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General Medicine

SERUM URIC ACID LEVELS IN ESSENTIAL HYPERTENSION AND ITS CORRELATION WITH MICROALBUMINURIA

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ABSTRACT Raised serum uric acid has been reported to be associated with an increased risk of coronary Heart disease and is commonly encountered with essential hypertension, even untreated Hypertension, and type 2 diabetes, which are in turn associated with coronary heart disease. Increased serum uric acid level combined with hypertension might cause an endothelial dysfunction and result in glomerular hypertension, which would induce microalbuminuria and hyper filtration.

AIM : This study was done to determine whether raised serum uric acid levels was an independent risk factor for developing hypertension.

OBJECTIVES:

(1)To study the relationship between serum uric acid levels and hypertension.

(2)To study the relationship between serum uric acid levels and severity of hypertension.

(3)To study the relationship between serum uric acid levels and microalbuminuria (marker of target organ damage) in hypertensives.

STUDY DESIGN: Prospective observational study

MATERIAL AND METHODS: 200 patients who attended in-patient or out-patient clinic in the department of Medicine, MGM hospital, Warangal during the period of one year were evaluated for Serum Uric Acid levels and urinary Microalbumin levels of which 100 were cases and 100 were controls.

INCLUSION CRITERIA:-

1) Known cases of essential hypertension; according to JNC VIII classification.

2) Male and Female patients >18 years and < 65 years of age.

EXCLUSION CRITERIA:-

- Diabetes Mellitus,
- Ischemic Heart Disease,
- All cases of secondary hypertension,
- Clinical findings of Gout or extraarticular manifestations of hyperuricemia
- Obesity (BMI > 25)
- H/o alcohol abuse
- H/o drugs known to cause hyperuricemia, e.g. thiazide diuretics, anticancer therapy.
- History of leukemia, polycythemia, lymphoma or any neoplastic disease.
- H/o Renal disease, Patients with UTI
- H/o pre-eclampsic toxemia

RESULTS: In the present study patients are in the age group of 31-65 years with mean age of 51.7 years. Mean serum uric acid in stage 1 hypertensives was 6.21±2.05 and in stage 2 hypertensives were 4.79±1.85. The serum uric acid was significantly higher in all stages of Hypertension when compared to the normotensives, but hyperuricemia did not correlate with the severity of hypertension.

CONCLUSION: Serum uric acid is higher in hypertensives and did not correlate with the severity of hypertension. Serum uric acid is higher in hypertensives with microalbuminuria and hence a surrogate marker for target organ damage.

KEYWORDS :

Hypertension and Hyperuricemia:

Uric acid is also commonly associated with hypertension. It is present in 25% of untreated hypertensive subjects, in 50% of subjects taking diuretics, and in >75% of subjects with malignant hypertension. Hypertensive people with raised serum uric acid had a significantly higher relative risk (RR) for both heart attack and stroke. The NHANES III data support the hypothesis that uric acid is an independent risk factor for hypertension-associated morbidity and mortality.

High serum uric acid concentrations may increase serum sodium reabsorption at nephron sites proximal to the distal tubule, and it has been proposed that metabolic perturbations such as hyperinsulinaemia may mediate some of the effects of hypertension. . It seems safe to say that hyperuricaemia in hypertension may be an early indicator of hypertensive cardio renal disease, which is commonly associated with a multimetabolic syndrome.

Increased SUA in Hypertension

The increase in serum uric acid in hypertension may be due to the decrease in renal blood flow that accompanies the hypertensive state, since a low renal blood flow will stimulate urate reabsorption. Hypertension also results in micro vascular disease, and this can lead to local tissue ischemia[6]. In addition to the release of lactate that blocks urate secretion in the proximal tubule, ischemia also results in increased uric acid synthesis. With ischemia, ATP is degraded to adenine and xanthine, and there is also increased generation of xanthine oxidase. The increased availability of substrate (xanthine) and enzyme (xanthine oxidase) results in increased uric acid generation as well as oxidant (O_2^-) formation.

MICROALBUMINURIA

Albumin excretion in healthy individuals ranges from 1.5 to 20 mcg/min with geometric mean in the range 6.5mcg/min, these have been termed normoalbuminuria. The persistent excretion of abnormal levels of urinary albumin, equivalent to between 30 and 300 mg/day, is below the level that can be detected by a standard urine protein dipstick and termed microalbuminuria.

EFFET OF MICROALBUMINURIA AND TARGET ORGAN DAMAGE :

Hypertensive target organ damage is more common in microalbuminuric patients[9]. Patients with elevated UAE have higher left ventricular mass, a higher prevalence of hypertensive retinopathy and an increased thickness and presence of plaques in the carotid

artery. Furthermore, the presence of microalbuminuria in essential hypertensive patients has been interpreted as a marker of early intrarenal vascular dysfunction in essential hypertension.

An absence of the capacity of the renal vasculature to vasodilate in response to an intravenous amino acid infusion or to an ACE inhibitor is present in patients with microalbuminuria. These findings could be of great relevance for two reasons, first because the existence of functional renal vasoconstriction since the very early stages of essential hypertension contributes to the development of high blood pressure; second because microalbuminuria could be a marker of the presence of nephrosclerosis.

Microalbuminuria is an independent predictor of cardiovascular morbidity and mortality in both men and women with essential hypertension. This could, in turn, be facilitated by the frequent association of an elevated urinary albumin excretion to a series of alterations, such as endothelial dysfunction, insulin resistance, altered lipid levels, higher body mass index, increased serum uric acid and salt-sensitivity[10–14]. All these alterations could facilitate the accompanying risk for atherosclerosis.

MICROALBUMINURIA AND HYPERURICEMIA:- Studies have revealed the association of microalbuminuria and elevated serum uric acid level with cardiovascular disease among patients with diabetes mellitus and hypertension. Some investigators have suggested that uric acid plays a causal role in the development of cardiovascular disease whereas others have concluded that uric acid merely reflects other concomitant risk factors, such as hypertension, insulin resistance, obesity, or lipid abnormality. The independent association of uric acid with cardiovascular disease appears to be stronger in persons with hypertension than in the general population.

It is unknown whether increased uric acid level and high blood pressure have synergistic effects on microalbuminuria or whether serum uric acid level is another marker of target organ damage by high blood pressure.

Several mechanisms have been proposed to explain a possible causal relationship it has been shown previously that hyperuricemia induced endothelial dysfunction, glomerular hypertension, and renal hypertrophy, even in conditions of mild hypertension in experimental rat model.

MATERIALS AND METHODS:

In the following hospital based study of **Serum Uric Acid Levels in Essential Hypertension and its correlation with Microalbuminuria.** 200 patients who attended in-patient or out-patient clinic in the Department of Medicine, MGM hospital, Warangal during the period of May 2016 to August 2017 were evaluated for Serum Uric Acid levels and urinary microalbumin levels of which 100 were cases and 100 were controls.

Data collection and measurements:

- Clinical examination, blood pressure measurement, anthropometric measurements (height and weight), urine for protein and sugar ,fasting serum uric acid levels, haemogram and Renal function tests.
- Lipid profile, Electrocardiogram, Chest X-ray.
- After a 5 min rest, systolic and diastolic blood pressures were measured in the sitting position on the right arm with a standard mercury sphygmomanometer on three separate occassions. The body mass index was calculated as the weight in kilograms divided by the height in m^2

Method of Uric Acid estimation Principle:

Blood sample of 5cc was drawn, collected in to dry plain bottle and sent to biochemistry laboratory. The enzymatic method (Uricase method) is used for analysis.

In our laboratory, normal range of Uric Acid 3.4-7.0 for males and 2.4-6.0 mg/dl for females.

Estimation of Urinary Microalbumin by Turbidimetric Immunoassay:

Presence of albumin in the test specimen forms an insoluble complex producing a turbidity which is measured at wavelength 340nm. The resulting turbidity corresponds to the concentration of the albumin in test specimen .

RESULTS AND ANALYSIS

In the study, a total of 200 subjects were studied of which 100 patients were cases that were categorized into Stage 1 or Stage 2 hypertension (based on JNC VIII classification) and 100 were controls who were subjects without hypertension or any other condition known to cause raised serum uric acid levels. The total number of male cases was 65 and the total number of female cases was 35. The total number of male controls was 65 and the total number of female controls were 35. The controls were adjusted with the cases for age and sex. The age group was between 25 to 65 years.

Sex Distribution: - Both cases and controls had 65 males and 35 females.The serum uric acid in male cases ranged from 2.2mg/dl – 11.5mg/dl and in female cases ranged from 2.2mg/dl – 8.8mg/dl.The serum uric acid in male controls ranged from 1.2mg/dl – 7.2mg/dl and in female controls ranged from 1.2mg/dl – 7.4mg/dl.

The urinary albumin in male controls ranged from 1.1mg/day – 331.5mg/day and in female cases ranged from 2mg/day – 119.2mg/day.The urinary albumin in male controls ranged from 2mg/day - 188mg/day and in female controls ranged from 2mg/day – 176mg/day.

The data was entered in excel sheet and transported to SPSS V.21 and analysed. Independent sample t test was used to test significance.
The total number of cases were 100 (both male and female), the data analysis of the cases showed the mean SUA level to be 4.17 with a standard deviation of 2.29 (4.17 ± 2.29). The total number of controls were 100 (both male and female), the data analyzed showed a mean SUA level of 2.14 with a standard deviation of 1.51 (2.14 ± 1.51).

Independent sample t test was applied and p value was found to be <0.001 which is statistically significant. This showed that there was a significant rise in serum uric acid levels in patients with hypertension when compared to normotensives.

Serum Uric Acid in Normoalbuminuric and Microalbuminuric Hypertensives:-

In this study of 100 hypertensives 54 were found to be normoalbuminuric (UAE<30mg/day) and 46 were found to be microalbuminuric (UAE>30mg/day).

Serum uric acid in normoalbuminuric hypertensives was 4.26 with a standard deviation of 1.46. Serum uric acid in microalbuminuric hypertensives was 7.11 with a standard deviation of 1.51.

The data was analysed using independent sample t test and p value was found to be <0.001 which is statistically significant.

DISCUSSION

Elevated SUA levels have been associated with an increased risk for cardiovascular disease. The potential mechanisms by which SUA may directly affect cardiovascular risk include enhanced platelet aggregation and inflammatory activation of the endothelium.

Because elevated serum uric acid is correlated with several risk factors including renal dysfunction, hypertension, insulin resistance, hyperhomocystenemia and hyperlipidemia, it is debated whether SUA is an independent cardiovascular risk factor.

SERUM URIC ACID LEVELS (SUA) AND SEVERITY OF HYPERTENSION

In the present study mean serum uric acid in stage 1 hypertensives was 6.21±2.05 and in stage 2 hypertensives was 4.79±1.85. The serum uri acid was significantly higher in all stages of hypertension when compared to the normotensives, but hyperuricemia did not correlate with the severity of hypertension.

In our study the incidence of hyperuricemia in cases with stage 1 hypertension was 38% and those with stage 2 hypertension was 23 %. In our study of 100 hypertensives 54 were normoalbuminuric and 46 were microalbuminuric. Out of the 46 cases with UAE >30 mg/day, 27 cases had hyperuricemia (58.6%) which was statistically significant i.e., serum uric acid was significantly higher in microalbuminuric than in normoalbuminuric hypertensives.

Several mechanisms have been proposed to account for the association between SUA and renal abnormalities, and include:
(1) Increased uric acid production to counteract oxidative stress and

endothelial damage in the context of the atherosclerotic process.
(2) The severity of hypertension itself.
(3) A subtle reduction in glomerular filtration rate leading to impaired renal uric acid clearance.
(4) Increased SUA level and hypertension induced endothelial dysfunction leads to glomerular hypertension and hyperfiltraion leading to microalbuminura.

Two possibilities can be drawn from the association of hypertension with raised SUA levels: - Hypertension can cause hyperuricemia and Hyperuricemia may lead to hypertension.

Mechanisms explaining hyperuricemia in hypertension:-

(1) Hyperuricemia reflects decreased renal blood flow, presumably a reflection of nephrosclerosis associated with hypertension, leading to increase urate reabsorption.
(2) Hypertension is associated with microvascular disease leading to local tissue ischemia, which results in release of lactate that blocks urate secretion in proximal tubule. Local tissue ischemia is also associated with increased uric acid synthesis.[14]

Mechanisms explaining how hyperuricemia may lead to hypertension:-

(1) Hyperuricemia induced endothelial dysfunction secondary to oxidant stress.
(2) Impaired endothelial NO release.
(3) Uric acid induced vascular smooth cell proliferation.
(4) Elevated SUA levels associated with insulin resistance, high serum triglyceride levels, chronic inflammation and increased arterial stiffness all of which may affect the development of hypertension.[15]

It is certainly possible that uric acid may be an earlier and more sensitive marker of decreased renal blood flow than serum creatinine. It has been suggested that serum uric acid may play a role in the formation of free radicals and oxidative stress, the increased risk of hypertension in subjects with raised serum uric acid levels might be associated with this increased generation of free radicals.

An antioxidant deficiency in diet which produces hyperuricemia contributes to the aetiology of hypertension and the antioxidant drugs also show a blood pressure lowering effect in both diabetic and hypertensive patients. In our study we found that there is definite relation in SUA levels between hypertensive patients and normotensive patients but there is no direct proportional relation between the levels of SUA and severity of hypertension.

STUDY LIMITATIONS:

1) The sample size is small.
2) Design study is cross sectional, hence only a point of time value can be found.
3) The impact of lowering the serum uric acid levels on hypertension could not be studied longitudinally.

CONCLUSION

1) Serum uric acid is higher in hypertensives.
2) Serum uric acid did not correlate with the severity of hypertension.
3) Serum uric acid is higher in hypertensives with microalbuminuria and hence a surrogate marker for target organ damage.

Graph 1:- serum uric acid and stages of hypertension.

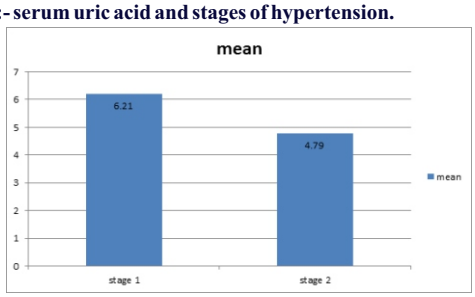
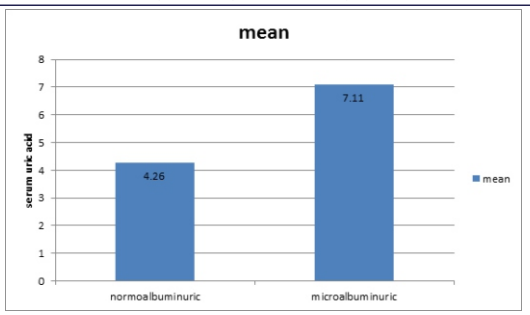


Table 1:- Serum uric acid levels between cases and controls.

category	number	mean±SD
cases	100	4.17±2.29
controls	100	2.14±1.51



Graph 2: SUA in normoalbuminuric and microalbuminuric hypertensives.

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