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RESEARCH ARTICLE

A STUDY OF SERUM GLUCOSE IN RELATION TO SERUM URIC ACID IN PREDIABETES, TYPE 2 DIABETES MELLITUS PATIENTS AND NORMOGLYCAEMICS

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ABSTRACT

Background: Several epidemiologic studies have reported that high serum uric acid levels are strongly associated with prevalent health conditions such as obesity, insulin resistance, metabolic syndrome, essential hypertension and renal disease. There has been a growing interest in the association of hyperuricemia with hyperglycaemia. Thus, the study is conducted to investigate the association of serum uric acid with deterioration in glucose metabolism.

Objectives:

1) To measure Serum fasting blood glucose (FBG) and Serum Uric Acid in prediabetics, Type 2 Diabetes Mellitus patients and normoglycaemics.
2) To assess the correlation between Serum FBG and Serum Uric acid in the above patients.

Material and Methods: Case Control study of 30 prediabetics, 30 Type 2 DM patients of age group 20-85 years in Victoria Hospital, attached to Bangalore Medical College and Research Institute, Bangalore and 30 healthy individuals of same age group with no family history of Type 2 DM from general population. Data analysis was done by Pearson's Correlation analysis, Chi square test and Student's t test.

Results: Mean serum uric acid levels in prediabetics is 6.903±0.42mg/dl, Type II Diabetes Mellitus is 2.97±1.01mg/dl and in normoglycaemics is 3.5±0.54mg/dl respectively. There is a positive correlation of FBG and Uric acid in prediabetes and a negative correlation in type II DM and both are statistically significant ($p<0.00001$). In normoglycaemics, uric acid shows a positive correlation but statistically insignificant ($p=0.424$)

Conclusion: Fasting serum uric acid levels were higher in prediabetic population but lower in people with diabetes than in normoglycaemic people. Therefore uric acid may serve as the potential biomarker of deterioration in glucose metabolism.

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INTRODUCTION

Diabetes Mellitus refers to a group of common metabolic disorders that share the phenotype of hyperglycemia which is caused by complex interaction of genetics and environmental factors. DM occurs due to reduced insulin secretion, decreased glucose utilization and increased glucose production. (Alvin C Powers, 2015) Type 2 DM is a heterogeneous group of disorders characterised by variable degrees of insulin resistance, impaired insulin secretion and increased glucose production. Insulin, a hormone involved in the regulation of glucose metabolism is released by the beta cells of the Islets of Langerhans in the pancreas (Park, 2015) In India, DM prevalence ranges from 0.4 to 3.9% in rural areas and from 9.3 to 16.6% in urban areas. The prevalence of diabetes has been growing rapidly from 135 million in 1995 to an estimated 380 million cases in 2025 worldwide. Diabetes causes long term dysfunction of various organs. Age adjusted mortality rates among diabetics is 1.5 to 2.5 times higher than general population. Much of this mortality is due to cardiovascular disease. (Park, 2015) In humans and higher primates, uric acid is the final oxidation (breakdown) product of purine nucleotide metabolism. (Robert L. Wortmann *et al*., 2012) Serum urate levels vary with age and sex. (Robert L. Wortmann *et al*., 2012; Victor W Rodwell *et al*., 2009) In human body, about 70% of daily uric acid disposal occurs via the kidneys and remaining through intestines. (Robert L. Wortmann *et al*., 2012) Normal reference range of uric acid : (Robert L. Wortmann *et al*., 2012; Carl A Burtis *et al*., 2013)

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Children - 180 to 240 µmol/L (3.0 to 4.0 mg/dl).
Males - 208 to 428 µmol/L (3.5 to 7.2 mg/dl).
Females - 155 to 357 µmol/L (2.6 to 6.0 mg/dl).

Hence, this study was taken up to assess the relation between serum uric acid levels in prediabetes, diagnosed patients with Type 2 Diabetes Mellitus and its relation with fasting blood glucose.

MATERIALS AND METHODS

The study comprised of 90 subjects with 30 subjects of prediabetes, 30 diagnosed cases of Type 2 Diabetes Mellitus and 30 age and sex matched healthy controls. The 30 prediabetes were of age group 21-60 years, 30 diagnosed patients Type 2 DM who were of age group 35-83 years in Victoria Hospital, attached to Bangalore Medical College and Research Institute, Bangalore and 15 normoglycemics of age group 21-60 and 15 normoglycemics of age group 35-83years with no family history of Type 2 DM from general population. It was a case control study done at Victoria Hospital, attached to Bangalore Medical College and Research Institute, Bangalore. An informed oral and written consent was taken from all the study participants.

Inclusion criteria were diagnosed patients with Type 2 Diabetes Mellitus of age group 35-83 years, prediabetic both diagnosed as per American Diabetes Association (ADA) criteria and Age and sex matched healthy normoglycaemics as controls.

Exclusion criteria were as follows:

a. Smoking and alcoholism,
b. Patients with metabolic syndrome
c. Patients diagnosed with gout and other diseases leading to hyperuricemia or hypouricemia.
d. Patients with liver dysfunction.
e. Patients with renal dysfunction.
f. Patients with any other comorbid conditions.
g. Patients with neoplastic diseases and on its treatment.
h. Pregnant and lactating mothers

After obtaining written informed consent from the cases and controls, about 5 ml of fasting venous blood was obtained by venepuncture under aseptic conditions in a plain tube, centrifuged and separated serum was used for measuring fasting blood glucose and uric acid. Parameters was measured in BECKMAN COULTER AU480. Statistical analysis was done with SPSS software.

RESULTS

This study shows that serum uric acid level increased from controls to pre-diabetic subjects. The serum uric acid level further decreased in diabetic subjects. The confounding factors like age and number patients with other diseases and drug intake which can affect uric level were comparable in all the three groups. Mean age cases were 35.67 years and SD was +/- 9.8years and mean age of the controls were 39.8years with SD +/- 13.28 years shown in Table 1. Age distribution in the cases and controls studied-in diabetes in cases were 54.4+/-10.93 years and in controls were 57.87+/-15.14years with p= 0.192, not significant. Gender distribution in the cases and controls studied- in prediabetes is shown in table 2(a) and 2(b) with p is 0.4. (*not* significant). The gender distribution is shown in the Table 2. The mean value of FBG in prediabetic cases were 111+/- 8.4 mg/dl; and in controls were 86.6+/- 7.54 mg/dl while in the diabetic cases FBG was 190.3+/-56.9 mg/dl and in controls were 86.6+/-7.54mg/dl. The mean value of S.uric acid in the prediabetic cases were 6.86+/- 0.40 mg/dl; and in the controls were 3.6+/- 0.63mg/dl. In the prediabetes group there was a strong positive correlation of FBG with serum uric acid with r=6.9033; and p <0.00001 where as in the controls there was slight positive correlation of r= 0.2956 and p is 0.2847which is not significant. The mean value of S.uric acid in the diabetes group were 2.97+/- 1.01mg/dl and in controls were 3.41+/- 0.41mg/dl. In the diabetes group there was a strong negative correlation of FBG with serum uric acid (r=-0.8394; and p <0.0001) where as in the controls there was a slight positive correlation (r= 0.1517 and p is 0.423574 which is not significant) and are shown in the tables respectively.

Table 1(a), 1(b). Age distribution of cases and controls studied-in pre diabetes and diabetes

AGE DISTRIB	LS STUDIED-IN
AGE GROUP (IN YEARS)	TOTAL (45)
20-30	14 (31.1%)
31-40	16 (35.5%)
41-50	7 (15.5%)
51-60	8 (17.7%)

AGE DIST	CONTROLS
AGE GROUP (IN YEARS)	TOTAL (45)
31-40	6 (13.3%)
41-50	6 (13.3%)
51-60	16 (35.5%)
61-70	10 (22.2%)
71-80	2 (4.4%)
81-90	3 (6.6%)

Table 2(a), Table 2(b)-Gender distribution of the cases and controls studied- in Prediabetes and diabetes

GENDER DISTR	ROLS STUDIED-IN
GNDR	
MAL	
FMAL	
TAL	

GENDER DISTRIBUTION OF THE CA DIABE		IN
GENDER	CASES	
MALE	15	
FEMALE	15	
TOTAL	30	

COMPARISON OF MEANS OF FBG AND URIC ACID PRE-DIABETES-PEARSON'S CORRELATION ANALYSIS

SUBJECTS	NUMBER	FBG(mg/dl)	S.URIC ACID(mg/dl)
Cases	30	111+8.4	6.86+0.40
Control	15	86.6+7.54	3.6+0.63

PARAMETER IN CASES		Uric Acid
FBG	r score	6.9033 STRONG POSITIVE CORRELATION
	P value	<0.00001**

PARAMETER IN CONTROL		Uric Acid
FBG	r score	0.2956 SLIGHT POSITIVE CORRELATION
	P value	0.2847 NOT SIGNIFICANT AT P<0.05

COMPARISON OF MEANS OF FBG AND URIC ACID DIABETES-PEARSON'S CORRELATION ANALYSIS

SUBJECTS	NUMBER	FBG(mg/dl)	S.URIC ACID(mg/dl)
CASES	30	190.3+56.9	2.97+1.01
CONTROL	15	86.6+7.5	3.41+0.41

PARAMETER IN CASES		Uric Acid
FBG	r score	-0.8394 STRONG NEGATIVE CORRELATION
	P value	<0.0001**

PARAMETER IN CONTROL		Uric Acid
FBG	r score	0.1517 SLIGHT POSITIVE CORRELATION
	P value	0.423574 NOT SIGNIFICANT AT <0.05

DISCUSSION

Uric acid is a strong reducing agent (electron donors) and potent antioxidant. (Maxwell *et al*., 1997) Studies have shown association of serum uric acid with Diabetes mellitus, Cardiovascular disease, Hypertension, Vascular Stroke and Chronic Kidney Disease in various previous studies. (Stephen Waring *et al*., 2006) Recent studies have suggested that uric acid plays a role in cytokine secretion and has been identified as a mediator of endothelial dysfunction and systemic inflammation. (Kanellis and Kang, 2005) In humans, over half of the antioxidant capacity of blood plasma comes from uric acid which is the most abundant aqueous antioxidant, accounting for up to 60% of serum free radical scavenging capacity. Uric acid is an important intracellular free radical scavenger during metabolic stress. Serum uric acid concentrations are reduced in patients with type 1 diabetes and in regular smokers, which could increase susceptibility to oxidative damage and account for the excessive free radical production characteristically found in both groups of prediabetes and diabetes. (Hairong Nan *et al*., 2010) Hyperglycaemia induce both an oxidative stress (glucose autoxidation and advanced glycosylation end products (AGE) – ROS oxidation products) and a reductive stress through pseudo-hypoxia with the accumulation of NADH and NAD(P)H in the vascular intima. (Hayden and Tyagi, 2002; Williamson *et al*., 1999; Aronson and Rayfield, 2002) This redox stress consumes the natural occurring local antioxidants such as: SOD, GPX, and catalase. Once these local intimal antioxidants are depleted, uric acid can undergo the paradoxical antioxidant – prooxidant switch or the urate redox shuttle. (Santos *et al*., 1999; Abuja, 1999) Insulin activate the renin – angiotensin system with subsequent increase in Angiotensin II(Ang II). Ang II is the most potent endogenous inducer of NAD(P)H oxidase, increasing NAD(P)H, which increases vascular – intimal reactive oxygen species and superoxide (O_2-•). (Hayden and Tyagi, 2002; Griendling *et al*., 2000) Now in the background of the complex cellular environment of insulin resistance and hyperglycaemia which is associated with oxidative stress, antioxidant properties of uric acid might get converted to a pre-oxidant state owing to reactive oxygen species (ROS) accumulation. (Chien *et al*., 2008) This may also lead to adverse affects on endothelial function and a pro-inflammatory response, both of which are known to be associated with new onset of type 2 diabetes. (Hayden and Tyagi, 2004)

At the time of first clinical presentation, children and young adults have detectably low serum antioxidant defences and increased plasma oxidizability. Epidemiologic studies suggest that serum uric acid levels are heritable. (Hairong Nan *et al*., 2010) Genetic correlations between serum uric acid and other cardiovascular risk factors, such as body mass index, waist circumference, systolic BP, and pulse pressure, were identified, suggesting that the genes associated with uric acid level are also associated with these phenotypes. (Subrata D. Nath, *et al*., 2007) Measurement of uric acid is easy in terms of preanalytics, can be performed with simple methods in routine laboratories, and is inexpensive. Thus, a preventive, cost effective approach is available with potential implications for public health. (Editorial. Uric Acid, Type 2 Diabetes, and Cardiovascular Diseases: References :Fueling the Common Soil Hypothesis? 2008) Choi, *et al*. in their study of Haemoglobin A1c, fasting glucose, serum C-peptide and insulin resistance in relation to serum uric acid levels, observed that serum uric acid levels and the frequency of hyperuricemia increased with moderately increasing levels of HbA1c and FPG and then decreased with further increasing levels of HbA1c (a bell- shaped relation). (Choi and Ford, 2008) Hairong Nan, *et al*. in their study Serum uric acid, plasma glucose and diabetes showed that serum UA concentration increased with increasing FPG levels up to the FPG level of 7.0 mmol/l, but notably decreased when FPG over 7.0 mmol/l. An increasing trend in the UA concentration at the 2hPG and a decreasing trend at 2hPG ≥10.0 mmol/l was also observed. (Hairong Nan *et al*., 2010) Ohlson *et al*., showed that the baseline serum uric acid level has also been found to independently predict the 2hPG levels during 13.5 years follow-up in a Swedish male population. (Ohlson *et al*., 1988) A biological mechanism underlying the bell-shaped relation between blood glucose

levels and serum uric acid levels is thought to be due to the uricosuric effect of glycosuria, which occurs when the blood glucose level is greater than 180 mg/dl. Higher insulin levels are known to reduce renal excretion of urate. Insulin may enhance renal urate reabsorption via stimulation of the urate-anion exchanger URAT1 and/or the sodium-dependent anion cotransporter in brush border membranes of the renal proximal tubule. Many studies have reported that there is a positive association between high serum uric acid level and diabetes (Chien *et al*., 2008; Hayden and Tyagi, 2004; Thorand *et al*., 2006). Whereas other studies show no association (Barzilay *et al*., 2001) or inverse association (Choi and Ford, 2008; Editorial. Uric Acid, Type 2 Diabetes, and Cardiovascular Diseases: References:Fueling the Common Soil Hypothesis? 2008)

This study shows that the serum uric acid level was higher in pre-diabetes than in controls and lower in diabetes mellitus than pre-diabetes. The present study focuses on simple cost effective biochemical test like uric acid when used, can guide the deterioration in glucose metabolism instead of using complex tests for measurement of insulin resistance. Uric acid level can also guide as a marker of cardiovascular disease which is the commonest cause of mortality in diabetes mellitus. The limitations of the present study include being a hospital based study; a community based study would yield better information. The number of participants is small for subgroup analysis. The Uric acid level is subjected to vary based on other co morbidities.

Conclusion

The serum uric acid level was higher in pre-diabetes than in controls and lower in diabetes mellitus than in pre-diabetes. The uric acid may serve as a potential biomarker of deterioration of glucose metabolism.

No conflict of interest.

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