

Serum Uric Acid and its Correlation with Inflammation in Hypertension, a Hospital Based Case-control Study

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ABSTRACT

Background

Our lifestyle has a significant impact on levels of serum uric acid. We have attempted to correlate the patients' uric acid levels with predictors of inflammation, such as C-reactive protein, obesity and dyslipidemia among hypertensive cases.

Objective

To investigate the association of uric acid with systolic and diastolic blood pressure, body mass index and waist circumference in essential hypertension. To correlate uric acid with C-reactive protein, fasting blood sugar, serum creatinine, triglycerides, high density lipoprotein and total cholesterol.

Method

This hospital-based case-control study included 280 participants. 150 were hypertensive cases and 130 were normotensive controls. Anthropometric measurements including waist circumference and blood pressure were taken. Body mass index was calculated from height and weight. Blood was collected for total cholesterol, triglyceride, C-reactive protein, high density lipoprotein, uric acid, creatinine and fasting blood sugar. Data were analyzed using SPSS 24, distribution expressed in frequency and percentage and correlations examined through Spearman's rho correlation, interquartile range and median. Categorical variables each were compared between groups using χ^2 test.

Result

There were 150 hypertension cases and 130 normotensive controls. The predictors of inflammation like waist circumference, systolic and diastolic blood pressure, body mass index, uric acid and triglyceride were significantly high among hypertensives; ($p=0.000$). High density lipoprotein was low among hypertensives ($p=0.000$). Uric acid showed significant positive correlation with waist circumference in females ($p=0.000$), but not in males. Body mass index, systolic and diastolic blood pressure, C-reactive protein, triglyceride and low levels of high density lipoprotein showed significant positive correlation; ($p=0.000$). A significant positive correlation of uric acid was seen with creatinine, ($p=0.005$). Fasting blood sugar and Total cholesterol failed to show any association with uric acid.

Conclusion

This study demonstrated that there is a strong correlation between serum UA and the metabolic predictors of inflammation, such as hypertension, C-reactive protein, triglyceride, low high density lipoprotein, high body mass index, high waist circumference, and serum creatinine, as shown by other studies that imply the interplay between metabolic disorders and inflammation.

KEY WORDS

C-reactive protein, Dyslipidemia, Hypertension, Inflammation, Uric acid

INTRODUCTION

Uric acid is an end product of purine metabolism. It can be generated from amino acid precursors or from purines provided in the diet. Breakdown of nucleic acids, heat stress, ischemia, dehydration can also generate uric acid.¹ Our eating habits and way of life make us more susceptible to hyperuricemia. High salt diets and high glycemic diets can induce the expression of aldose reductase that leads to increased fructose generation and metabolism in the liver, resulting in an increase in intracellular uric acid production.² Oxidative stress within cells due to uric acid has been linked with the activation of the renin-angiotensin system (RAS) and inhibition of endothelial nitric oxide (NO) resulting in systemic and renal vasoconstriction.³ Often considered as an extracellular antioxidant, experimental studies have suggested the proinflammatory role of hyperuricemia.^{4,5} The production of tumor necrosis factor-alpha (TNF-alpha), toll-like receptor 4 (TLR4), and cluster of differentiation (CD) 11c is significantly increased by uric acid.⁶

Our dietary and lifestyle choices put us at risk for a number of inflammatory and metabolic diseases. One such condition is hyperuricemia. According to a number of studies, hyperuricemia may be a predictor of the onset of hypertension.^{7,8} Low grade inflammation, hyperuricemia, hypertension, obesity, insulin resistance and coronary artery disease often coexists.⁹ When it comes to hypertension, mild hyperuricemia is largely neglected in the most parts of the world.

Over a past few decades there substantial urbanization and the Nepalese diet is shifting away from agricultural staple based foods to modern processed foods with higher total energy, total fat, and sugar. Although prevalence of overweight/obesity, hypertension, hyperuricemia and diet related metabolic diseases are increasing among the Nepalese population, only a few studies have been done suggesting the interrelationship of hyperuricemia, hypertension and inflammation.¹⁰ Keeping in mind the paucity of data, our main objective is to study the relationship of serum uric acid with inflammation among hypertensive patients. Confounding factors like body mass index (BMI), fasting blood sugar (FBS), triglycerides (TG), total cholesterol (T-CHO), High density lipoprotein-cholesterol (HDL-C) and C-reactive protein (CRP) is correlated with uric acid to strengthen this study.

METHODS

This hospital-based case control study was conducted at Dhulikhel Hospital, from December 2023 to March 2024, after an ethical approval granted by Institutional Review Committee Kathmandu University and School of Medical Science (IRC-KUSMS, Approval no: 251/23).

Sample size of 280 was calculated using the Cochran's formula with the expected prevalence of hyperuricemia to

be 25% in hypertension¹¹, 95% confidence interval, and margin of error of 5%.

Formula: $n = Z^2 pq / (d^2)$

Where Z= 1.96 at 95% of the Confidence interval

p = prevalence of hyperuricemia in hypertension= 25%

q = 100-p = 75

d = maximum tolerable error 5%

Convenient sampling was done and 150 were hypertensive cases, and those who are under anti-hypertensives were included in the study. Age and sex matched 130 normotensives controls were included. Age group between 29-80 years willing to participate after the informed consent were included. We categorized age to five group (29-40, 41-50, 51-60, 61-70, 71-80) years. These age groups were chosen to reflect meaningful life stages, as defined by previous research.¹² Medical history was taken and physical examination was performed by the physician. The participants were excluded if they were taking alcohol, hypoglycemic agents, thiazides, antihyperuricemic agents. Pregnant ladies and patients on steroids, oral contraceptive pills (OCPs), lipid-lowering drugs for dyslipidemia were excluded. Major comorbidities like thyroidal illness, cancer, diabetes mellitus (DM), respiratory, cardiac, renal, and hepatic problems were not included. Anthropometric measurements were collected after receiving informed consent and allowing only light clothes. Hypertension was defined according to Joint National Committee (JNC) 7 as cut off point of 140 mmHg and above for systolic blood pressure (SBP) and / or 90 mmHg and above for diastolic blood pressure (DBP), or reported about the use of antihypertensive medication during the study.¹³ A digital portable scale was used to measure body weight as kilogram (kg). Height was measured in centimeter (cm) with a stadiometer. The waist circumference was measured midway between the bottom of ribs and the iliac crest ensuring that the person is standing upright with arms relaxed at the sides and feet evenly spread. The recommended cut-off points are 90 cm (male) and 80 cm (female), for South Asians as per World Health Organization (WHO).¹⁴ BMI (kg/m^2) was calculated and classified according to their BMI into three groups: Normal weight BMI: 18.5 - 24.9 kg/m^2 , Overweight BMI: 25.0 - 29.0 kg/m^2 and Obesity class I with BMI: 30-34.9 kg/m^2 , Obesity class II with BMI: 35-39.9 kg/m^2 , Extreme obesity with BMI > 40 kg/m^2 as per WHO.

Three and half ml of venous blood was collected in serum vial, prior which the patients were advised 12 hours overnight fasting. Serum was estimated for total cholesterol, triacylglycerol, high density lipoprotein, FBS, Uric acid, creatinine, CRP. Using commercial kits by Biosystems (BA-400 Biosystems S.A. Spain) analyzer, serum samples were evaluated. TC, HDL-C and TG were determined directly using enzymatic spectrophotometric

techniques. For serum lipid reference level, National Cholesterol Education Programme (NCEP) Adult Treatment Panel III (ATP III) guideline was referred. FBS was estimated enzymatically by Glucose-oxidase/ Peroxidase method and 60-100 mg/dl was considered as the normal range. Uric acid was estimated enzymatically using Uricase method and 3.4 - 7.0 mg/dl was considered the normal range in males and females. Creatinine was estimated using Jaffe's kinetic method and 0.7 - 1.3 mg/dl was considered normal range in males and 0.6 - 1.1 mg/dl in females. CRP < 0.5 mg/dl was considered normal and was estimated by immunoturbidimetry technique.

Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 24 software. A low p-value (< 0.05) in Shapiro-Wilk test indicated that our data deviated from normal distribution. Hence, non-parametric tests like Chi-square χ^2 test and Spearman's rho correlation were used. Descriptive statistics were presented in frequency and percentages. The original continuous variables were categorized based on their values. χ^2 test was used to observe the difference of frequency distribution between two groups. Spearman's rho correlation, interquartile range (IQR) and medians were used to find the association of uric acid with demographic characteristics, anthropometric measurements and biochemical parameters. All tests were two tailed and p value of < 0.05 was considered statistically significant at 95% confidence interval.

RESULTS

A total of 280 participants were enrolled in the study. Table 1 shows frequency and percentage of demographic and anthropometric variables. There were 89 male and 69 female participants among hypertensive cases. Likewise, normotensive controls had 89 male and 41 female participants. Age was divided into five categories. The one between 51 - 60 years of age were present in highest percentage (32%) among cases and 37.7% of controls were between 41 - 50 years of age. Among hypertensive cases 60.7% and 76.6% exhibited high SBP and DBP respectively, and 2.3% of controls had high DBP and normal SBP was seen in all the controls. Obesity was high (41.3%) among hypertensive cases and 14.6% in controls. However 60.8% of controls were overweight, which was higher than cases (50%). WC was found to be high in all the male controls and 96.6% of male hypertensive cases. Both female hypertensive cases (98.4%) and controls (22%) had high WC.

Table 2 shows the frequency distribution of biochemical variables. In the hypertensive group, hyperuricemia was in high percentage (59.3%). Hyperuricemia was identified in 52.4% of female hypertensive cases and 64% of male hypertensive cases. 4.5% of male controls had high uric acid levels compared to none in female controls. TG was high and borderline high in 74.7% and 23.3% of cases

Table 1. Frequency table of categories of demographic and anthropometric variables.

Variables		Categories	Case (150)		Control		Total	
			n	%	n	%		
Age		29-40 years	14	9.3	25	19.2	39	
		41-50 years	42	28	49	37.7	91	
		51-60 years	48	32	16	12.3	64	
		61-70 years	38	25.3	37	28.5	75	
		71-80 years	8	5.3	3	2.3	11	
Gender		Male	89	59.3	89	68.5	178	
		Female	61	40.7	41	31.5	102	
SBP		Normal	59	39.3	130	100	189	
		High	91	60.7	0	0	91	
DBP		Normal	35	23.3	127	97.7	162	
		High	115	76.7	3	2.3	118	
BMI		Normal	13	8.7	32	24.6	45	
		Overweight	75	50	79	60.8	154	
		Obese	62	41.3	19	14.6	81	
WC	Male	High	86	96.6	89	100	175	
		Normal	3	3.4	0	0	3	
	Female	High	60	98.4	9	22.0	69	
			normal	1	1.6	32	78.0	33

Table 2. Frequency table of categories of biochemical variables.

Variables	Categories		Case (150)		Control (130)		Total (280)(N)
			n	%	n	%	
TG		Normal	3	2	30	23.1	33
		Borderline high	35	23.3	64	49.2	99
		High	112	74.7	36	27.7	148
Total cho- lesterol		Desirable	95	63.3	76	58.5	171
		Borderline High	46	30.7	47	36.2	93
		High	9	6	7	5.4	16
HDL-C		Low	60	40	0	0	60
		Normal	90	60	130	100	220
Uric acid	Male	Normal	32	36	85	95.5	117
		High	57	64	4	4.5	61
	Female	Normal	29	47.5	41	100	70
		High	32	52.5	0	0	32
FBS		Normal	146	97.3	130	100	276
		High	4	2.7	0	0	4
CRP		≤ 5	61	40.7	116	89.2	177
		≥ 5	89	59.3	14	10.8	103
Creatinine		Normal	140	93.3	129	99.2	269
		High	10	6.7	1	0.8	11

respectively. However high percentage of controls (36.2%) had borderline high TG. Total cholesterol was high in 6% cases and 5.4% controls, while it was borderline high in 30.7% cases and 36.2% controls. Low HDL was seen in 40% of hypertensive cases. FBS and creatinine was high among

2.7% and 6.7% of hypertensive cases respectively. High CRP (≥ 5 mg/dl) was present in 59.7% cases and 10.8% controls.

Table 3 and 4 compare the anthropometric and biochemical parameters of the study group and the control group using the chi-square. SBP was significantly high among cases χ^2 (1, 91) = 116.8, $p=0.000$ than controls. DBP was also significantly high among hypertensive cases χ^2 (2, 115) = 157.92, $p=0.000$. The hypertensive cases had significant obese and overweight BMI reflected by χ^2 (1, 62) = 175.9, $p=0.000$ and χ^2 (1, 75) = 175.9, $p=0.000$ respectively. Waist circumference was high among female cases than control

groups χ^2 (1, 60) = 65.4, $p=0.000$. However, there was no significant difference in the WC of male case and controls. Triglyceride was significantly high among study group groups χ^2 (2, 112) = 68.53, $p=0.000$. A significant Low HDL-C was present among cases χ^2 (1, 60) = 66.18, $p=0.000$. However total cholesterol and FBS were not high among study groups with p -value 0.622 and 0.061 respectively. Uric acid and creatinine were high among study group compared to controls with χ^2 (2, 89) = 101.11, $p=0.000$ and χ^2 (1, 10) = 6.41, $p=0.011$ respectively. Similarly CRP showed higher values among cases with χ^2 (1, 89) = 70.63, $p=0.000$.

Table 3. Comparison of the anthropometric variables between two groups.

Variables	Categories	Group		Total (280) N (%)	p-value	χ^2	df
		Case (150) n (%)	Control (130) N (%)				
SBP	Normal	59 (39.3)	130 (100)	189 (67.5)	0.000	116.8	1
	High	91 (60.7)	0 (0)	91 (32.5)			
DBP	Normal	35 (23.3)	127 (97.7)	162 (57.9)	0.000	157.92	2
	High	115 (76.7)	3 (2.3)	118 (42.1)			
BMI	Normal	13 (8.7)	32 (24.6)	45 (6.1)	0.000	175.99	1
	Overweight	75 (50.0)	79 (60.8)	154 (55.5)			
	Obese	62 (41.3)	19 (14.6)	81 (28.9)			
WC	Female	Normal	1 (1.6)	32 (78.0)	0.000	65.4	1
		High	60 (98.4)	9 (22.0)			
	Male	Normal	3 (3.4)	3 (3.4)	0.123	3.056	1
		High	86 (96.6)	86 (96.6)			

A p-value of <0.05 shows that there is a significant difference between two variables.

Table 4. Comparison of biochemical variables between two groups.

Biochemical variables	Categories	Group		Total (280) N (%)	p-value	χ^2	df
		Case (150) N (%)	Control (130) N (%)				
TG	Normal	3 (2%)	30 (23.1)	33 (11.8)	0.000	68.53	2
	Borderline high	35 (23.3)	64 (42.9)	99 (35.4)			
	High	112 (74.7)	36 (27.7)	148 (52.9)			
Total cholesterol	Desirable	95 (63.3)	76 (58.5)	171 (61.1)	0.622	0.94	2
	Borderline High	46 (30.7)	47 (36.2)	93 (33.2)			
	High	9 (6.0)	7 (5.4)	16 (5.7)			
HDL-C	Low	60 (40)	0 (0)	60 (21.4)	0.000	66.18	1
	Normal	90 (60)	130 (100)	220 (78.6)			
FBS	Normal	146 (97.3)	130 (100)	276 (98.6)	0.061	3.51	1
	High	4 (2.7)	0 (0)	4 (1.4)			
CRP	<5	61 (40.7)	116 (89.2)	177 (63.2)	0.000	70.63	1
	≥ 5	89 (59.3)	14 (10.8)	103 (36.8)			
Creatinine	Normal	140 (93.3)	129 (99.2)	269 (96.1)	0.011	6.41	1
	High	10 (6.7)	1 (0.8)	11 (3.9)			
Uric acid	Normal	61 (40.7)	126 (96.9)	185 (65.4)	0.000	101.11	2
	High	89 (59.3)	4 (3.1)	93 (33.2)			

*A p-value of <0.05 shows that there is a significant association between two variables.

Table 5 shows the association of uric acid with study variables. Uric acid showed significantly positive correlation with TG ($p=0.582$, $p=0.000$), creatinine ($p=0.169$, $p=0.005$) and CRP ($p=0.562$, $p=0.000$). FBS and total cholesterol failed to show any significance with the uric acid levels ($p=0.044$, $p=0.460$) and ($p=-0.034$, $p=0.567$) respectively. HDL showed significant negative correlation with uric acid level ($p=-0.533$, $p=0.000$). Among the anthropometric variables SBP, DBP and BMI were positively and significantly associated with uric acid levels with ($p=0.421$, $p=0.000$), ($p=0.492$, $p=0.000$) and ($p=0.361$, $p=0.000$) respectively. Waist circumference among female participants were negatively and significantly associated with uric acid ($p=-0.468$, $p=0.000$), however WC of male participants failed to do so ($p=-0.087$, $p=0.251$). No significant association age was seen with uric acid ($p=0.74$, $p=0.217$).

DISCUSSIONS

The primary goal of this study was to understand the concept of hyperuricemia as an important predictor of inflammation among hypertensive subjects. According to some studies uric acid up-regulates CRP expression in cultured human vascular smooth muscle cells (VSMCs) and endothelial cells.¹⁵ CRP is an acute phase reactant protein and has been used as a biomarker to suggest inflammation. The elevation of CRP is not limited to hypertension and hyperuricemia, but it has been linked to several systemic comorbidities associated with low grade systemic inflammation like renal, cardiovascular, infections, neoplastic and autoimmune diseases.¹⁶ However some studies have shown that minor CRP elevation is associated with a mild degree of tissue stress or injury, rather than a resulting inflammatory response. Even minor elevation of CRP suggest poor prognosis in apparently healthy individuals.¹⁷ Other studies have suggested that elevated uric acid can promote macrophage mediated systemic inflammatory response.⁶ Surprisingly, our study showed positive and significant correlation of CRP with uric acid. Interesting was, 10.5% of our controls showed CRP ≥ 5 mg/dl.

To establish a link between hypertension and hyperuricemia many studies proposed that hyperuricemia contributes to the endothelial dysfunction reducing nitric oxide, activation of renin angiotensin system, upregulation of aldose reductase, superoxide generation intracellularly and deposition of urate crystals in endothelial cells of blood vessels, increased insulin resistance and hyperinsulinaemia, causing decreases excretion of uric acid, sodium, potassium from renal tubules.¹⁸⁻²⁰ In a study done on hypertensive population which showed 28.8% had hyperuricemia, we found that hyperuricemia was diagnosed in majority of hypertensive cases (59.3%) and 4% of normotensive controls exhibited hyperuricemia.²¹ When systolic and diastolic blood pressure were independent variables, a

Table 5. Median, interquartile range (IQR) and Spearman's rank correlation of Uric acid with study Variables.

Correlation of the data with study variables:					
Variables		Median	IQR (Q3-Q1)	Rho (ρ)	p-value
Uric acid		0.5	1.8		
TG		201	109	0.582	0.000
Total cholesterol		190	40	-0.034	0.567
HDL-C		42	8	-0.533	0.000
FBS		90	11	0.044	0.460
Creatinine		0.8	0.3	0.169	0.005
CRP		4	4	0.562	0.000
Age		53.5	17	0.74	0.217
SBP		120	30.0	0.421	0.000
DBP		80	10	0.492	0.000
BMI		28	4.47	0.361	0.000
WC	Male	105.0	10.2	-0.087	0.251
	Female	101.0	27.80	-0.468	0.000

*A p-value of <0.05 shows that there is a significant association between two variables.

Korean study revealed that when blood pressure rose, so did the concentration of serum uric acid.²⁰ SBP and DBP were also significantly affected by serum UA levels in our research.

Adult women have lower serum UA levels than men of the same age, which is related to women's higher UA clearance rates, maybe as a result of their higher plasma estrogen levels.²² Male participants were predominantly affected in our study, which was similar to other studies.¹⁸ Another gender-specific study showed that; BP-elevating function of serum UA > 6 mg/dl seemed to affect the SBP in males.²³ Hyperuricemia commonly precedes the development of both insulin resistance and diabetes.²⁴ Urbanization and consumption of carbohydrate rich diet have given rise to metabolic disturbances in low and middle income countries, leading to metabolic syndrome and comorbidities.²⁵ According to some studies on metabolic syndrome, serum UA was found to be positively associated with indices like BMI, dyslipidemia and WC.^{26,27} In our study hyperuricemia was significantly associated with WC and BMI. Although many studies have shown UA has a significant role in the disturbance of glucose metabolism, a strong role of insulin is revealed.²⁸ Surprisingly there was no correlation between FBS and serum UA as our study group was normoglycemic. Hypertriglyceridemia was associated with high UA levels in our research, like other studies.^{29,30} Dyslipidemia often associated with high TG/HDL ratio is present in gout as confirmed by studies.³¹ Similarly, in our study, high UA was linked to low HDL. A Chinese study suggested that diet control and management of uric acid level might be advisable in patients with hyperuricemia so that those at an increased likelihood of developing dyslipidemia and further CVDs can be minimized. In their study hypercholesterolemia was linked to hyperuricemia, which contradicts our findings.⁷ Uric acid seems to have

been the important factor leading to decreased nitric oxide production, endothelial dysfunction and vascular changes in the kidney.³ Like serum UA, high normal serum creatinine is also a risk factor for hypertension.³² This study also shows a positive and significant correlation of serum UA with creatinine.

The primary limitations of our study were its short study period and single site design. Secondly, the sample size was small and did not accurately reflect Nepal's total population. In addition, it is unable to demonstrate a causal link between inflammation and hyperuricemia, for which a well-designed longitudinal study is required. Finally, this research did not gather information on ethnicity, environmental, dietary habits, alcohol intake, smoking and the lifestyle of the study population in order to assess their impact on uric acid levels.

CONCLUSION

We found that hyperuricemia was diagnosed in majority of hypertensive cases (59.3%). Hypertension, serum creatinine, raised CRP, hypertriglyceridemia, low HDL-C, high BMI, high WC are some of the metabolic predictors of inflammation. In this study we found serum uric acid levels are in positive correlation with these predictors of inflammation. Therefore it would be wise to avoid separating hyperuricemia from other comorbidities such as diabetes, obesity, insulin resistance, hypertension as they are associated with low grade chronic inflammation. Finally, it is possible that the CRP response is influenced by factors other than those examined in this study, which needs to be considered.

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