Original Article

A Study to find out the Association and Correlation between the Serum Uric Acid Levels with the Patients having Impaired Glucose Tolerance

Bapilal Bala[1], Pradip Kumar Chowdhury[2], Ujjwal Kumar Roy[3], Aneek Ghosh[4]

Background : The Impaired Glucose Tolerance (IGT) is a pre-diabetic condition having high risk of developing T2DM. Hence, the most important measures to prevent development of T2DM are to target the subjects with IGT. In Metabolic Syndrome the Insulin resistance as well as Hyperinsulinemia are associated with Hyperuricemia[1,2]. Furthermore, the risk of progression to type 2 diabetes are increased in presence of Hyperuricemia in patients having an IGT[3-5]. Hence, we have designed our study to detect any association and congruence between the Uric acid level and the patients having IGT.

Materials and Methods : A cross-sectional cum observational study was carried out involving the 151 individuals of >40 years but <80 years. The patients with Glucose level 140 to 199 mg/dl after 2 hours of 75 g oral Glucose was considered as IGT. The control groups having Glucose level <140 mg/dl. The patients with overt Diabetes Mellitus, altered serum Uric acid level, taking any drugs that may lead to altered Uric acid metabolism, Renal disease, Chronic liver disease, Heart failure and carcinoma were excluded from this study.

Results and analysis : The mean value of Uric acid of persons with normal GTT was 4.57 mg/dL and standard deviation was 0.528; whereas IGT groups had mean Uric acid level 7.01 mg/dL with standard deviation of 1.194. The value of serum Uric acid >5.15 mg/dL might predict impaired Glucose tolerance with the sensitivity 82.7% and specificity 89%. The area under the curve revealed a value of 0.915 and the 95% confidence interval was in between 0.859 and 0.970. The details of statistical analysis revealed the statistically significant correlation (*p value<0.001*) between the serum Uric acid levels and Glucose tolerance.

Conclusion : The IGT population those may turn into overt diabetes can be predicted by their increasing serum Uric acid concentration. Thus early recognition of IGT population by a simple measurement of uric acid in serum can help to undertake the preventive measures of the development to overt diabetes.

[*J Indian Med Assoc* 2021; **119(12):** 40-4]

As Impaired Glucose Tolerance (IGT) is a pre-diabetic condition, so it may be used to identify people at high risk of developing Diabetes Mellitus. Now it has been well recognized that IGT is a noticeable primary stage in the natural course of Type 2 Diabetes Mellitus (T2DM) which carries a significant risk of producing cardiovascular disease and mortality[6,7]. There are increasing evidence proving that diabetes can be prevented or halted by modifications of lifestyle or using anti-diabetic drugs. Therefore, majority of the preventive

> **Editor's Comment :**
> - A statistically significant correlation found between serum uric acid levels and impaired glucose tolerance.
> - A simple test like estimation of serum uric acid may predict the person having IGT.
> - Thus early recognition of IGT population can help to undertake the preventive measures of the development to overt diabetes mellitus.

measures targets the population with Impaired Glucose Tolerance[8,9]. Now American Diabetic Association (ADA) recommends screening for IGT among population of ≥45 years of age especially those with overweight or obese. The IGT remains unrecognized in many subjects in the field of clinical practice after the revised diagnostic criteria for diabetes ascertained by ADA and World Health Organization (WHO)[10].

Impaired Insulin secretion as well as its resistance can lead to Glucose intolerance, and finally give rise to Diabetes Mellitus. But, which defect originate first and which relates IGT with various alterations in Glucose Homeostasis is still remains unclear[11]. The

---

[1]MD (Gen Medicine), Associate Professor, Department of General Medicine, Maharaja Jitendra Narayan Government Medical College and Hospital, Cooch Behar 736101

[2]MD (Gen Medicine), Assistant Professor, Department of General Medicine, Diamond Harbour Government Medical College, Diamond Harbour, South 24 Parganas 743331 and Corresponding Author

[3]MD (Gen Medicine), Specialist Medical Officer (General Medicine), Islampur Sub-divisional Hospital, Uttar Dinajpur 733202

[4]MBBS, Resident Medical Officer, Department of Critical Care Medicine, Rabindranath Tagore International Institute of Cardiac Sciences, Mukundapur, Kolkata 700099

subjects with IGT shows Hyperinsulinemia and or increasing Insulin resistance or may have defective insulin secretion in response to Glucose load[12]. The "Insulin Resistance" denotes the impaired biochemical response to exogenously administered or endogenously secreted Insulin. It is manifested by impaired Insulin mediated transport and metabolism of Glucose in Liver, Adipose Tissue, and Skeletal Muscle[13]. The insulin resistance plays a major role in the development of IGT and Diabetes Mellitus. It is present for years before the onset of diabetes. So, IGT is the pre-diabetic condition in asymptomatic patient who may have Insulin resistance. There are several biochemical markers including Uric acid, which have consistent correlation with IGT. When there is derangement of Glucose Metabolism, there is alteration of blood Uric acid level also. So, in the reverse way, when elevated Blood Uric acid level is found in biochemical report, it can be predicted that there might be presence of impairment of glucose tolerance. Uric acid is the end product of the purine metabolism. A positive association was well observed between elevated serum Uric acid levels and the development of Type 2 Diabetes Mellitus (T2DM)[5,14,15]. Moreover, the individuals with Impaired Glucose Tolerance having elevated serum uric acid level was shown more risk of developing T2DM[11,16,18].

The Uric acid can play a role of pro-oxidant; hence it may be used both as a marker of oxidative stress as well as an antioxidant therapeutically[19]. The soluble form of Uric acid, Urate can chelate the transition metals and can scavenge both the superoxide as well as the Hydroxyl Radicals[20]. Hyperuricemia is associated with Insulin resistance and or hyperinsulinemia in the Metabolic Syndrome[21]. While some studies clearly demonstrated an elevated Serum Uric acid levels in Pre-diabetes and Diabetes mellitus patients, some other studies have shown a declining trend of the serum uric acid levels with increasing blood glucose concentration[22-24]. However, in a recently conducted meta-analysis including eleven studies, the elevated Serum Uric Acid level was closely associated with a higher risk of developing Diabetes Mellitus[3,25,26]. In addition, Hyperinsulinemia, Owing to insulin resistance in patients with metabolic syndrome, can increase serum uric acid levels by decreasing urinary excretion of Uric acid as well as accumulating the substrates for Uric acid production[11,22].

Therefore, this study was designed to find out any association and or correlation of serum Uric acid level with IGT, considering the relevant clinical, biochemical and the anthropometric data.

MATERIALS AND METHODS

A hospital based cross-sectional observational study was carried out in Medical College & Hospital, Kolkata from 01/02/ 2012 to 31/07/2012. The 151 patients of >40 years but <80 years were selected from Outpatient department of General Medicine and Diabetic Clinic after detailed history and clinical examination. The patients having blood Glucose level between 140 mg/dl and 199 mg/dl after two hours of a 75 g oral Glucose challenge were only included in this study. The control population group was considered having no Impaired Glucose Tolerance. The patients with overt Diabetes Mellitus, having altered serum Uric acid level, taking any drugs that may lead to altered Uric acid metabolism, Renal disease, Chronic liver disease, Heart failure, Carcinoma etc were excluded from this study. About 2.5 ml whole blood was collected in sodium fluoride containing vial for estimation of blood glucose concentration by Hexokinase Method and about 3.5 ml clotted blood was used for determination of serum uric acid level by Trinder reaction (Enzymatic, Uricase PAP) method. The entire biochemical tests and other relevant routine investigations were performed in the Department of Biochemistry of this College. The statistical analysis was done applying standard statistical methods with the help of SPSS, EPI INFO and assuming a null hypothesis.

ANALYSIS AND RESULTS

Among the 151 study subjects, 55% (83 persons) were male and 45% (68 persons) were female. About 65.6% (N =99) subjects have shown normal OGTT, whereas impaired OGTT (IGT) were observed in 34.4% (N= 52) of the study subjects. The 51.5% (n = 51) of subjects were contributed by male and 48.5% (n = 48) by female among the subjects having normal Glucose Tolerance Test (n= 99). In contrast, among the IGT group (n = 52) the male subjects were significantly more in number; ie, 61.5% (n = 32) compared to female subjects which is 38.5% (n = 20). In age group 41- 50 years IGT found in 43.8 %, in 51-60 years it was 30.3 %, in 61-70 years it was 58.3 % and in the age group 71-80 years IGT was found in 16.7% among male subjects. On the other hand in female subjects in age group 41-50 years IGT found in 26.5 %. In age group 51-60 years it was 30%, in age group 61-70 years it was 40% and in 71-80 years it was 25 %. The more number of IGT cases were found in lower age groups (ages between 41 and 60 years) whereas less cases were found in higher age group (ages between 71 and 80 years) among subjects having IGT(n = 52)(Table 1).

The mean value of Uric acid of persons with normal GTT was 4.57 mg/dl and standard deviation was 0.528 and IGT groups showed mean Uric acid level 7.01 mg/dl and standard deviation of 1.194 (Tables 2 & 3).

Serum Uric acid level $\geq$5.15 mg/dl may predict Impaired Glucose Tolerance with sensitivity 82.7% and specificity 89%. AUC = 0.915 with 95% confidence interval is in between 0.859 -0.970 (Vide ROC curve and Table 4).

The Tables 5 & 6 with descriptive statistics of serum Uric acid and GTT shows significant co-relation between Uric acid and GTT. p value is <0.001 with a correlation of 0.847.
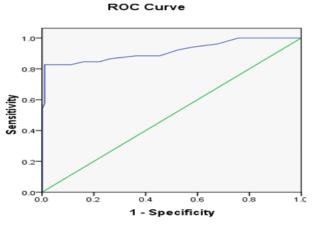
DISCUSSION

Though diabetes is a global epidemic disease but with modern therapy the management of diabetes is very effective and increases the life span of diabetic patients. Thus it can actually increase the morbidity and obviously the cost of therapy. Hence, prevention of diabetes is always desirable. Pre-diabetic patient shows insulin resistance as well as glucose intolerance[1]. Therefore patient with pre-diabetic state should be diagnosed earlier for taking preventive measures. There are several costly investigations like serum Insulin assay available for uses. In day to day practice, we need to look for some cost effective investigations. The oral glucose tolerance test and the serum uric acid level estimation are essay to perform

Table 1 — Sex and age-wise distribution of the normal and IGT group among the study population

Total Patients n = 151		OGTT		Total
		Normal	IGT	
Age (years) :				
41 – 50	Number	18	14	32
	Percentage	56.3%	43.8%	100%
51 – 60	Number	23	10	33
	Percentage	69.7%	30.3%	100%
Male (Total n = 83) :				
61 – 70	Number	5	7	12
	Percentage	41.7%	58.3%	100%
71 – 80	Number	5	1	6
	Percentage	83.3%	16.7%	100%
Total	Number	51	32	83
	Percentage	61.4%	38.6%	100%
Female (Total n = 68) :				
41 – 50	Number	25	9	34
	Percentage	73.5%	26.5%	100%
51 – 60	Number	14	6	20
	Percentage	70%	30%	100%
61 – 70	Number	6	4	10
	Percentage	60%	40%	100%
71 – 80	Number	3	1	4
	Percentage	75%	25%	100%
Total	Number	48	20	68
	Percentage	70.6%	29.4%	100%

Table 2 — Age and sex wise distribution of mean uric acid level (mg/dL) among normal and IGT population

Normal Glucose Tolerance		Impaired Glucose Tolerance (IGT)	
Age Group	Mean uric acid level	Age Group	Mean uric acid level
Male (Total n =51)		**Male (Total n = 32)**	
41 - 50	4.63	41 - 50	6.62
51 – 60	4.54	51 – 60	7.13
61 – 70	4.56	61 – 70	7.89
71 +	4.44	71 +	7.60
Total	4.56	Total	7.09
Female (Total n = 48)		**Female (Total n = 20)**	
41 - 50	4.61	41 - 50	7.09
51 – 60	4.56	51 – 60	6.93
61 – 70	4.62	61 – 70	6.32
71 +	4.43	71 +	6.90
Total	4.59	Total	6.88
All Sex (Total n = 99)		**All Sex (Total n = 52)**	
41 - 50	4.62	41 - 50	6.80
51 – 60	4.55	51 – 60	7.06
61 – 70	4.59	61 – 70	7.32
71 +	4.44	71 +	7.25
Total	4.57	Total	7.01

Table 3 — Mean uric acid level (mg/dL) in persons with normal and impaired GTT

OGTT	Mean	Number	Std. deviation
Normal	4.57	99	0.528
Impaired (IGT)	7.01	52	1.194
Total	5.41	151	1.419

OGTT – Oral glucose tolerance test, IGTT – Impaired glucose tolerance test, GTT – Glucose tolerance test

and are less costly. Whether there is any relationship present in between them is a matter of interest to clinical investigators. According to published literature the serum uric acid level is increased in patients with IGT. For this reason several prospective and cross-sectional studies have been or being performed over this matter[9,16,23].

ROC Curve

Diagonal segments are produced by ties.

Table 4 — Area under the curve (AUC) : Test result variables – Uric acid				
Area	Std. error	Asymptomatic Significance	Asymptomatic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.915	0.028	0.000	0.859	0.970

Table 5 — Correlation of uric acid and GTT			
Correlations		Uric acid	GTT
Uric acid	Pearson Correlation	1	0.847**
	Sig. (2-Tailed)		0.000
	Number	151	151
GTT	Pearson Correlation	0.847**	1
	Sig. (2-Tailed)	0.000	
	Number	151	151
**Correlation is 0.01 (2-Tailed) and it is significant.			

Table 6 — Correlation between serum uric acid level and GTT			
	Mean	Standard deviation	Number
Uric acid level	5.41	1.419	151
GTT	135.75	25.948	151

In our study, out of 151 study subjects IGT subjects were 52 in which 32 were male and 20 were female. Among the total study population, only 6.6% people had age in between 71-80 years. The majority of the study population (43.7%) had age in between 41-50 years, and 35% and 14.6% people were of age group between 51-60 years and 61 – 70 years respectively. 34.4% subjects had Impaired Glucose Tolerance test (IGTT). Among the person with IGT 44% subjects had age in between 41-50 years and 51% in between 51-70 years. Person with IGT were mostly male (61.5%) in this study population. But if we consider the age distribution of subjects with IGTT; there were no significant difference in IGT cases between male and female in the age group of 51-70 years (88.6% male *versus* 70% female). But in the age group of 71-80 years, the significant number of subjects with IGT were female (25% *versus* 16.7%). Serum Uric acid had been measured in all study population. The mean uric acid level was 5.41 mg/dl with a Standard Deviation (SD) of 1.419. In the subjects with normal Glucose Tolerance Test, the mean serum uric acid level was 4.57 mg/dl with a SD of 0.528, whereas in the subjects with IGT the mean serum Uric acid level was 7.01 mg/dl with a SD of 1.194. Therefore, in our study there was no significant sex and age specification of increased serum Uric acid level and IGT but with this statistical analysis it was found that there was a significant correlation in between elevated serum Uric acid level and IGT (r = 0.847), P value <0.001. It was also observed that the serum uric acid level $\geq$5.15 mg/dl had 82.7% sensitivity and 89% specificity rate to predict the presence of IGT.

The results of our study were similar with results of other studies of same interest conducted across the world. In many populations it was shown that this association is more in female population[27-29].

CONCLUSSION

In this study, both the male and female subjects were included having different age groups with no such variations found; and in all age groups of both sexes there were linear relationships between the serum uric acid level and IGT. As only two important variables (IGT and Uric acid) were included in this study, so different association were not observed but an obvious correlation was found between IGT and Serum Uric acid level. By excluding other modifiable factors (which may alter the results of the variables) it is concluded that elevated serum uric acid level is associated with almost all Impaired Glucose Tolerance persons. So a simple test like Serum Uric acid level may predict the person having IGT, that in near or distant future may turn it to overt diabetes.

Limitations :

Some noticeable limitations of this study were – the patients with Diabetes Mellitus were excluded, Serum Insulin Estimation was not done, small sized study population, the constant time limit, and different variables were excluded owing to limitations of funds. In the future a large population based prospective long term follow up study with different variables may be conducted to overcome such limitations.

Conflict of Interest : None.

REFERENCES

1 Krishnan E, Pandya BJ, Chung L, Hariri A, Dabbous O — Hyperuricemia in young adults and risk of insulin resistance, prediabetes, and diabetes: A 15-year follow-up study. *Am J Epidemiol* 2012; **176(2):** 108-16.

2 Modan M, Halkin H, Karasik A, Lusky A— Elevated serum uric acid-a facet of hyperinsulinaemia. *Diabetologia* 1987; **30(9):** 713-8.

3 Whitehead TP, Junger I, Robinson D, Kolar W, Pearl A, Hal A— Serum urate, Serum glucose and Diabetes. Ann Clin Biochem. 1992; **29:** 159-61.

4 Hairong N, Zengchang P, Shaojie W — Serum uric acid, plasma glucose and diabetes. *Diab Vasc Dis Res* 2010; **7(1):** 40-6.

5 Cook DG, Shaper AG, Thelle DS, Whitehead TP— Serum uric acid, serum glucose and diabetes: relationships in a population study. *Postgrad Med J* 1986; **62:** 1001-6.

6   Agamah ES, Srinivasan SR, Webber LS, Berenson GS — Serum uric acid and its relation to cardiovascular disease risk factors in children and young adults from a biracial community: The Bogalusa Heart Study. *J Lab Clin Med* 1991, **118:** 241-9.

7   Bhole V, Choi JW, Kim SW, de Vera M, Choi H— Serum uric acid levels and the risk of type 2 diabetes: A prospective study. *Am J Med* 2010; **123(10):** 957-61.

8   Yamashita S, Matsuzawa Y, Tokunaga K, Fujioka S, Tarui S — Studies on the impaired metabolism of uric acid in obese subjects: marked reduction of renal urate excretion and its improvement by a low-calorie diet. *Int J Obes* 1986; **10:** 255-64.

9   Niskanen L, Laaksonen DE, Lindstrom J — Serum uric acid as a harbinger of metabolic outcome in subjects with impaired glucose tolerance: The finnish diabetes prevention study. *Diabetes Care* 2006; **29(3):** 709-11.

10 (a) Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia. Geneva: World Health Organization; 2006. (b) Report of a World Health Organization consultation. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus, *Diabetes Res Clin Pract* 2011; **93:** 299-309. (c) American Diabetes Association, Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2014; **37(Suppl. 1):** S81–S90.

11 Kodama S, Saito K, Yachi Y, Asumi M, Sugawara A, Totsuka K, *et al* — Re - association between serum uric acid and development of type 2 diabetes mellitus. A Meta-Analysis. *Diabetes Care* 2009; **32(9) :** 1737-42.

12 Sluijs I, Beulens JW, van der ADL, Spijkerman AM, Schulze MB, van der Schouw YT— Plasma uric acid is associated with increased risk of type 2 diabetes independent of diet and metabolic risk factors. *J Nutr* 2012.

13 Quinones Galvan A, Natali A, Baldi S, Frascerra S, Sanna G, Ciociaro D, Ferrannini E — Effect of insulin on uric acid excretion in humans. *Am J Physiol* 1995; **268:** E1-5

14 Adlija C, Sabina S, Amra MD, Bakira C, Tanza D, Maja M, *et al* — Relevance of Uric Acid In Progression of Diabetes Mellitus. *Journal of Basic Science* 2010; **10(1):** 54-9.

15 Matsuura F, Yamashita S, Nakamura T, Nishida M, Nozaki S, Funahashi T, et al — Effect of visceral fat accumulation on uric acid metabolism in male obese subjects: visceral fat obesity is linked more closely to overproduction of uric acid than subcutaneous fat obesity. *Metabolism* 1998; **47:** 929-33.

16 Kramer CK, von Muhlen D, Jassal SK, Barrett-Connor E— A prospective study of uric acid by glucose tolerance status and survival: The rancho bernardo study. *J Intern Med* 2010; **267(6):** 561-6.

17 Perry IJ, Wannamethee SG, Walker MK, Thomson AG, Whincup PH, Shaper AG — Prospective study of risk factors for development of non-insulin dependent diabetes in middle aged British men. *BMJ* 1995; **310:** 560-4.

18 Chien K-L, Chen M-F, Hsu H-C, Chang W-T, Su T-C, Lee Y-T, Hu FB — Plasma uric acid and risk of type 2 diabetes in a Chinese community. *Clin Chem* 2008; **54:** 310-6.

19 Glantzounis GK, Tsimoyiannis EC, Kappas AM, Galaris DA — Uric acid and oxidative stress. *Current Pharmaceutical Design* 2005; **11:** 4145-51.

20 Sautin YY, Nakagawa T, Zharikov S, Johnson RJ — Adverse effects of the classic antioxidant uric acid in adipocytes: NADPH oxidase- mediated oxidative/nitrosative stress. *Am J Physiol Cell Physiol* 2007; **293:** C584-96.

21 Chiou WK, Wang MH, Huang DH, Chiu HT, Lee YJ, et al. — The relationship between serum uric acid level and metabolic syndrome: differences by sex and age in Taiwanese. *J Epidemiol* 2010; **20:** 219-24.

22 Bandaru P, Shankar A — Association between serum uric acid levels and diabetes mellitus. *International Journal of Endocrinology* 2011; **2011:** 1-6.

23 Rabari K, Samadhiya A, Saha S, Sharma A, Mirza AA, Naithani M — A study to assess serum uric acid level and its association with glycemic parameters in individuals with prediabetes and diabetes mellitusin a North Indian tertiary care hospital. *Yuva J Med Sci* 2018; **4:** 12-8.

24 Nan H, Dong Y, Gao W, Tuomilehto J, Qiao Q — Diabetes associated with a low serum uric acid level in a general Chinese population. *Diabetes Res Clin Pract* 2007; **76:** 68-74.

25 Causevic A, Semiz S, Macic Dzankovic A — Relevance of uric acid in progression of type 2 diabetes mellitus. *Bosn J Basic Med Sci* 2010; **10(1):** 54-9.

26 Herman JB, Goldburt U — Uric acid and Diabetes: Observation in a population study. The Lancet 1982; **2(7):** 240-3.

27 Meisinger C, Thorand B, Schneider A, Stieber J, Döring A, *et al* — Sex differences in risk factors for incident type 2 diabetes mellitus. The MONICA Augsburg Cohort Study. *Arch Intern Med* 2002; **162:** 82-9.

28 Finn R, Jones PO, Tweedie MCK, Hall SM, Dinsdale OF, Bowidillon RE — Frequency distribution curve of uric acid in the general population. *Lancet* 1966, **2:** 185-7.

29 Yuan HJ, Yang XG, Shi XY, Tian R, Zhao ZG — Association of serum uric acid with different levels of glucose and related factors. *Chin Med J (Engl)* 2011; **124(10):** 1443-8.