Original Article

Study of association of serum uric acid with albuminuria and carotid atherosclerosis in type 2 diabetes mellitus patients

Kuldeep Singh[1], Pardeep Kumar[1], Arun Joshi[2], Dileep Kumar Shivhare[3], Subodh Kumar Mahto[1], Akanskha Singh[1], Ankita Aneja[1], Brinder Mohan Singh Lamba[1]

[1]Department of Medicine, PGIMER and DR. RML Hospital, New Delhi, [2]Department of Nephrology, Army Research and Referral Hospital, New Delhi, [3]Department of Medicine, Haryana Mulitispecility Hospital, Haryana, India

ABSTRACT

Introduction: Type 2 diabetes mellitus is a heterogeneous group of metabolic disorders of disturbance of carbohydrate, fat, and protein metabolism causing macrovascular (like coronary artery disease) and microvascular (kidney damage) complications. Microalbuminuria is the first manifestation of injury to glomerular filtration barrier and carotid intima-media thickness (IMT) of common carotid artery serves as an excellent marker for early lesion of atherosclerosis. **Method:** A cross-sectional observational study was carried out over a period of 1.5 years in PGIMER, DR. RML Hospital, New Delhi. Patients with type 2 diabetes mellitus, aged between 35 and 60 years, were investigated for uric acid (UA), urine albumin levels, and common carotid IMT during this period. Patients on drugs that affect serum UA level, patients with acute illness, patients with serum creatinine >1.5 mg/dL, or with coronary artery disease were excluded from study. **Result:** Prevalence of hyperuricemia was found to be high (46%) in type 2 diabetic patients. It was also higher in females (73.7%) than males (25.8%). There was positive correlation between serum UA concentrations with logarithm of urine albumin excretion ($P < 0.023$) and carotid intima-media thickness (IMT) ($P < 0.027$). Plaque index also showed a positive correlation with UA ($P < 0.019$). However, there was no positive correlation with UA and other variable such as age, duration of diabetes, systolic blood pressure, diastolic blood pressure, HbA1c, lipid profiles, urea, and creatinine. **Conclusion:** Serum UA concentration thus serves as an early marker of renal dysfunction and cardiovascular diseases in type 2 diabetic patients.

Keywords: Albuminuria, atherosclerosis, carotid intima media thickness, serum uric acid, Type 2 diabetes mellitus

Introduction

Diabetes mellitus is a heterogeneous group of metabolic disorders causing macrovascular (like coronary artery disease) and microvascular (kidney damage) complications.[1] Type 2 diabetes mellitus is characterized by deficiency of insulin, variable degree of insulin resistance, impaired insulin secretion, and impaired glucose utilization. Among individuals with type 2 diabetes mellitus, death from macrovascular disease is more common.[1] Higher levels of serum insulin may decrease uric acid (UA) clearance by kidneys and predispose to UA injury.[2] Several large epidemiologic studies have reported that elevated serum UA concentration is associated with cardiovascular disease.[3] Microalbuminuria means significant increase in albumin excretion rate (AER)[4] and may reflect a generalized defect in vascular permeability and a concomitant atherogenic diathesis.[5]

Access this article online

Quick Response Code:

Website:
www.jfmpc.com

DOI:
10.4103/jfmpc.jfmpc_777_19

How to cite this article: Singh K, Kumar P, Joshi A, Shivhare DK, Mahto SK, Singh A, *et al*. Study of association of serum uric acid with albuminuria and carotid atherosclerosis in type 2 diabetes mellitus patients. J Family Med Prim Care 2019;8:4027-31.

The earliest lesion of atherosclerosis is a focal thickening of the vessel wall, especially the intima media layer.[6]

Methods

It was a cross-sectional observational study conducted at the department of medicine, PGIMER, Dr RML Hospital, New Delhi, India, over a span of 1.5 year. The study was approved by institutional review board and ethical committee (Number: 01-40/18/2011/IEC/Thesis/PGIMER-RMLH/10234, date of the approval- 13 Nov 2011). The target population consisted 50 Type 2 diabetes mellitus patients, aged between 35 and 60 years. New cases of type 2 diabetes were diagnosed based on The National Diabetes Data Group and World Health Organization diagnostic criteria.[1] Patients on drugs that affect serum UA levels, patients with acute illness, patients with serum creatinine >1.5 mg/dL, or with coronary artery disease and those not giving consent were excluded. Bilingual consent was taken from cases. They were subjected to a detailed history and physical examination and standardized laboratory tests.

UA was measured by enzymatic photometric test in the fully automated biochemistry analyser. Urine albumin was measured by immunoturbidimetric assay using COBAS Tina quant albumin kit. Urine creatinine was measured using creatinine Jaffe method on Olympus AU400 analyzer.

Albumin creatinine ratio (ACR) was calculated by dividing urine albumin concentration with urine creatinine concentration. Patients were further divided into three groups based upon ACR values---normoalbuminuria (ACR < 30 mg/g), microalbuminuria (ACR 30.1 to 300 mg/g), and macroalbuminuria (ACR > 300 mg/g).

These patients were evaluated for common carotid artery and internal carotid artery intima-media thickness (in centimetres) of both sides by color Doppler using Philips HD11 ultrasound system equipped with color flow imaging and pulse Doppler, with an electrical linear transducer (mid frequency of 7.5 MHz).[7]

Plaque was defined as a visually distinct area with an intima media thickness greater than that of than surrounding areas.[8]

The degree of plaque was graded for each segment using the following criteria:[9]

Grade 0: no observable plaque

Grade 1: one small plaque (less than 30% of the vessel diameter)

Grade 2: one medium plaque (30--50% of the vessel diameter) or multiple small plaques

Grade 3: one large plaque (greater than 50% of the vessel diameter) or multiple plaques with at least one medium plaque

The grades were then summed to create a variable called the plaque index, which is used as a measure of the extent of atherosclerosis.

Statistical analysis

The analysis was carried out in Microsoft Excel 2007 and SPSS software (IBM Corp. Statistics for Windows, Version 20.0, Released 2011, Armonk, NY, USA). The quantitative variables were reported as mean ± standard deviation. Statistical significance of outcomes with different variables was determined by Chi-square test. Simple linear regression analysis was done to identify the degree of relationship in the patterns of variation of two or more variables. Pearson's test was used to calculate the correlation. $P \leq 0.05$ was taken as level of statistical significance.

Results

A total of 50 cases of type 2 diabetes mellitus (T2DM) were recruited in this study. The mean age of the patients was 52.62 ± 8.26 years. Mean serum UA concentration was 6.10 ± 2.20 mg/dL. Mean UA in males was 5.50 ± 2.36 mg/dL and in females was 7.06 ± 1.52 mg/dL. This sex distribution of serum UA levels was statically significant ($P < 0.05$). The mean ACR was 473.16 ± 101.66 mg/g. Out of 50 T2DM patients, 23 (46.0%) had normoalbuminuria (ACR 0 to 30 mg/g), 21 (42.0%) had micromoalbuminuria (ACR 30.1 to 300 mg/g), and 6 (12%) had macromoalbuminuria (ACR > 300 mg/g). The mean IMT was 0.60 ± 0.15 cm. Out of 50 patients-,16 (32%) had IMT between 0.4 and 0.5 cm, 16 (32%) had IMT between 0.5 and 0.6 cm, 5 (10%) had IMT between 0.6 and 0.7 cm, 9 (18%) had IMT between 0.7 and 0.8 cm; 4 (8%) had IMT > 0.8 cm.

As the urinary ACR showed a positive skewed distribution (skewness = 1.491), a logarithmic transformation of ACR was carried out before calculating correlation and regression analysis. There was positive correlation between serum UA concentrations with logarithm of urine albumin excretion ($P < 0.023$) and carotid intima-media thickness (IMT) ($P < 0.027$) [Table 1 and Figure 1]. The relationship between serum UA concentrations and other variables such as age, duration of diabetes, systolic blood pressure, diastolic blood pressure, HbA1c, lipid profiles, urea, creatinine, and plaque index were examined by Pearson
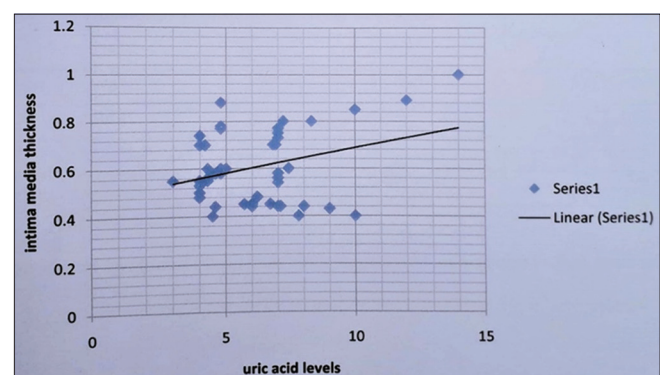

Figure 1: UA had positive correlation with IMT

correlation analyses.Plaque index showed a positive correlation with U.A. ($P < 0.019$) but no other variable showed a positive correlation with UA [Table 2]. Serum uric acid concentration was higher in patients with macroalbuminuria (10.55 ± 2.10 mg/dL) than in patients with microalbuminuria (6.79 ± 0.68 mg/dL) or normoalbuminuria (4.30 ± 0.43 mg/dL), and serum UA concentration was also higher in patients with microalbuminuria than in patients with normoalbuminuria.

Regression analysis

Simple linear regression analysis was done to identify the degree of relationship in the patterns of variation of two or more variables.Simple linear regression analysis demonstrated that serum UA concentration ($P < 0.023$), age ($P < 0.009$), duration of diabetes ($P < 0.037$), plaque index ($P < 0.026$) were independent determinants of logarithm of urinary albumin excretion. There was no significant degree of relationship between logarithm of urinary albumin excretion and IMT ($P < 0.052$) [Table 3].

Discussion

Our study showed the prevalence of hyperuricemia (UA > 6 mg/dl) in 23 (46%) out of 50 study subjects. The probable reason for this could be that

1. the study subjects were not taking any treatment for hyperuricemia,
2. suppression of UA excretion by exogenous insulin (it is known that hyperinsulinemia reduces the urinary excretion of uric acid by activating the transporter of UA).

Our study showed that the prevalence of UA was more in females (73.7%). Hyperuricemia was not much prevalent in males (25.8%). This could possibly be explained by the fact that in normal healthy adult males, serum urate levels exceed those in females of reproductive age due to enhanced renal urate clearance by oestrogenic compounds. After menopause, serum urate values in healthy females (the average age of females in our study was 51.16 ± 9.16 years) increases and approximate those in healthy males of corresponding age and a significant part of this variability in prevalence of UA. is certainly attributable to different values used to define it, as well as the techniques and protocols used to evaluate it, differences in ethnicity, and in some cases to the small number of patients studied. Similar to our study, Fang *et al.*[10] described that the serum UA level was higher in diabetic women. Ito H *et al.*[11] in a cross-sectional study found that the frequency of hyperuricemia was significantly higher in the diabetic patients.

In our study, a positive correlation was found between UA and logarithm of urinary albumin excretion (log ACR) ($P = 0.023$). Simple linear regression analysis also demonstrated that UA was an independent determinant of logarithm of urinary albumin excretion ($P < 0.023$). Urinary ACR has been an established early marker of renal injury and in our study it is causally related with the UA. Thus UA may itself have served as a marker of renal injury in our study. It could possibly be because of-

Table 1: UA had positive correlation with logarithm of urine albumin excretion and IMT

	Pearson correlation	Significance (*P*)
Log urine albumin : creatinine	0.320	0.023
IMT (carotid intima-media thickness)	0.312	0.027

Table 2: Correlation between serum uric acid concentration and other variables

	Pearson correlation	Significance (*P*)
Age	0.254	0.075
Duration of diabetes mellitus	0.247	0.084
Systolic blood pressure	0.175	0.223
Diastolic blood pressure	0.190	0.185
BMI	0.061	0.672
waist: hip circumference	0.122	0.400
HbA1c (%)	0.080	0.581
Total Cholesterol	0.097	0.504
Triglyceride	0.090	0.534
LDL	0.023	0.876
VLDL	0.035	0.812
HDL	0.105	0.467
Urea	0.020	0.893
Creatinine	0.025	0.863
Plaque index	0.330	0.019

Table 3: Independent determinants of logarithm of urinary albumin excretion

	R	*R*²	*P*
Serum uric acid levels	0.320	0.103	0.023
age	0.365	0.133	0.009
IMT	0.277	0.077	0.052
Duration of diabetes mellitus	0.295	0.087	0.037
Plaque index	0.315	0.099	0.026

R=coefficient of correlation
*R*²=coefficient of determination

1. Hyperuricemia-induced endothelial dysfunction, glomerular hypertension, and renal hypertrophy.
2. Uric acid causing an inhibition of endothelial nitric oxide bioavailability[8]
3. Activation of the rennin angiotensin system,[12] and
4. Direct actions on endothelial cells and vascular smooth muscle cells.[13]

Similar correlation between UA and log ACR has been observed by Kim ES[14] who conducted a study to determine the relationship between UA, metabolic syndrome (MetS), and albuminuria in type 2 diabetic patients. They concluded that an elevated UA was significantly associated with MetS and was an independent predictor of albuminuria after adjusting for conventional risk factors and MetS. In a similar study by Bonakdaran S[15] including 1,276 patients with type 2 DM, UA correlated positively with urine ACR.

In a study by Fukui M *et al.*[3] including 343 men with T2DM, multiple regression analysis demonstrated that serum UA concentration, duration of diabetes, serum triglyceride concentration, and systolic blood pressure were independent determinants of logarithm of urinary albumin excretion. Cai X *et al.*[16] in a cross-sectional study including 2108 type 2 diabetic patients in China concluded that high-normal SUA was associated with albuminuria and impaired glomerular filtration.

In a recent study by Petter Bjornstad *et al.*[17] in Chinese adolescent population, higher baseline UA independently increased the risk for onset of hypertension and elevated UAE (urinary albumin excretion).

In our study, a positive correlation was found between serum UA concentration and IMT ($P = 0.027$). The possible mechanism for raised IMT in hyperuricemic diabetic patients could be attributed to –
1. Hyperuricemia-induced endothelial dysfunction causing impaired acetylcholine induced vasodilatation and impaired endothelial nitric oxide (NO) release.
2. Deleterious effect of UA on oxidative metabolism, platelet adhesiveness, and aggregation. Urate crystals being proinflammatory, activate complement, stimulate neutrophils to release protease and oxidants, stimulate macrophages, and activate platelets and the coagulation cascade.
3. Role of UA in causing hypertension and thus contributing to atherosclerosis.

Though our study showed an overall positive correlation between serum UA concentration and IMT ($P < 0.027$). A positive correlation was also found between UA and IMT ($P < 0.038$) in males. But no correlation was found between UA and IMT ($P = 0.086$) in females. In the past, few studies have found positive correlation between UA and IMT in both males and females while others have found no correlation in both or either sex. This variability in results could be because of:
1. Presence of other risk factors such as smoking, hypertension, dyslipidemia, obesity
2. Patients on UA lowering agents
3. Difference in study protocols, methods of evaluation, and differences in ethnicity
4. Smaller size of study.

Krishnan E *et al.*[18] conducted a study in 2,498 participants in the Coronary Artery Risk Development in Young Adults (CARDIA) in which hyperuricemia was found to be an independent risk factor for subclinical atherosclerosis in young adults. In a prospective cohort study by Song M *et al.*[19] in north Chinese adult UA was found to be an independent risk factor for incidence of extracranial carotid atherosclerosis in both genders. Also José Carlos Arévalo-Lorido *et al.*[20] in a study concluded that the effects of UA on the vascular wall contribute to the development of atherosclerosis and carotid disease. Similar relation between UA and atherosclerosis was found in various studies.[21-23]

Conclusion

1. Asymptomatic hyperuricemia is highly prevalent in type 2 diabetic patients.
2. Serum UA concentration serves as early and independent marker of renal dysfunction in type 2 diabetic patients.
3. Serum UA concentration serves as early marker of carotid atherosclerosis in type 2 diabetic patients.

Thus in light of our findings we propose that:

1. Hyperuricemia combined with diabetes might be associated with an increased risk of progression of diabetic nephropathy and atherosclerosis and thus T2DM patients with asymptomatic hyperuricemia should be further evaluated for development of early diabetic nephropathy and atherosclerosis.
2. In general, little attention has been paid to UA as a factor for progression of diabetic nephropathy as well as atherosclerosis. However, hyperuricemia is common among diabetic patients and it is easy to lower serum UA concentration with lifestyle modifications and medications. Therefore, it is of clinical significance to clarify the role of UA in the development and progression of diabetic nephropathy as well as atherosclerosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Powers AC, Niswender KD, Molina CE. Diabetes mellitus: Diagnosis, classification and pathophysiology. In: Kasper DL, Hauser SL, Jamerson JL, Fauci AS, Longo DL, Loscalzo J, editors. Harrison's Principles of Internal Medicine. 20th New York: McGraw-Hill Education; 2018. p. 2896-9.
2. Berbari AE. The role of uric acid in hypertension, cardiovascular events and chronic kidney disease. European Society of Hypertension. Scientific Newsletter: Update on. Hypertension Management 2010;11:49-50.
3. Fukui M, Tanaka M, Shiraishi E, Harusato I, Hosoda H, Asano M, *et al.* Serum uric acid is associated with microalbuminuria and subclinical atherosclerosis in men with type 2 diabetes mellitus. Metabolism 2008;57:625-9.

4. Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R. Intimal plus medial thickness of arterial wall: A direct measurement with ultrasound imaging. Circulation 1986;74:1399-406.

5. Fredrick JS. Blood vessels. In: Kumar V, Abbas, AK, Fausto N, editors. Pathologic Basis of Disease. 9th ed. India: Saunders Philadelphia Company; 2014. p. 818-28.

6. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima media thickness: A systemic review and meta-analysis. Circulation 2007;115:459-67.

7. Hunt KJ, Williams K, Rivera D, O'Leary DH, Haffner SM, Stern MP, *et al.* Elevated carotid artery intima-media thickness levels in individuals who subsequently develop type 2 diabetes. Arterioscler Thromb Vasc Biol 2003;23:1845-50.

8. Khosla UM, Zharikov S, Finch JL, Nakagawa T, Roncal C, Mu W, *et al.* Hyperuricemia induces endothelial dysfunction. Kidney Int 2005;67:1739-42.

9. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, *et at.* Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: A consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr 2008;21:93-111; quiz 189-90.

10. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study; 1971-1992. National Health and Nutrition Examination Survey. JAMA 2000;283:2404-10.

11. Ito H, Abe M, Mifune M, Oshikiri K, Antoku S, Takeuchi Y, *et al.* Hyperuricemia is independently associated with coronary heart disease and renal dysfunction in patients with type 2 diabetes mellitus. PLoS One 2011;6:e27817.

12. Mazzali M, Hughes J, Kim YG, Jefferson JA, Kang DH, Gordon KL, *et al.* Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. Hypertension 2001;38:1101-6.

13. Kang DH, Park SK, Lee IK, Johnson RJ. Uric acid induced C-reactive protein (CRP) expression: Implication on cell proliferation and nitric oxide production in human vascular cells. J Am Soc Nephrol 2005;16:3553-62.

14. Kim ES, Kwon HS, Ahn CW, Lim DJ, Shin JA, Lee SH, *et al.* Serum uric acid is associated with metabolic syndrome and microalbuminuria in Korean patients with type 2 diabetes mellitus. J Diabetes Complications 2011;25:309-13.

15. Bonakdaran S, Hami M, Shakeri MT. Hyperuricemia and albuminuria in patients with type 2 diabetes mellitus. Iran J Kidney Dis 2011;5:21-4.

16. Cai XL, Han XY, Ji LN. High-normal serum uric acid is associated with albuminuria and impaired glomerular filtration rate in Chinese type 2 diabetic patients. Chin Med J 2011;124:3629-34.

17. Bjornstad P, Laffel L, Lynch J, El Ghormli L, Weinstock RS, Tollefsen SE, *et al.* Elevated serum uric acid is associated with greater risk for hypertension and diabetic kidney diseases in obese adolescents with type 2 diabetes: An observational analysis fromthe treatment options for type 2 diabetes in adolescents and youth (TODAY) study. Diabetes Care 2019;42:1120-8.

18. Krishnan E, Pandya BJ, Chung L, Dabbous O. Hyperuricemia and the risk for subclinical coronary atherosclerosis-data from a prospective observational cohort study. Arthritis Res Ther 2011;13:R66.

19. Song M, Li N, Yao Y, Wang K, Yang J, Cui Q, *et al.* Longitudinal association between serum uric acid levels and multiterritorial atherosclerosis. J Cell Mol Med 2019;23:4970-9.

20. Arévalo-Lorido JC, Carretero-Gómez J, Robles Pérez-Monteoliva NR. Association between serum uricacid and carotid disease in patients with atherosclerotic acue ischemic stroke. Vascular 2019;27:19-26.

21. Pacifico L, Cantisani V, Anania C, Bonaiuto E, Martino F, Pascone R, *et al.* Serum uric acid and its association with metabolic syndrome and carotid atherosclerosis in obese children. Eur J Endocrinol 2009;160:45-52.

22. Neogi T, Ellison RC, Hunt S, Terkeltaub R, Felson DT, Zhang Y, *et al.* Serum acid is associated with carotid plaques: The National Heart, Lung and Blood Institute Family Heart Study. J Rheumatol 2009;36:378-84.

23. Li Q, Yang Z, Lu B, Wen J, Ye Z, Chen L, *et al.* Serum uric acid level and its association with metabolic syndrome and carotid atherosclerosis in patients with type 2 diabetes. Cardiovasc Diabetol 2011;72:1475-2840.