

Serum Uric Acid Levels in Type 2 Diabetes Mellitus: Is There a Linear Relationship with Severity of Carotid Atherosclerosis?

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Abstract

Aims: The aim of this study was to correlate serum uric acid (SUA) levels and carotid intima-media thickness (CIMT) in patients with type 2 diabetes mellitus (DM). **Settings and Design:** This study was a cross-sectional observational study on 103 diabetic patients conducted from September 2015 to May 2017. **Subjects and Methods:** We screened 103 patients with type 2 DM between the ages of 30–65 years. SUA levels and the CIMT were measured. The patients were divided into quartiles based on uric acid level. The CIMT of the quartiles is compared and analyzed. **Statistical Analysis Used:** Chi-squared test, Analysis of Variance, and Pearson's correlation. **Results:** Uric acid levels were positively associated with CIMT ($P = 0.001$). The association remained significant after further adjustment for potential confounders. Strong correlation was found among them as depicted by correlation coefficient ($r = 0.779$). **Conclusions:** Carotid atherosclerosis as measured by IMT is associated with SUA levels in patients with type 2 DM.

Keywords: Atherosclerosis, intima-media thickness, serum uric acid

INTRODUCTION

In general population, it was suggested that one of the risk factor for cardiovascular disease (CVD) is hyperuricemia.^[1,2] However, still there was consideration of the fact that the association was confounded by certain established CVD risk factors.^[3,4] There is scarcity of data among the Indian population as most of the studies are from Japan and China and very few have studied the association in type 2 diabetes mellitus (DM) patients. In the modern era of 21st century, it was observed that hyperuricemia has a role in the development of metabolic syndrome (MetS), coronary artery disease, and DM.^[5] We studied the carotid intima-media thickness (CIMT) in diabetic patients and analyzed with the uric acid levels.

SUBJECTS AND METHODS

Study subjects

A cross-sectional study was performed among 103 diabetic patients. The duration of the study was conducted from September 2015 to May 2017. The patients who are on uric acid lowering drugs such as allopurinol and febuxostat, patients on diuretics especially thiazides, patient who is not

abstinent from alcohol consumption for the last 2 months, patients on drugs affecting serum uric acid (SUA) levels (salicylates, cyclosporine, ethambutol, pyrazinamide, and cytotoxic agents), patients with other comorbidities (cardiac disorders, renal disorders, and malignancies), and patients whose creatinine clearance is <60 ml/min/1.73 m² were excluded from the study. The study was approved by the Ethics Committee of the Hospital, and written informed consents were obtained from all participants.

Laboratory measurements

Each patient was given a questionnaire regarding the history of DM (duration and the present medications), history of hypertension (HTN), smoking and alcohol history, and family history of diabetes. Individual patient's glycated hemoglobin, fasting lipid profile (total cholesterol, triglycerides, and high-density lipoprotein cholesterol), and SUA level (measured using uricase/peroxidase calorimetric method) were

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measured. Estimated glomerular filtration rate was estimated using the modification of diet in renal disease equation.

Bilateral images of common carotid arteries, internal carotid artery, and carotid bulb is obtained by a lateral view by a single experienced radiologist who has expertise in cross-sectional imaging. The gap between the media-adventitia interface and lumen-intima interface is the IMT. The thickness was measured at 1 cm proximal to the dilatation of the carotid bulb. The mean of maximum IMT of both the common carotid artery is taken as the average CIMT.

Statistical methods

The normally distributed data are expressed as the means \pm standard deviation. The categorical variables are expressed in frequency and percentage. Analysis of Variance (ANOVA) is performed for continuous variables. For the categorical variables, multivariate linear regression analysis was performed for comparison according to the uric acid quartiles. Other categorical variables were analyzed using Chi-squared test. Potential confounding variables including gender, smoking, waist circumference, low-density lipoprotein cholesterol (LDL-C), alcohol, and HTN were controlled in the regression models. Correlation coefficients between uric acid and metabolic features were calculated by correlation analysis (Pearson's correlation). For data management and statistical analysis, SPSS version 23.0 (IBM, Chicago, Illinois, USA) for Windows was used. A value of $P < 0.05$ is considered statistically significant.

RESULTS

Our study included 103 diabetic patients with age group between 30 years and 65 years of age. The baseline characteristics of the patients under study in mean or in percentage are shown in the Table 1.

The mean age of the study patients was 54.5 ± 8.4 years with 65% being males and 40.8% having history of HTN. When analyzed mean uric acid levels among males was high compared to females, but was not statistically significant ($P = 0.35$).

The patients were divided into four quartiles based on the uric acid level. The baseline characteristics and medical characteristics of both genders as per the quartile are tabulated as given in Table 2.

Association between serum uric acid and carotid atherosclerosis

The mean of CIMT in each quartile is calculated and tabulated [Table 3]. A bar diagram comparing mean CIMT in each quartile is depicted in Figure 1. A scatter plot was constructed with SUA levels on X-Axis and average CIMT (Average of the right and left CIMT) on Y-Axis [Figure 2].

Significant differences between these four quartiles were found as analyzed by one-way ANOVA ($P = 0.001$). A Tukey *posthoc* test revealed that the CIMT was statistically significantly higher in the 1st quartile (0.07396 ± 0.0045)

Table 1: Baseline characteristics of the patients

Parameter	Values in percentage or mean \pm SD	Range
<i>n</i>	103	
Age (years)	54.5 \pm 8.4	31-65
Gender	Male: 65 Female: 35	
BMI (kg/m ²)	24.8 \pm 3.7	17.1-35.6
WC (cm)	90.34 \pm 6.7	78-106
Duration of diabetes (years)	10 \pm 2	1-20
HbA1c	9.1 \pm 2.5	4.1-17.2
Serum uric acid (mg/dl)	4.24 \pm 1.3	1.7-7.7
TC (mg/dl)	162.8 \pm 50.1	70-379
HDL-C (mg/dl)	32.4 \pm 15.4	4-72
LDL-C (mg/dl)	97.1 \pm 42.1	19.2-277
Serum TG (mg/dl)	170.8 \pm 42.1	49-568 mg/dl
History of HTN	40.8	
Carotid intima-media thickness (cm)	0.082 \pm 0.014 cm	0.055-0.120

SD: Standard deviation, BMI: Body mass index, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, HbA1c: Glycosylated hemoglobin, TC: Total cholesterol, TG: Triglycerides, WC: Waist circumference, HTN: Hypertension

and 4th quartile (0.07396 ± 0.0045) ($P = 0.001$) compared to the 1st quartile (0.07396 ± 0.0045) and 2nd quartile (0.07626 ± 0.0058) ($P = 0.643$).

Multiple linear regression analysis was performed with CIMT and uric acid, HTN, LDL-C, sex, waist circumference, smoking, and alcohol intake. HTN ($P = 0.003$) and SUA ($P = 0.001$) were found to be statistically significant [Table 4].

Pearson's correlation analysis was performed to find the correlation between SUA and CIMT. A strong correlation for CIMT with SUA was obtained with correlation coefficient of $r = 0.779$ (with $P = 0.001$) which was statistically significant.

DISCUSSION

Our study is a cross-sectional study, conducted at a tertiary care center. We enrolled 103 diabetic patients. It was found that there was a positive correlation between SUA levels and CIMT, and hence, to the carotid atherosclerosis.

The patients were divided into four quartiles, based on uric acid levels and compared. The rationale for using quartiles of uric acid is that in this descriptive study there are neither comparative groups nor controls. The values of uric acid levels were almost in the normal range and there were only few patients with high uric acid levels. Hence, quartiles based on uric acid levels were computed such that the mean CIMT can be compared among quartiles to find a correlation.

It was found that the mean CIMT in the last quartile (0.095 cm) was higher compared to the first quartile (0.074 cm) and this observation was statistically significant ($P = 0.001$).

The GREek Atorvastatin and Coronary heart disease Evaluation study,^[6] and the Losartan Intervention for Endpoint reduction

Table 2: Baseline characteristics of patients in each quartile

Uric acid quartile	Mean±SD								
	Mean Age (In years)	WC	BMI	HbA1c	TC	TG	HDL-C	LDL-C	CIMT-average
1.00 (1.7-3.3) (n=27)	52.85±9.67	89.33±5.74	24.2852±3.64	9.819±2.53	159.70±44.68	170.41±104.44	28.56±18.28	99.933±40.52	0.074±0.004
2.00 (3.4-4.1) (n=27)	55.33±7.33	87.56±7.18	23.8789±4.004	8.554±2.30	170.37±43.71	173.33±97.67	37.19±14.49	99.252±37.89	0.076±0.005
3.00 (4.2-5.2) (n=25)	55.76±7.80	91.28±6.28	25.6640±2.86	9.084±2.10	165.76±46.97	160.88±85.47	34.68±15.71	97.880±41.19	0.085±0.008
4.00 (≥5.3) (n=24)	54.21±9.11	93.62±6.27	25.7500±3.99	9.079±3.26	155.04±65.43	185.33±118.66	29.08±11.43	90.391±54.02	0.094±0.009

SD: Standard deviation, BMI: Body mass index, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, HbA1c: Glycosylated haemoglobin, TC: Total cholesterol, CIMT: Carotid intima-media thickness, TG: Triglyceride, WC: Waist circumference

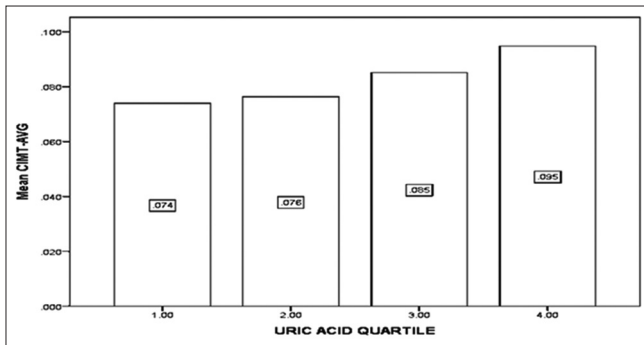


Figure 1: Bar diagram depicting mean carotid intima-media thickness in each quartile

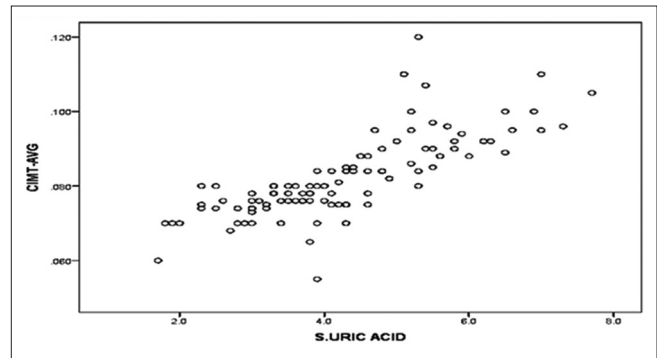


Figure 2: Scatter plot for the Serum Uric acid and Average carotid intima-media thickness

in HTN study^[7] have shown the possible causal relationship between SUA and cardiovascular risks.

In this study, 103 diabetic patients were studied in between the age groups of 30 years and 65 years. The mean age of the patients in the study is 54.5 ± 8.4 years. Similar study by Li *et al.*,^[8] recruited Chinese patients (65.57 ± 11.70 years). A study by Ishizaka *et al.*^[9] studied Japanese patients (56.6 ± 10.4 years). The mean baseline values of the patients under study compared to similar studies is shown in Table 5. Ishizaka *et al.* published a similar study in 2005 among Japanese individuals, while Li *et al.* published a study similar to the study in 2011 among Chinese individuals.

Uric acid levels are generally higher in males than in females. This is thought to be due to higher levels of estrogen in the plasma of females compared to males leading to higher renal clearance of urate by estrogen in females.^[10]

In this study, males made up to 65% while females were 35%. This is similar to the study by Ishizaka *et al.*^[9] The mean uric acid levels among males is 4.50 ± 0.21 mg/dL and among females is 4.08 ± 0.15 mg/dL. Although it was found that the uric acid levels in males are slightly higher than in females in the study, the finding was not statistically significant ($P=0.35$).

For comparison among groups and to find an association between uric acid levels and CIMT, quartiles were computed based on uric acid levels. There were 27 patients grouped into

first quartile and second quartile with uric acid levels ranging from 1.7 mg/dL to 3.3 mg/dL and 3.4 mg/dl to 4.1 mg/dl, respectively. About 25 patients were grouped into third quartile with uric acid levels ranging from 4.2 mg/dL to 5.2 mg/dL. Twenty-four patients were grouped into fourth quartile with uric acid levels above 5.3 mg/dL.

The mean CIMT in each uric acid quartile is calculated and compared. In this study, it is observed that the mean CIMT showed a gradual increase with each quartile. This implies that high uric acid level is seen with patients with high CIMT thereby representing higher degree of atherosclerosis. 0.074 cm in the 1st quartile, 0.076 cm in the 2nd quartile, 0.085 cm in the 3rd quartile, and 0.095 cm in the 4th quartile. Increasing level of uric acid although within the normal range seems to be associated with increase in the CIMT in a linear way.

ANOVA between the uric acid groups and CIMT was performed, and it was observed that the increase in mean CIMT with the increase in uric acid as per the quartile range was statistically significant ($P = 0.001$).

Aposthoc Tukey test was performed among the quartile groups and it was observed that increase in mean CIMT among the 1st and 2nd quartile group is not statistically significant, but the difference in CIMT among the 1st quartile when compared to 3rd and 4th quartile is statistically significant. This signifies that

Table 3: Mean carotid intima-media thickness in each uric acid quartile

Uric acid quartile	Mean	n	SD
1.00	0.07396	27	0.004536
2.00	0.07626	27	0.005822
3.00	0.08516	25	0.008773
4.00	0.09479	24	0.008925
Total	0.08214	103	0.010803

SD: Standard deviation

Table 4: Linear regression analysis of carotid intima-media thickness with other variables

	Beta coefficients	95% CI for beta coefficients		
		P	Lower bound	Upper bound
CIMT	0.053	0.001	0.034	0.072
LDL-C	-3.336E-6	0.833	0.000	0.000
Sex	-0.001	0.351	-0.005	0.002
WC	5.085E-5	0.635	0.000	0.000
HTN	0.005	0.003	0.002	0.008
Smoking	0.001	0.616	-0.003	0.004
Alcohol	0.000	0.886	-0.003	0.004
Serum uric acid	0.006	0.001	0.004	0.007

LDL-C: Low-density lipoprotein cholesterol, CIMT: Carotid intima-media thickness, WC: Waist circumference, HTN: Hypertension, CI: Confidence interval

Table 5: Baseline characteristics of our study compared to similar studies

Parameter	Present study (2017)	Li <i>et al.</i> , 2011	Ishizaka <i>et al.</i> , 2005
Age (years)	54.5±8.4	65.28±11.27	56.6±10.5
Gender (%)			
Male	65	38.4	67
Female	35	61.6	33
BMI (kg/m ²)	24.8±3.7	25.2±3.3	21.7±3.9
WC (cm)	90.34±6.7	84.8±9.2	82.4±8.8
Duration of diabetes (years)	10±2	7.52±3.6	NA
HbA1c (%)	9.1±2.5	7.04±1.02	5.5±1.2
TC (mg/dl)	162.8±50.1	208.8±22.4	205±32
LDL-C (mg/dl)	97.1±42.1	118.5±18.6	NA
HDL-C (mg/dl)	32.4±15.4	50.95±15.4	55±14
CIMT (cm)	0.082±0.014	0.085±0.024	Measured carotid plaque instead of CIMT
Uric acid (mg/dl)	4.24±1.3	4.88±1.2	5.5±1.1

BMI: Body mass index, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, HbA1c: Glycosylated hemoglobin, TC: Total cholesterol, CIMT: Carotid intima-media thickness, WC: Waist circumference, NA: Not available

there is an association of SUA with the CIMT (representing the carotid atherosclerosis) at higher levels of uric acid.

A multiple linear regression analysis was performed on CIMT with various variables [Table 4]. It was found that only HTN

and SUA had a positive impact on CIMT while sex, history of smoking, waste circumference, and LDL-cholesterol had no effect on the CIMT.

Experimental studies have also shown the harmful effects of uric acid on vascular smooth muscle cells (VSMCs) apart from its damage to the endothelium. The entry of uric acid causes the proliferation of VSMCs through the mitogen-activated protein kinase pathway,^[11] stimulates the production of pro-inflammatory chemokine monocyte chemoattractant protein-1 (MCP-1),^[12] and enhances angiotensinogen mRNA expression and reactive oxygen species production in VSMCs.^[13]

SUA possesses oxidative properties by mediating the production of radicals that have pro-oxidant effect on LDL-C. Increased uric acid levels causes endothelial dysfunction and reduces the bioavailability of NO.^[14] It enters into the VSMCs by urate transporters and increased levels induces the proliferation of VSMC's. This causes thickening of the vessel wall or the increase in the IMT.

The possible association of increased uric acid levels and coronary heart disease and their independence had been analyzed in several previous studies. Some showed a positive association^[15] and some did not.^[16,17] Most of the studies showed that the association was not independent. In alcohol abstainers, it was shown to have an independent association.

Pan *et al.*^[18] studied a population of 145 ($n = 145$), and after adjusting for age and sex, uric acid showed no significant correlation with carotid plaque. A total of 10,000 are included in the Atherosclerosis Risk in Communities Study and the possible associations between carotid atherosclerosis and uric acid were extensively studied.

Li *et al.*^[8] revealed a uric acid significantly correlated with carotid atherosclerosis (CIMT) ($P = 0.02$). The correlation coefficient was 0.07. Ishizaka *et al.*^[9] revealed a positive association between SUA, metabolic syndrome, and carotid plaque. However, when multivariate analysis was performed with adjustment of age, and smoking, the association was statistically significant only in men. For the presence of carotid plaque, it was found that uric acid is a risk factor in men without metabolic syndrome.

Kawamoto *et al.*^[19] revealed that uric acid had an independent association with carotid atherosclerosis in males without metabolic syndrome. Gomez-Marcos *et al.* revealed that there is no association between SUA levels and CIMT ($P = 0.39$), while Erdogen *et al.* showed a positive association ($P = 0.002$).

CONCLUSIONS

In conclusion, our data indicate that SUA levels are significantly associated with carotid atherosclerosis in patients with type 2 diabetes, even after adjustment for other potential confounders.

Limitations

The study includes the subset of population which may not represent the entire population with respect to region or

ethnicity. This study is a descriptive cross-sectional study with no control group. Even though there is a correlation found between SUA levels and CIMT, further studies to be carried out to establish uric acid as an independent risk factor for CIMT (atherosclerosis).

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Conflicts of interest

There are no conflicts of interest.

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