Original Research Paper

Volume - 11 | Issue - 07 | July - 2021 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Biochemistry

SERUM URIC ACID LEVELS IN NEWLY DIAGNOSED CASES OF TYPE 2 DIABETES MELLITUS IN ASSAM: A CASE CONTROL STUDY

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ABSTRACT **INTRODUCTION:** T_2DM is a metabolic disorder characterized by hyperglycemia with disturbances of carbohydrate, fats and protein metabolism. Hyperuricaemia has often been associated with diabetes mellitus. **METHOD:** 100 patients with T_2DM diagnosed according to ADA guidelines and 100 age sex matched normal healthy individuals as controls were selected. Serum Uric acid and Fasting blood sugar levels were measured and the results were analyzed statistically **RESULTS:** Statistical analysis of the results shows significant increase in Serum Uric acid in the cases ($P<0.001$) **CONCLUSION:** the mean Serum Uric acid level was found to be significantly higher in newly diagnosed cases of T_2DM

KEYWORDS : Type 2 Diabetes Mellitus, uric acid, hyperuricaemia

INTRODUCTION:

Diabetes mellitus comprises of a group of chronic metabolic disorders involving the principal metabolic fuels, carbohydrate, fats as well as proteins. The disorder results from absolute or relative deficiency of insulin secretion often associated with defect in insulin action. Diabetes is due to either pancreas not producing enough insulin or the cells of the body not responding properly to the insulin produced.[1]

India is the second most populous country in the world and in terms of numbers of people with diabetes, with an estimated 69.2 million affected in 2015, a figure that is projected to rise to 123.5 million by 2040.[2] with the increasing consumption of high energy food, increased adoption of sedentary lifestyle and urbanization, increasing numbers of individuals are developing T_2DM and the age at which individuals are being diagnosed is decreasing. If left untreated complications such as diabetic ketoacidosis, hyperosmolar hyperglycemic non ketotic state or death may occur.[3] various microvascular complications such as diabetic retinopathy, neuropathy and nephropathy are often seen at the time of the diagnosis

Uric acid in serum is the metabolic end product of the purine nucleotide and its overproduction and decreased excretion through the kidneys lead to hyperuricaemia in humans [4,5]. It is generated in the liver. Purine nucleotides decompose to hypoxanthine and guanine, some of which can be recycled and phosphorylated into hypoxanthine nucleotides, while the remaining part is metabolized by xanthine dehydrogenase/oxidase (XDH/XO) enzymatic reaction to the terminal product uric acid[29]. The circulating uric acid is easily filtered from the glomeruli into the renal tubule. About 90% of filtered UA is reabsorbed by the middle of the proximal convoluted tubule mainly by urate transporter1 (URAT1) and glucose transporter 9 (GLUT9)[30], and the remaining excreted 10% is responsible for 60–70% of total body uric acid excretion [12,13]. Changes in the uric acid content in body fluids can reflect the state of metabolism, immunity, and other functions of the human body. Hyperuricaemia was defined as the circulating uric acid levels of more than 5.7 mg/dl for women and more than 7.0 mg/dl for men[31]. When the blood uric acid concentration exceeds the norm, the human body fluid becomes acidic; this affects the normal function of the human cells, subsequently leading to metabolic disease in the long term[32,33,34]. UA directly inhibits the trigger of insulin signaling pathway by an ectonucleotide pyrophosphatase/ phosphodiesterase-1 (ENPP1) recruitment at the receptor level[29]. High Uric acid concentration in blood can lead to gout and are associated with several medical conditions including metabolic syndrome, cardiovascular diseases, diabetes and renal dysfunction[4,6,7]. However there is still a controversy about the association between serum Uric acid and diabetes.

Previously some studies reported a positive association between elevated serum Uric acid and diabetes.[8,9,10,11] whereas other studies reported no inverse correlation [12,13] or an inverse relationship [14,15] A metanalysis reported an association between serum Uric acid and increased risk of developing T_2DM[11,12]. A prospective study indicated that diabetes is related to a lower risk of gout development in the UK general population (21). As there are no studies about serum Uric acid in relation to fasting blood glucose level, so we aimed to do a comparative study on the levels of serum Uric acid in diabetic patients and healthy subjects in a tertiary care hospital of Assam

AIMS AND OBJECTIVE:

1. To estimate the levels of serum glucose and Uric acid in patients of T_2DM and healthy subjects
2. To compare the levels of serum glucose and Uric acid in both the above groups

STUDY DESIGN:

The study is a hospital based case control study conducted in Central Clinical Laboratory (Biochemistry) department in collaboration with the department of Endocrinology, Gauhati Medical College, Guwahati.

STUDY POPULATION:

The subjects were divided into 2 groups
a) Cases: patients diagnosed with T_2DM
b) Controls: normal healthy individuals with normal BMI, no hypertension, no history of impaired blood sugar, renal failure or any other endocrine disorder.

SAMPLE SIZE:

200 Samples were taken out of which 100 were cases and 100 controls

STUDY DURATION:

1 (one) **year**

INCLUSION CRITERIA:

Criteria for newly diagnosed T_2DM:
As per the ADA guidelines, patients are diagnosed with T_2DM according to the following criteria within 3months of presentation to the hospital OPD.

- Symptoms of diabetes plus Random blood glucose ≥11.1 mmol/L (200mg/dl)
- Fasting blood glucose ≥ 7.0 mmol/L (126mg/dl)
- Two-hour plasma glucose ≥11.1 mmol/L (200mg/dl)
- $HbA_{1C} > 6.5$

EXCLUSION CRITERIA:

i. Severe depression or psychotic cases
ii. Head trauma
iii. Renal failure
iv. Rickets
v. Gout

vi. Osteomalacia
vii. Patients on medications which interfere with uric acid excretion

METHODS:

With all aseptic and antiseptic measures 5 ml whole blood is to be drawn from the median cubital vein and centrifuged in a centrifuge machine for 5 minutes at the rate of 3000 rpm.Then the serum is taken for analysis of serum uric acid and serum plasma glucose by micro slide using photometry, both in vitreos 5600.

STATISTICALANALYSIS:

The results were expressed as mean ± SD. The data analysis is carried out using student "t" test (θ). The Parameters between normal healthy subjects (controls) and T_2DM patients (cases) is compared. A 'P' value<0.05, P<0.01 and P<0.001 are considered statistically significant.Data are analyzed with the help of Minitab-19 and in MS-excel.

RESULTS:

Figure 1: Frequency Distribution Curve Of Fpg In Diabetic Patient (case)

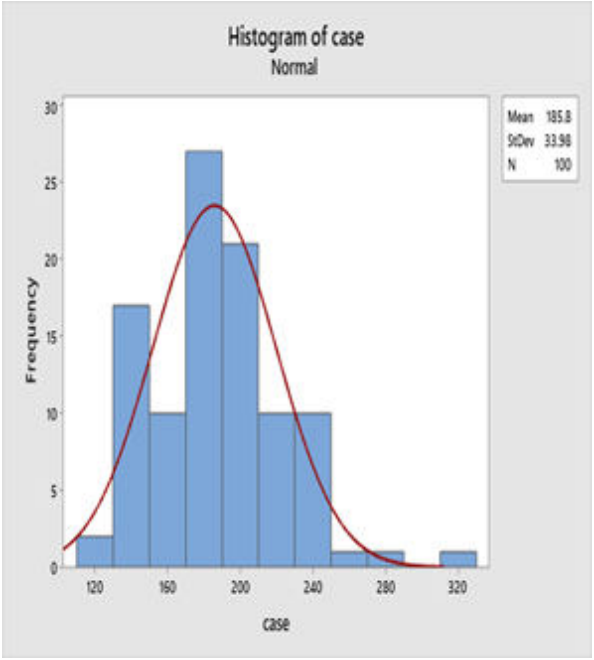


Figure 2: Frequency Distribution Curve Of Fpg In Healthy Individual (control)

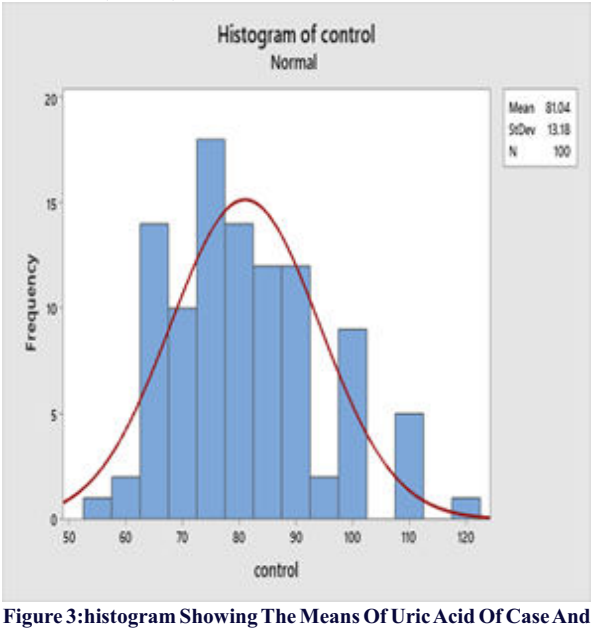


Figure 3:histogram Showing The Means Of Uric Acid Of Case And Control Group

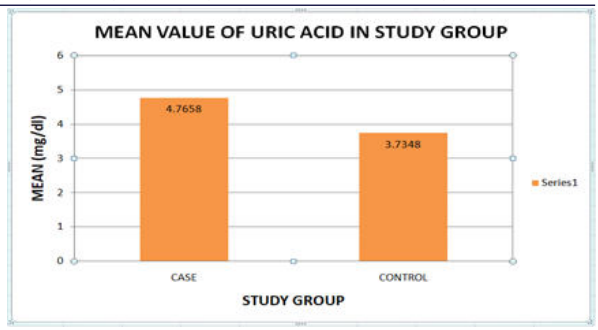


Figure 4: Frequency Distribution Curve Of Uric Acid In Case And Control

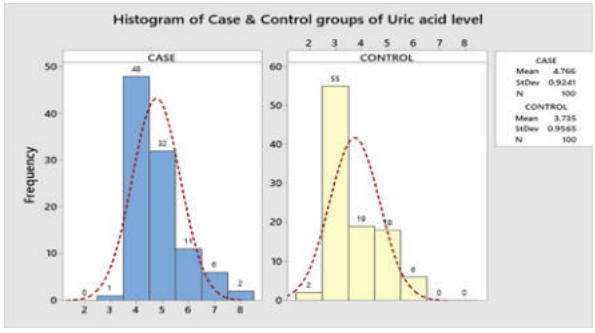


Table 1: Statistical Analysis Of Fpg, Sua And Hba_{1c}

	FPG		SUA		HBA1C	
	Normal	Case	Normal	Case	Normal	Case
Mean+/-SD	81.04+/-13.18	185.78+/-33.98	4.95+/-0.59	8.39+/-1.0	3.73+/-0.96	4.77+/-0.92
Median	78	185	4.9	8.4	3.41	3.41
SE	1.32	3.40	0.06	0.1	0.10	0.09
Min-Max	56-120	123-310	3.8-6.2	6.4-10.2	2.3-6.4	3.4-7.6
variance	173.65	1154.96	0.343	1.0	0.92	0.854
Coefficient variance	16.26	18.29	0.339	0.991	0.906	0.845

TABLE 2: P and t value when compared with normal healthy subjects

Patients with type2 diabetes mellitus		FPG	SUA	HBA1C
	P value	<0.0001	<0.0001	<0.0001
	t value	28.74	29.61	7.71

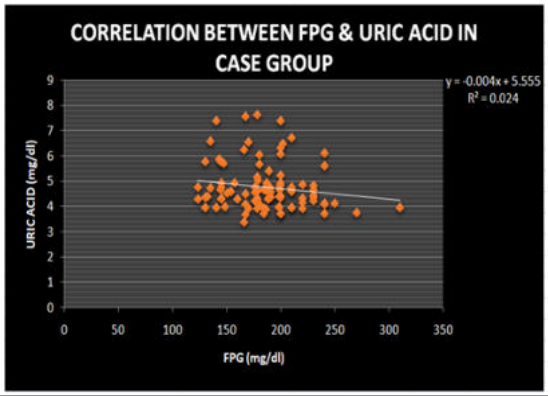
TABLE 3: Gender variation among the healthy subjects and diabetic cases

Total	Case (100)		Control(100)	
	Male	Female	Male	Female
200	46	54	76	24

Table 4:correlation Of Fpg With Uric Acid

R value(Pearson)	-0.153
t value	53.24
P value	<0.0001

FIGURE 6:



As can be seen from the above, R- value is -0.1563, t-Value is 53.24, and p-Value is <0.0001, there is a weak negative linear correlation between FPG & serum Uric acid in type 2 diabetes mellitus.

DISCUSSION:

In this study, the plasma fasting glucose level is seen to increase in the case group consisting of diabetes mellitus patients when compared to the healthy subjects. The mean value +/- SD of FPG in diabetic patients is 185.78 +/- 33.98 with a coefficient variance of 18.29. It is highly significant P0.0001 and t value is 28.74. This occurs as we have taken diabetic patients confirmed by the HbA_{1C}. This might be due to the continuum of clinical scenarios ranging from severe insulin resistance (IR) with relative insulin deficiency to severe insulin deficiency with some degree of insulin resistance (IR) according to American diabetic association (ADA). Both IR and insulin secretary defect are essential for T2DM to develop. The homeostasis of glucose metabolism is carried out by 2 signaling cascades: insulin mediated glucose uptake (IMGU) and glucose stimulated insulin secretion (GSIS). The IMGU cascade allows insulin to increase the uptake of glucose from skeletal muscle and adipose tissues as well as suppress glucose generation by hepatic cells. In the liver insulin affects glycogen metabolism by stimulation of glycogen synthesis. Insulin also increases expression of some lipogenic enzymes and this is due to glucose stored as a lipid within adipocytes. Thus an increase in fatty acid generation will increase glucose uptake by the cells.

In this study the serum uric acid (SUA) level is seen to increase in the case group consisting of patients having Diabetes mellitus when compared to the healthy control subjects. The mean value +/- SD of SUA in the case group is 4.77+/- 0.924 with a coefficient variance of 0.845. It is highly significant P□0.0001 and t value is 7.75. Tirkey et al reported mean serum Uric acid in prediabetic (n=12) ie 4.88+/-0.79 was more than control (n=34) ie 3.84+/-0.88 and was statistically significant [18] which supported our study. Hasmi N et al reported that elevated serum uric acid level in prediabetic is statistically significant with mean serum uric acid of cases was 5.31+/-0.87 which was more than the control having mean 3.84+/-0.63. It was found to be statistically significant (p□0.0001). Serum uric acid levels effect insulin resistance and show a significant correlation with risk factors for metabolic syndrome (high BMI, blood pressure, fasting blood glucose and triglyceride levels) and low HDL cholesterol values [19]. Excessive uric acid will lead to an increase in reactive oxygen species (ROS) production which leads to inflammation and dysfunction in the vessels. SUA mediated oxidative stress induced lipid peroxidation; DNA damage and activation of inflammatory factors finally lead to cellular damage [(20)] Oxidative stress can affect the expression of insulin gene causing a decrease in insulin secretion [21]. SUA directly inhibits signaling pathway by an ectonuclear pyrophosphate phosphodiesterase-1 (ENPP1) recruitment at the receptor level[24] All these interfere with glucose homeostasis and insulin sensitivity promotes development of diabetes.[22,23]. T Murali Venkateswar Rao et al 2016[25] conducted an analytical cross sectional study with 70 cases of T2DM and 30 healthy subjects and found that mean SUA of cases was 4.30 +/- 0.7 in diabetic patient (2 to 4 yrs.) mean +/-SD is 4.57+/-1.01 in diabetic patients (5 to 8 yrs.) and mean+/-SD was 6.47+/-1.07 in diabetic patient (9 to 12 yrs.) This suggests that the association of diabetes and serum uric acid level was statistically significant. Anju Gill et al.2013 [26] conducted a case control with 50 cases and 50 controls and found that parameters FPG, SUA and HbA1c levels raised in diabetic patients when compared to healthy individuals. This supported our study. Grover et al [27] conducted a study in 50 newly diagnosed T2DM patient and found that hyperuricaemia was seen >7mg/dl (male) and >6mg/dl (female) was present in 64% of patients. Shani et al found that the women who had normal uric acid level had an increased level of uric acid in newly diagnosed diabetic patients when compared with the women having low normal uric acid level[35]. This supported our study as expressed in Table 4. If elevated serum uric acid levels plays casual role in T2DM, serum uric acid levels might also indirectly affect the prevalence of diabetic complications. Moreover, high serum uric acid levels were shown to predict metabolic syndrome in a Japanese cohort. A link between serum uric acid levels and insulin resistance has repeatedly been shown and uric acid itself reportedly plays an important role in the exacerbation of insulin resistance[28]

CONCLUSION

From this study we have found that there is increase in the serum uric acid level in diagnosed cases of diabetics confirmed by HbA_{1C} when we compared with normal healthy subjects. a more elaborate study with longer duration would have been desirable to precisely establish the role of uric acid in diagnosing the early complications of type2 Diabetes Mellitus.

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