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Original Article

Biochemistry Section

Comparison of Uric Acid Levels in Hypertensive Patients with and without Heart Disease: A Case-control Study

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ABSTRACT

Introduction: Hypertensive heart disease is the 13th leading cause of death worldwide. Uric Acid (UA) is an end product of purine metabolism in humans and higher serum UA is a potential independent risk factor for Cardiovascular Disease (CVD).

Aim: To compare the levels of serum UA in hypertensive individuals with and without cardiovascular disease.

Materials and Methods: This case-control study was done at RIMS, Telangana, India from October to December 2021 including 50 individuals with hypertension and without CVD enrolled as controls and 100 individuals with Hypertensive Heart Disease (HHD) as cases. The HHD cases were subdivided into group 2A (age <=55 years) and 2B (age >55 years). Samples were collected and analysed for UA, lipid profile, serum creatinine, fasting blood sugar, etc. Independent samples t-test was used for statistical analysis using Statistical Package for Social Sciences (SPSS) software version 28.0.1.1 (15).

Results: Males and females were taken in a ratio of 1:1. Mean age for control group was 54.6±9.6 years, for HHD ≤55 years was 50±3.232 and for HHD >55 years was 63.26±6.137 years. In males, mean values of serum UA was 5.1±0.5 mg/dL in controls, 9.2±1.0 mg/dL in HHD ≤55 years (p-value=0.03), 6.4±0.8 mg/dL in HHD >55 years (p-value=0.1). In females, mean values of serum UA was 4.8±0.4 mg/dL in controls, 10.5±0.4 mg/dL in HHD ≤55 years (p-value=0.009), 6.9±0.5 mg/dL in HHD >55 years (p-value=0.09) Standard Deviation (SD). Serum UA levels were significantly higher in patients of HHD less than 55 years of age than that of controls.

Conclusion: Based upon the findings of the study, it was concluded that hypertensive individuals with cardiac disease had higher levels of serum UA than controls, especially in females.

Keywords: Blood pressure, Cardiovascular disease, Lipid profile, Purine metabolism

INTRODUCTION

Hypertension (HTN) is a well-known and strong risk factor for CVD [1]. Experimental and clinical evidences support the possibility that an elevated serum UA level may independently lead to or worsen hypertension [2].

Hypertensive Heart Disease (HHD) refers to a constellation of changes in the left ventricle, left atrium, and coronary arteries as a result of chronic blood pressure elevation, which increases the workload on the heart inducing structural and functional changes [3]. International Classification of Diseases (ICD)-10 definition for HHD includes heart failure and other cardiac complications of hypertension when a causal relationship between the heart disease and hypertension is stated or implied [4]. Hypertension precedes heart failure in 90% of cases [5]. Hypertensive heart disease was estimated to be responsible for 1.0 million deaths worldwide in 2004 (or approximately 1.7% of all deaths globally), and was ranked 13th in the leading global causes of death for all ages [6].

Uric Acid (UA) is an end product of purine metabolism in humans [7]. Increased serum UA levels are independently and significantly associated with risk of cardiovascular morbidity and mortality [8]. The relationship of UA with cardiovascular events is particularly strong, especially in patients at high-risk for heart disease [9]. Several studies suggested a U-shaped relationship between serum UA and risks of total and cardiovascular mortality, with lower UA levels mainly increasing stroke-related mortality, and higher UA levels mainly increase heart-related mortality [1,10,11].

The three main factors that affect the mechanism of angiopathy due to hyperuricaemia include the effects of oxidative stress during UA production, the urate transporter disorders and hyperuricaemia induced vascular disorders (facilitation of arteriosclerosis by deposition of monosodium urate crystals) [12]. In ischaemic state, hypoxanthine is converted to xanthine by Xanthine Oxidase (XO) which is further converted to UA. During this conversion, reactive oxygen is produced. Reactive Oxygen Species (ROS) stimulate proliferative effect on vascular wall and is involved in arteriosclerosis as ROS binds to Nitric Oxide (NO) and supresses its function [12].

Dyslipidaemia (Dyslipidaemia is characterised by the elevation of total cholesterol, Triglycerides (TGs), or both, or a low High-Density Lipoprotein (HDL) cholesterol level that contributes to the development of atherosclerosis), smoking, obesity and lack of physical activity were recognised as prominent risk factors for cardiovascular disease in a study by Ciumornian L et al., [13]. Infectious diseases are one of the precipitating factors for cardiovascular disease in addition to lack of compliance to proper diet [14]. Hyperuricaemia is associated with gout, chronic kidney disease and diabetes mellitus [15]. Age also is a major risk factor for CVD as in India, approx 40% of myocardial infarction occur in people aged <45 years and approx 33% occurs in people aged ≤55 years [16].

Serum UA assessment is less expensive when compared to assessment of other cardiac biomarkers (Troponins, CK-MB, NT-proBNP). The evidence regarding the link between serum UA levels and cardiovascular mortality in hypertensive individuals is unclear. Identifying this association may provide new insights into the management of UA levels in hypertension and in reducing mortality from HHD.

Studies were done previously to know the relationship between cardiovascular disease and serum UA levels in hypertension [1,2,17,18] but no similar study was done previously in Adilabad, Telangana. Hence, present study was conducted to compare the levels of serum UA in hypertensive individuals with and without cardiovascular disease coming to this institution.

MATERIALS AND METHODS

This case-control study was done at RIMS, Adilabad, Telangana, India for a duration of three months, from October to December 2021.

The protocol and procedure for this study was approved by the Institutional Ethical Committee (IEC/RIMS/21/2021). Oral and written consent was taken from all participants before participating in the study.

Inclusion criteria: Individuals above 30 years of age, with both hypertension and cardiovascular disease were taken as cases. Hypertension was defined by present history of intake of blood-pressure lowering drugs (Telmisartan in our institution) and/or baseline systolic/diastolic blood pressure >140/90 mmHg [5]. Age matched individuals with hypertension alone were taken as controls.

Exclusion criteria: Individuals below 30 years of age and with diabetes mellitus, gout, chronic kidney disease, infective diseases and on hyperuricaemia treatment were excluded.

Sample size: A total of 150 hypertensive individuals with and without heart disease, coming to the Department of General Medicine, RIMS, Adilabad during the three months of study period and meeting the above criteria were enrolled in the study by purposive sampling.

- **Group 1:** 50 individuals with hypertension alone were taken as controls and
- **Group 2:** 100 individuals with HHD were taken as cases

Group 2 was further subdivided into two groups with 50 individuals each:

Group 2A: Age 30-55 (<=55 years)

Group 2B: Age >55 years.

Study Procedure

History was taken from all the participants regarding age, smoking, physical activity and use of lipid lowering medications. Physical activity was assessed based on World Health Organisation (WHO) guidelines [19] and those not meeting the criteria were considered as inactive. Participants were examined for waist circumference and blood pressure. Waist circumference was measured according to CDC NHANES guidelines [20]. Normal reference range for waist circumference was taken as less than 90 cm in males and less than 80 cm in females. Central obesity was defined as waist circumference more than 102 cm in males and more than 88 cm in females [21,22].

Blood samples (5 mL) were collected in Ethylenediaminetetraacetic Acid (EDTA) vacutainers, in the morning, after participants had been fasting for atleast eight hours and sitting for 15 minutes. Aliquots of serum were immediately obtained by centrifugation (3000 RPM for 10 minutes) and stored at 2-8°C. Samples were analysed within 12 hours of collection to avoid deterioration in UA levels. The collected samples were analysed for total cholesterol, triglyceride, HDL cholesterol, fasting blood glucose, creatinine, White Blood Cell (WBC) count and UA. The test methods used and normal reference ranges for the analysed parameters are given in [Table/Fig-1] [23-28].

Variables	Test method	Normal reference range
Total cholesterol	CHOD-POD Method [23]	Normal range: <200 mg/dL Borderline: 200-239 mg/dL
Triglycerides	GPO-POD Method [24]	Normal range: <150 mg/dL Borderline: 150-199 mg/dL
HDL cholesterol	Enzyme selective inhibition method [25]	Normal range: >60 mg/dL Borderline: 40-59 mg/dL
Fasting plasma glucose	Hexokinase method [26]	70-100 mg/dL
Creatinine	Enzymatic method [27]	Women: 0.5-1.0 mg/dL Men: 0.7-1.2 mg/dL
WBC count	Flowcytometry method [28]	4.0-10.0×10^3/µL

[Table/Fig-1]: Test methods and normal reference ranges [23-28].

Serum UA estimation: Serum UA analysis was done using Beckmann Coulter AU480 analyser by Uricase based method (Modified Fossati Method). In women, the values between 2.6-6.0 mg/dL were taken as biological reference interval and values >6.0 mg/dL were taken as hyperuricaemia. In men, the value between 3.5-7.2 mg/dL were taken as biological reference interval and values >7.2 mg/dL were taken as hyperuricaemia [29].

STATISTICAL ANALYSIS

Continuous data were expressed as mean±SD. Categorical data were expressed as percentage. Independent samples t-test was used for statistical analysis using SPSS software version 28.0.1.1 (15). A p-value <0.05 was considered significant.

RESULTS

Overall, 150 participants (75 males and 75 females) with hypertension were identified. The mean age was 54.6±9.6 years in group 1 (controls), 56.63±8.259 years in group 2 (cases total). Triglycerides were 114.16±26.234 mg/dL in group 1, 116.29±32.781 mg/dL in group 2, 114.66± 36.212 mg/dL in group 2A and 117.92±29.231 mg/dL in group 2B. HDL Cholesterol were 44.29±0.662 mg/dL in group 1, 44.25±0.675 mg/dL in group 2, 44.39±0.666 mg/dL in group 2A and 44.11±0.661 mg/dL in group 2B. No significant difference was observed in smoking history, physical activity levels, waist circumference, obesity, total cholesterol, triglyceride, HDL cholesterol, fasting blood glucose, creatinine or WBC count between the case and control groups [Table/Fig-2].

General characteristics (age, number of males and females, smoking, physical activity, waist circumference, central obesity, total cholesterol, triglycerides, HDL cholesterol, fasting blood glucose, creatinine, WBC count) of total case and control groups and that of males and females of each group is shown in [Table/Fig-3]. The mean values for total cholesterol were higher among males 151.72±29.811 mg/dL in group 2A. The mean values of WBC count, triglycerides, and FBS were highest among females [Table/Fig-3].

Serum UA levels were significantly more in group 2A p<0.00001 in comparison to controls than those in group 2B (p=0.003). It was also seen that, females in group 2A had significantly elevated serum UA levels (p<0.00001) than males (p=0.00062). A comparison of serum UA levels among the case and control groups is shown in [Table/Fig-4].

In this study, significant elevation in blood pressure levels was seen in all patients with HHD (group 2A and 2B) as compared to individuals with hypertension alone (group 1) (p<0.05). Both males and females showed significant elevations (p<0.00001). A comparison of blood pressure levels among the case and control groups is shown in [Table/Fig-4].

DISCUSSION

In this study, hypertensive individuals had cardiovascular disease at an early age when serum UA levels were elevated. Even though significant association for serum UA was seen in both males and females, but females had greater significance, implying that females are at higher risk of cardiovascular disease than males. Total cholesterol, HDL cholesterol, triglyceride, glucose, creatinine levels and WBC count were similar between the case and control groups. These findings were consistent with other similar studies such as that done by You H et al., [1]. However, they found that the mortality rates were similar in both sexes. In another study done by Turak O et al., the findings were consistent with the present study but, in contrast their study showed higher levels of HDL cholesterol, triglycerides, glucose, creatinine levels and WBC count in those with elevated UA levels [30]. Similar to the present study, An Li-Na et al., study had shown no significant rise in HDL cholesterol in hyperuricaemic individuals but, in contrast creatinine and glucose levels were raised [31].

Hyperuricaemia is known as an independent risk factor for hypertension but, whether it is an independent risk factor for

Variables	Group 1 (controls)	Group 2 cases (total)	p-value	Group 2A (cases ≤55 years)	Group 2B (cases >55 years)	p-value
Age (years)	54.6±9.6	56.63±8.259	0.234	50±3.232	63.26±6.137	Group 1 vs 2A: 0.0009 Group 1 vs 2B: <0.0001
Smoking n (%)						
Never	31 (62%)	61 (61%)	0.837	30 (60%)	31 (62%)	Group 1 vs 2A: 0.772 Group 1 vs 2B: 1.000
Former	6 (12%)	14 (14%)	0.674	8 (16%)	6 (12%)	Group 1 vs 2A: 0.415 Group 1 vs 2B: 1.000
Current	13 (26%)	25 (25%)	0.871	12 (24%)	13 (26%)	Group 1 vs 2A: 0.744 Group 1 vs 2B: 1.000
Physical activity n (%)						
Inactive	26 (52%)	59 (59%)	0.319	28 (56%)	31 (62%)	Group 1 vs 2A: 0.57 Group 1 vs 2B: 0.153
Moderate	24 (48%)	41 (41%)	0.319	22 (44%)	19 (38%)	Group 1 vs 2A: 0.57 Group 1 vs 2B: 0.153
WC (cm)	85.68±10.255	84.95±9.808 (74.3)	0.631	85.5±8.862	84.4±10.732	Group 1 vs 2A: 0.463 Group 1 vs 2B: 0.272
Central obesity n (%)	9 (18%)	18 (18%)	1.000	10 (20%)	8 (16%)	Group 1 vs 2A: 0.718 Group 1 vs 2B: 0.707
TC (mg/dL)	148.18±26.993	147.06±24.43 (74.81)	0.787	148.62±24.74	145.52±24.267	Group 1 vs 2A: 0.466 Group 1 vs 2B: 0.301
TG (mg/dL)	114.16±26.234	116.29±32.781 (75.92)	0.873	114.66±36.212	117.92±29.231	Group 1 vs 2A: 0.469 Group 1 vs 2B: 0.250
HDL-C (mg/dL)	44.29±0.662	44.25±0.675 (74.54)	0.704	44.39±0.666	44.11±0.661	Group 1 vs 2A: 0.226 Group 1 vs 2B: 0.088
FBS (mg/dL)	92.44±5.779	91.07±5.407 (71.65)	0.126	91.08±5.671	91.06±5.188	Group 1 vs 2A: 0.119 Group 1 vs 2B: 0.106
Creatinine (mg/dL)	0.71±0.036	0.71±0.054 (76.76)	0.617	0.7±0.065	0.72±0.04	Group 1 vs 2A: 0.291 Group 1 vs 2B: 0.116
WBC Count (x10^3)	7.71±0.534	7.73±0.957 (75.22)	0.912	7.55±0.434	7.92±1.26	Group 1 vs 2A: 0.054 Group 1 vs 2B: 0.141
Lipid ↓ Meds n (%)	11 (22%)	30 (30%)	0.197	14 (28%)	16 (32%)	Group 1 vs 2A: 0.327 Group 1 vs 2B: 0.111

[Table/Fig-2]: General characteristics of case and control group.
WC: Waist circumference; TC: Total cholesterol; TG: Triglycerides; FBS: Fasting blood sugar; lipid ↓ meds: lipid lowering medications.
For statistical analysis of normally distributed continuous data Independent-samples t-test was used. For continuous data not normally distributed Mann Whitney U test was used. For categorical data Chi-square test was used

	Group 1 (controls)		Group 2A (cases ≤55 years)		Group 2B (cases >55 years)	
Variables	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**
Number	25	25	25	25	25	25
Age (years)	52±10.843	57.2±7.517	47.4±2.363	52.6±1.291	62.52±5.621	64±6.646
Smoking n (%)						
Never	25 (100%)	6 (24%)	25 (100%)	5 (20%)	25 (100%)	6 (24%)
Former	0	6 (24%)	0	8 (32%)	0	6 (24%)
Current	0	13 (52%)	0	12 (48%)	0	13 (52%)
Physical activity n (%)						
Inactive	14 (56%)	12 (48%)	14 (56%)	14 (56%)	16 (64%)	15 (60%)
Moderate	11 (44%)	13 (52%)	11 (44%)	11 (44%)	9 (36%)	10 (40%)
WC (cm)	79.4±8.421	91.96±7.85	81.52±8.312	89.48±7.632	78.16±7.936	90.64±9.543
Central obesity n (%)	5 (20%)	4 (16%)	6 (24%)	4 (16%)	4 (16%)	4 (16%)
TC (mg/dL)	145.72±28.868	150.64±25.329	145.52±18.464	151.72±29.811	144.84±28.441	146.16±19.813
TG (mg/dL)	113.88±25.31	114.44±27.65	115.84±37.353	113.48±35.764	122.48±21.762	113.36±35.037
HDL-C (mg/dL)	44.2±0.736	44.39±0.578	44.3±0.735	44.49±0.587	44±0.736	44.23±0.569
FBS (mg/dL)	93.08±6.103	91.8±5.485	90.52±5.966	91.64±5.423	91.92±5.251	90.2±5.083
Creatinine (mg/dL)	0.68±0.023	0.74±0.023	0.65±0.042	0.76±0.036	0.69±0.026	0.75±0.026
WBC count (x10^3)	7.64±0.691	7.78±0.308	7.5±0.548	7.6±0.283	7.99±1.268	7.85±1.277
Lipid ↓ meds TC	5 (20%)	6 (24%)	7 (28%)	7 (28%)	7 (28%)	9 (36%)

[Table/Fig-3]: General characteristics of case and control group.
WC: Waist circumference; TC: Total cholesterol; TG: Triglycerides; FBS: Fasting blood sugar; lipid ↓ meds: lipid lowering medications

Variables	Group 1 (controls)	Group 2A (cases ≤55 years)	Group 2B (cases >55 years)	p-value
Serum UA levels				
Total	6.03± 0.939	7.73± 0.775	6.496± 0.742	Group 1 vs Group 2A: <0.00001 Group 1 vs Group 2B: 0.003

Female	5.384± 0.789	8.216± 0.597	5.936± 0.504	Group 1 vs Group 2A: <0.00001 Group 1 vs Group 2B: 0.002
Male	6.676± 0.553	7.244± 0.615	7.056± 0.466	Group 1 vs Group 2A: 0.00062 Group 1 vs Group 2B: 0.006
Systolic blood pressure levels				
Total	125.2± 5.241	146.92± 3.562	146.82± 4.406	Group 1 vs Group 2A: <0.00001 Group 1 vs Group 2B: <0.00001
Female	121.72± 4.316	146.48± 3.765	146.52± 3.885	Group 1 vs Group 2A: <0.00001 Group 1 vs Group 2B: <0.00001
Male	128.68± 3.497	147.36± 3.365	147.12± 4.936	Group 1 vs Group 2A: <0.00001 Group 1 vs Group 2B: <0.00001
Diastolic blood pressure levels				
Total	78.52± 2.401	87.32± 3.513	88.66± 3.532	Group 1 vs Group 2A: <0.00001 Group 1 vs Group 2B: <0.00001
Female	77.32± 2.116	86.08± 3.161	87.88± 3.678	Group 1 vs Group 2A: <0.00001 Group 1 vs Group 2B: <0.00001
Male	79.72± 2.072	88.56± 3.465	89.44± 3.267	Group 1 vs Group 2A: <0.00001 Group 1 vs Group 2B: <0.00001

[Table/Fig-4]: Comparison of Serum UA levels and blood pressure levels among case and control groups.

Association of UA with cardiovascular disease

cardiovascular disease or not is under debate. The association of serum UA levels with cardiovascular risk in general population has been reported but most of them observed that elevated UA levels increased the risk of cardiovascular disease [8,32-36]. A few of them reported that serum UA elevations was not an independent risk factor for cardiovascular disease but only a marker of the pathological condition [1,37]. The heterogeneous conclusions may be partly due to the discrepancy in subjects, clinical characteristics, sample size, grouping strategy, and adjustment for confounders [1].

Recently, a few cohort studies have noted an association between serum UA levels and cardiovascular disease in hypertensive individuals [8,10]. A nationwide study conducted in China by You H et al., suggested a U-shaped relationship between serum UA and risk of mortality in hypertensive individuals, concluding that cardiovascular risk increases with elevated UA levels [1]. Other studies have demonstrated that both high and low serum UA levels were related to CVD risk in hypertensives [11,38,39]. Consistent with the above studies, the present study also showed a similar association between elevated serum UA levels and cardiovascular risk in hypertensive individuals.

A cross-sectional study conducted on 207 hypertensive women in Brazil, have demonstrated that elevated serum UA was associated with internal carotid resistive index only in women, suggesting a gender-related difference in the relationship between serum UA and vascular damage in subjects with systemic hypertension [36]. Female hormones lower the serum UA levels. Hence, in postmenopausal women there is an increase in serum UA levels. So, the diagnostic evaluation of UA levels is more difficult in these women [40,41].

The mechanism by which UA leads to cardiovascular risk remains unclear. Several studies have shown the beneficial role of antioxidant property of UA [42-44]. But, under pathological conditions like atherosclerosis, UA acts as a pro-oxidant and produce reactive oxygen species, instead of acting as an antioxidant. This pro-oxidant effect of UA encourages the development and progression of cardiovascular disease [1,7].

Monosodium urate crystals activate polymorphonuclear leucocytes, which engulf monosodium urate crystals resulting in super oxides, LDL oxidation. Disorders of endothelial cells and blood platelets facilitate arteriosclerosis [12].

Experimental data also showed that UA stimulates proliferation, inflammation and oxidative stress in vascular smooth muscle cells, induces endothelial dysfunction and activates the renin-angiotensin system [36,45]. The hypothesis of causal link between hyperuricaemia and endothelial dysfunction might be a possible mechanism for the development of cardiovascular disease in hypertensive individuals [31].

Various factors are involved in the process of UA production and secretion. For example, aggravated anaerobic metabolism in tissues due to reduced oxygen leads to increased lactic acid levels, which increases reabsorption of UA by kidneys, thus increasing serum UA levels. These factors complicate the process of identification of the reasons for the fluctuation of serum UA levels. Medications are also one of such factors which has an impact on serum UA levels. Angiotensin receptor blockers (losartan), antidyslipidemic drugs (fenofibrate) inhibit URAT1 and facilitate UA excretion. Diuretics (thiazide, furosemide) also increases serum UA [46,47].

Treatment of hyperuricaemia with allopurinol for three months have shown results in a significant decrease in inflammation biomarkers [48]. Antihyperuricaemic medications showed improved angina symptoms and prevented vascular disease. Few studies have proposed that the incidence of cardiovascular event was lower in hyperuricaemic individuals on urate-lowering treatment. Hence, it can be taken as a new approach for cardiovascular risk reduction [49,50]. Large controlled trials are ongoing to assess the effect of serum UA-lowering drugs on cardiovascular events [51].

This study also showed significant rise in blood pressure levels in cases when compared with the control group. This raise could be linked to elevated serum UA levels as hyperuricaemia is an independent risk factor for hypertension. Many studies have proved that elevated serum UA levels can lead to hypertension [52-54].

Limitation(s)

First, the effects of unmeasured confounders may not be completely ruled out. Second, the causality of the link between serum UA and cardiovascular disease in hypertensive individuals could not be determined. Third, limited sample size and sampling from single institution, so further studies need to be done to generalise the findings of this study.

CONCLUSION(S)

In present study, serum UA level was significantly higher in hypertensive individuals with cardiac disease than hypertensive controls without cardiac disease. No significant difference was observed in smoking history, physical activity levels, waist circumference, obesity, total cholesterol, triglyceride, HDL cholesterol, fasting blood glucose, creatinine or WBC count between the case and control groups. Hence, routine screening of UA levels in hypertensive individuals and taking necessary corrective steps would help prevent early progression to hypertensive heart disease, especially in females. Further follow-up

studies on larger sample size are needed to establish the causality of link between elevated UA levels and cardiovascular disease in hypertensive individuals.

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