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A Study on Serum Uric Acid in Patients with Heart Failure

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Abstract

Introduction: Elevated serum Uric Acid levels have been observed in clinical conditions associated with hypoxia. Cell death can cause accumulation of purine bodies and hence hyperuricemia. Increased activation of Xanthine Oxidase can be caused by tissue hypoxia, which itself is a consequence of vascular (and cardiac) dysfunction.

Methodology: A detailed history was taken including past or current morbidities. A structured clinical examination and the laboratory investigation profile of the subjects was recorded on a predesigned proforma. Height was measured by a Stadiometer, weight was recorded using a spring based weighting scale. BMI was calculated using formula of BMI = Weight (in kg)/ Height (in metre2).

Results: Serum Uric Acid level (SUA) estimation done in our study group of 85 patients diagnosed as congestive heart failure showed the following results – Patients with SUA <5 mg/dl consisted of 8.2% of the study group (n=7); patients with SUA 5.1–7 mg/dl consisted of 28.2% of the study group (n=24); the maximum number of patients had their SUA 7.1–9 mg/dl contributing 44.7% of the study group (n=38); whereas those with SUA >9 mg/dl contributed 18.8% of the group (n=16).

Conclusion: Thus, a total of 49 patients (65.33%) had hyperuricemia. The mean SUA was 7.68 ± 2.26 mg/dl.

Keywords: Serum Uric Acid; Heart failure; Hyperuricemia.

Introduction

The diagnosis of heart failure is mainly clinical but various investigations help us to understand the underlying cause and assessment of severity of Heart Failure. The classical clinical symptoms of heart failure are exertional dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, fatigue and the signs are elevated jugular venous pressure, pulmonary rales, third heart sound and peripheral oedema. No single symptom or sign is pathognomic of heart failure.[1,2]

Signs of HF are also non-specific. These include basal crepitations, oedema, raised jugular venous pressure and hepatomegaly. These signs may be absent in patients with compensated heart failure or those on drug therapy.[3]

Uric Acid is the end product of Purine Metabolism in Humans. It is the breakdown product of Xanthine and Hypoxanthine involving the enzyme Xanthine Oxidase. In human bloodplasma, the reference range of uric acid is typically 3.4–7.2 mg/dL (200–430 μmol/L) for men (1 mg/dL=59.48 μmol/L), and 2.4–6.1 mg/dL for women (140–360 μmol/L).

Hyperuricemia can be secondary to either an exaggerated production of Uric Acid that follows high cellular turn over conditions or, most

frequently, to a low renal excretion in patients with impaired renal function.[4]

Elevated serum Uric Acid levels have been observed in clinical conditions associated with hypoxia. Cell death can cause accumulation of purine bodies and hence hyperuricemia. Increased activation of Xanthine Oxidase can be caused by tissue hypoxia, which itself is a consequence of vascular (and cardiac) dysfunction.[5]

In numerous population studies, uric acid has been shown to be a predictor of cardiovascular mortality and serum UA has been reported to increase in patients with chronic congestive heart failure (CHF). Recent reports suggest that increased Uric Acid production through activation of xanthine oxidase is an important mechanism involved in the elevation of the serum UA level in CHF.[10] Xanthine Oxidase is also known as one of the main sources of free radicals and may contribute to oxidative damage in the myocardium.

A chronic increase in myocardial oxidative stress can cause subcellular abnormalities, and may lead to cardiomyopathic changes, depressed contractile function and failure.

Thus, an elevated serum level of Uric Acid may relate to cardiac dysfunction and progression of heart failure through oxidative stress by increased Xanthine Oxidase activity in patients with CHF.

For prognostication in CHF, the following 3 principal areas of relatively independent importance emerge: (1) a hemodynamic factor (for example, left ventricular ejection fraction [LVEF]); (2) the patient's functional status (e.g., peak oxygen consumption [V–O2]); and (3) a metabolic factor, including the neuroendocrine and immunologic processes.[6]

In CHF, hyperuricemia (independent of kidney function and diuretic dose) is a marker of impaired oxidative metabolism and hyper insulinemia, inflammatory cytokine activation, and impaired vascular function. The relationship of Uric Acid to kidney function and diuretic dose may additionally increase the value of Uric Acid as prognostic marker. Additionally, via degradation of accumulated purines, Uric Acid is a general marker of cell death.

Methodology

The target population consisted of patients of either sex diagnosed as Congestive Heart Failure according to the Framingham Criteria for Congestive Heart Failure, either admitted to the In-Patient Department (IPD) or visiting the out-patient department. They were contacted, explained about the purpose of study and requested for enrolment. They were provided with a patient information sheet either in Kannada, Hindi or English. Only those patients who volunteered for participation after fully satisfying themselves about the nature of the study were included into the study.

A written informed consent was obtained from these patients. 85 consecutive patients fulfilling all inclusion and exclusion criteria were included in the study as cases after obtaining a written informed consent.

A detailed history was taken including past or current morbidities. A structured clinical examination and the laboratory investigation profile of the subjects was recorded on a predesigned proforma. Height was measured by a Stadiometer, weight was recorded using a spring based weighting scale. BMI was calculated using formula of BMI = Weight (in kg)/ Height (in metre^2). BMI < 18.5 was classified as being underweight, 18.5–24.9 Normal, 25.0–29.9 were considered over-weight, > 30 were considered obese, > 40 were considered morbidly obese. All enrolled patients were randomly included into a group of patients with congestive heart failure, according to the Framingham Criteria and arranged for 2D- Echocardiographic examinations and relevant blood investigations at Hospitals. Patients underwent thorough examination and investigated as per inclusion and exclusion criteria.

Fasting Blood samples were withdrawn under aseptic precautions into a Plain/Serum vial from the cases in this study and sent to the Biochemistry Laboratory without significant delay. Uric acid estimation was done by Uricase-Peroxidase method, following the standard protocols.

In human blood plasma, the reference range of uric acid is typically 3.4–7.2 mg/dL (200– 430 μmol/L) for men (1 mg/dL=59.48 μmol/L), and 2.4–6.1 mg/dL for women(140–360 μmol/L).

Hyperuricemia was defined as serum uric acid level greater than 7 mg/dl; while serum uric acid level below 7 mg/dl was considered normal.

Results

Serum Uric Acid level (SUA) estimation done in our study group of 85 patients diagnosed as congestive heart failure showed the following results – Patients with SUA <5 mg/dl consisted of 8.2% of the study group (n=7); patients with SUA 5.1–7 mg/dl consisted of 28.2% of the study group

(n=24); the maximum number of patients had their SUA 7.1–9 mg/dl contributing 44.7% of the study group (n=38); whereas those with SUA >9 mg/dl contributed 18.8% of the group (n=16). Thus, a total of 49 patients (65.33%) had hyperuricemia. The mean SUA was 7.68 ± 2.26mg/dl. (Table 1,2)

Table 1: Distribution of study subjects according to uric acid.

Uric acid	Frequency	Percent
< 5	7	8.2
5.1 – 7	24	28.2
7.1 – 9	38	44.7
> 9	16	18.8
Total	85	100.0

Discussion

This study showed that hyperuricemia was found in majority (65.33%) of heart failure patients with increased prevalence in females. The mean uric acid level among females (n=21) was 7.57 mg/dl in comparison to a lower reading of 7.5 mg/dl among males (n=56). Normally, serum uric acid levels are higher in males as compared to that in females, but there are some studies 7,8that showed female dominance. In our study, we found higher levels of serum uric acid among females probably because moderate (LVEF 31–40%) to severe (LVEF

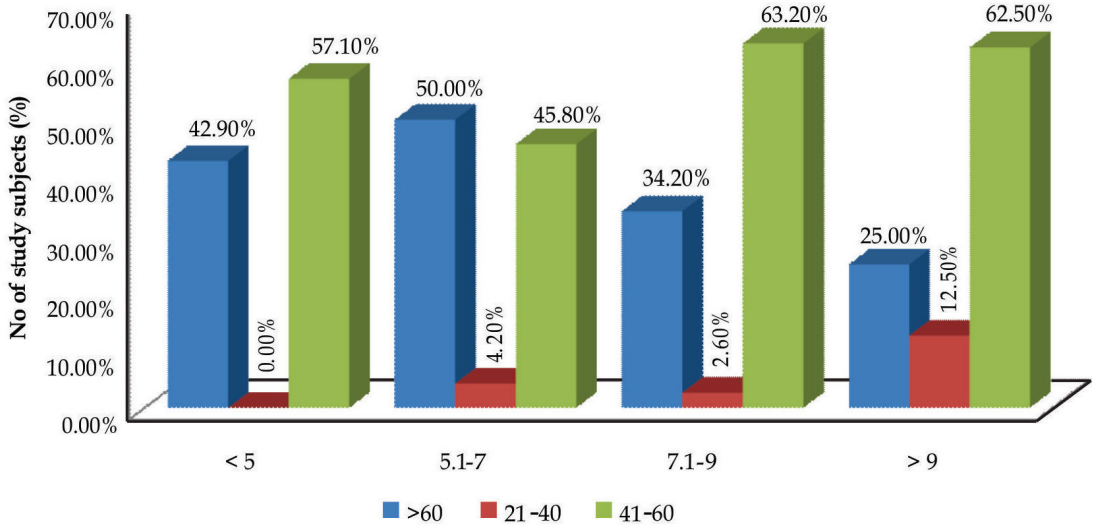

Fig. 1: Age category and Uric acid grade.

Table 2: BMI and Uric acid.

BMI	Uric Acid Grade				Total	Chi square	p value
	< 5	5.1–7	7.1–9	> 9			
<18.5	0	2	2	0	4	16.207	0.368
	0.0%	50.0%	50.0%	0.0%	100.0%		
18.5–24.9	3	11	15	6	35		
	8.6%	31.4%	42.9%	17.1%	100.0%		
25–29.9	1	8	17	8	34		
	2.9%	23.5%	50.0%	23.5%	100.0%		
30–34.9	2	3	2	1	8		
	25.0%	37.5%	25.0%	12.5%	100.0%		
25–39.9	1	0	2	0	3		
	33.3%	0.0%	66.7%	0.0%	100.0%		
>=40	0	0	0	1	1		
	0.0%	0.0%	0.0%	100.0%	100.0%		
Total	7	24	38	16	85		
	8.2%	28.2%	44.7%	18.8%	100.0%		

<30%) cardiac dysfunction was seen in 85.7% females while it was found in 64.1% males. Also, in the study group, the mean left ventricular ejection fraction was also lower in females (28.95%) in contrast to that in males (34.02%). This observation explained the reason for a higher serum uric acid levels among female population in our study.

The patients that were included had a renal function with estimated GFR > 30 ml/min/1.73m2 body surface are. As the renal functions declined, the serum uric acid levels increased, as evident by 73% patients having hyperuricemia (SUA >7 mg/dl) with eGFR above 90 ml/min/1.73m2 (n=26); 51.5% patients having hyperuricemia with eGFR between 60–89 ml/min/1.73m^2 (n=33); and 69.2% patients having hyperuricemia with eGFR between 30–59 ml/min/1.73m^2 (n=26). This association held showed a p-value of 0.33. Thus, this study showed a negative correlation between eGFR and serum uric acid levels but was not stastically significant (correlation coefficient = –0.423).

However, because uric acid is primarily eliminated via the kidneys, hyperuricaemia in heart failure patients with CKD (eGFR<60 ml/min/1.73m^2) may in large part be considered due to impaired renal excretion of uric acid. On the other hand, hyperuricaemia in patients without CKD (eGFR≥ 60 ml/min/1.73m^2) may be considered primarily due to increased production of uric acid and thus a marker of increased xanthine oxidase activity.[9,10]

The mean serum uric acid level in patients with CKD was higher (8.8 mg/dl), in contrast to that in patients without CKD (7.04 mg/dl). Despite a higher mean serum uric acid level among patients with CKD, such patients had a less severe cardiac dysfunction as compared to those without CKD. This was evident by a higher mean LVEF among patients with CKD (34.48%) than those without CKD (29.63%), as also shown by Gerasimos S. Filippatos, et al (2011).

From the above findings, it was made clear that elevated uric acid levels served as a clinical marker for the multiple pathological processes viz.: metabolic, inflammatory and neuro- endocrine, in the progression of heart failure as evident by decreasing left ventricular ejection fraction. Elevated uric acid levels indicated cardiac dysfunction and progression of heart failure through oxidative stress and free radical injury by increased xanthine oxidase activity.

Hyperuricaemia was common in patients with advancing heart failure. However, this association was only observed in patients without CKD but not in those with CKD, despite a higher mean serum uric acid level among the latter group. Hyperuricaemia in patients without CKD was likely primarily due to increased production and thus a marker of increased xanthine oxidase activity.

Conclusion

- The prevalence of hyperuricemia was significantly higher in patients with congestive heart failure.
- Hyperuricaemia in patients without chronic kidney disease is primarily a marker of increased xanthine oxidase activity, while in patients with chronic kidney disease it is primarily due to impaired renal excretion of uric acid.

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