

Relationship Between Serum Uric Acid and Incident Hypertension in Patients with Type 2 Diabetes

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Manuscript submitted August 24, 2017; resubmitted October 15, 2017; accepted November 12, 2017

■ Abstract

BACKGROUND: Little is known about the relationship between high baseline serum uric acid (SUA) and incident hypertension in patients with type 2 diabetes (T2D). **OBJECTIVES:** To evaluate the ability of baseline SUA to predict the incidence of hypertension in non-hypertensive patients with T2D. **METHODS:** The association between SUA and mean 20-year incidence of hypertension was examined in 1,666 non-hypertensive patients with T2D from Isfahan Endocrine and Metabolism Research Center outpatient clinics, Iran. The primary outcome was incident hypertension defined as systolic blood pressure (BP) of 140 mmHg or higher and/or diastolic BP 90 mmHg or higher and/or use of antihypertensive medications. The mean (standard error (SE)) age of

participants was 49.4 years (0.25 years) with a mean (SE) duration of diabetes of 6.1 years (0.15 years) at initial registration. We used multiple logistic regression to estimate the odds ratio (OR) for the incidence of hypertension across quartiles of SUA, and plotted a receiver operating characteristic (ROC) curve to assess discrimination. **RESULTS:** The highest quartile of SUA was not associated with hypertension compared with the lowest quartile in multivariable adjusted models (OR: 1.22, 95% CI: 0.87, 1.73). The area under the ROC curve for SUA was 51.7% (95% CI: 48.9, 54.5). **CONCLUSIONS:** High initial SUA levels are not a predictor of incident hypertension in an Iranian T2D population.

Keywords: diabetes · hypertension · uric acid · diabetes incidence · risk factor · eGFR · fasting plasma glucose

1. Introduction

 Hypertension is an increasing public health issue worldwide, in particular among patients with type 2 diabetes (T2D), and a leading cause of morbidity and mortality [1, 2]. Although the cause of essential hypertension is unclear, serum uric acid (SUA), the end-product of purine metabolism, has been hypothesized to activate the renin-angiotensin system, which can cause injury to pre-renal blood vessels [3]. Lowering SUA with either allopurinol or probenacid has been reported to reduce blood pressure (BP) in pilot studies of adolescents with hypertension or pre-hypertension [4, 5], while effects on adults with primary hypertension are less pronounced [6, 7].

While several epidemiological studies have reported that elevated SUA is likely to be associated with risk of hypertension in people without T2D [3, 8-19], some studies have reported no such association [20-23]. Also, the relationship may be confounded by several factors. However, the nature of this association remains unknown [15], and it is also not clear whether high SUA is cause or effect of hypertension [16]. Bjornstand *et al.* in a cross-sectional and longitudinal study of the association between SUA levels and hypertension risk in patients with type 1 diabetes (T1D), found that high SUA levels were inversely associated with systolic BP, but not with diastolic BP [24]. The authors postulated that the relationship between SUA and BP may differ in people with T1D.

T1D patients have decreased SUA levels, which may cause a change of the association between SUA and BP. Although many studies have examined the relationship between SUA and hypertension in people without diabetes, there is little information on whether SUA is an independent risk factor or predictor of future hypertension in patients with T2D, and whether the role of SUA in hypertension may be affected by other interactive risk factors. If this is the case, the association between SUA and hypertension may vary across different populations, such as patients with T1D and those with T2D. A better understanding of how SUA predisposes to hypertension may bring about more rational approaches to the prevention and treatment of hypertension in patients with T2D.

Therefore, the objective of this cohort study was to investigate the relationship between SUA and mean 20-year incidence of hypertension in non-hypertensive patients with T2D, while controlling for several known confounders, including age, gender, BMI, estimated glomerular filtration rate (eGFR), and several metabolic factors.

2. Methods and patients

2.1 Study population and data collection

The present study was a prospective registry analysis that used data from the clinical information system at Isfahan Endocrine and Metabolism Research Center, Iran, an ongoing data collection initiative in central Iran to collect, analyze, and disseminate data in a standardized manner. Clinical data were collected from all consecutive patients at the first attendance and at review consultations (usually annually) using standard examination procedures. These included an examination of ocular fundus, lens, limbs, and BP, and construction of a problem list by the clinician. At the time of each examination, the patients underwent anthropometric measurements and laboratory tests, including measurement of fasting plasma glucose (FPG), glycosylated hemoglobin A1c (HbA1c), urine protein, triglyceride, cholesterol, low-density lipoprotein cholesterol (LDLC), high-density lipoprotein cholesterol (HDLC), SUA, and serum creatinine. The examinations also included information on smoking and education as part of a questionnaire on demography, family history, and smoking status completed by the patients.

All patients were referred to the diabetes education program by qualified nutritionists following the start of the therapy. The diabetes education program consisted of six 2-h sessions emphasizing

Abbreviations:

ANOVA	analysis of variance
BP	blood pressure
BMI	body mass index
CI	confidence interval
eGFR	estimated glomerular filtration rate
FPG	fasting plasma glucose
HbA1c	glycosylated hemoglobin
HDLC	high-density lipoprotein cholesterol
LDLC	low-density lipoprotein cholesterol
MDRD	modification of diet in renal disease
OR	odds ratio
ROC	receiver operating characteristic curve
SE	standard error
SUA	serum uric acid
T1D	type 1 diabetes
T2D	type 2 diabetes

the importance of carbohydrate counting, exercise, and oral and injectable medications, and explaining the microvascular and macrovascular complications of diabetes. The mechanisms of action of diabetes medications along with proper dosing and use were reviewed, the definition and proper treatment for hypoglycemia were explained, and the importance of exercise and proper foot care were described. A computerized patient registry provided data on patient characteristics, medications, and laboratory values.

All patients were attendees at outpatient clinics at the Isfahan Endocrine and Metabolism Research Center, which is part of Isfahan University of Medical Sciences, Iran. The recruitment methods and examination procedures of the Isfahan Endocrine and Metabolism Research Center outpatient clinics have been described elsewhere [25].

Predictors of hypertension were assessed using the following data from the patients' registration consultation: gender, age at diagnosis, current age, educational level, time since diagnosis of diabetes, BMI (kg/m²), smoking status (never, current), FPG, HbA1c, serum creatinine, SUA, triglyceride, cholesterol, HDLC (measured using standardized procedures), LDLC (calculated by the Friedwald equation [26]), and BP (systolic and diastolic) at initial registration, and number of follow-up visits and follow-up duration.

2.2 Ethics statement

The study protocol followed the Iranian ethical guidelines for epidemiological studies in accordance with the current version of the Declaration of Helsinki. Isfahan University of Medical Sciences ethical committee approval was granted. This was a retrospective study based on a routine medical

procedure; additional written consent was not required. The data was processed and analyzed by authorized medical personnel only, the patients remained anonymous, and the information was concealed prior to analysis.

2.3 Follow-up and diagnosis of hypertension

Between 1992 and 2016, a total of 16,571 patients with gestational diabetes, T1D, and T2D were registered in the system. Patients with T1D, women with diabetes diagnosed only during pregnancy, and patients taking drugs that might interfere with SUA metabolism were excluded. Patients were included in the analyses if they had at least one follow-up examination during a mean (standard error (SE)) follow-up period of 20.3 (0.09) (range 6-25) years. For this study, data from 1,666 (667 (40.0%) men and 999 (60.0%) women) hypertension-free patients with T2D at baseline were used. These patients participated in at least one follow-up examination, and complete data were available.

The participants had a mean (SE) age of 49.4 (0.25) (range 30-82) years, and all of them had at least one subsequent review during a mean (SE) follow-up period of 20.3 (0.09) (range 6-25) years. Hypertension was defined as follows:

1. Systolic BP ≥ 140 mmHg and /or
2. Diastolic BP ≥ 90 mmHg and/or
3. Current use of antihypertensive medication [27]

For calculating incidence rates, we used the first occasion of documented hypertension per subject as the index event. As part of the medical interview, participants were asked whether they had ever been told by a physician that they had high or elevated BP, and whether they were taking antihypertensive medication.

2.4 Measurements

Height (assessed at baseline) and weight were measured with subjects in light clothes and without shoes using standard apparatus. Weight was measured to the nearest 0.1 kg on a calibrated beam scale. Height was measured to the nearest 0.5 cm with a measuring tape. Resting systolic (phase I) and diastolic (phase V) BP were recorded at each examination by a physician, after participants had rested in a sitting position, with legs uncrossed, and feet placed firmly on the floor, for at least 10 min, using a mercury column sphyg-

momonometer and appropriately sized cuffs. Average BP was calculated from two consecutive measurements.

FPG was measured using the glucose oxidase method. T2D was defined by a physician using the following procedure:

1. If FPG ≥ 200 mg/dl or pharmacological treatment, the participant was considered as T2D patient.
2. If FPG was ≥ 126 mg/dl and < 200 mg/dl, a second FPG was measured on another day.
3. If the second FPG was also ≥ 126 mg/dl, the participant was considered as persons with T2D.

SUA levels were measured using a direct colorimetric method. Serum creatinine was measured using a kinetic alkaline picrate assay. The eGFR was calculated using the modification of diet in renal disease (MDRD) formula [28]: $eGFR = 186.3 \times (\text{serum creatinine in mg/dl})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ for women})$. The subjects were subdivided into four groups based on their SUA level. All blood sampling procedures were performed in the central laboratory at Isfahan Endocrine and Metabolism Research Center.

2.5 Statistical analysis

Participants were followed until the occurrence of hypertension, the date of the last completed follow-up, death, or end of follow-up on October 1, 2016, whichever came first.

The statistical methods included:

- Student's *t*-test or Mann-Whitney U test
- One-way analysis of variance (ANOVA) with Scheffe's method as *post hoc* analysis or Kruskal-Wallis test with the Dunn procedure for continuous variables
- Chi-squared test for categorical variables
- Multiple logistic regression

Since no hypertension events had been registered between the examination cycles, crude and multivariate binary logistic regression equations were fitted to calculate the ORs with 95% confidence intervals (CI) and p-values for new-onset hypertension in relation to SUA quartiles using the SPSS version 18 for Windows (SPSS Inc., Chicago, IL, USA). SUA was also analyzed as a continuous variable. These multivariable models were adjusted for the following covariates:

Table 1. Age, age-adjusted means (SE), and proportions of selected baseline characteristics in 931 type 2 diabetes patients with and 736 without hypertension at baseline

Variable	Developed hypertension	Not developed hypertension	p
	Mean (SE)	Mean (SE)	
Age (yr)	50.1 (0.33)	48.6 (0.38)	0.003
Age at diagnosis (yr)	43.9 (0.33)	42.7 (0.37)	0.011
Years since diabetes diagnosis	6.0 (0.19)	6.1 (0.21)	0.617
Number of follow-up visits	37.3 (0.73)	14.8 (0.82)	<0.001
Height (cm)	159.3 (0.30)	160.8 (0.33)	0.001
Weight (kg)	70.3 (0.38)	68.7 (0.44)	0.007
Body mass index (kg/m ²)	27.6 (0.14)	26.5 (0.16)	<0.001
Follow-up duration (yr)	20.1 (0.12)	20.6 (0.14)	0.009
eGFR (ml/min)	89.9 (1.10)	91.9 (1.37)	0.238
GFR (ml/min/1.73 m ²)	85.2 (2.60)	80.5 (3.41)	0.275
Systolic BP (mmHg)	120.4 (0.45)	115.8 (0.50)	<0.001
Diastolic BP (mmHg)	76.0 (0.32)	73.4 (0.36)	<0.001
Baseline FG (mg/dl)	195.0 (2.44)	199.7 (2.75)	0.196
Creatinine (μM/l)	0.98 (0.03)	1.02 (0.04)	0.455
HbA1c (%)	8.9 (0.09)	8.5 (0.14)	0.003
Triglyceride (mg/dl)	228.8 (5.03)	231.8 (5.69)	0.693
Cholesterol (mg/dl)	221.2 (1.62)	219.2 (1.82)	0.421
HDL cholesterol (mg/dl)	44.3 (0.50)	43.8 (0.93)	0.629
LDL cholesterol (mg/dl)	131.0 (2.09)	128.2 (3.85)	0.524
Serum uric acid (mg/dl)	5.4 (0.11)	5.1 (0.13)	0.150
	No. (%)	No. (%)	
Men	344 (36.9)	329 (43.9)	0.004
Therapeutic regimen (%)			
Diet	265 (28.5)	234 (31.8)	0.338
Oral agent	552 (59.3)	424 (57.5)	-
Insulin	99 (10.6)	72 (9.8)	-
Insulin and oral agent	15 (1.6)	7 (0.9)	-
Education (%)			
Lower than high school	658 (75.4)	462 (67.2)	0.007
High school	129 (14.8)	126 (18.3)	-
College graduate	86 (9.6)	99 (14.4)	-
Smoking (%)			
Non-smoker	717 (86.7)	541 (82.3)	0.024
Current-smoker	110 (13.3)	116 (17.7)	-
HbA1c (%)			
<7%	122 (19.2)	68 (27.3)	0.007
7%-9.0%	230 (36.2)	95 (38.2)	-
>9.0%	283 (44.6)	86 (34.5)	-
Weight category (%)			
Normal (BMI <25.0 kg/m ²)	246 (27.2)	255 (35.8)	<0.001
Overweight (BMI 25-29.9 kg/m ²)	416 (46.1)	314 (44.0)	-
Obese (BMI ≥30.0 kg/m ²)	241 (26.7)	144 (20.2)	-

Legend: Data are expressed as mean (SE) or number (%). Data show differences in mean or percentage values of variables between participants who developed and those who did not develop hypertension. Age-adjusted means were calculated using general linear models. *Abbreviations:* BP – blood pressure; BMI – body mass index; eGFR – estimated glomerular filtration rate; FG – fasting glucose; GFR – glomerular filtration rate; HbA1c – glycated hemoglobin; HDL – high-density lipoprotein; LDL – low-density lipoprotein.

- Age
- Gender
- Cholesterol
- HDLC
- Triglycerides
- BMI
- eGFR
- Systolic BP
- FPG
- Smoking
- Education
- Therapeutic regimen

Diastolic BP was not included in multivariate analysis to avoid collinearity between systolic and diastolic BP. When a new case of hypertension was identified, we used the examination date to document the new case. A general linear model was used to examine the significance of trends in potential predictors of hypertension across SUA quartiles, and to compare age-adjusted means. The interaction term between gender and SUA revealed no difference, allowing us to combine them in the analysis. The ability of SUA to predict the incidence of hypertension was examined with receiver operating characteristic (ROC) curves and their respective areas under the curve, in which sensitivity was plotted as a function of 1-specificity. The area under the ROC curve is a global summary statistic of the discriminating value of a model, describing the probability that SUA is higher in an individual developing than in an individual not developing hypertension.

Reported p-values were two-tailed and p-values <0.05 were considered to be statistically significant.

3. Results

3.1 Characteristics

Table 1 shows the baseline characteristics of those participants who did and who did not progress to hypertension. As expected, those who progressed to hypertension were older and had higher age-adjusted mean weight, BMI, systolic and dia-

Table 2. Age, age-adjusted means (SE), and proportion of selected baseline characteristics of patients with type 2 diabetes by baseline serum uric acid (SUA) quartiles

Characteristic	SUA quartiles (mg/dl)				p
	1 st (<3.7)	2 nd (3.7-4.6)	3 rd (4.6-5.7)	4 th (>5.7)	
Number (%)	432 (25.9)	431 (25.9)	390 (23.4)	413 (24.8)	-
SUA (%)	2.9 (0.13)	4.2 (0.13)	5.2 (0.13)	9.0 (0.13)	<0.001
Age (yr)	48.9 (0.49)	49.2 (0.49)	48.8 (0.52)	50.7 (0.50)	0.028
Age at diagnosis (yr)	43.8 (0.27)	43.1 (0.27)	43.5 (0.29)	43.1 (0.28)	0.251
Height (cm)	158.4 (0.43)	159.4 (0.43)	160.9 (0.46)	161.3 (0.44)	<0.001
Weight (kg)	67.4 (0.56)	69.3 (0.56)	70.5 (0.59)	71.6 (0.57)	<0.001
BMI (kg/m ²)	26.9 (0.21)	27.3 (0.21)	27.1 (0.22)	27.4 (0.21)	0.296
Follow-up duration (yr)	20.3 (0.18)	20.7 (0.18)	20.5 (0.19)	19.8 (0.18)	0.002
Yr since diabetes diagnosis	5.7 (0.27)	6.2 (0.27)	6.0 (0.29)	6.3 (0.28)	0.251
FG baseline (mg/dl)	211.6 (3.55)	192.9 (3.56)	193.6 (3.75)	189.5 (3.65)	<0.001
HbA1c (%)	8.9 (0.15)	9.08 (0.15)	8.5 (0.15)	8.8 (0.14)	0.151
Cholesterol (mg/dl)	218.6 (2.37)	220.7 (2.38)	220.5 (2.51)	221.5 (2.43)	0.859
LDL-cholesterol (mg/dl)	130.4 (3.67)	132.2 (3.75)	125.2 (3.70)	133.5 (3.51)	0.391
HDL-cholesterol (mg/dl)	45.4 (0.89)	45.3 (0.90)	42.7 (0.88)	43.5 (0.84)	0.078
Triglyceride (mg/dl)	218.1 (7.39)	233.9 (7.36)	218.3 (7.78)	249.6 (7.54)	0.008
Systolic BP (mmHg)	117.0 (0.66)	119.0 (0.67)	118.1 (0.70)	119.3 (0.68)	0.068
Diastolic BP (mmHg)	73.9 (0.47)	75.3 (0.48)	75.0 (0.50)	75.0 (0.49)	0.191
Serum creatinine (μM/l)	0.92 (0.05)	1.01 (0.05)	1.05 (0.05)	1.00 (0.05)	0.289
eGFR (ml/min/1.73 m ²)	91.0 (1.69)	89.1 (1.70)	92.2 (1.80)	90.6 (1.70)	0.644
GFR (ml/min)	79.7 (4.00)	81.9 (4.10)	86.7 (4.36)	86.3 (4.07)	0.558
Men	140 (21.0)	149 (22.3)	181 (27.1)	197 (29.5)	<0.001
Therapeutic regimen, n (%)					
Diet	123 (24.6)	126 (25.3)	127 (25.5)	123 (24.6)	0.260
Oral agent	267 (27.4)	264 (27.0)	213 (21.8)	232 (23.8)	-
Insulin	38 (22.2)	36 (21.1)	47 (27.5)	50 (29.2)	-
Insulin and oral agent	6 (27.3)	5 (22.7)	3 (13.6)	8 (36.4)	-
Education, n (%)					
Lower than high school	203 (50.0)	303 (75.2)	249 (68.4)	252 (65.4)	0.312
High school	52 (12.8)	59 (14.6)	69 (19.0)	75 (19.4)	-
College graduate	39 (9.6)	41 (10.2)	46 (12.6)	59 (15.2)	-
Smoking, n (%)					
Non-smoker	343 (27.3)	327 (26.0)	288 (22.9)	300 (23.8)	0.284
Current-smoker	50 (22.1)	62 (27.4)	62 (27.4)	52 (23.0)	-
HbA1c, n (%)					
<7%	47 (21.4)	39 (17.5)	55 (27.4)	49 (20.4)	0.047
7%-9.0%	77 (35.0)	77 (37.5)	81 (40.3)	90 (37.5)	-
>9.0%	96 (43.6)	107 (48.0)	65 (32.3)	101 (42.1)	-
Weight category, (%)					
Normal weight (BMI <25.0 kg/m ²)	149 (35.2)	123 (29.5)	113 (30.1)	116 (28.9)	0.159
Overweight (BMI 25-29.9 kg/m ²)	179 (42.3)	189 (45.3)	169 (45.1)	193 (48.1)	-
Obese (BMI ≥30.0 kg/m ²)	95 (22.5)	105 (25.2)	93 (24.8)	92 (22.9)	-

Legend: Age-adjusted means were calculated using general linear models. Data are expressed as mean (SE) or number (%). Comparisons across all four groups. *Abbreviations:* BMI - body mass index; BP - blood pressure; eGFR - estimated glomerular filtration rate; FG - fasting glucose; GFR - glomerular filtration rate; HbA1c - glycated hemoglobin; HDL - high-density lipoprotein; LDL - low-density lipoprotein; SUA - serum uric acid.

stolic BP, and HbA1c at baseline. A higher proportion of these patients had obesity, while a lower proportion smoked and had attended higher education. The mean (SE) age was 50.1 (0.33) years for those progressing to hypertension and 48.6 (0.38) years for those who did not progress to hypertension. The mean (SE) SUA was 5.4 mg/dl (0.11) for those who progressed to hypertension and 5.1 (0.13) for those who did not.

Baseline characteristics of the study participants by SUA quartiles are shown in **Table 2**. In comparisons by variables at baseline, age, SUA, height, weight, triglyceride, and obesity were more likely to increase, while FPG was more likely to decrease across all four subject groups. The mean (SE) SUA of all participants was 5.3 mg/dl (0.09). The mean (SE) SUA levels per group were 2.9 (0.13), 4.2 (0.13), 5.2 (0.13), and 9.0 (0.13) at the

Table 3. Incidence rates and odds ratios (OR) of hypertension by serum uric acid (SUA) quartiles

Characteristic	Quartiles of SUA (mg/dl)			
	1 st (<3.7)	2 nd (3.7-4.6)	3 rd (4.6-5.7)	4 th (>5.7)
Number of cases (%)	241 (25.9)	234 (25.1)	210 (22.6)	246 (26.4)
Person-years	8822	8921	7988	8180
Incidence/1000 person-years (95% CI)	27.3 (23.9, 30.7)	26.2 (22.9, 29.5)	26.3 (22.8, 29.8)	30.1 (26.4, 33.8)
Odds ratio (95% CI)				
Unadjusted	1.00	0.95 (0.73, 1.24)	0.93 (0.71, 1.23)	1.18 (0.90, 1.55)
Gender-adjusted	1.00	0.96 (0.74, 1.26)	0.98 (0.74, 1.30)	1.24 (0.94, 1.63)
Age- and gender-adjusted	1.00	0.96 (0.73, 1.25)	0.98 (0.75, 1.30)	1.21 (0.92, 1.59)
Age-, gender-, and BMI-adjusted	1.00	0.95 (0.72, 1.25)	0.97 (0.73, 1.28)	1.14 (0.86, 1.52)
Age-, gender-, triglyceride-, and BMI-adjusted	1.00	0.92 (0.70, 1.22)	0.95 (0.71, 1.26)	1.12 (0.84, 1.49)
Age-, gender-, triglyceride-, BMI-, and cholesterol-adjusted	1.00	0.93 (0.70, 1.22)	0.95 (0.71, 1.26)	1.12 (0.84, 1.49)
Age-, gender-, triglyceride-, BMI-, cholesterol-, FPG-, and eGFR-adjusted	1.00	0.98 (0.72, 1.32)	1.03 (0.76, 1.42)	1.12 (0.82, 1.52)
Age-, gender-, triglyceride-, BMI-, cholesterol-, FPG-, eGFR-, smoking-, and education-adjusted	1.00	1.07 (0.77, 1.49)	1.03 (0.74, 1.45)	1.30 (0.92, 1.49)
Age-, gender-, triglyceride-, BMI-, cholesterol-, FPG-, eGFR-, smoking-, education-, and systolic BP-adjusted	1.00	1.02 (0.73, 1.42)	1.01 (0.72, 1.43)	1.23 (0.87, 1.74)
Age-, gender-, triglyceride-, BMI-, cholesterol-, FPG-, eGFR-, smoking-, education-, systolic BP-, and therapeutic regimen-adjusted	1.00	1.02 (0.73, 1.42)	1.00 (0.71, 1.41)	1.22 (0.87, 1.73)

Legend: Odds ratio (with 95% CI) calculated by the multiple logistic regression. *Abbreviations:* BMI - body mass index; BP - blood pressure; CI - Confidence interval; eGFR - estimated glomerular filtration rate; FPG - fasting plasma glucose.

first, second, third, and fourth quartile, respectively.

3.2 Incidence of hypertension

931 (344 men and 587 women) incident cases of hypertension were recorded during 33,863 (13,347 men and 20,516 women) person-years of follow-up. Within this cohort of patients with T2D but without hypertension at baseline, the overall incidence of subsequent hypertension was 27.5 (95% CI: 16.9, 20.6) events per 1000 person-years. Incidence rates were higher in women (28.6, 95% CI: 26.3, 30.9 per 1000 person-years) than men (25.8, 95% CI: 23.1, 28.5), but the differences were not statistically significant.

3.3 Association with hypertension

The incidence of hypertension (95% CI) was 27.3 (23.9, 30.7) per 1000 person-years for the 1st quartile, 26.2 (22.9, 29.5) for the 2nd quartile, 26.3 (22.8, 29.8) for the 3rd quartile, and 30.1 (26.4, 33.8) for the 4th quartile. No overall association was observed. In multivariable-adjusted models, the odds ratio (OR) (95% CI) was 1.22 (0.87, 1.73) in those in the 4th quartile, 1.00 (0.71, 1.41) in

those in the 3rd quartile, and 1.02 (0.73, 1.42) in those in the 2nd quartile when compared with participants in the 1st quartile at baseline. Controlling for gender, age, BMI, triglyceride, cholesterol, FPG, eGFR, smoking, education, therapeutic regimen, and systolic BP did not significantly alter the OR compared to the unadjusted model (**Table 3**).

In another model, an appropriate interaction term was included to test the impact of gender on the relation of SUA to hypertension incidence. The interaction term was not statistically significant for developing hypertension ($p > 0.05$). When the analyses were repeated using SUA levels as a continuous variable, the results were similar and a higher SUA level was not associated with a higher risk of hypertension (OR 1.02; 95% CI: 0.98, 1.06) (**Table 4**). When the association between SUA (continuous variable) and incident hypertension within subgroups of BMI, eGFR, gender, and the therapeutic regimen at baseline was examined, SUA was not associated with incident hypertension within these subgroups (**Table 4**).

The ROC curves for the incidence of hypertension according to SUA levels are shown in **Figure 1**. The area under the ROC curve was 51.7% (95% CI: 48.9, 54.5).

Table 4. Odds ratios (OR) of hypertension by baseline serum uric acid levels and within subgroups

Group	OR (95% CI)
Unadjusted	1.02 (0.99, 1.05)
Gender-adjusted	1.02 (0.99, 1.05)
Age- and gender-adjusted	1.02 (0.99, 1.05)
Age-, gender-, and BMI-adjusted	1.02 (0.99, 1.05)
Age-, gender-, triglyceride-, and BMI-adjusted	1.02 (0.99, 1.05)
Age-, gender-, triglyceride-, BMI-, and cholesterol-adjusted	1.01 (0.99, 1.05)
Age-, gender-, triglyceride-, BMI-, cholesterol, FPG-, and eGFR-adjusted	1.01 (0.98, 1.04)
Age-, gender-, triglyceride-, BMI-, cholesterol, FPG-, eGFR, smoking-, education-, and systolic-BP adjusted	1.02 (0.98, 1.06)
Age-, gender-, triglyceride-, BMI-, cholesterol, FPG-, eGFR, smoking-, education-, systolic BP-, and therapeutic regimen-adjusted	1.02 (0.98, 1.06)
Subgroup	Multivariable-adjusted* OR (95% CI)
Body mass index	
Normal weight	0.95 (0.87, 1.04)
Overweight	1.05 (0.99, 1.11)
Obese	1.00 (0.94, 1.07)
eGFR	
60 or above	1.01 (0.98, 1.06)
Below 60	1.08 (0.92, 1.25)
Gender	
Male	1.04 (0.96, 1.12)
Female	1.01 (0.97, 1.05)
Therapeutic regimen	
Diet	0.97 (0.91, 1.03)
Oral agent	1.05 (0.99, 1.11)
Insulin	1.20 (0.98, 1.46)

Legend: Odds ratio (95% CI) calculated by multiple logistic regression. *Adjusted for age, gender, triglyceride, BMI, cholesterol, FPG, eGFR, smoking, education, systolic BP, and therapeutic regimen. *Abbreviations:* CI - confidence interval, eGFR - estimated glomerular filtration rate.

4. Discussion

This long-term cohort study indicated that among patients with T2D, high SUA levels were not a predictor of hypertension incidence. However, even though not high, predictive power was existent, as reflected by non-significant ORs and area under the ROC curve, which was close to 0.5. This suggests that high SUA levels may be recognized as a weak risk factor for hypertension in patients with T2D, although lowering SUA levels in patients with T2D is not able to prevent hypertension. Using SUA measurements as a continuous variable did not change the finding. To the best of our knowledge, this is the first study to explore the

association between SUA and hypertension in patients with T2D.

The lack of an association between SUA and hypertension in our study population should be explained. Although many studies have suggested that SUA is an independent risk factor for hypertension in people without diabetes [3, 8-18], some studies have reported no such association in men or the elderly [17, 18]. There are also studies which suggest that SUA does not play a role in hypertension [19-23]. It is conceivable that there is a difference in the relationship between SUA and hypertension reported in people without diabetes and that reported in our study in people with T2D, which may be explained by the following reasons:

1. SUA has not only antioxidant properties, including the clearance of oxygen radicals and the chelation of metals, but also pro-oxidant features (reduction of nitric oxide bioavailability and increase of reactive oxygen species). The pro- or antioxidant features of SUA depend on its chemical microenvironment [29]. Therefore, SUA can play different roles in T2D depending on the chemical microenvironment, and thus may be differently associated with T2D and metabolic patterns in different populations.
2. Many cardiovascular risk factors, such as obesity and hyperlipidemia, can accumulate in patients with T2D and may affect the role of SUA in incident hypertension.

However, the lack of association between SUA and hypertension in patients with T2D cannot be fully explained to date. Our longitudinal data should provide information for the generation of further hypotheses. Other reasons why the relationship between SUA and hypertension was not statistically significant may be that the statistical power was rather low and that clustering according to covariate occurred. SUA levels have been shown to be higher in those with better diabetes control and in obese patients and lower in patients with T2D [30]. So, SUA may be decreased in patients with T2D, particularly when they are poorly controlled, despite high intracellular levels. Thus, a possible explanation is that patients with T2D with poor glycemic control may have reduced SUA levels, which could alter the relationship between SUA and hypertension. We clearly need more longitudinal studies to address mechanistic differences among individuals with and without T2D, to explain the different findings regarding the association between SUA and hypertension in patients with T2D.

The role of elevated SUA levels in the pathogenesis of hypertension in people without diabetes is not entirely clear. Putative mechanisms include [31-36]:

1. Oxidative stress
2. Renal vascular inflammation (through stimulation of nuclear transcription factor and release of proinflammatory cytokines)
3. Activation of the vascular renin-angiotensin system (through a preglomerular arteriopathy, attributable to increased vascular smooth cell proliferation via increased expression of mitogen-activated protein kinases, cyclooxygenase-2, and platelet-derived growth factor)
4. Impairment of nitric oxide production
5. Vascular endothelial dysfunction

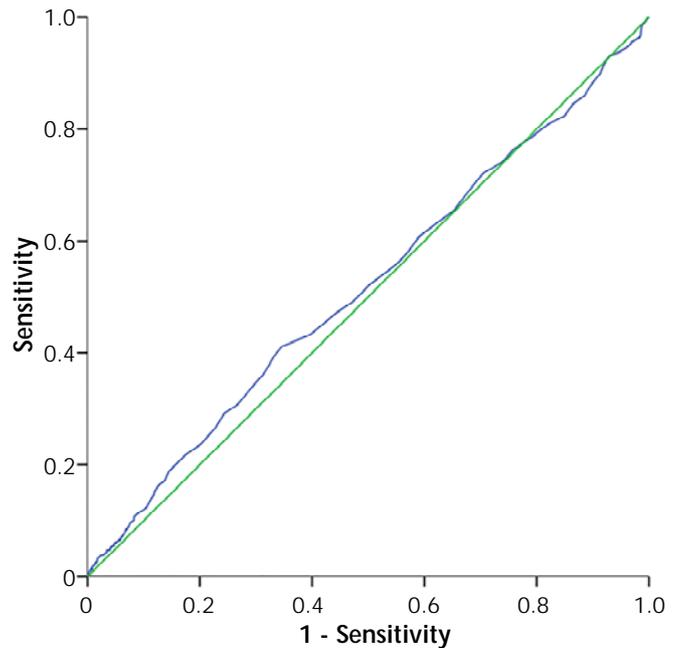
There are also studies that suggest SUA has no role in hypertension [23]. One of the arguments is based on genome-wide association studies that have been able to link polymorphisms in urate transporters with hyperuricemia and gout, but not with hypertension [37]. One proposed explanation for this discordance is that SUA is not the critical determinant of hypertension, but rather intracellular uric acid may be the key factor, and this may be dissociated from SUA in the various genome-wide association studies [38].

In Iran, the prevalence of T2D has increased so rapidly that 9.3% of Iranian adults aged 20-79 years had T2D in 2010 [39], and more than 1% of the Iranian urban population older than 20 years develops T2D each year [40]. Patients with T2D have an increased incidence of cardiovascular disease [41], and individuals diagnosed with both coronary artery disease and T2D belong to a very high-risk population that warrants increased attention [42].

The main advantages of these real-life data include:

- The observation of patients for a mean of 20 years.
- The use of standardized protocols for exposure and outcome assessment.
- The ability to assess several important confounding factors in the association between SUA and hypertension in patients with T2D in our center.

This study also has some limitations. Because it was single-centered and selection of patients was non-random, a selection bias in the registry and



Area under the curve (95% CI)	
Serum uric acid	0.517 (0.489, 0.545)

Figure 1. Receiver operating characteristic (ROC) curves for serum uric acid (SUA) to predict hypertension in patients with type 2 diabetes. Estimates of the area under the ROC curves and their 95% confidence intervals are shown in the table.

the results cannot be excluded. The results may not be applicable to regional populations therefore. However, this helped to limit confounding, and our previous studies showed that these patients are a representative sample of known diabetic patients from the region of Isfahan [43]. We used clinical characteristics of patients only at baseline and at the last follow-up visit. We could not rule out the possibility of residual confounding because of unmeasured or inaccurately measured covariates. Our study was limited by a possible survival bias in that the study was restricted to patients alive during the whole study period. As SUA levels relate to mortality [44], selective survival may have resulted in underestimation of the true association. It is possible that the people with diabetes who had the most severe disease or whose disease was the most poorly controlled died before the end of the study, and were not included in the sample.

In conclusion, these data provide evidence that high SUA levels are not a robust predictor of hypertension, independent of age, gender, triglyceride, cholesterol, HDLC, FPG, BMI, eGFR, smoking, education, systolic BP, and therapeutic regi-

men in patients with T2D in Iran. This is the first report of the relationship between SUA and incident hypertension in patients with T2D in a Middle-East country and provides new data from Iran which has been under-represented in earlier studies. More studies are necessary to confirm the observations.

Acknowledgments: We wish to thank M. Abyar for technical computer assistance. This study was supported in part by Isfahan University of Medical Sci-

ences, grant IR.MUI.REC.1396.1.005, dated 10 July 2017.

Author contributions: MJ designed the study, performed the statistical analyses, interpreted the data, and drafted the manuscript; AA and MA recruited samples, contributed to the interpretation of results, and revised the manuscript. All authors approved the final version submitted for publication.

Disclosures: The authors reported no conflict of interests.

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