

A CROSS-SECTIONAL STUDY ON CORRELATION BETWEEN SERUM URIC ACID LEVEL AND CAROTID ATHEROSCLEROSIS IN PATIENTS OF TYPE 2 DIABETES

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ABSTRACT

Objective: The objective of the study was to assess correlation between uric acid (UA) level and carotid intima media thickness (CIMT) in type 2 diabetes mellitus (DM) patients.

Methods: The study was conducted in the Department of Medicine, SMS Medical College and Attached Hospital, among adults with type 2 DM. It was cross-sectional study conducted from April 1, 2019, to December 31, 2020. Sample size is calculated 60 patients of Type 2 DM. As per previous study show correlation coefficient between serum UA (SUA) level and CIMT ($r=0.779$)⁵² (For 90% power and 1% α error). CIMT and carotid artery plaques were measured through Doppler ultrasound. 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.

Results: Most patients (60%) were diabetics since 5 years and nearly 30% had diabetes since 5–15 years while only 10% had diabetes since more than 15 years. Mean duration of diabetes was 6.91 ± 5.88 years. Two thirds of diabetic individuals (67%) had HDL cholesterol level above 40 mg/dL. About 42% of diabetic individuals had triglyceride level <150 mg/dL and 5% of diabetic individuals had LDL cholesterol level <100 mg/dL. Mean HDL cholesterol, Triglycerides, and LDL cholesterol were 47.4 ± 15.49 mg/dL, 153.78 ± 81.56 mg/dL, and 92.33 ± 57.28 mg/dL, respectively. Mean bilirubin and serum creatinine in study population were 0.65 ± 0.48 mg/dL and 0.96 ± 0.18 mg/dL, respectively. Mean CRP was 3.95 ± 2.40 mg/L. Mean SUA level in study population was 5.78 ± 2.18 mg/dL. Mean of average CIMT was found to be 8.0 ± 1.16 mm. Glycated hemoglobin (HbA1c) and UA had negative weak linear correlation which was statistically significant. HbA1c and average CIMT had no or weak negative correlation which was not statistically significant and SUA and average CIMT showed positive moderate linear correlation which was statistically significant.

Conclusion: Carotid atherosclerosis as measured by IMT is associated with SUA levels in patients with type 2 DM. In type 2 DM patients, HbA1C is negatively correlated with UA while HbA1C has no correlation with CIMT.

Keywords: Serum uric acid, Carotid intima media thickness, Glycated hemoglobin, Carotid atherosclerosis.

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INTRODUCTION

Diabetes mellitus (DM) is one of the most common diseases in the world. As per the International Diabetes Federation (2017), approximately 50% of all people with diabetes live in just three countries: China (98.4 million), India (65.1 million), and the USA (24.4 million) [1]. DM is a type of metabolic disorder which is characterized by the disturbances in body's capacity to utilize glucose, protein, and fat due to impairment in insulin secretion and/or insulin resistance leading to chronic hyperglycemic state. Long-term complications of diabetes are macrovascular and microvascular which include retinopathy with potential loss of vision; nephropathy leading to renal failure; peripheral neuropathy with risk of foot ulcers, amputations, and Charcot joints; and autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular symptoms and sexual dysfunction. Patients with diabetes have an increased incidence of atherosclerotic cardiovascular, peripheral arterial, and cerebrovascular disease. Hypertension and dyslipidemia are often associated with diabetes. Diabetes has been defined as an independent factor for the presence of high-grade carotid-artery stenosis (CAS) in the general population [2]. Type 2 diabetes poses a substantial risk factor for the progression of atherosclerosis, measured by rise in carotid intima-media thickness (CIMT) [3,4]. CAS, atherosclerotic narrowing of the extracranial carotid arteries, is clinically significant because CAS is a risk factor for ischemic stroke [5]. The uric acid (UA) is a potent antioxidant which is considered beneficial in the presence of oxidative stress in cell. However, despite the potential antioxidant effect of UA itself, numerous studies have revealed close associations of serum UA

(SUA) concentrations and various disorders, most of which are included in the metabolic syndrome category. Thus, UA metabolism may be a so-called double-edged sword as regard the inflammatory and/or oxidative responses in many organs, though on the whole, its harmful effects appear to outweigh the benefits of UA in most cases.

It has been recognized that SUA is positively associated with serum glucose levels in healthy subjects [6]. Recent studies have demonstrated that UA levels are higher in subjects with prediabetes and early Type 2 diabetes than in healthy controls [7,8]. Studies examining the relation of hyperuricemia with cardiovascular disease (CVD) have had conflicting results. Many studies have found an independent association of higher serum uric acid (SUA) concentrations with increased risk of adverse cardiovascular outcomes, [9,10,11] others studies have not found same association of higher serum uric acid (SUA) concentrations with increased risk of adverse cardiovascular outcomes [12,13]. Biological mechanisms linking hyperuricemia to CVD risk exist, but direct effects of uric acid on the vasculature remain controversial [14,15].

Objectives

The objectives of the study were to assess the correlations between UA level and carotid intima thickness, UA level and glycated hemoglobin (HbA1c) and HbA1c and carotid intima thickness among type 2 DM patients.

METHODS

This cross-sectional observational study was conducted in the Department of medicine, SMS Medical College and Attached Hospital,

Jaipur, Rajasthan. It comprises of 60 patients with type 2 DM during the period of April 2019–December 2020. Ethical clearance was taken from ethical committee of university and medical college before start the study.

Inclusion criteria

The following criteria were included in the study:

1. All patients of T2DM (baseline HbA1c $\geq 6.5\%$)
2. Age >18 years
3. Patients willing to give written informed consent.

Exclusion criteria

The following criteria were excluded from the study:

1. Patient presented with sign and symptoms of cardiac dysfunction
2. Known cardiovascular disorder, renal disorder and malignancy
3. Major burn
4. Severe trauma
5. The patients who are on UA lowering drugs such as allopurinol and febuxostat
6. Patients on drugs affecting SUA levels (salicylates, cyclosporine, ethambutol, pyrazinamide, and cytotoxic agents)
7. Patients whose creatinine clearance is <60 mL/min/1.73 m²
8. Patients on diuretics especially thiazides.

The frequency distribution of the study subjects according to age, gender, duration of DM type 2, smoking status, Family history of diabetes, History of CVD, Waist circumference, body mass index, systolic blood pressure, diastolic blood pressure, high density lipoprotein, triglycerides, low-density lipoprotein, and SUA, was analyzed. Qualitative data were presented as percentage. Quantitative data were presented as mean and standard deviation. Correlation coefficient was calculated by Pearson correlation. Values of $p < 0.05$ were considered statistically significant. Microsoft Word and Microsoft Excel were used to generate graphs and tables.

CIMT

A bilateral image of common carotid arteries, internal carotid artery and carotid bulb are obtained by a lateral view in CANON APLIO 500 USG machine 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.

Above figure shows that Intima-media thickness is accepted as a marker of subclinical atherosclerosis and IMT screening can help the clinician to reclassify a substantial proportion of intermediate cardiovascular risk patients into a lower or higher risk category.

OBSERVATION AND RESULTS

The study was conducted among 60 patients, out of which nearly, half of the individuals belonged to below 60 years of age and rest of the individual belonged to above 60 years of age. Most common age group was 60–69 year of age. The mean age of the study patients was 59.11 ± 6 years. Total number of males included were 55 % (n=33) while, females were 45% (n=27). Most patients (60%) were diabetics since 5 years and nearly thirty percent had diabetes since 5–15 years while only ten percent had diabetes since more than 15 years. Mean duration of diabetes was 6.91 ± 5.88 years.

Two thirds of diabetic individuals (67%) had HDL cholesterol level above 40 mg/dL. About 42% of diabetic individuals had triglyceride level <150 mg/dL and 5% of diabetic individuals had LDL cholesterol level <100 mg/dL. Mean HDL cholesterol, Triglycerides, and LDL cholesterol were 47.4 ± 15.49 mg/dL, 153.78 ± 81.56 mg/dL, and 92.33 ± 57.28 mg/dL, respectively. Ten percent males and 8% females had UA level below the reference limit.

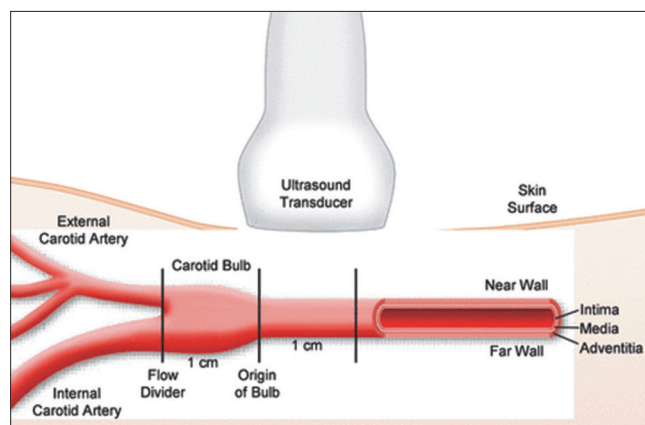


Fig. 1: Proper location for intima media thickness measurement

Table 1: Age-wise distribution of cases

Age group	Frequency (n=60), n (%)
30–39	3 (5.0)
40–49	8 (13.3)
50–59	17 (28.3)
60–69	22 (36.7)
70–79	8 (13.3)
80–89	2 (3.3)
Total	60 (100)

Table 2: Distribution of cases according to duration of diabetes mellitus

Duration (years)	Frequency (n=60), n (%)
0–5	36 (60.00)
5–10	17 (28.33)
10–15	2 (3.33)
15–20	4 (6.67)
>20	2 (3.33)
Total	60 (100)

Table 3: Distribution of cases according to uric acid level

Uric acid level (mg/dL)	Frequency (n=60), n (%)
Male	
<3.6	6 (10.00)
3.6–7.7	19 (31.67)
>7.7	8 (13.33)
Female	
<2.5	5 (8.33)
2.5–6.8	11 (18.33)
>6.8	11 (18.33)
Total	60 (100.00)

DISCUSSION

Age and sex distribution

The mean age in our study sample was 59.11 ± 06 years. Venishetty *et al.* 2019 studied on “SUA Levels in Type 2 DM: Is There a Linear Relationship with Severity of Carotid Atherosclerosis” reported mean age of their study population was 54.5 ± 8.4 years [16].

There were 55% (n=33) males and 45% (n=27) females in present study sample. Venishetty *et al.* 2019 reported 65% male and 35% female [16]. Li *et al.* 2011 reported 38.4% males and 61.6% females [17]. Ishizaka *et al.* 2006 reported of 67% male and 33% females [18].

Table 4: Correlation of HbA1c and serum uric acid level

Type of variable	HbA1c	Uric acid
HbA1c		
Pearson correlation	1	-0.362**
Significance (two-tailed)		0.004
n	60	60
Uric acid		
Pearson correlation	-0.362**	1
Significance (two-tailed)	0.004	
n	60	60

**Correlation is significant at the 0.05 level (two-tailed). HbA1c: Glycated hemoglobin

Table 5: Correlation of serum uric acid with average carotid intima media thickness

Type of variable	Uric acid	CIMT
Uric acid		
Pearson correlation	1	0.613**
Significance (two-tailed)		0.000
n	60	60
CIMT		
Pearson correlation	0.613**	1
Significance (two-tailed)	0.000	
n	60	60

**Correlation is significant at the 0.01 level (two-tailed). CIMT: Carotid intima media thickness

Table 6: Correlation of HbA1c with average carotid intima media thickness

Type of variable	HbA1c	CIMT
HbA1c		
Pearson correlation	1	-0.078
Significance (two-tailed)		0.553
n	60	60
CIMT		
Pearson correlation	-0.078	1
Significance (two-tailed)	0.553	
n	60	60

**Correlation is not significant at the 0.05 level (two-tailed). CIMT: Carotid intima media thickness, HbA1c: Glycated hemoglobin

Table 7: Multiple linear regression between carotid intima media thickness and other variable

Variables	B coefficients	p	95.0% CI for B	
			Lower bound	Upper bound
Constant	7.258	0.001	3.302	11.214
Age	0.007	0.597	-0.031	0.018
Sex	0.271	0.310	-0.260	0.803
HbA1c	0.085	0.264	-0.066	0.236
HTN	0.165	0.540	-0.372	0.702
Waist circumference	0.019	0.293	-0.054	0.017
BMI	0.012	0.836	-0.131	0.107
TG	0.000	0.930	-0.009	0.010
LDL	0.000	0.968	-0.015	0.014
CRP	0.029	0.657	-0.102	0.160
Smoker	0.472	0.142	-1.108	0.164
Uric acid	0.382	0.001	0.163	0.602

*Dependent variable: CIMT, R²=0.466. LDL: Low-density lipoprotein, CI: Confidence interval, CRP: C-reactive protein, BMI: Body mass index, HbA1c: Glycated hemoglobin, HTN: Hypertension, TG: Triglycerides

Duration of DM and HbA1c

The mean duration of DM in our study was 6.91±5.88 years. Venishetty *et al.* 2019 found mean duration of DM was 10±2 years [16]. Li *et al.*

2011 found mean duration of DM was 7.53±3.6 years. This finding is almost similar to present study [17].

Mean HbA1c in our study population was 8.98±1.87. Venishetty *et al.* 2019 found mean HbA1c was 9.1±2.5 [16] which is similar to our study. Li *et al.* 2011 reported mean HbA1c was 7.04±1.02 [17]. While Ishizaka *et al.* 2006 reported, mean HbA1c in their study individuals was 5.5±1.2 [17].

HbA1c and SUA

In our study, HbA1c has statistically significant weak negative linear relationship with SUA. A case-control study done by Sushilendu *et al.* 2019 on "SUA level and its correlation with HbA1c in type 2 DM" in 100 individuals found that SUA level is inversely associated with HbA1c in patients with type 2 DM [19] which is also similar to the present study. Similar findings were seen in the research by Shirsath *et al.* 2016 that there is an inverse correlation between UA and HbA1c [20].

HbA1c and average CIMT

In our study, HbA1c and Average CIMT has no or week negative correlation and however it not found to be statistically significant. $r(58)=0.078=0.553$ Ma *et al.* 2015 suggested that HbA1c was positively correlated with CIMT ($r=0.135$ and $p<0.01$) [21]. A cross sectional study conducted by Olt *et al.* suggested that HbA1c could not be a marker for subclinical atherosclerosis in diabetic patients as there is no statistically significant relationship between this variable [22] which is similar to our study.

SUA and average CIMT

In this study, we found positive moderate linear correlation between SUA and average CIMT which was statistically significant $r(58)=0.613=0.000$. Venishetty *et al.* 2019 suggest that UA levels were positively associated with CIMT ($p=0.001$). The association remained significant after further adjustment for potential confounders. In their study strong correlation was found among them as depicted by correlation coefficient ($r=0.779$) [16] which was similar to our study. Li *et al.* 2011 suggest that UA significantly correlated with carotid atherosclerosis CIMT ($p=0.02$). The correlation coefficient was 0.07 [17]. SUA possesses oxidative properties by mediating the production of radicals that have pro-oxidant effect on LDL. Increased UA levels causes endothelial dysfunction and reduces the bioavailability of NO [23]. It enters into the VSMCs by urate transporters and increased levels induce the proliferation of VSMC's. This causes thickening of the vessel wall or the increase in the IM.

CONCLUSION

On the basis of our study findings, we conclude that UA can be used as proxy indicator of carotid atherosclerosis among type 2 diabetes patients. However, further larger prospective studies would be needed to establish the causal association.

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CONFLICT OF INTEREST

None declared.

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