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Original Research Article

Hyperuricemia in patients with pulmonary hypertension: A study in a tertiary care center

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ABSTRACT

Background: Pulmonary Hypertension is one of a life-threatening disease with high rate of patient mortality. Decreased cardiac output and tissue hypoxia is measured using Uric acid as a marker for assessment of pulmonary hypertension.

Materials and Methods: 75 patients who were diagnosed with a mean pulmonary arterial pressure of >22mmHg were categorized as group A and 75 healthy patients were considered to be Group B. Blood was collected for Uric acid, creatinine and total Bilirubin estimation. Pulmonary arterial systolic pressure as well as the ventricular function of the patients was evaluated using Colour Doppler ECG and a value of ≥50 mmHg, or a mean pulmonary arterial pressure (at rest) of ≥25 mmHg was taken and the right arterial pressure was calculated. Using the Simpson's formula, the right and left ventricular ejaculation factors (RVEF, LVEF) were calculated.

Results: The serum uric acid levels among the patients were 8.3±1.4mg/dL, creatinine levels were 2.1 ± 0.5 mg/dL, and the total bilirubin levels were 1.9 ± 0.8 mg/dL all of which was significantly higher than the controls. The uric acid levels were also positively correlated to the NHYA class. The blood pressure and the pulmonary arterial pressure were also higher than that of the controls. The correlation was done between the elevated uric acid and ejection fractions and the correlation coefficients of MPAP, LVEF, RVEF and the NYHA class were all significantly associated and the values were 0.394, -0.513, -0.467 and 0.38 respectively.

Conclusions: High serum uric acid levels is significantly associated with higher blood pressure, pulmonary arterial pressure and NYHA class. High serum uric acid levels can be a reliable prognostic marker for the detection of pulmonary hypertension. Early therapy may help in the reduction of mortality rate.

1. Introduction

Pulmonary Hypertension is one of a life-threatening disease with high rate of patient mortality. It is estimated that the approximate survival rate of the patient is 2.8 years.[1,2] It is not just a single disorder but consists of a group of disorders due to proliferative and obstructive pulmonary vessels remodeling which result in pulmonary arterial pressure and vascular resistance ultimately causing heart failure and death.[3,4] It is defined as a resting mean pulmonary arterial pressure which is higher than 25 mmHg and is measured by right heart catheterization, which is considered to be the gold standard for the diagnosis of PH.[5,6] PH can be seen at all ages – from infancy to elderly.[6] It is progressive and if untreated, it is a singular cause for death. However, since the symptoms are nonspecific, it is difficult to identify the condition.

Diagnosis of pulmonary hypotension is a challenge for the clinicians as the signs and symptoms are nonspecific and difficult to recognize. Most of the time, PH is due to an

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underlying condition and therefore, the symptoms of the PH are obscured with those of the underlying disease. Specific diagnosis is done for PH only when it is suspected, to check its presence and severity and cause. But at times, the ECG also may not suggest PH, making the diagnosis difficult and the clinician has to rely only on the clinical suspicion. The need for Right heart catheterization is required only when the PH is high, otherwise, in lower PH, other alternatives methods of treatment can be done.[7]

Decreased cardiac output and tissue hypoxia is measured using Uric acid as a marker for assessment of pulmonary hypertension.[6] Uric is found to be elevated even in diseases such as chronic heart disease, chronic obstructive lung disease and cyanotic congenital heart disease.[8–10] Increased levels of uric acid has been observed in left or right heart failure.[11] The test for uric acid estimation is simple and noninvasive, therefore it is one of the preferred methods.

Uric acid, being the final product of purine degradation is elevated when there is an over production of uric acid such as in myelo and lymphoproliferative diseases or during decreased excretion as in renal insufficiency and as a part of metabolic syndrome like in insulin resistance.[12] The mechanism of impaired oxidative mechanism in these diseases is due to depletion of adenosine triphosphate by tissue ischemia and hypoxia, and also the promotion is degradation of the adenosine nucleotides into inosine, xanthine, hypoxanthine and Uric acid.[13,14]

A strong correlation has been reported between elevated uric acid levels and pulmonary hypertension. This study was therefore done to investigate if uric acid levels can be used as a marker to predict the presence of pulmonary hypertension.

2. Materials and Methods

This prospective study was done by the department of Pulmonary medicine Kamineni Institute of Medical Sciences and Research Centre, and Maheswara Medical College over a period of 18 months i.e., March 2019 to Jully 2020 after getting the Institutional Ethical Clearance. 75 patients who were diagnosed with a mean pulmonary arterial pressure of >22mmHg were included into the study and categorized as group A. 75 healthy patients without pulmonary hypertension were also included into the study as controlled and assigned into Group B. Patients with renal dysfunction, hepatic diseases, pulmonary diseases, interstitial lung disease, hepatic diseases, congenital cardiac abnormalities and Diabetes mellitus were excluded from the study.

The nature of the study was explained in detail to the patients and controls and their relatives and informed consent was taken from all of them. A thorough demographic details were taken from all of them and they were all subjected to physical and clinical examination. ECG, chest X-rays (Posterio-anterior view), pulmonary function test, ventilation or perfusion scintigraphy was also done for all of them.

Pulmonary arterial systolic pressure as well as the ventricular function of the patients was evaluated using Colour Doppler ECG and a value of ≥50 mmHg, or a mean pulmonary arterial pressure (at rest) of ≥25 mmHg was taken and the right arterial pressure was calculated. Using the Simpson's formula, the right and left ventricular ejaculation factors (RVEF, LVEF) were calculated

The level of clinical impairment was classified according to the New York Heart Association (NYHA) into Class I-IV (Table 1).

Table 1: New York heart association functional classification

Class	Impairment
Class I	Asymptomatic – no limitation in physical activity, No breathlessness, fatigue or palpitations
Class II	Mild - Slight limitation in physical activity, Comfortable at rest but ordinary activity results in breathlessness, fatigue or palpitations
Class III	Moderate - Marked limitation in physical activity, comfortable at rest and less than ordinary activity results in breathlessness, fatigue or palpitations
Class IV	Severe - Unable to carry on physical activity without discomfort. Symptoms at ret may be present

For Uric Acid analysis, blood was collected by from medial cubital vein into vacutainers without anticoagulants so as to get serum and was transported to the Central lab for estimation. This Estimation of blood glucose level, creatinine, lipid profile was also done.

Statistical analysis was done using SPSS version 13.0 software and the data was expressed as mean ± SD. The comparison was analyzed using Pearson's correlation coefficient with $p<0.05$ considered to be significant.

3. Results

Among the 50 patients, 28 (56%) were females and 22 (44%) were males, while among the controls, 26 were females (52%) and 24 (48%) were males (Figure 1)

The predominant NYHA classification to which the patients belonged to were Class II, with 28 patients (56%), followed by Class III with 19 (38%) patients and 3(6%) belonged to Class IV (Figure 2).

The, mean ages of the patients were 40.67 ± 7.6years, and the same in controls was 36.4 ± 4.2 years. The serum uric acid levels among the patients were 8.3 ± 1.4mg/dL, which was significantly higher than the controls which was 4.1 ± 0.8 mg/dL. The creatinine levels were also higher in the patients which was 2.1 ± 0.5 mg/dL, while in controls, it was 0.9 ± 0.1 mg/dL. The total bilirubin levels among the patients were 1.9 ± 0.8 mg/dL and among the controls it was 0.7 ±0.2 mg/dL (Table 1).

Table 2: Uricacid levels among controls and cases

Variables	Controls	Cases	Significance
Mean Age ± SD	36.4 ± 4.2	40.67 ± 7.6.	
Uric Acid (mg/dl)	4.1 ± 0.8	8.3 ± 1.4	< 0.001
Creatinine (mg/dl)	0.9 ± 0.1	2.1 ± 0.5	< 0.001
Total Bilirubin (mg/dl)	0.7 ±0.2	1.9 ± 0.8	< 0.001

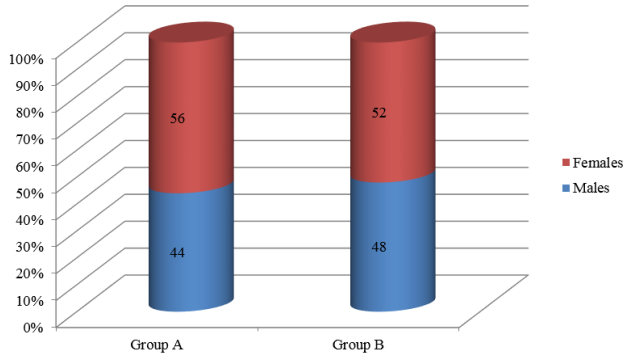

Fig. 1: Gender wise distribution of patients and controls

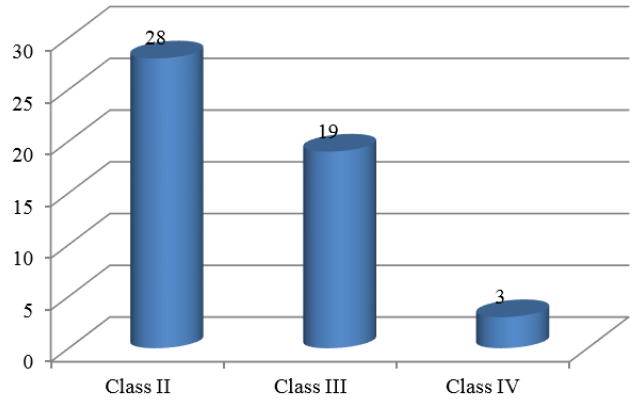

Fig. 2: NYHA classification of patients

The uric acid levels of patients in the NYHA Class II category were 3.87 ± 0.5 mg/dl, Class III was 4.61 ± 1.2 mg/dl and in Class IV, it was 8.84 ± 2.8 mg/dl. Out of the 3 patients in Class IV, all had very high Uric levels and all died during treatment (Table 2).

There was no significant difference between the pH of the blood of the patients and the controls, which was 7.44 ± 0.7 and 7.41 ± 0.4 respectively. However, there was significant difference in all the other blood parameters. The mean saturation of the blood oxygen levels in the patients was 65 ± 12% and in controls it was 91 ± 7.0 %, the blood CO2 levels were 37.7 ± 0.9 and in controls it was 28.4 ±3.1%. The blood pressure was higher among the patients with systolic being 129 ± 11 mmHg and diastolic being 91 ± 9 mmHg, while among the cases it was 113 ± 15mmHg and 78 ± 8 mmHg respectively, while the arterial pressure was 21.7 ± 3.8 in systolic and 12.4 ± 2.9 diastolic in patients and 14.7 ± 2.8 systolic and 9.1 ± 0.8 diastolic in controls and the MPAP was 15.9 ± 4mmHg in patients and 11.9 ± 5 mmHg in controls.

The cardiac output was 2.3 ± 1.6 L/min in cases and 3.9 ± 0.7 L/min in controls. The RVEF% and LVEF% was 41.6 ± 2.7 and 40.9 ± 2.1 in patients and 47.8 ± 4.1 and 45.1 ± 5.3 in controls respectively (Table 3).

The correlation was done between the elevated uric acid and ejection fractions and the correlation coefficients of MPAP, LVEF, RVEF and the NYHA class were all significantly associated and the values were 0.394, -0.513, -0.467 and 0.38 respectively (Table 4)

4. Discussion

The mechanism of the higher uric acid levels in patients with heart failure is not yet clear. As Uric acid is one of the final by product of purine metabolism, impairment of adenosine triphosphate (ATP) production occurs due to hypoxia, resulting in the degradation of ATP to diphosphate (ADP) and monophosphate (AMP). This further results in the increase in purine metabolite and thereby increase in uric acid levels.[15]

In the present study, there was no significant difference of the gender among the patients and controls. The mean age of the patients was 40.67 ± 7.6 years and we found no correlation of age with the uric acid levels. However, in a study by Seyyedi et al., they found an inverse relationship between the age and uric acid levels, with the younger group being more affected.[16] However a study by Kuzuya et al., reported an increase in the uric acid levels with increase in age.[17]

56% of the patients in the present study belonged to the NYHA Class II, while 38% belonged to Class III and 6% belonged to the Class IV in the present study.

The serum Uric acid levels, creatinine levels as well as Total bilirubin levels were significantly higher in the patients compared to the controls. The blood pressure and the pulmonary arterial pressure were also higher than that of the controls. The uric acid levels of patients in the NYHA Class II category were 3.87 ± 0.5 mg/dl, Class III was 4.61 ± 1.2 mg/dl and in Class IV, it was 8.84 ± 2.8 mg/dl. Out of the 3 patients in Class IV, all had very high Uric levels and all died during treatment. Similar results were observed in a study by Seyyedi et al., where

Table 3: Correlation ofuric acid levels with NYHA Class

NYHA Class	Uric Acid levels (Mean ± SD)
Class II	3.87 ± 0.5 mg/dl
Class III	4.61 ± 1.2 mg/dl
Class IV	8.84 ± 2.8 mg/dl

Table 4: Blood and pulmonary arterial pressure

Variables	Controls	Cases	Significance
pH of Blood	7.41 ± 0.4	7.44 ± 0.7	
Blood oxygen saturation %	91 ± 7	65 ± 12	< 0.001
Blood CO2 mmHg	28.4 ±3.1	37.7 ± 0.9	<0.001
Heart beats / min	88 ± 9	76 ± 8	< 0.001
Blood pressure – systolic (mmHg)	113 ± 15	129 ± 11	< 0.001
Blood pressure – diastolic (mmHg)	78 ± 8	91 ± 9	< 0.001
Pulmonary arterial pressure –systolic	14.7 ± 2.8	21.7 ± 3.8	< 0.001
Pulmonary arterial pressure –diastolic	9.1 ± 0.8	12.4 ± 2.9	< 0.001
MPAP mmHg	11.9 ± 5	15.9 ± 4	< 0.001
Cardiac output (L/min)	3.9 ± 0.7	2.3 ± 1.6	< 0.001
Right ventricular ejection fraction %	47.8 ± 4.1	41.6 ± 2.7	< 0.001
Left ventricular ejection fraction %	45.1 ± 5.3	40.9 ± 2.1	< 0.001

Table 5: Correlation between Uric acid and ejection fractions

Factors	Correlation coefficient	P value
MPAP	0.394	<0.01
LVEF	-0.513	<0.01
RVEF	-0.467	<0.01
NYHA Class	0.38	<0.01

high uric acid levels were seen in patients with severe pulmonary hypertension compared to moderate and mild hypertension.[16] Higher creatinine levels and higher uric nitrogen levels were observed in patients with high uric acid levels in a study by Zhang et al.[18] In contrast, Castillo-Martinez et al, in their study on patients with systemic lupus erythematosus, found no association between uric acid and PASP or any other markers.[19] They however concluded that a serum uric acid level of >7 did predict the development of pulmonary hypertension in the future.[19] Similar was the case in another study by Jamali et al.[20] Zhang et al also reported mortality to be associated with higher uric acid levels in patients.[18] Nagaya et al reported that patients with primary pulmonary hypertension who had high uric acid levels had a higher mortality rate compared to patients with lower uric acid levels, corroborating our study.[21]

The high levels of uric acid were positively correlated with the MPAP and NYHA class, while they were negatively correlated to the RVEF and LVEF. RV dysfunction, Pulmonary artery systolic pressure and the WHO functional class was significantly related to the high uric acid levels in another study by Seyyedi et al.[16] A positive correlation of the mean right arterial pressure was seen in the patients with high uric acid levels in a study by Voelkel et al[22] and Zhang et al.[18]

5. Conclusions

High serum uric acid levels is significantly associated with higher blood pressure, pulmonary arterial pressure and NYHA class. The mortality rate of patients with higher NYHA class and higher serum uric acid levels is also very high. Moreover, these levels are also related to the ventricular dysfunction and severity of the pulmonary hypertension. Thus, we conclude that high serum uric acid levels can be a reliable prognostic marker for the detection of pulmonary hypertension. Early therapy may help in the reduction of mortality rate.

6. Acknowledgments

None.

7. Conflict of Interests

The authors declare that there are no conflicts of interest in this paper.

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None.

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