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Research Article

BIOMARKERS IN SERUM, URIC ACID AS A RISK FACTOR FOR TYPE 2 DIABETES ASSOCIATED WITH HYPERTENSION

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ABSTRACT

Objectives: Uric acid (UA) is the end product of purine metabolism in humans. UA is the final oxidation product of purine catabolism and has been implicated in diabetes mellitus (DM) as well as in hyperlipidemias. Hyperuricemia can cause serious health problems including renal insufficiency. Hyperuricemia is associated with many diseases including hypertension (HTN), DM, hypertriglyceridemia, and obesity. The aim was to determine the serum UA (SUA) level in Patients of Type 2 DM with HTN.

Methods: Out of 100 samples, 50 were found as cases of Type 2 diabetic with HTN, and the 50 control samples were without Type 2 diabetic HTN.

Results: SUA, glycosylated hemoglobin, and low-density lipoprotein of male and female cases of Type 2 DM with HTN compared to control were ($p<0.05$) highly significant and also serum triglycerides and total cholesterol of both sex groups of Type 2 DM with HTN compared to control were found to be ($p<0.05$) highly significance.

Conclusion: It is concluded from our present study that level of SUA >7.0 mg/dl were significantly seen in cases of diabetes with HTN. SUA ≤5.0 mg/dl was significantly seen in subjects without diabetes with HTN. Our data showed hyperuricemia and glycated hemoglobin as significant risk factors in the progression of DM, atherosclerosis, myocardial infarction, renal disorder, hypertriglyceridemia, and obesity. Further large sample size studies are needed to be done in the direction with more focused mechanistic approaches to fortify the fact. Very little is known about the relationship between UA, DM, and HTN in India.

Keywords: Diabetes mellitus, Hypertension, Uric acid, Glycosylated hemoglobin, Lipid profile

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia and disturbances in carbohydrate, fat, and protein metabolism caused by defects in insulin secretion, action or both [1]. Serum uric acid (UA), an end product of purine metabolism, has been shown to be associated with an increased risk of hypertension (HTN) [2,3]. Recently, it has been recognized that serum UA (SUA) is positively associated with serum glucose levels in healthy subjects [4].

DM and HTN are interrelated diseases that strongly predispose an individual to atherosclerotic cardiovascular disease (CVD). Data obtained from death certificates show that hypertensive disease has been implicated in 4.4% of deaths coded to diabetes, and diabetes was involved in 10% of deaths coded to hypertensive disease. Indeed, an estimated 35% to 75% of diabetic cardiovascular and renal complications can be attributed to HTN [5,6].

More than 75% of adults with diabetes have blood pressure (BP) levels ≥ 130/80 mm Hg or are using antihypertensive medication [7]. In contrast, in the Atherosclerotic Risk in Communities Study and in the Framingham Heart Study, there was no association between SUA and incidence of CVD [8,9].

The difficulties in the assessment of the role of SUA independently from other traditional risk factors and the different methodologies used in the epidemiological studies may be responsible for the conflicting data regarding the relationship between the SUA level and cardiovascular disease. The prevalence of the metabolic syndrome was 18.9% for the SUA levels <6 mg/dL; in contrast, the prevalence of metabolic syndrome increased at 70.7% for the SUA levels of 10 mg/dL or greater. Moreover, hyperuricemia might independently predict the development of different components of the metabolic syndrome obesity, hyperinsulinemia, and diabetes [10,11]. The role of UA as an independent risk factor for the CVD is controversial since hyperuricemia is associated to other traditional risk factors. Elevated SUA level also represents a strong prognostic marker for cardiovascular events, particularly in patients at high cardiovascular risk or with established CVD [12].

Hyperuricemia is a condition that is significantly associated with markers of metabolic syndrome such as dyslipidemia, glucose intolerance, high BP, and central obesity, which are accepted as risk factors for developing CVD. Hyperuricemia is probably associated with glucose intolerance due to various mechanisms; however, the most important is the association between insulin and renal resistance to absorption of urates [13-15]. We, therefore, aim to determine the SUA level in patients of Type 2 DM with HTN.

METHODS

The criteria used for selection of both DM with HTN and without HTN controls were according to well-established diagnostic criteria as recommended by the Word Health Organization and 7th Joint National Committee. The present case-controlled study was conducted on 100 patients out of them, 50 cases were of Type 2 DM with HTN patients and 50 control cases with normotensive Type 2 diabetes. Blood samples from clinically diagnosed and confirmed cases of a diabetic with HTN in the age group 35-74 years, were collected from the Hind Institute of Medical Sciences Lucknow. The patients and the controls were further divided into different groups. The height and the weight of patients and the controls were measured, the body mass index (BMI) was calculated.

The waist/hip ratio (W/H ratio) was also calculated. All the patients were asked to fast overnight for a period of 12-hr before collection of blood. Plasma glucose, SUA, glycosylated hemoglobin (HbA1c), cholesterol, and triglycerides (TG) were evaluated according to the well-established protocol given in the literature and were as follows. Large sample size studies are needed to be done in the direction with more focused mechanistic approaches to fortify the fact.

Biochemical assessments

1. HbA1c: Estimated using direct enzymatic assay method [16]
2. Fasting blood sugar level: Glucose oxidase method commonly known as the GOD-PAP (end point) method [17]
3. TG: Estimated using enzymatic (Endpoint) method [18]
4. TCH: Estimated using enzymatic (end point) method [19,20]
5. Low-density lipoprotein (LDL) and high-density lipoprotein: by precipitation method using a reagent that consists of modified polyvinyl sulfonic acid and polyethylene-glycol methyl ether [21]
6. Very LDL cholesterol was calculated using the Friedewald's Formula [22]
7. UA: Estimated using Uricase-PAP method [23]

Statistical analysis

In our results, we analyzed by applying mean±standard error and percentage. Unpaired t-test was used to compare the study parameters between cases and controls. The Pearson correlation coefficient was calculated among the parameters. The p-value<0.05 was considered significant. All the analysis was carried out by SPSS 16.0 version (Chicago, Inc., USA).

RESULTS

Comparison of all the parameters between control and study subjects is clearly mentioned in Table 1. Table 2 shows the comparison of UA level between cases and controls. UA was found to be significantly raised both in males and females (diabetics with HTN) compared controls with p values (p=0.0011), and (p=0.0001), respectively. While the difference in the values of male and female study subjects was not significant (p=0.3458).

Table 3 shows the comparison of HbA1C level between cases and controls. HbA1C level was significantly raised as compared to control both the genders (with p=0.0001) difference in the values of males and females (diabetics with HTN) was extremely significant (p=0.0077).

Table 4 shows the comparison of TG level between cases and controls. While compared to control, the values were significantly raised in both male and females. Difference in the values of males and females (diabetics with HTN) was extremely significant (p=0.0001).

Table 5 shows the comparison of total cholesterol level between cases and controls. While comparing to control, the values were significantly raised in both male and females. Difference in the values of males and females (diabetics with HTN) was extremely significant (p=0.0001).

Table 6 shows the comparison of LDL level between cases and controls. While compared to control, the values were significantly raised in both male and females. Difference in the values of males and females (diabetics with HTN) was not significant (p=0.6674).

Table 1: Characteristics and medication of different groups

Variables	Diabetics with HTN		Controls	
	Males	Females	Males	Females
Age (years)	51.5±1.51	50.2±1.46	50.4±1.46	50.0±0.96
BMI	25.2±0.62	27.0±0.79	25.4±0.77	24.8±0.39
W/H ratio	0.90±0.01	0.83±0.01	0.80±0.019	0.69±0.01
FPG (mg/dl)	154.8±8.64	171±14.9	77.4±2.16	76.7±1.98
2hPG (mg/dl)	241.2±12.42	259.2±14.5	102.6±3.78	100.6±43.60
TC (mg/dl)	162.4±13.5	181.7±12.7	127.6±6.18	125.6±5.90
TG (mg/dl)	141.7±9.7	132.8±6.2	106.2±3.5	102.8±4.7
HDL-C (mg/dl)	39.4.1±5.23	35.31±7.1	45.6±8.0	42.4±6.8
LDL-C (mg/dl)	131.53±41.10	135.2±10.6	85.0±12.0	82.0±10.4
HbA1c (%)	9.1±2.6	7.4±1.6	5.8±0.7	5.5±0.4
UA (mg/dl)	6.95±2.65	6.40±1.28	4.9±1.3	4.2±1.7

UA: Uric acid, TC: Total cholesterol, TG: Triglycerides, FPG: Fasting plasma glucose, LDL-C: Low-density lipoprotein-cholesterol, HDL-C: High-density lipoprotein-cholesterol, 2hPG: 2 h postprandial glucose, W/H ratio: Waist/hip ratio, BMI: Body mass index, HbA1c: Glycosylated hemoglobin

DISCUSSION

UA is the final product of the purine metabolism in humans and plays a dual role, both as a pro-oxidant and as an antioxidant [24,25]. To our knowledge, this is the first report to show raised SUA levels at the onset of overt diabetes with HTN as a risk factor in comparison to decline

Table 2: Comparison of uric acid between different groups (cases and controls)

Gender	Cases (n=50)	Controls (n=50)	Significance	t value df
Male diabetics with HTN	6.95±2.65	4.9±1.3	p=−0.0011***	t=3.4726 df=48
Female diabetics with HTN	6.40±1.28	4.2±1.7	p=0.0001**	t=5.1692 df=48
Male+female Diabetics with HTN	6.95±2.65 6.40±1.28	-	p=0.3548	t=0.9344 df=48

HTN: Hypertension, df: Degree of freedom

Table 3: Comparison of HbA1C between different groups (cases and controls)

Gender	Cases (n=50)	Controls (n=50)	Significance	t value df
Male diabetics with HTN	9.1±2.6	5.8±0.7	p=0.0001**	t=6.1279 df=48
Female diabetics with HTN	7.4±1.6	5.5±0.4	p=0.0001**	t=5.7602 df=48
Male+female diabetics with HTN	9.1±2.6 7.4±1.6	-	p=−0.0077***	t=2.7843 df=48

HTN: Hypertension, df: Degree of freedom, HbA1c: Glycosylated hemoglobin

Table 4: Comparison of TG between three groups (cases and controls)

Gender	Cases (n=50)	Controls (n=50)	Significance	t value df
Male diabetics with HTN	141.7±9.7	106.2±3.5	p=0.0001**	t=4.4932 df=275
Female diabetics with HTN	132.8±6.2	102.8±4.7	p=0.0001**	t=29.5027 df=275
Male+female diabetics with HTN	141.7±9.7 132.8±6.2	-	p=0.0001**	t=4.4932 df=275

HTN: Hypertension, df: Degree of freedom

Table 5: Comparison of total cholesterol between three groups (cases and controls)

Gender	Cases (n=50)	Controls (n=50)	Significance	t value df
Male diabetics with HTN	162.4±13.5	127.6±6.18	p=0.0001**	t=11.7193 df=48
Female diabetics with HTN	181.7±12.7	125.6±5.90	p=0.0001**	t=20.0306 df=48
Male+female diabetics with HTN	141.7±9.7 132.8±6.2	-	p=0.0001**	t=5.2064 df=48

HTN: Hypertension, df: Degree of freedom

Table 6: Comparison of LDL between three groups (cases and controls)

Gender	Cases (n=50)	Controls (n=50)	Significance	t value df
Male diabetics with HTN	131.53±41.1	85.0±12.0	p=0.0001**	t=5.4337 df=48
Female diabetics with HTN	135.2±10.6	82.0±10.4	p=0.0001**	t=17.9126 df=48
Male+female diabetics with HTN	131.53±41 135.2±10.6	-	p=0.6674	t=0.4323 df=48

LDL: Low-density lipoprotein, HTN: Hypertension, df: Degree of freedom

UA levels in diabetic subjects without HTN thereby showing a close relationship to cholesterol levels in patients with Type 2 diabetes. In the present study, male diabetes cases with HTN showed mean UA and HbA1C value as 6.95±2.65 mg/dL and 9.1±2.6%, respectively, and females of the same group showed mean UA and HbA1C value of 6.40±1.28 and 7.4±1.6, respectively, which were significantly elevated as compared to control group (Diabetes Type 2 without HTN). The comparison of HbA1C among both the sexes showed a significant difference, whereas no significant difference was observed while comparison was made among both the sexes for UA. These two biochemical constituents are emerged as a strong and independent risk factor for diabetic dyslipidemia predisposing vascular complications and CVD.

These associations persisted in both gender and were independent of other known risk factors of Type 2 diabetes including age, BMI, W/H ratio, BP, HTN and levels of glucose, cholesterol, and TG. Overall, these findings provide prospective evidence that individuals with higher SUA, including younger adults, are at an increased future risk of Type 2 diabetes independent of other known risk factors. Nakanishi *et al.* [26] study found that SUA level is closely associated with an increased risk for HTN and Type 2 diabetes. In the present study, UA was significantly (p=0.0001) higher among cases (6.95±2.65) as compared with controls (4.9±1.3). Because elevated SUA is correlated with several risk factors including renal dysfunction, HTN, insulin resistance, hyperhomocystenemia, and hyperlipidemia, it is debated whether SUA is an independent cardiovascular risk factor. In another study, SUA >7.0 was found significantly raised in coronary artery disease (CAD) patients with DM Type 2 [27]. Thus, hyperuricemia is can be taken as a predictor or a risk factor for CAD. DM is associated with hyperglycemia and patients are at an increased risk of CVD. The outcome of our study and possible cause of elevated level of UA among diabetics with HTN can be better correlated from the previous findings and can be explained by the effects of UA on diurnal rhythms of NO levels and renin-angiotensin system activation [28]. However, since our study used an observational type, we could not suggest a cause-and-effect relationship between SUA and HTN, but we hypothesize that SUA may play a causal role in increased nighttime BP variation. In addition to SUA levels, DM and waist circumference were found to be independent predictors of nighttime diastolic BPV. In the present study, we show for the first time that SUA levels are associated with BPV in patients with essential HTN. It would be pertinent to perform genetic studies to clarify the gender differences in the SUA concentrations in relation to Type 2 DM which is associated with HTN.

CONCLUSION

The finding of the study suggests a significant correlation between UA, HbA1c, and lipid profile; As elevated was UA and HbA1c, dyslipidemia are independent risk factors of CVD, diabetic patients with elevated HbA1c and dyslipidemia can be considered as a very high-risk group for CVD. Improving glycemic control can substantially reduce the risk of cardiovascular events in diabetics. This data shows hyperuricemia is a significant risk factor for CAD in Type 2 DM. Hyperuricemia is significantly associated with progression of DM and can increase the morbidity and mortality from diabetes if not manage in time. Based on the study carried out it is concluded that SUA can be used as a biochemical marker to determine the severity and duration of HTN. Further research should attempt to determine whether it is effective to utilize SUA levels as a predictor in the prevention of Type 2 diabetes with HTN.

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