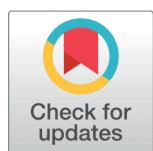


The relationship between uric acid and dyslipidemia in type 2 diabetic patients with urolithiasis

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ABSTRACT

Background and objectives: Type 2 diabetes mellitus (DM) is characterized by insulin resistance, which can increase the risk of kidney stone formation. This study aimed to find out the association between serum levels of uric acid and lipid profile in type 2 DM patients with urolithiasis in comparison to those without.

Methods: This cross-sectional study was conducted with the approval of the institutional ethical review committee for human studies. A total of 60 type 2 DM patients were included in the study and grouped as patients with urolithiasis and patients without urolithiasis. Biochemical parameters studied were glucose, urea, creatinine, uric acid, serum uric acid to creatinine ratio, lipid profile, HbA_{1c}, and triglyceride glucose index as a measure of insulin resistance.

Results: A significant increase was found in uric acid, urea, serum uric acid to creatinine ratio, and triglyceride glucose index level in type 2 DM urolithiasis cases as compared to DM cases without urolithiasis. It was also found that total cholesterol, triglycerides, LDL-cholesterol, and VLDL-cholesterol levels were significantly elevated and HDL-cholesterol was significantly decreased in urolithiasis cases. Serum uric acid level was positively correlated with total cholesterol, triglycerides, LDL-cholesterol, and VLDL-cholesterol and negatively correlated with HDL-cholesterol in diabetics with urolithiasis.

Conclusions: From this study, it is demonstrated that urolithiasis patients with type 2 DM have higher insulin resistance, altered lipoprotein metabolism, and an increased level of serum uric acid compared to type 2 diabetics without urolithiasis and their lipid components are strongly associated with increased serum uric acid.

Keywords insulin resistance, lipid profile, triglyceride glucose index, type 2 diabetes mellitus, uric acid, urolithiasis

INTRODUCTION

Urolithiasis is a systemic disease that represents an association with multiple metabolic risk factors.¹ The prevalence of urolithiasis varies from 1-12% and this value is continu-

ously rising due to worldwide socio-economical, nutritional, and environmental changes.² A significant economic burden is associated with urolithiasis, and is reflected directly by treatment costs and indirectly by lost work productivity.³

The prevalence of Type 2 Diabetes Mellitus (DM) is 8.8% worldwide and it is projected to escalate up to 9.9% by 2045. Insulin resistance is a characteristic of type 2 DM.⁴ Triglyceride glucose index is a simple, highly sensitive surrogate marker for measuring insulin resistance.⁵ Insulin resistance and compensatory hyper-insulinemia are associated with defective renal ammonium production, an increase in urinary calcium excretion along with low urinary pH, a decrease in uric acid clearance, and hypocitraturia which ultimately leads to urinary stone formation.^{6,7}

Uric acid, the most abundant antioxidant in plasma is now known for its utmost important role in glucose and lipid metabolism.⁸ An increase in uric acid excretion is highly associated with Type 2 DM and obesity.⁹ Dyslipidemia associated with diabetes can also increase the risk of stone formation.¹⁰

This study was done on patients diagnosed with type 2 DM and was aimed at finding out the association between serum uric acid and lipid profile in type 2 DM patients with urolithiasis and type 2 DM patients without urolithiasis.

MATERIALS AND METHODS

Study design and subjects

This is a cross-sectional study. The study was started after getting approval from Institutional Ethics Committee. Informed consent was taken from the 60 patients who were recruited for the study. They were classified into two groups: Group A) Type 2 DM patients diagnosed with urolithiasis based on ultrasonography or X-ray (n=30), and Group B) Those Type 2 DM patients who did not have urolithiasis and whose disease duration-matched the first group (n=30).

In this study, we included those patients who were taking oral hypoglycemic drug treatment for 5-10 years. We excluded those patients who have a history of other renal disorders like renal failure, infectious diseases, obstructive uropathy, and ischemic heart disease.

Biochemical analysis

A 5 ml fasting blood sample was collected from each study participant. Two ml of blood was collected in an EDTA tube for HbA_{1c} estimation. The remaining 3 ml was collected in tubes without anticoagulant. Serum glucose, urea, creatinine, uric acid, and lipid profile were estimated (Randox imola fully automated clinical chemistry analyzer by enzymatic method). HbA_{1c} was estimated by the HPLC method (Bio-Rad D-10).

Calculations

The body mass index (BMI) was calculated by using the formula:

$$BMI_{Kg/m^2} = \frac{Weight (Kg)}{Height (m^2)}$$

The insulin resistance was assessed by the triglyceride glucose index (Ty glucose index) method,⁵ the following formula was used:

$$TyG = Ln \left[\frac{Fasting triglycerides (mg/dl)}{Fasting plasma glucose (mg/dl)} \right]$$

The serum uric acid to creatinine ratio was also calculated.

Statistical analysis

SPSS version 21 was used to do the statistical analysis. Mean and standard deviation was used to present results for continuous variables and median and range were used for descriptive characteristics. For comparing biochemical parameters between the study groups (diabetic patients with and without urolithiasis), an independent student t-test was used for normally distributed data and Mann–Whitney U test was used for non–normally distributed data. The association between serum uric acid, triglyceride glucose index, and serum uric acid to creatinine ratio with various parameters were assessed by using Spearman's correlation. A *P*-value of <0.05 was considered statistically significant.

RESULTS

Table 1 shows the comparison of age, BMI, and other routine biochemical parameters between type 2 diabetes mellitus patients with urolithiasis and those without urolithiasis.

As shown in Table 1, the study groups showed age and BMI matching, and no significant differences were observed. In addition, there were no statistical differences observed in glucose, creatinine, HbA1c, and eGFR levels between groups. However, serum uric acid, urea, serum uric acid to creatinine ratio, total cholesterol, triglycerides, LDL-c, and VLDL-c were found to be significantly higher in diabetic patients with urolithiasis when compared to diabetic patients without urolithiasis. In contrast, HDL-c was significantly lower in urolithiasis patients.

Further statistical analysis was done to know the correlation among various biochemical parameters in Group A patients to understand the metabolic alternations among diabetic patients with urolithiasis.

Figure 1: A-E show the correlation between serum uric acid and lipid parameters in urolithiasis. Uric acid was found to have a positive and significant correlation with total cholesterol ($r = 0.586$, $P = 0.001$), triglyceride ($r = 0.413$, $P = 0.023$), LDL-c ($r = 0.540$, $P =$

Table 1 Anthropometric and biochemical properties of participants.

Parameter	Urolithiasis patients (n=30)	Non-urolithiasis patients (n=30)	P-value
Age (years)	55.30±12.04	52.90±12.01	0.443
BMI (Kg/m ²)	27.03±4.90	27.40±5.52	0.781
Glucose (mg/dl)	146.56±60.82	138±23.8	0.522
HbA _{1c} (%)	7.39±0.56	7.33±0.55	0.713
Uric acid (mg/dl)	6.51±1.27	5.30±1.10	0.001*
Urea (mg/dl)	33.33±24.75	22.93±6.97	0.031*
Creatinine (mg/dl)	1.11±0.50	0.967±0.13	0.128
eGFR (ml/min/1.73 m ²)	77.80±22.34	77.867±14.54	0.989
Serum UA:Cr	6.28±1.35	5.44±1.34	0.002*
Cholesterol (mg/dl)	208.36±55.34	174.83±39.70	0.009*
Triglyceride (mg/dl)	158.73±53.82	127.93±49.38	0.025*
HDL-c (mg/dl)	30.1±3.10	42.06±3.22	0.001*
LDL-c (mg/dl)	133.80±29.21	111.86±44.79	0.029*
VLDL-c (mg/dl)	33.53±10.68	27.73±9.91	0.033*
Triglyceride glucose index	9.22±0.47	8.96±0.44	0.031*

UA:Cr Serum uric acid to creatinine ratio.

The star (*) denotes statistically significant difference.

0.002), VLDL-c ($r = 0.462$, $P = 0.010$) and negatively correlated with HDL-c ($r = -0.751$, $P = 0.001$).

Table 2 shows the correlation between triglyceride glucose index and other parameters in type 2 diabetics with urolithiasis (group A).

Table 2 The association between triglyceride glucose index and other parameters.

Parameter	Triglyceride-glucose index	
	r	P
BMI (Kg/m ²)	-0.148	0.436
Glucose (mg/dl)	0.582**	0.001
Uric acid (mg/dl)	0.153	0.421
Urea (mg/dl)	0.089	0.641
Creatinine (mg/dl)	0.053	0.779
eGFR (ml/min/1.73 m ²)	0.013	0.944
Cholesterol (mg/dl)	0.168	0.375
Triglycerides (mg/dl)	0.862**	0.001
HDL (mg/dl)	0.057	0.763
LDL (mg/dl)	0.152	0.423
VLDL (mg/dl)	0.608**	0.001

Triglyceride glucose index had a statistically significant positive correlation with fasting glucose ($r = 0.582$, $P = 0.001$), triglyceride ($r = 0.862$, $P = 0.001$), and VLDL-C ($r = 0.608$, $P = 0.001$).

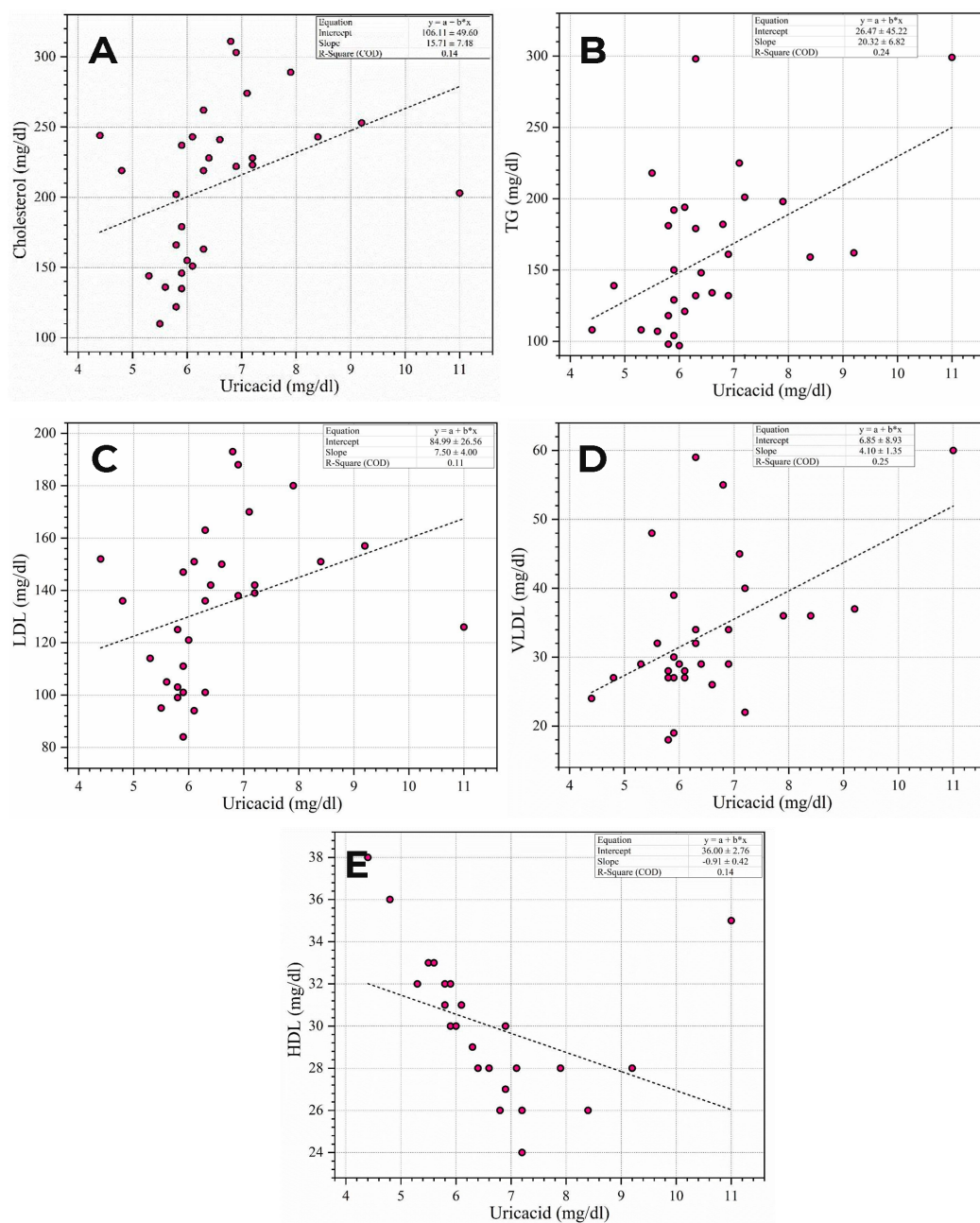


Figure 1 Correlation between serum uric acid and: A) total cholesterol, B) triglycerides, C) low-density lipoprotein, D) very-low-density lipoprotein, and E) high-density lipoprotein of diabetic patients with urolithiasis.

DISCUSSION

A characteristic feature of type 2 DM is insulin resistance.¹¹ The positive reciprocal relationship between Type 2 DM and stone formation suggests that some common metabolic defects cause the development of both diseases.⁷ The triglyceride glucose index is a novel and reliable indicator of insulin resistance. It is the logarithmic product of fasting triglyceride level and fasting glucose level.¹² In this study, we have observed that the triglyceride glucose index is significantly high in type 2 diabetic patients with urolithiasis patients compared to type 2 diabetic patients without urolithiasis.

Insulin plays a major role in renal acidification, by increasing ammonium production. High levels of free fatty acids are found in the circulation of patients with diabetes mellitus. These free fatty acids interfere with glutamine utilization in the proximal convoluted tubule and hence affect ammonia production. So a decrease in the ability to excrete acid load is noted in insulin resistance.^{13,14}

Tubular epithelium in the kidneys expresses insulin receptors. The reabsorption of hydrogen is increased by insulin which stimulates the renal tubular sodium hydrogen exchanger (Na^+/H^+ exchanger).¹⁵ This mechanism helps in trapping ammonia in the kidney tubules. Ammonia in turn is bound to hydrogen ions to form ammonium which gets trapped in the renal tubule.¹⁶

Insulin resistance in type 2 DM hence results in decreased buffering capacity due to reduced ammonia secretion and this leads to urinary acidification. Lowered urinary pH induces Uric acid to precipitate out of the urine, in turn leading to the formation of UA stones.⁷

Systemic acidosis can lead to bone demineralization, associated hypercalcemia, increased renal citrate reabsorption, and subsequent hypocitraturia. One of the risk factors for the formation of calcium stones is hypocitraturia.¹⁷ It is also observed that urinary excretion of calcium is high in Type 2 DM patients.¹⁸ This can be explained by diabetic osteopathy and other mechanisms due to insulin resistance, and associated inflammatory processes.^{19–21}

In our study, we found higher statistically significant levels of total cholesterol, triglyceride, LDL-cholesterol, and VLDL-cholesterol in type-2 diabetic urolithiasis patients compared to type-2 diabetes mellitus patients without urolithiasis. Metabolic derangements including dyslipidemia and alternation in the urinary composition can be associated with increased kidney stone formation in diabetes mellitus.¹¹

Stroller et al, in their cholesterol extraction studies on calcium oxalate stones, found an evident association between cholesterol and stone formation.²² They found that esterified cholesterol form 14-16% of the stones made of total cholesterol. Stone composition is appeared to be related to the esterified-to-free cholesterol ratio.²² A study performed by Inci et al shows that elevated total cholesterol and triglyceride levels were strongly associated with uric acid and calcium oxalate dehydrate stone formations.²³ The cholesterol part of the stone could be due to the increased production of free cholesterol from the vascular system associated with metabolic derangements of Type 2 DM.

We also found a decrease in HDL-cholesterol levels in type-2 diabetic urolithiasis patients compared to type-2 patients without urolithiasis. An increased level of HDL-cholesterol in the circulation can prevent stone formation.²⁴ HDL levels of < 45mg/dl in men and < 60mg/dl in females are correlated with an increased risk of stone formation.²⁵ Toricelli et al found a significant correlation between low HDL and high triglycerides with lower urinary pH. It can cause stone formation.¹⁰

In this study, we found that serum uric acid levels in diabetic urolithiasis (Group – A) patients are strongly related to their lipid profile. Serum uric acid level was found to be positively associated with serum total cholesterol, triglycerides, LDL cholesterol, and VLDL cholesterol. Serum HDL-cholesterol levels were found to be negatively related.

In a study by Son M et al, it was found that there was an association between dyslipidemia and uric acid.¹⁸ Serum total cholesterol, triglycerides, and LDL cholesterol levels were found to be positively associated with serum uric acid levels whereas serum HDL-cholesterol levels were inversely related to serum uric acid level.¹⁸

CONCLUSIONS

In conclusion, in the present study, it was found that Type 2 DM patients with urolithiasis had significantly increased levels of serum total cholesterol, triglycerides, LDL-C, and VLDL-C levels and lower levels of serum HDL-C compared to Type 2 DM patients without urolithiasis. They also had a significantly higher triglyceride glucose index which was used as a marker for insulin resistance. Increased serum uric acid levels in these patients were positively associated with increased serum total cholesterol, triglycerides, LDL-C, and VLDL-C levels and decreased serum HDL-C. Hence an amalgamation of all the factors like insulin resistance increased uric acid levels and deranged lipid profile form the central theme for nephrolithiasis in patients with Type 2 DM.

ABBREVIATIONS

BMI: Body Mass Index, eGFR: estimated glomerular filtration rate, HDL: high-density lipoprotein, LDL: low-density lipoprotein, TyG: Triglyceride Glucose Index, T2DM: type 2 diabetes mellitus, and VLDL: very low-density lipoprotein.

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DECLARATIONS

Authors' contributions

Both authors have equally contributed to this work.

Conflict of interest

The authors have no conflict of interest.

Ethical approvals

This study was started after getting approval from Institutional Ethics Committee. Informed consent was taken from patients who were recruited for the study.

Data availability

The data that support the findings of this study is available from the corresponding author, upon reasonable request.

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