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RESEARCH ARTICLE

HbA1C IN RELATION TO SERUM URIC ACID IN NEWLY DIAGNOSED TYPE 2 DIABETES MELLITUS.

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ABSTRACT

Uric acid is a strong reducing agent (electron donors) and potent antioxidant. In humans, over half the antioxidant capacity of blood plasma comes from uric acid.6 Serum uric acid has been shown to be associated with Diabetes mellitus, cardiovascular disease, hypertension, vascular stroke and chronic kidney disease in previous studies. 7 Recent evidence suggest that uric acid plays a role in cytokine secretion and has been identified as a mediator of endothelial dysfunction and systemic inflammation.8Hyperglycemia 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.9-11 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.12,13Insulin activate the renin –angiotensin system with subsequent increase in Angiotensin II (ANG II). AngII is the most potent endogenous inducer of NAD(P)H oxidase, increasing NAD(P)H, which increases vascular –intimal reactive oxygen species and superoxide (O2-•).9,14Now 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.15This may also lead to adverse effects on endothelial function and a pro-inflammatory response, both of which are known to be associated with new onset of type 2 diabetes.16Many studies have reported that there is a positive association between high serum uric acid level and diabetes.15-17 whereas other studies show no association18 or inverse association.19,20Most of studies are on serum uric acid levels in already existing type 2 DM. Hence, this study was taken up to assess the relation between serum uric acid levels in newly diagnosed type 2 diabetes mellitus and its relation with glycemic index. The Case control study included 30 newly diagnosed type 2 DM patients of age group 30-65 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. Diabetic patients diagnosed as per American Diabetes Association criteria. Patients already on treatment for Diabetes mellitus, liver dysfunction, renal dysfunction, essential hypertension, neoplastic diseases and on its treatment and Pregnant and lactating mothers were excluded from the study. After obtaining written informed consent from the cases and controls, about 5 ml of fasting venous blood was obtained by venepuncture under aseptic conditions and divided into 2 parts, first part of blood was taken in a sterile EDTA tube and was used for measuring HbA1C and second 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. Chi-Square test. Pearson's Correlation analysis. Student's t test. Statistical Tests were used to interpret results. And p value < 0.05 was considered significant. AIMS AND OBJECTIVES of the study was to measure HbA1C and Serum Uric Acid in newly diagnosed type 2 Diabetes mellitus patients and to assess the correlation between HbA1C and Serum Uric acid in the above patients. Type 2 diabetes mellitus is a heterogeneous disease which is characterized by variable degrees of insulin resistance and increased glucose production.1Pathogenesis: There is rising blood sugar levels (hyperglycaemia) and a drop in the energy production. To compensate for the insulin resistance and to keep the blood glucose levels from spiralling out of control the pancreas tries to restore the balance by producing more insulin. If they are left unchecked, the cells become even more resistant to insulin, even as the pancreas secretes ever greater amounts of insulin, in a desperate attempt to bring the system back under control. This results in dangerously high blood levels of insulin (hyper-insulinaemia). If this is not corrected, the pancreas eventually becomes exhausted, resulting in diabetes. In the present study, it was observed that the serum uric acid level of cases was significantly higher than that of controls ($p<0.001$).It can be postulated that compensatory hyper-insulinaemia which occurs in the insulin resistant individuals may impose an anti-uricosuric effect on the kidneys. Insulin mediates renal urate reabsorption via stimulation of the urate-anion exchanger URAT1 and/or the sodium-dependent anion co-transporter in brush border membranes of the renal proximal tubule.2Thus, the clearance of uric acid gets reduced, with an increase in the insulin resistance.[16] Similar results were reported by Joseph B. Herman *et al*.[21] , T P Whitehead *et al*.[22] , Causevic *et al*.[23] In the present study, it was also observed that when a comparison was made between the serum uric acid and HbA1C, there was a positive correlation ($r= 0.4688$) which was statistically significant($p< 0.01$), which meant that there was an increase in the serum uric acid with an increase in HbA1C.This can be explained on the basis of the mechanisms with suggested association with Hyper-insulinaemia. It is through increased uric acid production. The increased flux of glucose-6-phosphate through the hexose monophosphate pathway shunt due to impairment of the glycolytic pathway, has been suggested as an explanation for the increased uric acid and NADPH formation in impaired glucose tolerance [2,21,24] and this may also include excess carbohydrates and an enhanced lipogenesis in the presence of excess insulin.25Similar findings were explained by HK Choi *et al*. [26] This case control study showed that serum uric acid is seen increased in newly diagnosed type 2 DM patients and suggests that HbA1C very much correlates with serum serum uric acid levels. Hence, simple cost effective biochemical parameter, uric acid can be used as a potential biomarker to guide the deterioration in glucose metabolism instead of using complex tests for measurement of insulin resistance, but community based study comprising large group of representatives is necessary to generalise uric acid as more specific tool in type 2 DM.

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INTRODUCTION

Uric acid is a strong reducing agent (electron donors) and potent antioxidant. In humans, over half the antioxidant capacity of blood plasma comes from uric acid.[6] Serum uric acid has been shown to be associated with Diabetes mellitus, cardiovascular disease, hypertension, vascular stroke and chronic kidney disease in previous studies.[7]Recent evidence suggest that uric acid plays a role in cytokine secretion and has been identified as a mediator of endothelial dysfunction and systemic inflammation.[8] Hyperglycemia induce both an oxidative stress(glucose autoxidation and advanced glycosylation endproducts (AGE) – ROS oxidation products) and a reductive stress through pseudo-hypoxia with the accumulation of NADH and NAD(P)H in the vascular intima.[9-11]

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.12,13Insulin activate the rennin –Angiotensin system with subsequent increase in Angiotensin II ($^{ANG\ II}$). AngII is the most potent endogenous inducer of NAD (P) H oxidase, increasing NAD(P)H, which increases vascular –intimal reactive oxygen species and superoxide (O2-•).[9,14]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.[15]This may also lead to adverse effects on endothelial function and a pro-inflammatory response, both of which are known to be associated with new onset of type 2 diabetes.[16] Chien *et al*[15], reported a positive association between plasma concentration of uric acid and the incidence of type 2 diabetes in Chinese individuals. The association was somewhat attenuated after adjustment for metabolic syndrome, suggesting that the association between hyper-uricemia and diabetes was partly mediated through the metabolic syndrome in particular insulin resistance. Many studies have reported that there is a positive association between high serum uric acid level and diabetes.[15-17] whereas other studies show no association[18] or inverse association.[19,20]Most of studies are on serum uric acid levels in already existing type 2 DM. Hence, this study was taken up to assess the relation between serum uric acid levels in newly diagnosed type 2 diabetes mellitus and its relation with glycemic index.

METHODOLOGY

The Case control study included 30 newly diagnosed type 2 DM patients of age group 30-65 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. Diabetic patients diagnosed as per American Diabetes Association criteria. Patients already on treatment for Diabetes mellitus, liver dysfunction, renal dysfunction, essential hypertension, neoplastic diseases and on its treatment and Pregnant and lactating mothers were excluded from the study.

After obtaining written informed consent from the cases and controls, about 5 ml of fasting venous blood was obtained by venepuncture under aseptic conditions and divided into 2 parts, first part of blood was taken in a sterile EDTA tube and was used for measuring HbA_{1C} and second 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.Chi-Square test. Pearson's Correlation analysis. Student's t test. Statistical Tests were used to interpret results. And p value < 0.05 was considered significant.

AIMS AND OBJECTIVES of the study was to measure HbA1C and Serum Uric Acid in newly diagnosed type 2 Diabetes mellitus patients and to assess the correlation between HbA1C and Serum Uric acid in the above patients.

RESULTS

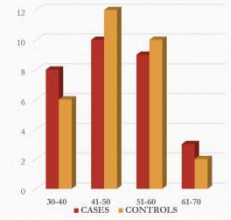
Age distribution in the cases and controls studied.

Table 1

Age group (in years)	Cases	Controls	Total
30-40	08(26.67%)	06(20%)	14(23.33 %)
41-50	10(33.33%)	12(40%)	22(66.67%)
51-60	09(30%)	10(33.33%)	19(31.67%)
61-70	03(10%)	02(6.67%)	5(8.33%)
TOTAL	30	30	60
Mean ± SD	49± 8.6	49.1±8.3	

P value: 1.00 not significant

Graph 1



Gender distribution in the cases and controls studied.

Table 2

Gender	Cases	Controls	Total
Male	21(70%)	20(66.67%)	41(68.33%)
Female	09(30%)	10(33.33%)	19(31.67%)
Total	30	30	60

P value: 0.78 ,chi square =0.077 not significant

Graph 2

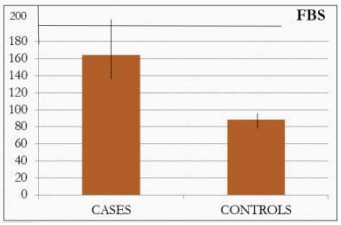
Comparison of Fasting blood sugar in two groups studied.

Table 3

Subjects	Total no.	Fasting blood sugar (mg/dl)	
		Range	Mean ± SD
Cases	30	127-273	164.1 ± 38
Controls	30	68-106	88.56 ± 9.2

P value: 0.0001** t score 10.58

Graph 3

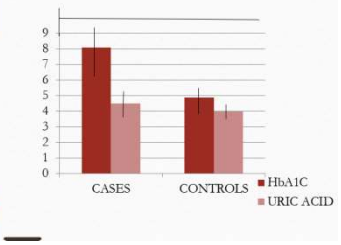


Comparison of means of HbA1C and Uric acid in two groups studied.

Table 4

Subjects	Total no.	Mean ± SD	
		HbA1C	Uric acid
Cases	30	8.1 ± 1.65	4.52 ± 0.69
Controls	30	4.94 ± 0.93	4.0 ± 0.5
t score		9.2538	3.3425
P value		0.0001**	0.0015**

Graph 4



Correlation between HbA1C and Uric acid in two groups studied.

Parameter		Uric Acid
HbA1C	r score	0.6488
	P value	0.000105**

Correlation between FBS and Uric acid in two groups studied.

Parameter		Uric Acid
FBS	r score	0.3912
	P value	0.032*

Parameter	Mean ± SD		Standard error		t score	P value
	CASES	CONTROLS	CASES	CONTROLS		
FBS	164.1 ± 38	88.56 ± 9.2	6.9378	1.6797	10.58	0.0001**
HbA1C	8.1 ± 1.65	4.94 ± 0.93	0.3012	0.1698	9.2538	0.0001**
Uric acid	4.52 ± 0.69	4.0 ± 0.5	0.1260	0.0913	3.3425	0.0015**

DISCUSSION AND CONCLUSION

Type 2 diabetes mellitus is a heterogeneous disease which is characterized by variable degrees of insulin resistance and increased glucose production.

[1]**Pathogenesis:** There is rising blood sugar levels (hyperglycaemia) and a drop in the energy production. To compensate for the insulin resistance and to keep the blood glucose levels from spiralling out of control the pancreas tries to restore the balance by producing more insulin. If they are left unchecked, the cells become even more resistant to insulin, even as the pancreas secretes ever greater amounts of insulin, in a desperate attempt to bring the system back under control. This results in dangerously high blood levels of insulin (hyper-insulinaemia). If this is not corrected, the pancreas eventually becomes exhausted, resulting in diabetes. In the present study, it was observed that the serum uric acid level of cases was significantly higher than that of controls ($p<0.001$).It can be postulated that compensatory hyper-insulinaemia which occurs in the insulin resistant individuals may impose an anti-uricosuric effect on the kidneys.Insulin mediates renal urate reabsorption via stimulation of the urate-anion exchanger URAT1 and/or the sodium-dependent anion co-transporter in brush border membranes of the renal proximal tubule.[2]Thus, the clearance of uric acid gets reduced, with an increase in the insulin resistance.[16]

Similar results were reported by Joseph B. Herman *et al*.[21] , T P Whitehead *et al*.[22] , Causevic *et al*.[23]In the present study, it was also observed that when a comparison was made between the serum uric acid and HbA1C, there was a positive correlation ($r= 0.4688$) which was statistically significant($p< 0.01$), which meant that there was an increase in the serum uric acid with an increase in HbA1C.This can be explained on the basis of the mechanisms with suggested association with Hyper-insulinaemia. It is through increased uric acid production. The increased flux of glucose-6-phosphate through the hexose monophosphate pathway shunt due to impairment of the glycolytic pathway, has been suggested as an explanation for the increased uric acid and NADPH formation in impaired glucose tolerance[2,21,24] and this may also include excess carbohydrates and an enhanced lipogenesis in the presence of excess insulin.[25]

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