Research Article

Evaluation of serum uric acid levels in type 2 diabetes mellitus: complex interplay with demographic and clinical parameters

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Abstract

Introduction: Type 2 Diabetes Mellitus presents potential risk factor for development of macro and microvascular complications because of certain metabolic as well as clinicodemographic variables. The association of uric acid with such parameters in diabetic environment is highly complex and inconclusive, which forms the basis of our study. **Materials and Methods:** OPD based cross sectional study including 100 cases of T2DM and 100 controls evaluated in a stepwise manner. Results were assessed by appropriate statistical software. **Observations and Results:** Significant difference was noted in mean values of age, SBP, BMI WHR, BSL and UA between cases and controls ($P < 0.05$); while DBP was not significant high compared to controls ($P = 0.12$). The number of males, smokers, alcoholics, physically inactive and mixed dietarians was high in cases compared to controls. Mean duration of diabetes was 6.7 ± 1.1 years. Hyperuricemia was observed 51 cases, with a mean level of 8.8 ± 1.7 mg%. Cases in hyperuricemic group were comparatively aged, with high BP, BMI and WHR than those with normal/ low UA. WHR showed strongest positive correlation with UA, while BSL and duration of diabetes showed negative correlation. The impact of central obesity shown by WHR is profound than general obesity shown by BMI. Inverse relationship of uric acid with duration of diabetes and blood glucose level shows uricosuric effect of glucose on kidneys. **Conclusion:** Impact of demographic and clinical variables on metabolic parameters like uric acid in diabetic settings often remains underevaluated in practice. Uric acid level in a patient is rather an ultimate outcome of several factors which must be taken into consideration before any precise causality is established.

Keywords: demographic variables, duration of diabetes, hypertension, obesity, Type 2 diabetes mellitus, uric acid.

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INTRODUCTION

Diabetes Mellitus is a heterogeneous, multifactorial, polygenic disease characterized by a defect in insulin's secretion, insulin action or a combination of both which ultimately leads to elevated glucose levels in blood[1]. Type 2 diabetes Mellitus (T2DM) is largely emerging as a global epidemic severely affecting Indian subcontinent. It increases the risk of number of macro and microvascular complications. The development of these complications in diabetic environment is largely a result of clustering of various modifiable and non modifiable risk factors which may be demographic, anthropometric or metabolic. Modifiable risk factors include physical inactivity, smoking, alcoholism, excessive stress, high calorie diet and central obesity while non modifiable risk factors are age, sex, duration of diabetes and hypertension. The interplay of such factors along with certain metabolic

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parameters is potentially responsible for adverse outcomes in diabetics. The role of uric acid (UA) has gained attention in this regard. Uric acid is the end product of purine metabolism in humans. Uric acid may act as prooxidant as well as antioxidant in diabetic environment and is known to be influenced by certain demographic and clinical factors by many diverse mechanisms[2]. Although positive association between uric acid and prediabetes has been known for quite some time; conflicting data exist about its association with established diabetes cases as well as the development of complications[3]. The study was aimed at evaluating the status of uric acid in diabetic individuals taking into consideration the apparently complex interplay of uric acid with demographic and clinical factors.

MATERIAL AND METHODS

Study population

It was an OPD based cross sectional Study carried out in a tertiary care hospital during period from January to may 2011. Research protocol was approved by institutional ethical committee. 100 patients of type 2 diabetes mellitus receiving treatment and 100 age and sex matched non diabetic healthy controls were enrolled for the study in random manner. They were in the age group of 35 to 60 years of either sex. Written and informed consent was obtained from all participants. Those with existing renal disease, cardiovascular disease, medications that influence uric acid levels like uricosuric drugs were excluded from the study.

Study protocol

Study was conducted as per prescribed proforma including history, clinical examination and laboratory investigations. Participants were asked to answer the Standard questionnaire consisting of personal details, age, sex, smoking, alcoholism, duration of diabetes, physical activity and diet (veg/ mixed / non veg diet). Smoker was defined as the one who smokes at least one cigarette per day. Alcohol intake was categorized as men $\geq$ 40 gm/day and women $\geq$ 20 gm / day. A person was labeled physically active if he if he engaged in moderate physical activity for at least 30 minutes for a minimum of 3 times in a week[4]. Clinical examination consisted of Blood pressure (mm of Hg), weight (Kg), Height (meters), Body Mass Index (BMI), Waist circumference (WC), Hip circumference (HC), and Waist/Hip ratio (WHR). Body weight was taken on a calibrated scale to the nearest 0.1 kg. Height was taken with a wall-mounted stadiometer to the nearest 0.5 cm. Body mass index (BMI) was calculated as body weight (kg) to the squared height (m^2). Waist circumference (WC) was measured at the mean point between the lowest rib margin and iliac crest with the participant standing and at the maximum point of normal expiration. Hip circumference was measured at the level of greatest protuberance of buttocks without compression of skin. Hypertension was defined as blood pressure of $\geq$ 130 / 85 mm of Hg. Obesity was defined as BMI $\geq$ 30 kg/ metre^2. Central obesity was defined as WC $\geq$ 102 cm for men and $\geq$ 88 cm for women [2]. WHR of < 1.0 for men and <0.85 for women was considered as normal[5]. 12 hour fasting venous blood samples were collected from all participants in Fluoride and plane bulbs for glucose and uric acid estimation respectively. Serum was separated after 1 hour by centrifugation at 3000 rpm for 10 minutes. Blood glucose level was estimated by glucose oxidase peroxidase method using kits from Erba Mannheim. Serum uric acid was estimated by Uricase end point method using kits from TECO diagnostics, USA

Statistical Analysis

The results were analyzed by appropriate statistical software (OPEN EPI version 2.3). The results were interpreted as mean $\pm$ S.D. for quantitative parameters and as number / percentage for qualitative data. Correlation coefficients were calculated between uric acid and other variables (r value) and P< 0.05 was considered statistically significant.

OBSERVATIONS AND RESULTS

100 cases of T2DM and 100 age and sex matched healthy controls were enrolled for the study. The tabular data reflects the finding in case and control group, their statistical significance, comparison of characteristics in cases in accordance with uric acid levels as well as correlation coefficients of uric acid with studied parameters.

Table 1: Demographic and clinical characteristics in study group

Sr. No.	Parameter	Cases (100)	Controls (100)	P value
	Values expressed as mean $\pm$ SD			
1	Age	56.6 $\pm$ 18.4	41.1 $\pm$ 13.8	< 0.01**
2	Duration of diabetes	6.7 $\pm$ 1.1	--	
3	Systolic blood pressure (SBP) (mm of Hg)	124.4 $\pm$ 9.5	118.4 $\pm$ 7.6	< 0.05 *
4	Diastolic blood pressure (DBP) (mm of Hg)	86.7 $\pm$ 7.8	81.6 $\pm$ 3.1	P = 0.12
5	Waist hip ratio (WHR)	0.90 $\pm$ 0.09	0.81$\pm$ 0.05	< 0.01 **
6	Body mass index (BMI)	27.7 $\pm$ 2.8	23.8 $\pm$ 2.9	<0.05 *
7	Blood glucose (Fasting) (mg / dl)	129.4 $\pm$ 14.8	89.9 $\pm$ 10.1	< 0.01 **

8	Sr. uric acid (mg / dl)	5.8 ± 1.3	3.9 ± 1.0	<0.05 *
	Values expressed as percentage (%)			
9	Sex (M/F ratio)	57/43	52/48	NA
10	Smokers	42	39	NA
11	Alcoholics	37	35	NA
12	Physical inactivity	58	42	NA
13	Diet (Veg / Mixed diet)	32/68	36/64	NA

*: significant P value, **: Highly significant P value

Table 1 shows that; mean levels of age, SBP, WHR, BMI, UA and blood glucose were found to be higher in cases than controls and the difference was statistically significant; while the DBP though higher than controls was not significant. The number of males, smokers, alcoholics and non vegetarian was higher than that of control group. There was a significant difference in number of people with physical inactivity in cases than controls. Mean duration of diabetes was 6.7 ± 1.1 years.

Table 2: Distribution of demographic and clinical parameters in T2DM cases according to uric acid levels

Sr. No.	Parameter	Overall N = 100	Uric acid (>7 mg/dl) N= 51	Uric acid (≤7 mg/dl) N = 49	P Value
		Values expressed as mean ± SD			
1	Serum Uric acid	5.8 ± 1.3	8.8 ± 1.7	4.6 ± 1.2	<0.01 **
2	Age	56.6 ± 18.4	57.4 ± 12.4	53.1 ± 9.8	<0.05 *
3	Duration of diabetes	6.7 ± 1.1	4.2 ± 1.8	9.8 ± 2.1	<0.01 **
4	SBP	124.4 ± 9.5	128.6 ± 10.1	122.5 ± 6.6	P=0.09
5	DBP	86.7 ± 7.8	86.3 ± 6.9	82.8 ± 7.1	P=0.1
6	Waist hip ratio (WHR)	0.90 ± 0.09	1.13 ± 0.23	0.84 ± 0.18	<0.01 **
7	Body mass index (BMI)	27.7 ± 2.8	28.1 ± 3.7	26.3 ± 4.4	<0.05 *
8	Blood glucose level	129.4 ± 14.8	119.2 ± 15.4	132.5 ± 12.3	<0.01 **
		Values expressed as percentage (%)			
9	Sex(M/F)	57/43	32/19	25/24	NA
10	Smokers	42	23	19	NA
11	Alcoholics	37	20	17	NA
12	Physical inactivity	58	35	23	NA
13	Diet (Veg / Mixed diet)	32/68	15/36	17/32	NA

Table 2 subcategorizes parameters on uric acid levels. The cases with UA >7 mg/dl were comparatively aged, with high BP, WHR, BMI and physically inactive than those with UA ≤7 mg/dl. The SBP and DSP values were not statistically significant in two groups. The percentage of males, Smokers, alcoholics and non vegetarians was also higher in high UA group. Mean duration of diabetes and blood glucose level was found to be low in hyperuricemic group and the difference was highly significant.

Table 3: Correlation coefficients of demographic and clinical parameters with uric acid

Sr. No.	Parameter	R value
1	Age	+ 0.41
2	Duration of diabetes	- 0.56
3	SBP	+ 0.34
4	DBP	+ 0.21
5	Waist hip ratio (WHR)	+ 0.63
6	Body mass index (BMI)	+ 0.39
7	Blood glucose (mg / dl)	- 0.63

Table 3: Uric acid was positively correlated with age, SBP, DBP, BMI and WHR while it was negatively correlated with duration of diabetes and blood glucose levels. UA shows strongest positive correlation with WHR.

DISCUSSION

Uric acid (UA) is the end product of the purine metabolism in humans. UA is a physiological free radical scavenger and one of the major contributors of the plasma antioxidant capacity. But at increased concentrations, it can act as a prooxidant and may be a marker of oxidative stress. Thus, UA plays a dual role, both as a prooxidant and antioxidant depending on various mechanisms[3]. Hyperglycemia of T2DM may lead to generation of free radicals, impairs the endogenous antioxidant defense

system and also causes depletion of the local antioxidants including its effect on uric acid homeostasis[3]. In T2DM, uric acid level has significant value; hyperuricemia being associated with insulin-resistance syndrome, impaired glucose tolerance and an early onset of nephropathy, while hypouricemia is associated with nonadequate metabolic control, hyper filtration and a late onset of overt nephropathy[6]. But uric acid levels are influenced by a variety of demographic and clinical factors in normal as well as diabetic persons. Thus ultimate value of uric acid in T2DM warrants consideration of this complex interplay to arrive at a conclusion. The underlying mechanisms to justify our findings are discussed hereunder. Negative correlation of UA was observed with blood glucose and duration of diabetes. It may be possibly because of antiuricosuric effect of insulin on kidneys initially. But as the duration and severity of disease progresses, hyperglycemia leads to hyper filtration and uricosuria. At this stage the effect of insulin becomes minimal[6]. H. K. Choi, *et al* in their study of HbA1c, fasting glucose, C-peptide and insulin resistance in relation to serum uric acid levels, observed negative correlation of uric acid with blood glucose and duration of diabetes[2]. The study by Shabana S *et al* found negative relationship between uric acid levels with duration of diabetes and blood sugar (r= -0.60). They found this inverse relation because of coexistance of glycosuria with uricosuria. They also observed uric acid levels to be more in males than females; and found negative association between hypertension and uric acid in T2DM[3]. Since estrogen promotes uric acid excretion higher incidence of hyperuricemia is evident in men and postmenopausal women. It may also explain the rise of serum UA in diabetic patients with aging[6]. Accumulated visceral fat stimulates endogenous production of uric acid, leads to an increase in free fatty acids and tumor necrosis factor alpha (TNF-α), together with a decrease in adiponectin concentration, which leads to reduced renal excretion of uric acid[2]. Thus UA levels might rise with increasing BMI and WHR. In a study by Meisinger C *et al*, subjects with impaired glucose status/ diabetes were older, had a higher BMI, waist circumference, higher systolic blood pressure, higher alcohol intake and lack of physical activity than normoglycemic counterparts[4]. *Rodrigues S* and his colleagues, demonstrated strong association of uric acid with BMI, central obesity and hypertension in males and females. Waist circumference in both genders presented the strongest correlations with SUA[2]. According to some epidemiological studies, there exists strong genetic correlation of uric acid with other factors, such as gender, body mass index, waist circumference, blood pressure suggesting that the genes associated with uric acid level are also associated with these phenotypes[7]. According to study by Zoppini G and colleagues, higher serum uric acid levels may indirectly contribute to the increased CVD risk through a close association with established risk factors, such as older age, hypertension, dyslipidemia, poor glycemic control, and chronic kidney disease. Serum uric acid might confer an excess risk over and above the risk expected as a result of the underlying established risk factors[8]. Thus it may be wisely said that, focusing on relatively well known and established parameter like uric acid from a new angle may reflect diverse interplay of important but rather less emphasized clinicodemographic factors which must be taken into consideration before any causality is established. Although Cross sectional design of this study poses limitation, this study definitely has some strengths. Strict exclusion criteria being followed, the confounders are kept to minimum. Most possible detailed analysis of T2DM cases as regards to clinical and demographic profile along with its linkage with uric acid widens the presentation. Uric acid offers a simple, cost effective and widely available metabolic parameter with potential implications on public health. Adding more depth to this study including renal functions, oxidant- antioxidant status, as well as genetic influences along with uric acid and clinicodemographic factors in diabetics will thoroughly explore this extremely important but often underestimated spectrum of interactions.

CONCLUSION

From the present study it appears that, several factors seem to influence uric acid levels in T2DM. Rather than an independent entity, uric acid may have more importance as a connecting link between clinical, demographic and metabolic events taking place in a diabetic individual and thus a detailed workout is mandatory before precise causality is established. Strategies to improve people's awareness about the necessity to urgently modify eating habits, physical activity, avoidance of stress as well as addictions, mainly focusing on the pursuit of healthy lifestyle warrants great deal of attention in order to minimize subsequent morbidity and mortality.

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