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Uric Acid in Relation to Type 2 Diabetes Mellitus Associated with Hypertension

Biochemistry Section

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ABSTRACT

Introduction: The role of uric acid in the progression of prediabetes to diabetes has been known. However, conflicting data exist as regards the serum uric acid (UA) levels in type 2 diabetes mellitus, which are associated with risk factors and complications.

Objective: The present study was designed to look for any association of serum uric acid with hypertension in type 2 diabetes mellitus, taking into consideration the relevant clinical, biochemical and the anthropometric data.

Material and methods: Fifty patients with type 2 diabetes mellitus and 50 healthy controls were included in this study. They were further divided into different groups, based on the sex, the duration of diabetes, and the diabetes which was complicated with hypertension.

Results: The circulatory levels of glucose, total cholesterol and triglycerides were found to be elevated in the diabetics of either sex as compared to those in the controls. There was no significant difference in the serum uric acid levels between the diabetics and the non-diabetics, either in males or females. A negative correlation was observed between the fasting plasma glucose and the serum uric acid levels in both male [r = –0.60] and female [r = –0.60] diabetic patients. The serum uric acid levels marginally decreased with an increased duration of diabetes. The hypertensive male and female diabetics were found to have significantly decreased ($P < 0.05$) serum uric acid levels as compared to the corresponding non-hypertensive diabetics.

Conclusion: It was concluded from the present study that there occurs a significant decrease in the serum uric acid levels in hypertensive diabetics (both in males and females) in comparison with the non-hypertensive diabetics.

Key Words: Type 2 diabetes mellitus, Serum uric acid, Hypertension

INTRODUCTION

Diabetes mellitus is a clinical syndrome which is characterized by hyperglycaemia due to an absolute or a relative deficiency of insulin. It may be associated with a number of complications which include macro and microvascular diseases. Uric acid (UA) is the end product of the purine metabolism. The association between the blood glucose and the serum uric acid levels has been known for quite some time [1]. A positive association between the serum uric acid levels and the development of type 2 diabetes mellitus (T2DM) has been reported [2]. In individuals with an impaired glucose tolerance, an elevated Serum Uric Acid (SUA) level was found to increase the risk for developing T2DM [3].

Uric acid can act as a prooxidant and it may thus be a marker of oxidative stress, but it may also have a therapeutic role as an antioxidant [4]. Urate, the soluble form of uric acid, can scavenge the superoxide and the hydroxyl radicals and it can chelate the transition metals [5]. Hyperuricaemia has been also added to the set of metabolic abnormalities which are associated with insulin resistance and/or hyperinsulinaemia in the metabolic syndrome [6]. While an increase in the uric acid levels in prediabetes and diabetes was demonstrated by some studies, a declining trend of the serum uric acid levels with increasing blood glucose levels was observed by other research workers [7].

Hypouricaemia has also been implicated in the development of diabetic nephropathy [8]. Although some studies have demonstrated the role of UA in the progression of prediabetes to diabetes, conflicting data exist about the uric acid levels in T2DM, which are associated with risk factors and complications [9,10]. Thus, the role of UA in the pathogenesis and the development of the diabetic complications is controversial. Therefore, the present study was designed to look for any association of serum uric acid with hypertension in T2DM, taking into consideration the relevant clinical, biochemical and the anthropometric data.

MATERIALS AND METHODS

A cross- sectional study was conducted on 50 patients with known type 2 diabetes mellitus and on 50 healthy controls who were in the age group of 30 -60 years. The patients were randomly selected from the Outpatients Medicine Department of Dr. Pinnamaneni Siddhartha Institute of Medical Sciences and Research Foundation, Chinna Avutapalli. The patients and the controls were further divided into different groups, based on

(i) The sex of the individual,

(ii) The duration of diabetes - group I (1- 5 years) and group II (5.1-10 years)

(iii) The patients with and without hypertension.

The study was approved by the institutional ethical committee of Dr. Pinnamaneni Siddhartha Institute of Medical Sciences and Research Foundation, Chinna Avutapalli. All the data were collected in a prescribed proforma and they were compiled. The questionnaire

contained questions regarding the duration of diabetes, the family history of diabetes, the dietary history and the history of hypertension, smoking, alcohol drinking, etc. A criterion for the selection of the patients which was included in the study, was that all the individuals who gave a history of diabetes and were under treatment with either oral antidiabetic drugs or insulin were considered to have diabetes. The patients with a history of gout and cardiovascular or renal diseases and those who were on drugs (other than antidiabetics) that could alter the blood glucose levels were excluded from the study. The controls were non-diabetic, non-hypertensives, non-smokers and non-alcoholics with normal plasma glucose levels.

A subject was considered to be on a mixed diet if non-vegetarian food was taken three or more than three times per week. The patients who gave a history of hypertension and were on antihypertensive treatment or whose blood pressure was more than 140/90 mm of Hg were considered to have hypertension. The height and the weight of patients and the controls were measured. The body mass index (BMI) was calculated by dividing the weight (Kg) by the height (m) squared. By measuring the waist circumference at the level of the iliac crest and the hip circumference at the maximal horizontal girth between the waist and the thigh, the waist/hip ratio (W/H ratio) was calculated.

All the patients were asked to fast overnight for a period of minimum eight hours. The blood samples which were taken for analysis were obtained from the antecubital vein. The post-prandial plasma glucose samples were collected two hours after the subjects had their breakfast. The analysis of plasma glucose was done by the glucose oxidase method, while the serum uric acid, cholesterol and triglycerides were evaluated by enzymatic methods. These tests were performed on a Randox Daytona analyser.

The statistical analysis was done by the unpaired two tailed 't' test and the Pearson's correlation coefficient by using the NCSS software. The data were presented as mean with SEM. The statistical significance was kept as a P value of < 0.05.

RESULTS

The mean ages (in years) of the male and female diabetic patients were 51.5±1.51 and 50.4±1.46 against 43.9±1.60 and 41.8±1.86 in the controls (males and females) respectively. The BMI, the W/H ratio, the fasting and the postprandial plasma glucose (FPG, 2hPG) levels and the total serum cholesterol and the serum triglycerides levels were higher in the diabetics as compared to the controls in both males and females. The serum uric acid levels in the diabetic males and females were marginally lower as compared to those in the controls, although this was not statistically significant [Table/Fig-1].

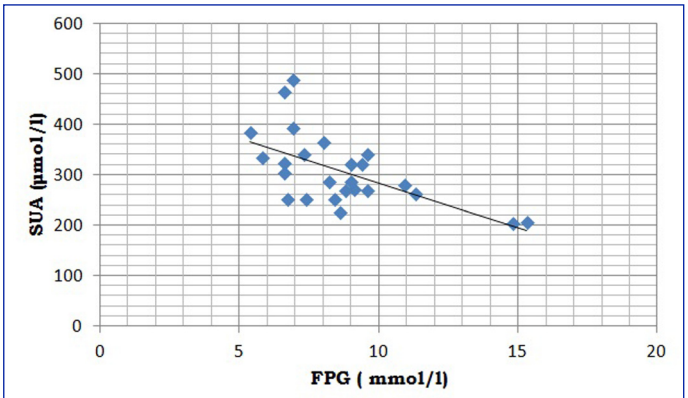
A negative correlation was observed between the fasting plasma glucose and the serum uric acid levels in both male [r = –0.60] and female [r = –0.60] diabetic patients [Table/Fig-2],[Table/Fig-3]. The serum uric acid levels decreased with an increased duration of diabetes, although it was not statistically significant [Table/Fig-4].

The comparison of the non-hypertensive and the hypertensive male and female diabetics showed decreasing serum uric acid levels, which was statistically significant (P<0.05). The decrease in the uric acid levels was more pronounced in the female diabetics (P<0.02) than in the male diabetics (P<0.03) [Table/Fig-5].

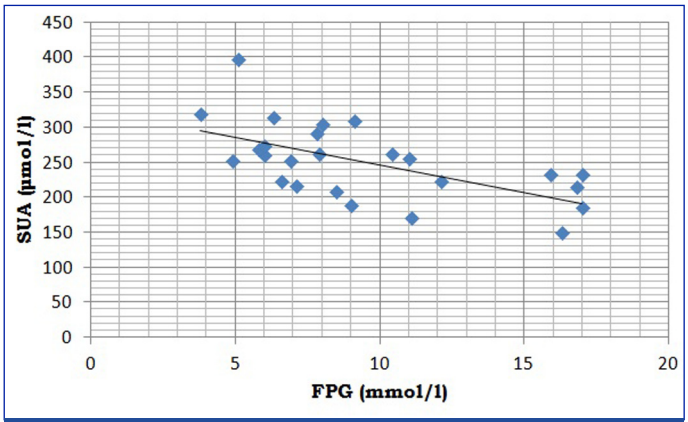
The percentage of the diabetics who gave a positive family history of diabetes and a history of hypertension was more among the females than among the males, while smoking and alcohol drinking were predominantly seen in the males. Dyslipidaemia in the form of increased serum total cholesterol levels was more pronounced in the female diabetics and hypertriglyceridaemia was more common in the male diabetics [Table/Fig-6].

Variables	Males		Females	
	Controls 25	Diabetics 25	Controls 25	Diabetics 25
Age (yrs)	43.9 ± 1.60	51.5 ± 1.51	41.8 ± 1.86	50.4 ± 1.46
BMI	23.9 ± 0.75	25.2 ± 0.62	25.4 ± 0.77	27.0 ± 0.79
W/H ratio	0.90 ± 0.01	0.92 ± 0.01	0.80 ± 0.01	0.83 ± 0.01
FPG (mmol/l)	4.5 ± 0.13	8.6 ± 0.48*	4.3 ± 0.12	9.5 ± 0.83*
2hPG (mmol/l)	6.1 ± 0.19	13.4 ± 0.69*	5.7 ± 0.21	14.4 ± 0.81*
T.Cholesterol (mmol/l)	3.1 ± 0.16	4.2 ± 0.35*	3.3 ± 0.16	4.7 ± 0.33*
Triglycerides (mmol/l)	1.1 ± 0.04	1.6 ± 0.11*	1.2 ± 0.04	1.5 ± 0.04*
Uric acid (µmol/l)	314.5 ± 16.48	306.8 ± 14.27	266.0 ± 18.45	250.1± 10.85

[Table/Fig-1]: Biochemical and anthropometric data Data presented as Mean ± SEM *Significant – p<0.05(comparison between controls and diabetics in males and females)



[Table/Fig-2]: Correlation (r= -0.60) between fasting plasma glucose (FPG) and serum uric acid levels (SUA) in male diabetics



[Table/Fig-3]: Correlation (r= - 0.60) between fasting plasma glucose (FPG) and serum uric acid levels (SUA) in female diabetics

Group	I	II
Female diabetics	285.7±28.68 (15)	236.6±13.76 (10)
Male diabetics	308.5±18.82 (15)	262.5±10.25 (10)

[Table/Fig-4]: Serum uric acid levels (µmol/l) associated with duration of T2DM Group I :1-5yrs, Group II : 5.1-10 yrs Data presented as Mean ± SEM Number in parentheses represent the sample size

Group	Non-hypertensive	Hypertensive
Female diabetics	320.3 ± 35.01	235.5 ± 17.63*
Male diabetics	311.9 ± 18.58	257.3 ± 8.24*

[Table/Fig-5]: Serum uric acid levels (µmol/l) associated with hypertension in T2DM Data presented as Mean ± SEM *Significant – p<0.05(comparison between non-hypertensive and hypertensive diabetics)

Characteristics	Males 25	Females 25
Diet(mixed)	17 (68)	15 (60)
Family history of diabetes	7 (28)	11 (44)
Hypercholesterolemia	5 (20)	8 (32)
Hypertriglyceridemia	10 (40)	7 (28)
History of hypertension	10 (40)	16 (64)
History of smoking	6 (24)	nil
History of alcohol intake	5 (20)	nil

[Table/Fig-6]: Clinical and biochemical characteristics in T2DM Data presented as number of patients with percentages in parentheses

DISCUSSION

Uric acid is the final product of the purine metabolism in humans. The 2 final reactions in its production which catalyze the conversion of hypoxanthine to xanthine and the latter to uric acid are catalyzed by the enzyme xanthine oxidoreductase, which may attain 2 inter-convertible forms, namely xanthine dehydrogenase or xanthine oxidase. The latter uses molecular oxygen as an electron acceptor and it generates a superoxide anion and other Reactive Oxygen Species (ROS), thus favouring an antioxidant – prooxidant urate redox shuttle [10,11]. UA is also a physiological free radical scavenger and one of the major contributors of the plasma antioxidant capacity [12]. Thus, UA plays a dual role, both as a prooxidant and as an antioxidant [13,14]. T2DM is associated with oxidative stress and increased free radical formation [15]. While on one hand, hyperglycaemia generates free radicals, on the other hand, it also impairs the endogenous antioxidant defense system [16]. Under the condition of increased oxidative stress, there occurs the depletion of the local antioxidants, which causes a reduction in the antioxidant status of the body [17].

Studies have reported the association of hypouricaemia with T2DM [18,19]. A positive relationship has been described between glycosuria and uricosuria [20]. Further, a higher degree of hyperglycaemia was observed to be associated with an increased rate of uric acid excretion and lowering of the plasma uric acid levels [20]. Hypouricaemia and the tubular transport of uric acid have been thoroughly reviewed [21]. An increased urate clearance due to increased glomerular hyperfiltration which is a result of an abnormality in the tubular urate handling, has been reported [22].

The SUA levels were found to be higher in males than in females [23]. We reported a similar finding in our study. The findings of the BMI, and the waist hip ratio in the diabetic males and females in our study were in accordance with the findings of others [24,25]. Our study reported a negative relationship between the fasting plasma glucose and the serum uric acid levels which were in agreement with the findings of other studies [26].

While the incidence of hypercholesterolaemia and hypertension and a family history of diabetes were more in the female diabetics, the incidences of hypertriglyceridaemia, smoking, and alcohol drinking were more in the male diabetic patients. These findings were in corroboration with those of other studies [24]. Although it was not statistically significant, the lowering of the serum uric acid levels with an increase in the duration of diabetes was observed in our study and this was in agreement with the findings of another study [1].

Johnson et al,. in their review, have reported a positive association of hyperuricaemia with hypertension in T2DM with complications [27]. In contrast, a statistically significant decrease in the serum uric acid levels in the hypertensive diabetics (both males and females) in comparison with the non-hypertensive diabetics, was observed in our study.

As a decrease in the serum uric acid levels was seen with high plasma glucose levels/increased glycosuria, hyperfiltration and a decreased antioxidant status, the lowering of the serum uric acid levels in diabetes which was complicated with hypertension, as was observed in our study, may be of pathogenic significance.

Several factors are known to alter the serum uric acid levels in T2DM. From the present study, it appears that uric acid alone cannot act as an independent risk marker for type 2 diabetes mellitus. Taking up more studies on the renal clearance and the uric acid excretion and on the antioxidant status in the hypertensive diabetics, by taking the glycaemic status into consideration, may help in better defining the role of uric acid in type 2 diabetes mellitus. Further, as the decrease in the serum uric acid levels is more significant in the hypertensive diabetic females with a family history of diabetes, it would be pertinent to perform genetic studies in order to clarify the gender differences in the serum uric acid concentrations in relation to type 2 diabetes mellitus which is associated with hypertension.

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