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Original Research

Study of Correlation of Serum Uric Acid and Lipid Profile in Type 2 Diabetes Mellitus

Dr. Neha Dalal[1], Dr. Ila Pahwa[2], Dr. Hemant Sharma[3]

[1]Post-graduate student, Department of Medicine, Muzaffarnagar Medical College and Hospital (MZN), U.P.;
[2]Head and Professor, Department of Medicine, Muzaffarnagar Medical College and Hospital (MZN) , U.P.;
[3]Professor, Department of Medicine, Muzaffarnagar Medical College and Hospital (MZN), U.P.

ABSTRACT:
Background: Diabetes mellitus (DM) refers to a group of common metabolic disorders that share a phenotype of hyperglycemia. The prevalence of dyslipidemia in type 2 diabetes is double with respect to the general population. Dyslipidemia is an important risk factor for cardiovascular disease (CVD) and plays a major role in the progress of atherosclerosis. In present study, the levels of biochemical parameters like serum uric acid and serum lipid profile were evaluated and correlated for the risk of macrovascular disease in type 2 diabetes mellitus. **Materials and method**: The study population was selected among patients attending the Medicine O.P.D, Muzaffarnagar Medical College, Muzaffarnagar. Controls for the study population were patients of age (30-60 years) with type 2 Diabetes Mellitus. The student t-test, chi-square test and Pearson's correlation test were used. **Results**: The correlation showed that uric acid showed a significantly positive correlation with Total cholesterol, triglyceride level and LDL. Whereas, there was a significantly negative correlation of uric acid with HDL. **Conclusion**: Diabetes mellitus is strongly associated with hyperuricemia. The present study shows a strong association between SUA and lipid profile among diabetic adults in our study. Early prevention of hyperuricemia and dyslipidemia can reduce the incidence of associated cardiovascular disease. The glycaemic control has got a strong impact on the serum lipid level and dyslipidemia is frequently encountered among individuals with poor glycaemic control.
Keywords: Diabetes Mellitus, Dyslipidemia, serum lipid level, Total cholesterol.

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Corresponding author: Dr. Dr. Neha Dalal, Post-graduate student, Department of Medicine, Muzaffarnagar Medical College and Hospital (MZN), U.P., India

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INTRODUCTION

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share a phenotype of hyperglycemia. Currently, the prevalence of diabetes worldwide is estimated to be around 415 million (8.8% of the whole population) and is predicted to reach 642 million by 2040. India has the second highest number of diabetics with estimated prevalence of 69.3 million, which is expected to reach 123.5 million by 2040.[1]

DM increases the risk of developing cardiovascular diseases (CVD). Incidence of sudden cardiac death is on the rise, especially in the urban regions of India, which may largely be attributed to the increase in prevalence of coronary artery disease (CAD), diabetes, and hypertension.[2] Indeed, type 2 DM (type 2 DM) is associated with a 2–4 fold increase in the risk of developing CAD. However, such an increased risk cannot be explained by hyperglycemia alone, as other cardiovascular risk factors such as hypertension and dyslipidemia also play a major role.[3,4] Moreover, it is observed that the prevalence of other cardiovascular risk factors such as smoking, sedentary lifestyle, and obesity are higher among diabetic compared to nondiabetic patients.[5]

Dyslipidemia and hypertension are major modifiable risk factors for T2DM and related CAD, which account for more than 87% of disability in low- and middle-income countries.[6,7] Furthermore, prediabetes (an intermediate metabolic state between normoglycemia and T2DM) has also been found to be associated with an increased risk for cardiovascular

disease.[8] The prevalence of dyslipidemia in type 2 diabetes is double with respect to the general population. Dyslipidemia is an important risk factor for cardiovascular disease (CVD) and plays a major role in the progress of atherosclerosis.[9] These are more complex abnormalities that are caused by interrelationship among obesity, insulin resistance and hyperinsulinism.[10]

Lipid abnormalities in patients with diabetes, often termed "diabetic dyslipidemia", are typically characterized by high total cholesterol (T-Chol), high triglycerides (Tg), low high density lipoprotein cholesterol (HDL-C) and increased levels of small dense LDL particles. Low density lipoprotein cholesterol (LDL-C) levels may be moderately increased or normal. Lipid abnormalities are common in people with T2DM and prediabetes[11,12] but the pattern of the different lipids may vary between ethnic groups, economic levels, and access to health care.[13,14] A recently published meta-analysis reported that abnormal levels of the above-mentioned lipid parameters reflect, to some extent, the risk of Type 2 DM.[15] Furthermore, studies in people with T2DM have found an increased association between CAD and high Tg and low HDL-C combined, compared to the two lipid parameters assessed separately.[16,17]

Uric acid is a weak organic acid, the final enzymatic end product of purine nucleotides degradation.[18] It represents a marker for high levels of damaging oxidative stress associated with the enzymes involved in uric acid production e.g. xanthine oxidase. There are reports, which implicate uric acid as a surrogate marker for oxidative stress.[19] Though there is controversial opinion about pro-oxidative and antioxidant properties of uric acid as it is also a powerful free radical scavenger in humans.[20]

Hyperglycemia and lipid metabolism disorder is also linked to a greater risk for vascular problems, kidney disease, nerve and retinal damage resulting in challenges in managing the disease adequately, especially in the presence of immune suppression, and predisposes individual to premature mortality. Moreover, this has cost and social implications for patients, their families, communities and the healthcare system.[21] Increasing evidence suggests that hyperuricemia is an independent risk factor for impaired fasting glucose (IFG) and type 2 diabetes. Patients with hyperuricemia are at a significantly higher risk of progressing to type 2 diabetes.[22,23] A large number of researchers have begun to consider uric acid as a serum indicator of glycometabolic disorders, because of a correlation between uric acid and glucose metabolism.[24,25] However, changes in serum uric acid and blood glucose do not exhibit a linear relationship, as some have assumed. Rather, the relationship follows more of a bell curve. Uric acid levels rise with increasing blood glucose concentrations in the normal and prediabetes population. However, in type 2 diabetes patients, uric acid levels tend to decline with increasing blood glucose concentrations.[26,27]

Framingham study has suggested that hyperuricemia is only a bystander in CVD and its association with the disease is indirectly influenced by confounding factors such as obesity, dyslipidemia, hypertension, use of diuretics, and insulin resistance.[28] On the contrary, several other studies have identified serum uric acid levels as an independent predictor of CVD in various population groups.[29]

Increased serum uric acid levels are commonly correlated with glucose intolerance, hypertension and dyslipidemia.[30-32] It is associated with smaller low-density lipoprotein-cholesterol (LDL-cholesterol) and high-density lipoprotein-cholesterol (HDL-cholesterol) particles[33] and insulin resistance.[34,35] In a recent study, the association between elevated serum uric acid and high circulating inflammatory cytokines has been reported.[36] The studies suggest that high serum uric acid triggers sterile inflammation[36] and may indicate an early sign of atherosclerosis in asymptomatic individuals.[33] Furthermore, the metabolic syndrome increases the risk of cardiovascular disease and type 2 diabetes mellitus and is associated with insulin resistance.[37,38] Serum uric acid has been shown to be associated with oxidative stress and production of tumor necrosis factor-α which are both related to the development of diabetes. Hyperuricemia is said to be a mediator of proinflammatory endocrine imbalance in the adipose tissue which may be one of the factors for dyslipidemia and the inflammatory process leading to atherogensis.[38]

Hyperuricemia and hyperlipidemia are the metabolic abnormalities frequently associated with type 2 diabetic patients. In present study, the levels of biochemical parameters like serum uric acid and serum lipid profile were evaluated and correlated for the risk of macrovascular disease in type 2 diabetes mellitus.

MATERIALS AND METHOD

This cross-sectional comparative study entitled "**Correlation of serum uric acid and lipid profile in type 2 diabetes mellitus**" was conducted after clearance from Board of Studies and Ethical committee in the Department of Medicine, Muzaffarnagar Medical College, Muzaffarnagar (U.P.) during the period 2018-2020.

Sample Size:

The study population was calculated by using G-power software with 80% of the power and 5% of the significance level. The total sample size was determined to be 200 ASA grade I/II patients of age 30-60 years, randomly divided into 2 groups of 100 each by closed envelope technique.

Inclusion and Exclusion criteria

The study subjects were chosen as per the inclusion and exclusion criteria:

Inclusion criteria

- Patients with type 2 diabetes mellitus in the age group of 30-60 years.
- Both genders (male & female) are included.
- Those who are on treatment with oral hypoglycemic drugs are included.

Exclusion criteria

- Type 1 diabetes mellitus
- Pregnant women with GDM
- Patients on treatment with statins, insulin, uricosuric drugs
- Patients with hypertension
- Individuals with history of alcoholism
- Patients with malignancy (leukemia, lymphoma, myeloma)
- Patients with arthritis, cardiac, renal disease and hypothyroidism.

Study procedure

The target population for the study was the patients attending the Medicine O.P.D and those admitted in the I.P.D. of Muzaffarnagar Medical College, Muzaffarnagar. Controls for the study population were patients of age (30-60 years) with type 2 Diabetes Mellitus and was selected from the Medicine O.P.D. and I.P.D. of M.M.C.

An informed and written consent was taken from all the selected participants. History in detail about symptoms of diabetes, including any relevant complication, any drug intake, any other illness and family history of diabetes.

5ml of fasting venous blood was drawn from antecubital vein of patients in a plain vacutainer tube under sterile conditions after fulfilling the selection criteria.

Assessment of Lipid levels

Programme guideline the optimal level of TC, TG, HDL and LDL were < 200mg/dl, < 150mg/dl, > 40 mg/dl and < 100 mg/dl, respectively.

Assessment of Serum uric acid level

Serum uric acid level also estimated in the fasting state, as purine rich diet may influence the serum uric acid levels significantly.

Statistical analysis

The data was entered into the Microsoft excel and the statistical analysis was performed by statistical software SPSS version 25.0. The Quantitative (Numerical variables) were present in the form of mean and SD and the Qualitative (Categorical variables) were present in the form of frequency and percentage. The student t-test was used for comparing the mean values between the 2 groups whereas chi-square test was applied for comparing the frequency. The correlation of serum uric acid level was done with lipid profile of the patient using the Pearson's correlation test. The p-value was considered to be significant when less than 0.05.

RESULTS

There were 101 (50.5%) males and 99 (49.5%) females among study population. No significant difference in mean age was found between Diabetes mellitus type 2 and control groups (48.34±5.24 and 50.33±5.50 respectively).

The mean Glucose level was significantly more among Diabetes mellitus type 2 (170.71±38.65) compared to control group (92.38±12.68).

The mean Total cholesterol level was significantly more among Diabetes mellitus type 2 (218.63±44.26) compared to control group (141.52±26.12). The mean Triglyceride level was significantly more among Diabetes mellitus type 2 (175.08±65.86) compared to control group (100.42±26.81). The mean HDL level was significantly more among control group (49.47±12.68) compared to Diabetes mellitus type 2 (24.39±5.53).

The mean LDL level was significantly more among Diabetes mellitus type 2 (170.71±38.65) compared to control group (92.38±12.68).

The correlation showed that uric acid showed a significantly positive correlation with Total cholesterol, triglyceride level and LDL. Whereas there was a significantly negative correlation of uric acid with HDL.

Table 1: Demographic characteristics of the study population

		Control group	Diabetes mellitus type 2	Total	p-value
Gender[a]	Male	49	52	101	0.203
		49.0%	52.0%	50.5%	
	Female	51	48	99	
		51.0%	48.0%	49.5%	
Age[b]		48.34±5.24	50.33±5.50		0.109

[a] Chi-square test [b] Unpaired t-test [#] Non-significant difference

Table 2: Comparison of mean Glucose level between Control group and Diabetes mellitus type 2

	Glucose level				
Groups	Mean	Std. Deviation	Mean Difference	t-test value	p-value
Control group	92.38	12.68	-78.33	-19.255	< 0.001*
Diabetes mellitus type 2	170.71	38.65			

Unpaired t-test * Significant difference

Table 3: Comparison of mean lipid parameters between Control group and Diabetes mellitus type 2

	Control group		Diabetes mellitus type 2		
Groups	Mean	SD	Mean	SD	p-value
Total cholesterol	141.52	26.12	218.63	44.26	< 0.001*
Triglyceride level	100.42	26.81	175.08	65.86	< 0.001*
HDL	49.47	4.29	24.39	5.53	< 0.001*
LDL	71.96	24.43	159.19	42.24	< 0.001*

Unpaired t-test *** Significant difference**

Table 4: Comparison of mean Uric acid level between Control group and Diabetes mellitus type 2

	Uric acid				
Groups	Mean	Std. Deviation	Mean Difference	t-test value	p-value
Control group	4.73	0.56	-0.86	-4.987	< 0.001*
Diabetes mellitus type 2	5.59	1.63			

Unpaired t-test *** Significant difference**

Table 5: Correlation of serum uric acid level with lipid parameters

		Uric acid		
		Over-all	Diabetes mellitus type 2	Control group
Total cholesterol	Pearson Correlation	0.564	0.545	0.321
	p-value	< 0.001*	< 0.001*	0.001*
Triglyceride level	Pearson Correlation	0.403	0.255	0.374
	p-value	< 0.001*	0.010*	< 0.001*
HDL	Pearson Correlation	-0.376	-0.347	-0.355
	p-value	< 0.001*	< 0.001*	< 0.001*
LDL	Pearson Correlation	0.537	0.535	0.199
	p-value	< 0.001*	< 0.001*	0.047*

*** Correlation is significant**

DISCUSSION

Uric acid is a final product of purine catabolism. It has been confirmed that elevated uric acid levels can increase the risk of metabolic syndrome, atherosclerosis, and chronic kidney disease.[39-41] Role of uric acid in subjects with type 2 diabetes with or without complication has been controversial since long. Some earlier studies have shown lower uric acid level in diabetic subjects suggesting that increased plasma glucose in diabetics imposes inhibitory action on renal reabsorption of uric acid in proximal convoluted tube of nephron leading to lower value of uric acid in diabetic subjects.[26,27]

On the other hand Kodama S et al have shown significant hyperuricemia in patients with type 2 diabetes mellitus, they have suggested that uric acid play an important role in worsening the insulin resistance by inhibiting the bioavailability of nitric oxide, which is essential for insulin stimulated glucose uptake.[42]

Comparison of lipid levels between Diabetes mellitus type 2 and Control groups

In present study, the mean Total cholesterol level was significantly more among Diabetes mellitus type 2 (218.63±44.26) compared to control group (141.52±26.12).

Our findings are mainly in agreement with two landmark studies namely the Framingham Heart Study[43] and the UK Prospective Diabetes Study (UKPDS).[44] In both studies, Type 2 DM subjects compared to those without T2DM, had higher plasma Tg levels and lower HDL-C levels. However, T-Chol level was found significantly increased in female diabetic subjects in the Framingham Heart Study. The LDL-C level in subjects with glucose intolerance did not differ from their non-diabetic counterparts in neither of the studies.

In our study, T2DM patients with hyperuricaemia had significantly higher triglyceride concentrations and triglyceride to HDL cholesterol ratios. It has been suggested that a high triglyceride to HDL cholesterol ratio is a risk factor for coronary heart disease.18 The triglyceride to HDL cholesterol ratio can be used to predict the presence and degree of coronary atherosclerosis.[45] Although high triglyceride to HDL cholesterol ratio has been reported to be a marker of insulin resistance,[46] a study of African Americans did not corroborate this finding.[47]

Hyperinsulinemia as a consequence of insulin resistance causes an increase in serum uric acid concentration by both inhibiting the renal uric acid secretion and retention of substrate responsible for uric acid production.[42] This leads to a vicious cycle which enhances level of uric acid in diabetic subjects. Quinones GA et al also have suggested that physiological hyperinsulinemia acutely reduces urinary uric acid and sodium excretion from the kidney in a coupled fashion.[48] Our finding is consistent with the former group of studies which

states lower level of uric acid in diabetic subjects compared to healthy controls.

Hyperinsulinemia could increase the activation of the hexose phosphate shunt, which would promote the biosynthesis and transformation of purine, thus increasing the rate of uricogenesis.[49] At the same time, insulin may increase reabsorption of uric acid from the kidneys by stimulating the urate anion transporter on the border membrane in the proximal tubular brush,[50] the end result of which is an increase in the concentration of serum uric acid.

These results agree with the results obtained in a study done by Safi et al,[51] who found the average level of serum uric acid in the diabetic patients was 6.07 mg/dl as compared to 5.01 mg/dl in the control group.

This is consistent with the finding of *Navin et al*,[52] where they have suspected the pro-oxidant role of uric acid in causation of oxidative stress leading to diabetic complication like diabetic retinopathy, though they could not clearly state that the hyperuricemia in diabetic retinopathy is either a protective response (due to its antioxidant role) or a primary cause of it (due to its pro-oxidant role).

This was an agreement with previous studies,[53-55] where a decreasing trend of SUA was observed with increasing blood glucose concentration whereas a follow-up study on Japanese individuals for 16 years, uric acid was found not to be correlated with a statistically significant increase in the risk of T2D.[56] Inverse correlation or decreased SUA concentration in diabetic individuals has been reported in other studies. For instance, a negative association between SUA and FBG has been reported in Austrian men.[57]

A plausible mechanism for the observed findings of the negative relationship between SUA and diabetes may be related to the inhibition of uric acid reabsorption in the proximal tubule of kidney by high glucose concentrations in diabetic individuals.[26,27] Studies demonstrated that the net concentration of uric acid in serum depends on its synthesis, secretion and reabsorption in the body.[58,59] The low concentration of uric acid in serum might be the results of the uricosuric effect of glucose on uric acid which may influence to increase the excretion and decrease reabsorption of uric acid from the kidney.[60] About 70% of the uric acid is excreted through kidney.[61] The exact mechanism is not clear but the proposed mechanism is that the 100% of uric acid is filtered in the glomerulus to the renal tubules with about 80% filtered load reabsorbed.[62]

Hyperuricaemia was associated with an increased creatinine concentration. Although hyperuricaemia may simply be a marker of renal disease, there are studies which suggest that elevated SUA levels might contribute to the development and progression of renal dysfunction.[63] Toda et al reported that hyperuricaemia was an independent risk factor for the development of chronic kidney disease,[64] and in studies in Japan, elevated baseline SUA and increases in SUA increased the risk of developing chronic kidney disease.[65] In another study, hyperuricaemia was associated with incident diabetic retinopathy among male patients with T2DM.[66]

Our results are also consistent with some prospective studies that established that high SUA levels increase the likelihood of dyslipidemia,[67] and this is independently associated with an increased likelihood of development of MetS.[68] These results also indicated that uric acid might contribute to the development of dyslipidemia. Uric acid has been widely recognized as a risk factor for the development of various cardiovascular diseases (CVDs), such as hypertension[69] and coronary heart disease.[70]

It is recognized that dyslipidemia is an independent risk factor for cardiovascular disease. Elevated blood glucose level combined with dyslipidemia increases atherosclerosis-related inflammation and makes it more extensive. A larger extent of coronary artery calcification in asymptomatic patients with newly-diagnosed T2DM has been demonstrated.[71] Dyslipidemia is not only an important risk for macrovascular complications;[72] studies have also observed the association of dyslipidemia with microvascular complications related to T2DM namely diabetic retinopathy, diabetic nephropathy and diabetic neuropathy.[73-75]

Uric acid was found to be positively correlated with serum triglyceride and negatively correlated with HDL-cholesterol levels in Peng et al's report.[76] A study conducted by Ching-Chao Liang et al., concluded that there were increased serum uric acid levels which correlated with the severity of diabetic Retinopathy in patients with type 2 DM.[77]

Limitations of the study

The present work has several limitations. First, with a cross-sectional study, it is very difficult to establish any causal relationship between SUA levels and dyslipidemia. Secondly, a selection bias could be introduced, for the study participants volunteered for the health examination. Third, parameters of lifestyle factors such as diet and physical activity were not included in the questionnaire, which may affect the SUA levels. Lastly, the relationship between uric acid and fractions of cholesterol could be very complex, and our study examined only the relationship between uric acid and lipid profiles as a variable to variable relationship.

CONCLUSION

Diabetes mellitus is strongly associated with hyperuricemia. The present study shows a strong association between SUA and lipid profile among diabetic adults in our study. Early prevention of hyperuricemia and dyslipidemia can reduce the incidence of associated cardiovascular disease. The glycaemic control has got a strong impact on the serum lipid level and dyslipidemia is frequently encountered among individuals with poor glycaemic control.

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