

# Prevalence of Hyperuricemia and the Relationship Between Serum Uric Acid and Hypertension in New Onset Diabetic Patients: A Cross-Sectional Indian Study

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**Objective:** Prevalence of hyperuricemia (HU) is increasing and it is associated with hypertension, metabolic syndrome, diabetes mellitus (DM), obesity, chronic kidney disease, gout and cardiovascular disease. Elevated level of serum uric acid (SUA) has been shown to be associated with hypertension and diabetes in many countries but there is lack of evidence from India. The aim of this study is to know the prevalence of HU and to know the relationship between SUA and hypertension in newly onset DM.

**Methods:** This is a cross-sectional study from a tertiary center. A total of 305 (males: 212; females: 93) newly diagnosed diabetic patients were enrolled. All patients were categorized as normotensive (<140/90) and hypertensive (≥140/90) based on ADA criteria. Based on SUA level participants were grouped into 3 tertile (T1: <4.52; T2: 4.52–5.64; T3: >5.64 mg/dl).

**Results:** The mean age, systolic blood pressure (SBP) and diastolic blood pressure (DBP) of the patients were 46.76 ±0.61 years, 130.6±1.06 mmHg and 84.11±0.63 mmHg, respectively. The mean level of SUA was 5.14±0.073 mg/dl and level was significantly higher in males compared with females (P <0.000). Overall prevalence of HU and hypertension was 12.13% and 44.59%, respectively. There was an increase in the prevalence of hypertension across the SUA tertile. SBP and DBP significantly increased across the SUA tertile (P <0.014 and <0.001, respectively). A multiple logistic regression analysis revealed that SUA tertile was independently associated with presence of hypertension (P <0.01).

**Conclusion:** This first report on the population of the eastern part of India indicates a significant positive relationship between SUA and hypertension among the newly onset Indian diabetic patients. Therefore, routine measurement of SUA is recommended in newly onset hypertensive diabetic patients to prevent HU and its related complications.

**Keywords:** serum uric acid, hypertension, newly onset diabetes mellitus, blood pressure, prevalence

## Introduction

Prevalence of diabetes mellitus (DM) is increasing and so is the associated cardiovascular disease (CVD).<sup>1,2</sup> Life expectancy is reduced by as much as 10 years in diabetics and CVD accounts for 2/3rds cause of death in these patients.<sup>3–5</sup> CVD in DM is related to dysglycemia, hypertension, dyslipidemia, obesity, hyperuricemia and other factors.<sup>6</sup> In DM one cannot effectively prevent CVD by controlling blood glucose only.<sup>7</sup> So we need a multifactorial and novel way to prevent CVD in DM. Controlling hypertension, dyslipidemia, obesity, hyperuricemia are the other ways to control CVD in DM.<sup>8</sup>

Uric acid (UA) is the byproduct of purine metabolism. Its level is high in patients with obesity, insulin resistance (IR), metabolic syndrome (MS) and DM.<sup>9–11</sup> Elevated serum level of UA is associated with various complications such as CVD,

endothelial dysfunction, chronic kidney disease (CKD), incident hypertension and prediabetes.<sup>12–14</sup> In the past few years, the relationship between serum uric acid (SUA) and the incidence of hypertension has received widespread attention. A positive association between SUA and hypertension has been reported in various epidemiological studies.<sup>15–19</sup> But it is unclear, whether SUA is a marker for hypertension or a risk factor for development of hypertension.<sup>20</sup> Some argue that both originate from common factors, such as a high fructose diet, which causes development of both hyperuricemia and hypertension.<sup>21</sup> SUA induces hypertension in two steps.<sup>22</sup> First it raises secretion of renin, reduces nitric oxide bioavailability and increases oxidative stress. This first step leads to renal vasoconstriction and a reversible uric acid (UA) dependent and salt inducible hypertension. After some weeks of persistently elevated UA, architectural vascular damage occurs with afferent arteriopathy and mild interstitial inflammation. At this second stage hypertension becomes salt sensitive and does not respond to UA-lowering therapy. Recently a few studies with small numbers of subjects have reported that UA-lowering therapy can reduce blood pressure in hypertensive patients with hyperuricemia.<sup>23,24</sup> This suggests that SUA might be a risk factor for development of hypertension. So, if we can reduce the uric acid with drugs (xanthine acid oxidase inhibitors) or lifestyle modification, we can prevent development of hypertension and thus CVD. A positive association has been found between SUA and hypertension in various countries. No studies have been performed until now to show an association between SUA and hypertension in newly diagnosed DM patients from the eastern part of India. Furthermore, level of SUA varies among different ethnicities due to difference in genetics, diet and lifestyle. Hence, we aimed to investigate the association of SUA with hypertension in newly diagnosed diabetic patients from the eastern part of India and further to know the prevalence of hyperuricemia and hypertension in these diabetic patients.

## Materials and Methods

This is a cross-sectional tertiary care center-based study conducted between April 2020 and May 2021. 305 consecutive patients with newly onset diabetes (duration <1 year) were enrolled over a period of one year. Patients with history of renal, cardiac, hepatic diseases, pregnant women, drug addicts and patients on antihyperuricemic treatment were excluded from the study.

Due care was taken not to include patients having alcohol intake in the last seven days.<sup>26</sup> Diagnosis of DM was done based on ADA criteria.<sup>27</sup> Data regarding age, sex, height, weight, BMI (body mass index), waist circumference (WC), BP (blood pressure), uric acid, lipid profile, glycosylated hemoglobin A1c (GlyHbA1c), glomerular filtration rate (GFR) were collected from patients on a predefined format. Weight was measured by a weighing machine with precision of 0.1 kg. Height was measured by a stadiometer with precision of 0.1 cm. For height measurement patients were asked to remove footwear and stand with head kept in Frankfort position. BMI was calculated by dividing the weight (in kg) by square of height (in meter). BP was measured with the help of a digital BP machine.

7 mL venous blood was collected in the morning for FPG (fasting plasma glucose), GlyHbA1c, vitamin D, creatinine and lipid profile. Blood glucose was estimated by glucose oxidase-peroxidase method. Vitamin D level was analyzed on Siemens ADVIA centaur, standardized against ID-LC/MS/MS, as per vitamin D standardization (Thyrocare). Creatinine was measured by creatinine enzymatic method. Lipid profile was carried out by standard enzymatic procedure. Ultrasonography was done to rule out cirrhosis in suspected cases.

The present investigation defined elevated SBP (systolic blood pressure) as  $\geq 140$  mmHg and/or DBP (diastolic blood pressure)  $\geq 90$  mm Hg as per ADA criteria.<sup>28</sup> All hypertensive patients were either on amlodipine or telmisartan as they do not influence the serum uric acid level.

Hyperuricemia was defined as SUA level  $>416.4$  micromole/mL ( $>7$  mg/dl) in men and  $>356.9$  micromole/mL ( $>6$  mg/dl) in women. All participants were divided into three tertile based on SUA levels (T1:  $<4.52$  mg/dl; T2:  $4.52$ – $5.64$  mg/dl; T3:  $>5.64$  mg/dl). Prevalence of hypertension was estimated in each tertile separately.

## Ethical Statement

All diabetic patients provided written informed consent and they agreed to participate in this study. The protocol was approved by the Ethics Committee for Research, Opal Hospital, Varanasi, India, dated February 1, 2020. The study was also conducted using good clinical practice following the Declaration of Helsinki.

## Statistical Analysis

All recorded data were summarized using descriptive analyses. Mean, standard error of mean, median, range (Min–Max) were used to describe continuous variables. Frequency and percentage were used to describe categorical variables. All data were analyzed using SPSS software ver. 20.0F.<sup>25</sup> The difference between sex groups for baseline variables was done by independent sample *t*-test (two-tailed). Pearson's correlation coefficient test was performed to assess the interrelationships between BP variables and SUA levels. One-way ANOVA determined the differences for variables among the groups. Box plot was used for showing the level of SUA in normotensive and hypertensive population. The relationship between SUA and hypertension was evaluated by logistic regression modeling. In Model-1, age and GFR were adjusted and in Model-2 age, GFR and sex were adjusted. In Model-3 age, GFR, sex and BMI were adjusted. A *p*-value <0.05 was considered as statistically significant.

## Results

### Baseline and Demographic Characteristics of Study Population

Baseline characteristics of newly diagnosed diabetic patients are summarized in Table 1. 305 (male: 212, female: 93) patients with mean age 46.76±0.61 years were recruited in the study. There was no significant age difference between male and female groups. Mean BMI of patients were 26.33±0.25, with a significant difference between gender groups (*P* <0.04). Mean HDL (high density lipoprotein) level was 41.32±0.56 mg/dl of all patients and mean HDL level was significantly higher in females compared with males (*P* <0.000). Females had a lower mean level of SUA compared with males (*P* <0.000). Mean levels of A1c, vitamin D, TG (triglyceride), WC, SBP, DBP, GFR, total cholesterol (TC) and LDL (low density lipoprotein) were similar in the two groups. Prevalence of hyperuricemia was 12.13%, 11.79% and 12.90% in all, males and females, respectively.

### SUA Tertile and Baseline Characteristics of Patients

Baseline characteristics of patients with different SUA tertile are presented in Table 2. Number of patients in tertile 1, tertile 2 and tertile 3 were 102, 102 and 101, respectively. Increasing trends for mean level of SUA were found across tertile (*P* <0.000). Mean value of SBP increases with increasing SUA tertile (*P* <0.014). With increasing SUA level, mean value of DBP also increased significantly (*P* <0.001). The mean values for BMI, A1c, HDL WC and GFR were

**Table 1** Baseline Characteristics of the Study Participants by Gender. *P*-values are Obtained from Independent Sample *t*-test in Comparison Between the Gender Groups

Characteristics	Total (n = 305)			Male (n = 212)			Female (n = 93)			P-value
	Mean±SEm	Min	Max	Mean±SEm	Min	Max	Mean±SEm	Min	Max	
AGE	46.76±0.61	21	76	46.72±0.76	21.00	76.00	46.86±1.01	29.00	70.00	0.914
BMI	26.33±0.25	16.3	50.6	25.99±0.27	16.30	42.70	27.10±0.53	16.30	50.60	0.041
A1c	9.85±0.15	4.8	17.8	10.02±0.18	4.80	17.80	9.46±0.27	5.30	15.60	0.091
VIT D	19.26±0.59	4.2	76.6	19.73±0.68	4.85	75.00	18.20±1.17	4.20	76.60	0.233
TG	197.85±6.55	51	800	205.71±8.29	51.00	800.00	179.95±10.05	57.00	671.00	0.070
HDL	41.32±0.56	15	71	39.87±0.63	15.00	71.00	44.62±1.06	28.00	69.00	0.000
WC	97.11±0.54	71.5	130	97.28±0.66	71.50	126.00	96.70±0.97	78.00	130.00	0.621
SBP	130.60±1.06	85	190	130.50±1.25	85.00	190.00	130.83±1.98	90.00	180.00	0.885
DBP	84.11±0.63	60	140	84.63±0.75	60.00	140.00	82.92±1.15	60.00	110.00	0.213
Uric Acid	5.14±0.073	2.1	8.5	5.39±0.09	2.10	8.50	4.58±0.12	2.35	8.12	0.000
GFR	109.11±0.81	60.5	143	108.86±1.03	60.50	143.00	109.70±1.24	91.00	297.00	0.602
TC	184.02±2.44	89	345	182.72±3.02	89.00	345.00	186.98±4.07	31.00	205.00	0.421
LDL	109.99±2.12	31	237	107.94±2.55	33.00	237.00	114.67±3.80	29.00	70.00	0.145
Hyperuricemia	37 (12.13%)	-	-	25 (11.79%)	-	-	12 (12.90%)	-	-	-

**Table 2** Baseline Characteristics of the Study Participants According to UA Tertile. Values are Presented as Mean  $\pm$  SE. P-values are Obtained from One-Way ANOVA

Characteristics	Ter I (<4.52)	Ter I (4.52–5.64)	Ter I (>5.64)	P-values for Trend
N	102	102	101	-
Sex, M/F	54/48	74/28	84/17	-
AGE	46.30 $\pm$ 1.06	46.16 $\pm$ 0.97	47.83 $\pm$ 1.15	0.405
BMI	24.86 $\pm$ 0.48	26.54 $\pm$ 0.40	27.59 $\pm$ 0.39	0.000
A1c	10.70 $\pm$ 0.27	10.05 $\pm$ 0.26	8.79 $\pm$ 0.23	0.000
VIT D	17.91 $\pm$ 1.02	19.54 $\pm$ 0.94	20.36 $\pm$ 1.10	0.063
TG	186.12 $\pm$ 10.14	194.06 $\pm$ 10.36	213.53 $\pm$ 13.25	0.059
HDL	43.39 $\pm$ 1.07	39.32 $\pm$ 0.91	41.25 $\pm$ 0.86	0.015
WC	94.14 $\pm$ 1.00	97.19 $\pm$ 0.90	99.99 $\pm$ 0.84	0.000
SBP	126.89 $\pm$ 1.82	132.13 $\pm$ 1.89	132.79 $\pm$ 1.75	0.014
DBP	80.67 $\pm$ 1.00	85.84 $\pm$ 1.31	85.84 $\pm$ 1.07	0.001
Uric Acid	3.76 $\pm$ 0.06	5.09 $\pm$ 0.03	6.60 $\pm$ 0.07	0.000
GRF	111.75 $\pm$ 1.40	110.39 $\pm$ 1.24	105.16 $\pm$ 1.49	0.003
TC	183.26 $\pm$ 4.26	182.11 $\pm$ 4.02	186.70 $\pm$ 4.40	0.318
LDL	111.26 $\pm$ 4.10	110.45 $\pm$ 3.49	108.24 $\pm$ 3.42	0.744

significantly increased with increasing concentration of SUA ( $P < 0.05$ ). Mean values for age, vitamin D, TG, total cholesterol and LDL was not significantly increased with increasing concentration of SUA.

### SUA Tertile and Prevalence of Hypertension

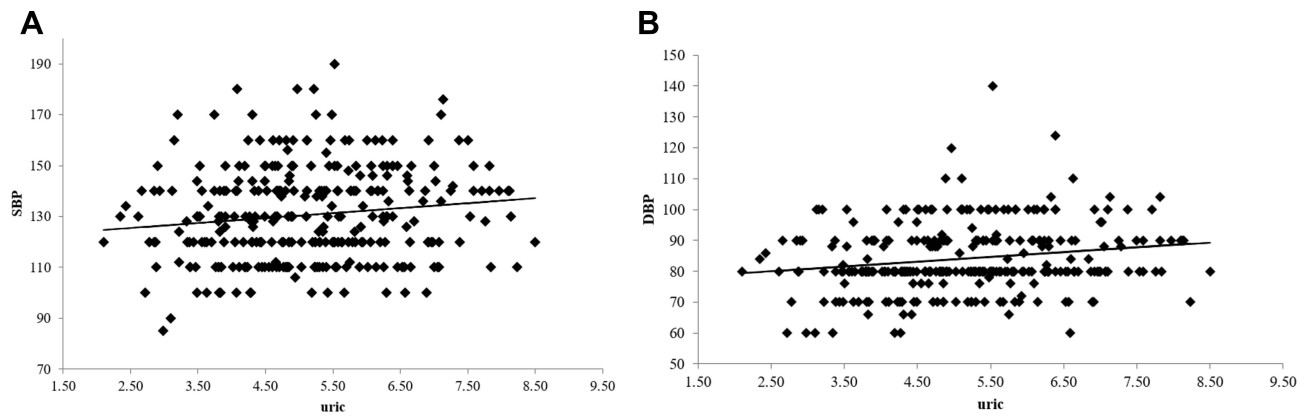
Prevalence of hypertension in each tertile is presented in Table 3. Prevalence of hypertension was 44.59%, 44.34% and 45.16% in all, males and females, respectively. Prevalence of hypertension was similar in males and females, however it increased with increasing concentration of SUA but more in females than males ( $P < 0.05$  for trends).

### Association of SUA Tertile with Blood Pressure

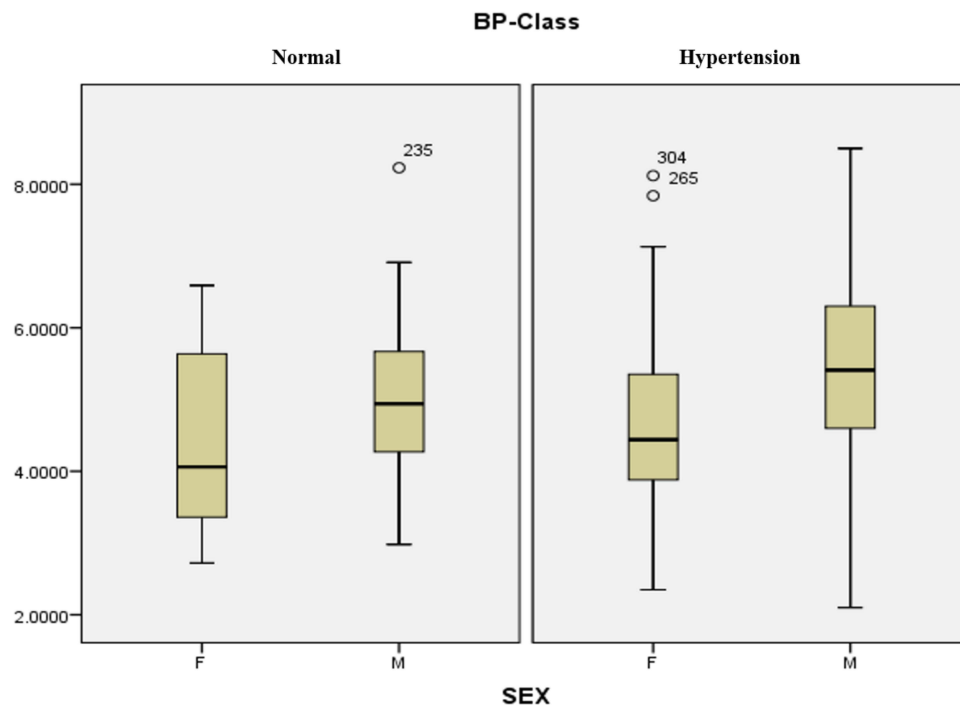
A significant positive correlation was found between SUA levels and SBP and DBP. Pearson's correlation coefficient test indicates that SUA level was significantly positively associated with SBP ( $r = 0.135$ ,  $P < 0.018$ ) and DBP ( $r = 0.181$ ,  $P < 0.001$ ) (Figure 1). In hypertensive patients SUA was elevated compared with normotensive patients (Figure 2). Mean level of SUA in normotensive and hypertensive males was 5.29 $\pm$ 0.114 and 5.53 $\pm$ 0.131 with median (interquartile range)

**Table 3** Prevalence of Hypertension. Blood Pressure (mmHg) Was Categorized as Normal (SBP < 140; DBP < 90) and Hypertensive (SBP  $\geq$  140; DBP  $\geq$  90)

Prevalence	Ter I (<4.52)	Ter2 (4.52–5.64)	Ter3 (>5.64)	Total
Male	21 (38.89%)	32 (43.24%)	41 (48.81%)	94 (44.34%)
Female	16 (33.33%)	16 (57.14%)	10 (58.82%)	42 (45.16%)
Sub-Total	37 (36.27%)	48 (47.06%)	51 (50.50%)	136 (44.59%)



**Figure 1** Association of SUA levels with (A) SBP and (B) DBP. The scale in the Y-axis is not similar between the figures.



**Figure 2** Box plot showing level of SUA in normal and hypertensive population by gender.

of 5.26 (2.06) and 5.49 (2.19) mg/dl, respectively. In females mean levels of SUA in normotensive and hypertensive patients were  $4.37 \pm 0.126$  and  $4.82 \pm 0.182$  with median (interquartile range) of 4.26 (1.80) and 4.87 (1.88) mg/dl respectively. The association of hypertension and SUA tertile for all diabetic patients is presented in Table 4 after applying logistic regression analysis. Hypertension was positively correlated with SUA tertile ( $P < 0.01$  for trends) in the present study. After adjusting age and GFR (model 1), the odds ratios (95% CI) were 1.092 (1.000–1.294) and 1.153 (1.048–1.436), respectively for T2 and T3 compared with T1. In model 2, after adjustment for age, sex and GFR, the odds ratios (ORs) were 0.980 (0.893–1.077) and 1.040 (1.001–1.336) for T2 and T3, respectively compared with T1. In model 3 after adjustment for age, sex, GFR and BMI, the ORs were 1.114 (0.994–1.248) and 1.287 (1.057–1.592), respectively for T2 and T3 compared with T1. This shows that SUA tertile was independently associated with increased prevalence of hypertension.

**Table 4** Association of UA Quartiles with Hypertension. The Logistic Regressions Were Applied to Evaluate the Association Between SUA Quartiles and BP-Class

	OR (95% CI)			P-values
	Tertile1	Tertile2	Tertile3	
Model 1	1.000	1.092 (1.000–1.294)	1.153 (1.048–1.436)	<0.01
Model 2	1.000	0.980 (0.893–1.077)	1.040 (1.001–1.336)	<0.01
Model 3	1.000	1.114 (0.994–1.248)	1.287 (1.057–1.592)	<0.01

**Notes:** Model 1: Age and GFR were selected. Model 2: Age, GFR and Sex were adjusted. Model 3: Age, GFR, SEX and BMI.

**Abbreviations:** UA, uric acid; SAU, serum uric acid; BP, blood pressure; GFR, glomerular filtration rate; BMI, body mass index.

## Discussion

Hypertension is a leading cause of CVD and premature death.<sup>29,30</sup> Worldwide prevalence of hypertension is rapidly increasing and this increase is more significant in low- and middle-income countries compared with developed countries.<sup>31</sup> Various reasons such as high sodium intake, obesity, hyperuricemia, alcohol intake, stress, physical inactivity, older age and unhealthy diet may explain the regional heterogeneity in prevalence of hypertension. Despite high prevalence, treatment and control of hypertension is low in developing countries. However various trials show that if we can control blood pressure we can reduce CVD. Meta-analysis shows that a 2 mmHg reduction in SBP can reduce stroke mortality by 10% and death from ischemic heart disease and other CVD by about 7% and a further 2 mmHg reduction in DBP in mean of population distribution can result in 6% decrease in occurrence of CHD and 15% risk reduction of stroke and transient ischemic attack.<sup>32,33</sup> Hyperuricemia has been reported to be commonly present in patients with primary hypertension and especially in malignant hypertension.<sup>34</sup> Recently a systematic review and meta-analysis by Agrawal et al reported that treatment with urate lowering drug reduces SBP by 3.3 mmHg and DBP by 1.3 mmHg.<sup>35</sup> Therefore, reduction of SUA can help in lowering of blood pressure and thus CVD. In the present study we tried to explore the prevalence of hypertension and hyperuricemia and potential association of SUA and hypertension. This is the first study from the eastern part of India that has evaluated the relationship between SUA and hypertension in new-onset DM.

In the present study, prevalence of hypertension was 44.59%, 44.34% and 45.16% in all, male and females, respectively. Similar trends in prevalence of hypertension were seen in previous studies also.<sup>36,37</sup> Prevalence of hyperuricemia was 12.13%, 11.79% and 12.90% in all, males and females, respectively. Similar results were found in other studies.<sup>38–40</sup> SUA was lower in females compared with males. Reasons for low SUA in females is due to high estrogen level.<sup>41</sup> Estrogen is known to have uricosuric properties.<sup>41</sup> Other reasons for high SUA in males are different eating habits, exercise and commuting methods.<sup>42</sup>

Our present finding confirms a strong association between SUA and hypertension. We observed that SBP and DBP increased progressively across the SUA tertile. We also found that prevalence of hypertension steadily increased across the SUA tertile even after adjusting the confounders such as age, sex, BMI and GFR. This proves that SUA is independently associated with hypertension. Consistent with present study, several epidemiological studies have also found a positive association between SUA and hypertension.<sup>15–19</sup> In a Japanese study hypertension OR was 1.2 for each 1 mg/dl increase in SUA concentration after adjusting of multiple confounders. In the same study OR in the highest quartile was 1.58 in male and 1.60 in females, compared with lowest SUA quartile.<sup>15</sup> Another study found that men with hyperuricemia had a higher risk of incident hypertension, with each unit increase in SUA associated with a 9% increase in the risk of incident hypertension.<sup>43</sup> Other studies also found elevated SUA common in subjects with new-onset hypertension, with prehypertension and with gestational hypertension.<sup>44–46</sup> SUA increases blood pressure through various mechanisms, such as activation of RASS, induction of oxidative stress, decrease in NO availability, smooth muscle cell proliferation, and induces inflammation and salt sensitivity.<sup>22</sup>

We also observed a relatively stronger relationship between SUA level and hypertension in females as compared to male diabetic patients. Other studies have also found the same. Gender-related differences were also reported in the association of SUA and MACE (major adverse cardiovascular event), arterial stiffness, metabolic syndrome, CAVI (cardio-ankle vascular index) and cardiac diastolic dysfunction.<sup>47</sup> Although the reason for these gender differences is still unclear, sex hormones may have a role. Further studies are required to investigate the exact role of sex hormones in development of hypertension and other related disorders in hyperuricemic patients.

Though vitamin D deficiency has been found associated with hyperuricemia in some reports the causal association has been always a point of enigma. In the present investigation no significant association was found between uric acid level and vitamin D level. Such observations are also reported.<sup>48,49</sup> Alcohol is known to increase serum uric acid level in blood. In the present study, patients were non-alcoholic except very few patients that too were not having alcohol consumption in last seven days while collecting the samples. Since effect of alcohol vanishes after 3 days, thus it has not influenced the statistical analysis.<sup>25</sup>

There are three primary limitations of this study. First, its cross-sectional nature prevents assessing cause–effect relationship. Second, sample size was moderate and from single center so there could be some bias. Third, we were not able to analyze dietary pattern in these patients as SUA level is also dependent upon diet.

The present investigation demonstrates that hypertension is strongly and independently associated with serum uric acid level thus early and aggressive treatment of hyperuricemia will be beneficial in prevention of the complication.

## Conclusion

The results of the present study show a significant positive association between SUA and hypertension. Prevalence of hypertension and hyperuricemia is high in new-onset DM. Multiple logistic regression analysis proves that there is an independent relationship between SUA and hypertension. Therefore, routine measurement and treatment of SUA and blood pressure in diabetic patients is recommended to prevent development of related complications.

## Abbreviations

HU, hyperuricemia; DM, diabetes mellitus; SUA, serum uric acid; SBP, systolic blood pressure; DBP, diastolic pressure; CVD, cardiovascular disease; UA, uric acid; IR, insulin resistance; MS, metabolic syndrome; CKD, chronic kidney disease; BMI, body mass index; WC, waist circumference; BP, blood pressure; GlyHbA1c, glycosylated hemoglobin A1c; GFR, glomerular filtration rate; FPG, fasting plasma glucose; HDL, high density lipoprotein; TG, triglyceride; TC, total cholesterol; LDL, low density lipoprotein; CHD, coronary heart disease; RASS, renin-angiotensin- aldosterone system; NO, nitric oxide; MACE, major adverse cardiovascular event; CAVI, cardio-ankle vascular index.

## Acknowledgments

The authors gratefully acknowledge Vanshika Singh, Praveer Anand and Yogender Singh for their critical comments. Authors also wish to thank Prof Dinesh Kumar, Department of Biotechnology, Central University of Haryana, for his constant motivation and critical comments.

## Author Contributions

SKS contributed in conceptualization, designing, acquisition of data and execution of the work. MAI and SJ analyzed the data. All authors made a significant contribution in interpretation. SKS took part in initial drafting, all authors contributed in revising the article and gave final approval of the version to be published. All authors have agreed on the journal to which the article has been submitted and further agreed to be accountable for all aspects of the work.

## Disclosure

Authors have no conflicts of interest related to this work to disclose.

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