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Correlation between serum uric acid level and hypertension: A case control study

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Abstract
The association of raised serum uric acid levels with various cardiovascular risk factors has often led to the debate of whether raised serum uric acid levels could be an independent risk factor in essential hypertension. Hence we carried out a study to examine the possibility of hyperuricemia causing hypertension. The study was carried out in Sri Adhichunchungiri institute of medical science the study period was of 18 months from April 2004 to September 2005 a total of 400 patients were studied of which 200 were cases and 200 controls. The patients were included if they satisfied the JNC VII criteria for hypertension. They were excluded if they were having any other condition known to cause raised serum uric acid levels & secondary hypertension. The study showed that serum uric acid levels were raised in patients with hypertension in comparison to normotensives. The Mean SUA levels between cases and controls were 6.104 ± 1.576 and 5.685 ± 1.338 respectively. t-value = 2.866, p - value =.004. SUA levels in the stages of hypertension showed a mean serum uric acid level in stage 1 hypertension of 5.0312 ±.77 and stage 2 hypertension 6.4421± 1.615 the t- value of 8.213 and p- value =.000 which was significant. SUA level in patients with hypertension 5 years was 5.163 ± 1.255 those with ≥ 5 years was 6.972 ± 1.326. t-value of 9.891, p-value =.000 which was also significant. Based on the study carried out we concluded that SUA can be used as an early biochemical marker to determine the severity and duration of hypertension.

Keywords: serum uric acid, hypertension, JNC VII, Hyperuricemia

Introduction
Association between hypertension and hyperuricemia was recognized when a family with a unique and unfortunate pedigree attended Hammer Smith hospital in 1957. The father and six of the seven siblings had hyperuricemia, while the mother and all the siblings had hypertension [1]. This raised the question whether a raised serum uric acid was common in patients with hypertension. 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. It is not known wheth raised serum uric acid increases the risk of hypertension and type 2 diabetes independently of known risk factors such as age, obesity, alcohol consumption, and physical activity [2].
Hypertension is the third leading killer disease in the world and is responsible for 1 in every 8 deaths. About 1 billion people are affected by hypertension worldwide [3]. The prevalence of hypertension is known to increase with age. Over 50% of individuals aged 60 to 69 and over 75% of those aged 70 years and older are affected. Recent Framingham Heart Study reported that lifetime risk of developing HTN is approximately 90% for men and women who are normotensive at 55-65 years old and survived to the age of 80-85 years [4]. This study was carried to determine correlation between serum uric acid level and hypertension.

Methods
In the following Hospital based study 400 patients who attended the out-patient and in-patient at the department of Medicine were evaluated for Serum Uric Acid levels of which 200 were cases and 200 were controls. The study was conducted over a period of 18 months starting from April 2004 to September 2005.
Adult male and female patients > 18 years of age diagnosed as hypertensive according to JNC VII classification for hypertension were included as cases; patients were excluded if they had any of the following - Diabetes Mellitus, Ischaemic Heart Disease, All cases of secondary hypertension, Clinical Findings of gout or extra- articular manifestations of hyperuricemia, Obesity (body weight exceeding 25% of body weight), H/o alcohol abuse, H/o drugs known to cause hyperuricemia, e.g. thiazide diuretics, H/o Renal disease, H/o pre-eclampsic toxemia. Controls were patients without hypertension or any other condition known to cause hyperuricemia and were matched for age and sex with that of the cases.

Data collection and measurements
The clinical examination consisted of a medical history, a physical examination, blood pressure measurement, anthropometric measurements, measurement of fasting serum uric acid levels and other parameters like Blood haemogram, Renal function tests (blood urea, serum creatinine), Electrocardiogram, Chest X-ray, Lipid profile (Total cholesterol, triglycerides, HDL- cholesterol, LDL-cholesterol), urine for protein and sugar.
The patients were asked to fast for 12 hours and to avoid smoking and heavy physical Exersice for more than 2 hours before the examinations. After a 5 min rest in a quite room, systolic and diastolic blood pressures were measured in the sitting position twice at an interval of a few minutes on the right arm with a standard mercury sphygmomanometer on three separate occassions. Anthropometric measurements included height and body weight, which were measured while the subject was wearing light clothing without shoes.

The body mass index was calculated as the weight in kilograms divided by the height in m^2.

Hypertension was defined according to the JNC VII classification of hypertension as those with SBP of < 120 mm hg and DBP of < 80 mm hg as normal, those with SBP of 120- 139 mm hg or DBP of 80 - 89 mm hg were labeled pre-hypertensive were not taken up for the study, those with SBP 140 -159 mm hg or DBP of 90 - 99 mm hg were labeled as having Stage 1hypertension, and those with SBP ≥ 160 or DBP ≥ 100 mm hg were labeled as Stage 2 hypertension.

Method of Uric Acid estimation

Sample: The Sample used was unhemolyzed serum or plasma separated from the cells as soon as possible. Recommended anticoagulants are heparin and EDTA. Uric acid is stable in serum or urine for 3 days at 20 - 25º C.

Mix and incubate for 5 minutes at 37º C. Read the absorbance of standard and each sample at 510 nm (500 - 550 nm) or 510/630 nm on biochromatic analysers against reagent blank.

Linearity: Upto 25mg/dl (1.5 mmol/L). For higher values, it is recommended to dilute the samples with normal saline, and repeat the assay. Multiply the results with dilution factor. The color developed is stable for 15 minutes. The reagent and sample volume may be altered proportionally to accommodate various analyzer requirements. Specimens with Uric acid concentration greater than 1.5 mmol/L should be diluted with saline and reassayed. Multiply results by dilution factor. S.I. unit conversion factor, mmol/L x 16.8 = mg/dl. Reference Values for SUA levels in Males was 3.4 - 7.0 mg/dl and in females 2.4 - 6.0 mg/dl

Results

During the 18 month study period from April 2004 to September 2005 a total of 400 patients were studied of which 200 patients were cases that were categorized into Stage 1 or Stage 2 hypertension (base on JNC VII classification) and 200 were controls who were patients without hypertension or any other condition known to cause raised serum uric acid levels. The total number of male cases was 145 and the total no of female cases 55. The age group ranged from 20 years to 90 years.

The total number of male controls was 145 and the total no of female controls were 55. The age group ranged from 20 years to 90 years. The controls were adjusted with the cases for age and sex, shown in fig-7. Total number of male patients was 145 and the total no female patients were 55 both in cases and controls table no. - 4

The Serum Uric Acid levels in male cases ranged from 3.8 mg/dl to 9.8 mg/dl and female cases ranged from 3.2 mg/dl to 9.5mg/dl. The Serum Uric Acid levels in male controls ranged from 2.8 - 9 mg/dl and female controls ranged from 3 - 8.4mg/dl. The statistical analysis was performed using the SPSS 10.0 software package. The data was analyzed using the t-test (Independent sample t-test) and p Value less than 0.05 was considered as significant.

The total number of cases were 200 (both male and female), the data analysis of the cases showed the mean SUA level to be 6.104 with a standard deviation of 1.576 (6.104 ± 1.576). The total number of controls of controls were 200 (both male and female), the data analyzed showed a mean SUA level of 5.685 with a standard deviation of 1.338 (5.685 ± 1.338), as shown in table no - 5. The t-value was found to be 2.866 and the p value =.004 which was significant. This showed that there was a significant rise in serum uric acid levels in patients with hypertension when compared to normotensive.

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 [5]. In few studies, the association of SUA with cardiovascular disease was uncertain after multivariate adjustment as in the Framingham Heart Study (1985) and the ARIC study (1996), but in others the association remained certain and significant. In the present study the incidence of hyperuricemia in controls was 17% and the incidence of hyperuricemia in cases was 37 %.

Various other studies have also shown that increased SUA levels were seen in hypertensive patients. Kinsey (1961) in his study with 400 hypertensive patients reported a 46 % incidence of hyperuricemia in hypertensives[5]. Kolbe (1965) in his study of 46 hypertensive patients found 26 to be having increased SUA levels (56 %) [6]. A. Breckenridge (1966) showed 274 of 470 patients on antihypertensive treatment (58%) had raised SUA levels and 90 of the 333 patients (27%) attending the clinic for the time had hyperuricemia[1]. In a study by C. J. Bulpitt (1975), 48 % male hypertensives and 40 % female hypertensives had their SUA level in the hyperuricemic range [7].

Ramsay (1979) in his study of 73 men with untreated hypertension had 18 with raised serum uric acid levels (25%) [8]. Messerli *et al.* (1980) had an incidence of 72 % raised SUA in their study population of 39 established hypertensives. Messerli and Frohlich *et al*. hypothesized that the frequent presence of hyperuricemia in hypertensive patients reflects underlying renal dysfunction or reduced renal perfusion [9]. It certainly is possible that uric acid may be an earlier and more sensitive maker of decreased renal blood flow than serum creatinine. It has been recently suggested that since 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.

Several observations support this concept of free radical mediated inhibition of endothelium dependent vasodilation. An antioxidant deficiency in diet which produces hyperuricemia, contributes to the etiology of hypertension, and the antioxidant drugs also show a blood pressure lowering effect in both diabetic and hypertensive patients [10]. In a study by Tykarski (1991), he showed SUA concentration and the prevalence of hyperuricemia were significantly higher in hypertensive patients. They further demonstrated that tubular secretion of uric acid was significantly lower in hypertensive patients in comparison with normotensive subjects. There was no difference in pre and post- secretory reabsorption of uric acid. They concluded that high prevalence of hyperuricemia in essential hypertension was caused by impaired renal excretion of uric acid [11].

In gouty patients without advanced tophi, however renal failure and hypertension are rare. In a group of 80 patient's attending the Hammer Smith hospital gout clinic only 2

were hypertensive. In a study of gouty patients of Northern India by Kumar *et al.* they found that only one out of 30 patients had hypertension [12]. Fessel *et al.* showed no appreciable loss of renal function in 112 patients with gout as compared to normal subjects followed up for 12 years [13]. In a study by Lawrence E Ramsay there was no evidence that hyperuricemia had a deleterious effect on renal function [14]. Canon *et al.* considered that an impairment of renal function will raise the SUA levels more commonly than an increased SUA will cause renal damage [15].

Hence it is unlikely that hypertension arises as a result of raised SUA levels, but the possibility that uric acid which plays 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. Hence the fact that raised SUA levels can lead to Hypertension cannot be entirely ruled out.

Table 1: Serum uric acid and hypertension

Variable	Conditions	Number	Mean ± SD	P Value
SUA level	Cases	200	6.104 ± 1.576	0.004
	Controls	200	5.685 ± 1.338	
Stage of hypertension	Stage 1	48	5.0312±.77	0.000
	Stage 2	152	6.4421± 1.615	
Duration of hypertension	< 5 years	96	5.163 ± 1.255	0.000
	≥ 5 years	104	6.972 ± 1.326	

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