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## Serum uric acid level in newly diagnosed essential hypertension in a Nepalese population: A hospital based cross sectional study

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## PEER REVIEW

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**Comments**

Over all the paper is very informative and gives very scientific information, which makes us to rethink about the relationship of uric acid and hypertension. It can be an eye-opener to further conducted research on uric acid levels with other disorders related to hypertension.

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## ABSTRACT

**Objective:** To develop the missing link between hyperuricemia and hypertension.

**Methods:** The study was conducted in Department of Biochemistry in collaboration with Nephrology Unit of Internal Medicine Department. Hypertension was defined according to blood pressure readings by definitions of the Seventh Report of the Joint National Committee. Totally 205 newly diagnosed and untreated essential hypertensive cases and age–sex matched normotensive controls were enrolled in the study. The potential confounding factors of hyperuricemia and hypertension in both cases and controls were controlled. Uric acid levels in all participants were analyzed.

**Results:** Renal function between newly diagnosed hypertensive cases and normotensive healthy controls were adjusted. The mean serum uric acid observed in newly diagnosed hypertensive cases and in normotensive healthy controls were (290.05±87.05) μmol/L and (245.24±99.38) μmol/L respectively. A total of 59 (28.8%) participants of cases and 28 (13.7%) participants of controls had hyperuricemia (odds ratio 2.555 (95% CI: 1.549–4.213), *P*<0.001).

**Conclusions:** The mean serum uric acid levels and number of hyperuricemic subjects were found to be significantly higher in cases when compared to controls.

## KEYWORDS

Newly diagnosed hypertension, Serum uric acid, Hyperuricemia, Joint National Committee

### 1. Introduction

Hypertension is the emerging public health problem of adult population across the globe, affecting one in every four individuals<sup>[1]</sup>. The etiological factors associated with hypertension is difficult to predict because hypertension results from a complex interaction of genes and environmental factors<sup>[1]</sup>. Different studies advocate the association between serum uric acid level and hypertension. The reasonable mechanism for the

development of hypertension in hyperuricemia includes: (a) uric acid induced activation of renin–angiotensin system and action on glomerular apparatus<sup>[2,3]</sup>; (b) increased insulin resistance and hyperinsulinaemia, causing decreases excretion of uric acid, sodium, potassium from renal tubules<sup>[4,5]</sup>; and (c) uric acid action in proliferation of vascular smooth muscle<sup>[6]</sup>, endothelial dysfunction with decrease nitric acid production<sup>[7,8]</sup>. However, there are numerous confounding factors including metabolic syndrome, diabetes mellitus, chronic kidney disease, obesity,

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alcohol consumption, salt intake, fluid volume status *ect.* in the association of hyperuricemia and hypertension. Thus our main objective was to find out the association between hyperuricemia and hypertension by controlling aforementioned potential confounding factors.

## 2. Materials and methods

### 2.1. Study design and the participants

This hospital based cross-sectional study was conducted in the Department of Clinical Biochemistry in collaboration with Department of Internal Medicine (Nephrology Unit), Tribhuvan University Teaching Hospital, Institute of Medicine (Tribhuvan University Teaching Hospital, Institute of Medicine). Tribhuvan University Teaching Hospital is a tertiary care hospital in capital city of Nepal and it provides the health services to patients who visit to Tribhuvan University Teaching Hospital from different part of Nepal. Hence this site was chosen for the study.

### 2.2. Data collection

This study was carried out from 2009 February to 2011 August. The study population included patients visiting medical out patients door (OPD) and nephrology unit of Tribhuvan University Teaching Hospital from different parts of Nepal. A medical history was taken and a physical examination was performed by a physician. Only newly diagnosed hypertensive cases were included in the study. Hypertension was defined by blood pressure  $\geq 140/90$  mm Hg<sup>[9]</sup>. Subjects were resting for at least 20 min before taking the blood pressure. Blood pressure measurement was done using aneroid sphygmomanometer with an adequate cuff size. Systolic blood pressure (SBP) was taken by the first heard sound (Korotkoff Phase I). Diastolic blood pressure (DBP) was recorded at the level when the sound just disappeared (Korotkoff Phase V) or sometimes the K4 point, where the sound is abruptly muffled<sup>[10]</sup>. Weight was taken using a platform weighing machine. Standing height measurement was done with the participants in bare foot, eyes looking ahead. After having the written consent from the participants, 205 newly diagnosed hypertensive cases, ranging from 16 years to 65 years were eligible for the assessment of biochemical profile. We measured biochemical profile including uric acid, creatinine, total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and triglyceride (TG). Furthermore, age-sex matched normotensive healthy controls were also enrolled and all biochemical profile was done similar to cases. Demographic data including age, sex, weight, height, body mass index (BMI), physical activity, smoking status, alcoholic status and family history of hypertension were collected from the participants. Participants with haemophilia and recent cancer chemotherapy were

excluded from the venipuncture. Five millilitres of blood was drawn after an overnight fast (12 h) by venous puncture and a routine urine sample were also collected. After clotting of blood, serum was separated within an hour by centrifugation at 5000 g for 5 min. Serum was used for analysis of biochemical profile. Laboratory standard operation procedures were maintained for all laboratory analysis. Internal quality control sera, both normal and pathological, were also run for each lot of the test, for the validation of the results.

#### 2.2.1. Inclusion criteria

Age between 16 years to 65 years with newly diagnosed hypertension and normotensive healthy controls were enrolled as a study group.

#### 2.2.2. Exclusion criteria

For study cases: Age <16 years and >65 years, gout, chronic alcoholics, leukemias, polycythemia, lymphoma, carcinoma, anti-cancer therapy, psoriasis, pregnancy, diabetes mellitus, chronic diseases causes tissue break down, tuberculosis, chronic obstructive pulmonary disease, chronic renal failure, end stage renal disease, endocrine disorder, patients under medication for diabetes mellitus, hypertension were excluded from the study.

For healthy controls: Age <16 years and >65 years, gout, chronic alcoholics, leukemia, polycythemia, lymphoma, carcinoma, anti-cancer therapy, psoriasis, pregnancy, chronic disease causes tissue break down, tuberculosis, chronic obstructive pulmonary disease, liver disease, endocrine disorder, any medical history of chronic kidney disease, chronic renal failure, end stage renal disease, patients with or without medication for diabetes mellitus, hypertension were excluded.

### 2.3. Measured variables

Serum level of uric acid (uricase method as described by Fossati *et al.*)<sup>[11]</sup>, creatinine (modified Jaffe reaction)<sup>[12]</sup>, TC (enzymatic method as described by Allain *et al.*)<sup>[13]</sup>, HDL-C (precipitation of LDL-C and VLDL-C with phosphotungstic acid and magnesium chloride and treat as TC), LDL-C (Friedewald formula)<sup>[14]</sup> and TG (Fossati and Prencipe method associated with Trinder reaction)<sup>[15]</sup> were also measured.

#### 2.3.1. Defining variables

Hypertension was categorized according to blood pressure readings by Joint National Committee VII definitions: normal (systolic <120 mm Hg and diastolic <80 mm Hg), pre-hypertension (systolic 120 to 139 mm Hg or diastolic 80 to 89 mm Hg), hypertension stage I (systolic 140 to 159 mm Hg or diastolic 90 to 99 mm Hg), and hypertension stage II (systolic  $\geq 160$  or diastolic  $\geq 100$  mm Hg)<sup>[9]</sup>. In this study only hypertensive patient were taken. So, patients having stage I hypertension and stage II

hypertension were taken.

The formula of Cockcroft and Gault was used<sup>[16]</sup>.

For creatinine clearance (Ccr) in males:

$$\text{Ccr} = [140 - \text{age (years)}] \times \text{weight (kg)} \times 88.4 / [72 \times \text{serum creatinine } (\mu\text{mol/L})]$$

A companion equation for women was proposed, based on their 15% lower muscle mass (on average):

$$\text{Ccr} = [140 - \text{age (years)}] \times \text{weight (kg)} \times 88.4 \times 0.85 / [72 \times \text{serum creatinine } (\mu\text{mol/L})]$$

BMI was calculated as weight in kilograms divided by height in meters squared.

### 2.3.2. Other variables

Age, sex, weight, height, smoking status (never, past, or current), physical activity, alcohol intake and family history of hypertension were collected after having a written consent from participants.

Ethical committee approval: Ethical approval was taken from the ethical board of Institute of Medicine, Kathmandu.

### 2.4. Data management and statistical analysis

The data was analyzed using Excel 2003, R 2.8.0 Statistical Package for the Social Sciences (SPSS) for Windows Version 16.0 (SPSS Inc; Chicago, IL, USA). Association between hypertension and hyperuricemia was tested by *Chi*-square test and odds ratio was also calculated. Comparison of mean of continuous data between hypertensive cases and normal healthy control group was tested by student *t*-test. A *P*-value of <0.05 (two-tailed) was used to establish statistical significance.

## 3. Results

Among the patients visiting medical OPD and nephrology unit of Tribhuvan University Teaching Hospital from 2009 February to 2011 August, only 205 patients with newly diagnosed hypertension and 205 normotensive healthy controls were included in this study. In the cases, 116 patients were males and 89 were females. Control comprised of 112 males and 93 females.

The demographic and biochemical characteristics of study participants are depicted in Table 1. The median age of the participants was 44 years. We matched the age and sex between the newly diagnosed hypertension cases and normotensive healthy controls. Table 1 shows that the hypertensive cases were less physically active compared with normotensive healthy controls. Moreover, hypertensive cases had higher BMI. We adjusted the estimated glomerular filtration rate (eGFR) in both cases and controls. Biochemical profile including serum uric acid, TC, LDL-C and TG were found to be higher in hypertensive cases. However, HDL-C was found to be lower in hypertensive cases.

Table 2 shows the categorical association between hyperuricemia and hypertension. To define hyperuricemia, we had taken cut off point 416  $\mu\text{mol/L}$  for males and 357  $\mu\text{mol/L}$  for females<sup>[17]</sup>. Hyperuricemia found in male hypertensive, female hypertensive and total hypertensive were found to be 28.4%, 29.2% and 28.8% respectively. Similarly, hyperuricemia found in male healthy controls, female healthy controls and total normal healthy controls were found to be 14.3%, 12.9% and 13.7% respectively.

Table 3 shows the partial (adjusted) spearman correlation between different biochemical markers, DBP and SBP. Most of the biochemical markers are associated to each other and with DBP and SBP.

**Table 1**

Demographic and biochemical characteristics of the study population.

Characteristics	Cases (n=205)	Controls (n=205)	P-value
Demographic			
Age (years) median (5th–95th percentile)	44 (24–65)	44 (24–65)	matched
BMI (kg/m <sup>2</sup> )	23.59±2.96 (23.19–24.00)	22.03±1.70 (21.79–22.27)	<0.001**
Physical activity (METS)	10.6	12.6	0.003*
Current smokers (%)	45 (22%)	30 (14.6%)	0.055
Past smokers (%)	18 (8.8%)	15 (7.3%)	0.586
SBP (mm Hg)	143.99±14.28 (142.02–145.96)	113.51±6.76 (112.58–114.4)	<0.001**
DBP (mm Hg)	96.61±7.24 (95.61–97.61)	74.44±5.12 (73.73–75.15)	<0.001**
Family history of hypertension (%)	112 (54.6%)	81 (39.5%)	0.002*
Fasting biochemical profile			
Uric acid ( $\mu\text{mol/L}$ )	290.05±87.05 (278.06–302.04)	245.24±99.38 (231.50–258.50)	<0.001**
Uric acid in male ( $\mu\text{mol/L}$ )	311.23±88.04 (295.04–327.42)	266.12±105.64 (246.33–285.90)	0.001*
Uric acid in female ( $\mu\text{mol/L}$ )	262.44±77.94 (246.02–278.85)	220.11±85.23 (202.55–237.70)	0.001*
Total cholesterol (mmol/L)	5.15±1.10 (4.99–5.30)	4.36±0.59 (4.27–4.44)	<0.001**
HDL-C (mmol/L)	1.050±0.320 (1.010–1.098)	1.080±0.200 (1.057–1.110)	0.233
LDL-C (mmol/L)	3.21±1.06 (3.06–3.36)	3.27±0.63 (3.18–3.36)	0.505
TG (mg/dl)	1.93±0.86 (1.81–2.05)	1.41±0.52 (1.34–1.48)	<0.001**

METS: metabolic equivalent task scores.

SI conversion factors: To convert cholesterol to milligram per liter, multiply by 38.61; triglycerides to milligram per liter, multiply by 88.49; and uric acid to milligram per liter, multiply by 0.0168.

Continuous variables were analyzed using the independent-student *t*-test and categorical variables using the  $\chi^2$  test. 95% CI was shown in the parenthesis. \*: *P* < 0.05, \*\*: *P* < 0.001.

**Table 2**Distribution of study population according to hyperuricemia in male and female (SUA  $\geq 416$   $\mu\text{mol/L}$  for male and  $\geq 357$   $\mu\text{mol/L}$  for female).

Hyperuricemia ( $\mu\text{mol/L}$ )	Male population		Female population		Total study population	
	Hypertension	Control	Hypertension	Control	Hypertension	Control
Total number	116	112	89	93	205	205
Hyperuricemia	33 (28.4%)	16 (14.3%)	26 (29.2%)	12 (12.9%)	59 (28.8%)	28 (13.7%)

Statistical significance at the level of  $P < 0.05$ .  $P$  value obtained from *Chi*-square test.Odds ratio (total): 2.555 (95% *CI*: 1.549–4.213),  $P < 0.001$ .Odds ratio (male): 2.386 (95% *CI*: 1.226–4.61),  $P < 0.01$ .Odds ratio (female): 2.786 (95% *CI*: 1.304–5.951),  $P < 0.01$ .**Table 3**

Partial spearman correlation among biochemical profile markers, age and BMI.

	SBP	DBP	BMI	TC	HDL-C	LDL-C	TG	Age
Uric acid	0.221 (0.000)*	0.201 (0.000)*	0.154 (0.002)*	0.115 (0.02)	-0.173 (0.000)	0.042 (0.392)	0.152 (0.002)*	-0.057 (0.251)
SBP	1	0.8 (0.000)*	0.289 (0.000)*	0.313 (0.000)	-0.083 (0.093)	-0.058 (0.238)*	0.307 (0.000)*	0.074 (0.134)
DBP		1	0.242 (0.000)*	0.32 (0.000)	0.058 (0.241)	-0.089 (0.073)*	0.346 (0.000)*	0.034 (0.0487)
BMI			1	0.093 (0.06)*	-0.02 (0.68)	-0.05 (0.309)*	0.168 (<0.001)**	-0.043 (0.382)
TC				1	-0.022 (0.655)	0.797 (0.000)**	0.204 (0.000)*	0.014 (0.782)
HDL-C					1	-0.235 (0.000)*	-0.004 (0.937)	-0.033 (0.502)
LDL-C						1	-0.094 (0.056)*	0.005 (0.919)
TG							1	-0.067 (0.174)
Age								1

UA: uric acid.

\*: Statistically correlated at the level of  $P < 0.05$ , \*\*: statistically correlated at the level of  $P < 0.001$ 

#### 4. Discussions

In this cross sectional case control study we observed the strong positive association between hyperuricemia and hypertension. We observed that 28.8% of patients had hyperuricemia with hypertension. Garrick *et al.* found 31% of their patients had hyperuricemia with hypertension[17]. We observed the mean level of serum uric acid in hypertension and control were (290.05 $\pm$ 87.05)  $\mu\text{mol/L}$  and (245.24 $\pm$ 99.38)  $\mu\text{mol/L}$  respectively ( $P < 0.001$ ). Significant high serum uric acid level in hypertensive patients were also observed by Eisen *et al.* and Grayson *et al.*[18,19]. Mean age of our study patients was close to those of Eisen *et al.*[18] and Grayson *et al.*[19]. Gender ratio (male/female) in our study was 1.25:1 which was less than Feig *et al.*[20], they showed male/female ratio 1.5:1. We found the mean value of systolic blood pressure and diastolic blood pressure in patients were 143.99  $\pm$ 14.28 and 96.61 $\pm$ 7.24 respectively which was higher than the mean values of SBP and DBP in patients of Feig *et al.* study; they found the mean level of SBP and DBP 139 mm Hg and 83 mm Hg respectively.

The serum level of uric acid has been associated with the incident of hypertension and may be important of developing hypertension. Several studies have reported regarding serum uric acid level and hypertension from different part of world including Asia[21–24]. However, to the best of our knowledge, this type of study has not been reported from Nepal. This is the first study in Nepalese population to find out the association of serum uric acid level with newly diagnosed

hypertension. In this study a positive association between the serum uric acid level and newly diagnosed hypertension was found.

The potential confounding factors including renal function, dyslipidemia, and metabolic syndrome were adjusted between the hypertensive patients and normal healthy control. Somewhat decreasing association was found between the serum level of uric acid and hypertension after adjusting the BMI advocating that associated mechanism may be mediated through obesity. BMI levels of a subject reflect the obesity. Qui *et al.*, also found the association between serum uric acid level and hypertension which was attenuated after the adjustment of waist circumference[24]. The report of our study is similar to Borges *et al.* Although uric acid has the antioxidant properties, it imparts strong oxidant properties in case of obesity[25]. Both the oxidative stress due to serum uric acid level and inflammation in obesity may influence the patient to an increase risk for hypertension.

In the study of Zang W *et al.*, incident of hypertension was significantly associated with the component of metabolic syndrome[24]. We had taken metabolic syndrome as a potential confounding factor and adjusted it in both cases and controls. In this study, hypertension was significantly correlated with the component of metabolic syndrome. Joint exposure of high serum uric acid level with higher BMI and TG has higher risk factor for progression of hypertension than hyperuricemia alone. Obesity associate with hyperinsulinaemia. Hyperinsulinaemia causes the marked reduction of uric acid excretion. Hyperinsulinaemia also causes decreased sodium and potassium excretion. Overall effect of hyperinsulinaemia is to produce hypertension. Thus

high chance of getting hypertension occurs in metabolic syndrome[26].

We use the Cock Croft Gault equation for the estimation of renal function *i.e.* eGFR. Uric acid excretion declines from the renal tubules with the declining renal function. As a result, level of serum uric acid increases. Furthermore, declining renal function is the potential risk factor for secondary hypertension. By considering this mechanism, we adjusted the renal function in our cases and controls. We also tried to exclude the persons who were chronic alcoholic. Chronic alcoholics can influence the uric acid concentration and may be the cause for hyperuricaemia[27]. However, limited information on feeding habit of our study subjects is our limitation which may influence the level of uric acid.

Study conducted by Cheng X *et al.* postulated the positive association between aldosterone synthase–344 C/T polymorphism and hypertension in Han[28]. This type of genetic variation may also have role to the association between serum uric acid and hypertension. Thus we could not exclude this fact for their relation which is also limitation of our study.

In conclusion, the mean value of serum uric acid and the number of hyperuricemia persons were significantly higher in newly diagnosed hypertensive cases compared with normotensive healthy controls. Though the serum uric acid level within the normal reference range, it was strongly and significantly associated with the newly diagnosed hypertension in the study population. In clinical practices, measurement of serum uric acid level may help to identify the risk of hypertension. Moreover, further studies can be carried out to lower the serum uric acid level to maintain a low risk of hypertension or to translate high risk of hypertension into a lower risk of hypertension.

### Conflict of interest statement

We declare that we have no conflict of interest.

### Acknowledgements

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### Comments

#### Background

Hypertension is one of the current emerging community

health problem, which is very common affecting one in four individuals and it is associated with the cardiovascular disorder, diabetes mellitus, dyslipidemia which is considered as Metabolic syndrome. Since there are various etiological factors associated with hypertension so it is very difficult to predict which one is the most common cause of hypertension. The current study is based on the association of hyperuricemic with hypertension. The study tries to exemplify the reasonable mechanism(s) through which higher uric acid levels inadvertently affects the blood pressure by controlling the confounding factors.

#### Research frontiers

The current work is an explicit link of uric acid with hypertension.

#### Related reports

The exclusion and inclusion criteria of the study are well documented. The study elucidates the various reasons causing hypertension by elevated uric acid levels.

#### Innovations and breakthroughs

The current study is innovative and gives us an idea to explore further and to re–think why and how uric acid affects the endothelial functions causing hypertension.

#### Applications

The levels of uric acid in individuals would prompt to check the blood pressure and this study proves that hyperuricemia is associated with hypertension. Though earlier study conducted by Kumar *et al.*, 2009 proves uric acid to be beneficial antioxidant in cardiovascular disorders, but this current study shows it as an etiological factor responsible for hypertension.

#### Peer review

Over all the paper is very informative and gives very scientific information, which makes us to rethink about the relationship of uric acid and hypertension. It can be an eye–opener to further conducted research on uric acid levels with other disorders related to hypertension.

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