Correlation of Serum C-peptide and Serum uric acid Levels with Glycated Hemoglobin in Patients of Type 2 Diabetes Mellitus

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Abstract

Background: Alterations in serum uric acid levels are associated with changes in Blood glucose. While impaired Glucose tolerance is accompanied with increased levels of Uric acid, the levels decrease once overt diabetes develops. This necessitates the screening of Type 2 Diabetes Mellitus to prevent the development of hyperuricemia and gout.

Material & Methods: It was a Cross-sectional observational study. The subjects included in the study were divided into two groups. **Group A** composed of 50 normal healthy individuals, in the age group of 40-65 years of either sex with no family history of diabetes mellitus. **Group B** comprised of 50 newly diagnosed patients of Type 2 Diabetes Mellitus in the age group of 40-65 years of either sex from the same population. Fasting blood sample was withdrawn and investigated for serum c-peptide, serum uric acid, fasting blood sugar and HbA1c.

Results: The values of the patients were compared with that of normal healthy subjects. The parameters, serum c-peptide and serum uric acid were found to be significantly increased in the patients of Type 2 Diabetes Mellitus as compared to controls ($p<0.001$). Uric acid showed a positive correlation with serum c-peptides ($r=0.224$).

Conclusion: The rising incidence of Type 2 Diabetes Mellitus (T2DM) indicates the importance of screening and thus Blood Glucose, C-peptides and HBA1c should be evaluated in all subjects over 40 years of age as recommended by American Diabetic Association. This should be accompanied by measurement of Serum uric acid levels as they rise in the early stages of the disease to prevent gout. This should be further monitored with the progression of disease and treatment as uric acid shows a bell shaped changes.

Keywords: Uric Acid, HBA1c, Type 2 Diabetes Mellitus.

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Introduction

Among the types of Diabetes Mellitus as grouped by American Diabetic Association, Type 2 Diabetes Mellitus accounts for approximately 90% of all cases. Although more prevalent after 40 years of age, it can occur in younger age groups, thus emerging as a significant problem in children and adolescents. Insulin, a major anabolic hormone secreted by the pancreatic β cells, has a major role in blood glucose regulation.(1) C – Peptides, derived from proinsulin is devoid of any biological activity but appears necessary to ensure correct structure of insulin. Although secreted in equimolar concentrations in the circulation, fasting C – peptide levels are five to ten fold higher than insulin due to its longer half life of approximately 35 minutes.(2) The liver does not extract C-peptides, which is excreted by renal mechanisms, with a fraction excreted unchanged in the urine. Moreover measurement of C- peptides has many advantages over insulin measurements, most important being the negligible hepatic metabolism. Secondly, it does not undertake exogenous insulin immunoassays.(3)

Glycated Hemoglobin, is the non- enzymatic irreversible addition of sugar residue to amino group of proteins and represents integrated values of glucose over preceding 8-12 weeks.(4) Due to a rising incidence of T2DM, irrespective of age group, American Diabetic Association, which previously did not support screening for T2DM, indicates screening all asymptomatic individuals over 45 years of age and new guidelines include HBA1c to be less than 5.7% and FPG < 100 mg% to prevent micro vascular complications in newly diagnosed or screened cases.(5) The International expert committee advised the use of HBA1c for both diagnosis and monitoring diabetes and has been firmly established as an index of long term blood glucose concentrations in such patients.(6)

Serum Uric Acid, an end product of purine metabolism, has been shown to be associated with an increased risk of hypertension, Cardiovascular disorder and Chronic Kidney disease by various authors.(7,8) Despite many efforts of many authors, to establish a link between uric acid and T2DM, the relationship between the two is still a matter of debate. Although hyperuricaemia and gout are associated with an increased future risk of diabetes, diabetes may reduce the future risk of gout through the uricosuric effect of

glucose or the impaired inflammatory response.[9] Some authors have depicted a positive correlation, some negative correlation whereas some have failed to depict any relation amongst the two. The present study was designed to establish the role of uric acid in newly diagnosed T2DM by correlating with serum C-peptides and HBA1c.

Material and Methods

The present study was a cross-sectional study undertaken in the Department of Biochemistry in collaboration with Department of Medicine, SGRDIMSAR, Amritsar. The subjects were included in the study after an informed consent and were further divided into 2 groups:

Group A: Comprised of 50 normal healthy individuals, in the age group 40-65 years of either sex and without family history of DM.

Group B: Comprised of 50 **newly diagnosed** patients of Type 2 Non Insulin Dependent Diabetes Mellitus (NIDDM), in the age group 40-65 years of either sex from the same population.

The permission of the ethical committee of the institution was taken prior to the start of this study.

Exclusion Criteria

Patients suffering from type-1 DM, acute complications of DM, history of acute infections, other ailments like gross congestive heart failure, tuberculosis, gout, rheumatoid arthritis and skeletal muscle injury were excluded from the present study. Patients with Serum creatinine > 1.5mg/dl, renal failure and those on hypoglycemic drugs and on insulin therapy were excluded from the study.

A detailed history and thorough clinical examination was carried out on each patient. Fasting blood sample was drawn and investigated for serum C-peptide, uric acid, blood sugar, HbA1C, and the values were compared with that of normal healthy subjects. Serum C-peptide was estimated by ELISA method[10] and Serum uric acid by Enzymatic colorimetric method.[11] Fasting blood sugar was estimated by GOD-POD Method[12] and HbA1C by Nycocard Reader.[13]

Statistical Analysis

The comparison between various parameters was done by student t test. Correlation was done by Pearson's correlation analysis. Logistic regression analysis was also done on the variables of each parameter.

Results

The statistical analysis showed no difference between males and females with regards to their mean age. Sex and number distribution in these groups were comparable. The mean FBS levels of group B, was significantly higher than group A ($p< 0.001$.) (Table 2). In the present study it was observed that the HbA1C values of group B were statistically significant higher than group A ($p<0.001$) (Table 3). Serum C-peptide levels in group B statistically significant higher than group A ($p<0.01$) (Table 4) Similar findings were observed in the values of serum uric acid levels which showed significantly higher values of group B as compared with group A ($p<0.001$) (Table 5).

Pearson's correlation coefficient for the relation between serum C-peptide and HbA1C showed negative correlation (r= -0.497) (Table 6). Similarly the correlation coefficient for the relation between serum uric acid and HbA1C showed positive correlation(r=0.092) whereas between uric acid and C-peptides was also positive i.e. 0.224 although not very significant.(Table 6)

Table 1: **Showing the comparison of age and sex in control and study groups (p= 0.229), not- significant**

Sex	Control Group	Study Group	Total
Male	26(52%)	20(40%)	46(46%)
Female	24(48%)	30(60%)	54(54%)
Total	50	50	100

Table 2: Showing FBS in control & study group where No number of is cases & SD is standard deviation. t = 10.849 (p= < 0.001), highly-significant

S. No.	Subjects	Number	Fasting Blood Sugar (mg/dl)		
			Range	Mean±SD	± SE
1.	Group A	50	60-90	75.14±8.43	1.19
2.	Group B	50	80-240	140.98±42.0	5.95

Table 3: Showing HbA1c levels in control & study group. t = 10.905 (p<0.001), highly-significant

S. No.	Subjects	Number	Glycated Hemoglobin/ HbA1C (%)		
			Range	Mean±SD	± SE
1.	Group A	50	3.2- 6.0	4.77±0.56	0.080
2.	Group B	50	4.5- 11	7.78±1.87	0.264

Table 4: Showing comparison of serum C-peptide levels in both the groups. t = 6.721(p<0.01), significant

S. No.	Subjects	Number	Serum C-peptide (ng/ml)		
			Range	Mean±SD	± SE
1.	Group A	50	0.5- 2.1	1.91±0.34	0.049
2.	Group B	50	0.3- 4.0	2.35±1.03	0.145

Table 5: Showing the comparison of serum uric acid in both the groups

S. No.	Subjects	Number	Serum Uric Acid (mg/dl)		
			Range	Mean±SD	± SE
1.	Group A	50	2-6.5	4.54±1.19	0.080
2.	Group B	50	4.9-7.8	6.6±0.591	0.264

Table 6: **Showing the correlation between HbA1c, serum C-peptide and serum uric acid levels**

		HbA1c	C-peptide
HbA1c	R		-0.497
	P		0.001
Uric acid	R	0.092	0.224
	P	0.526	0.118

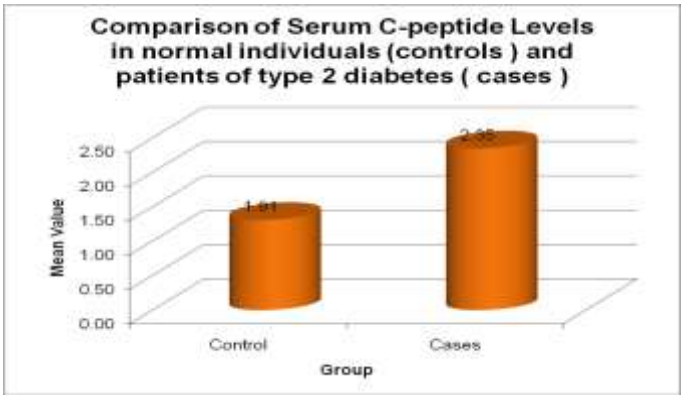

Fig. 1

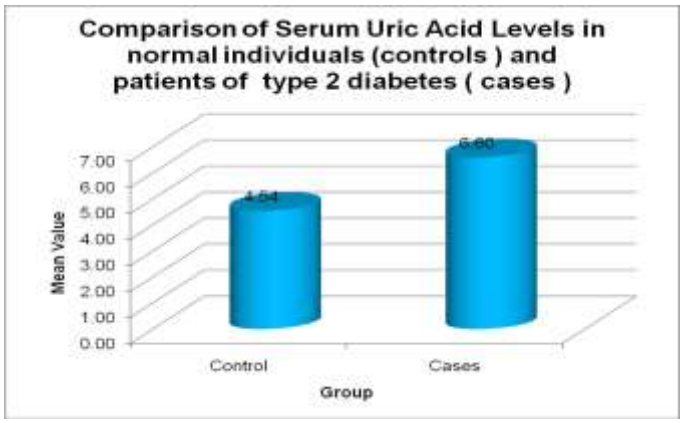

Fig. 2

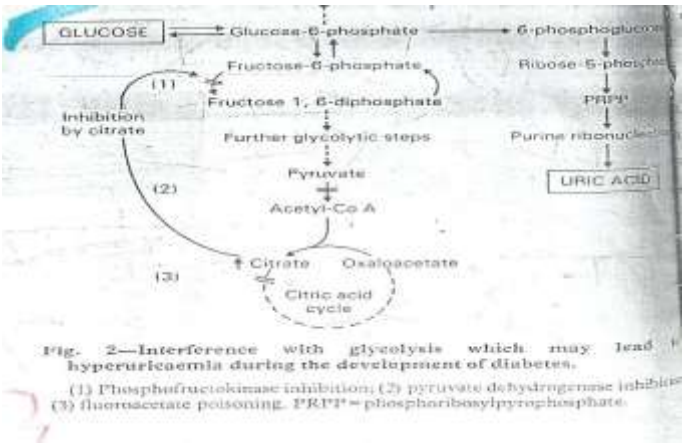

Fig. 2—Interference with glycolysis which may lead to hyperuricaemia during the development of diabetes.

(1) Phosphofructokinase inhibition; (2) pyruvate dehydrogenase inhibition; (3) fluoroacetate poisoning. PRPP = phosphoribosylpyrophosphate.

Fig. 3: Generation of uric acid due to interference in Glycolysis

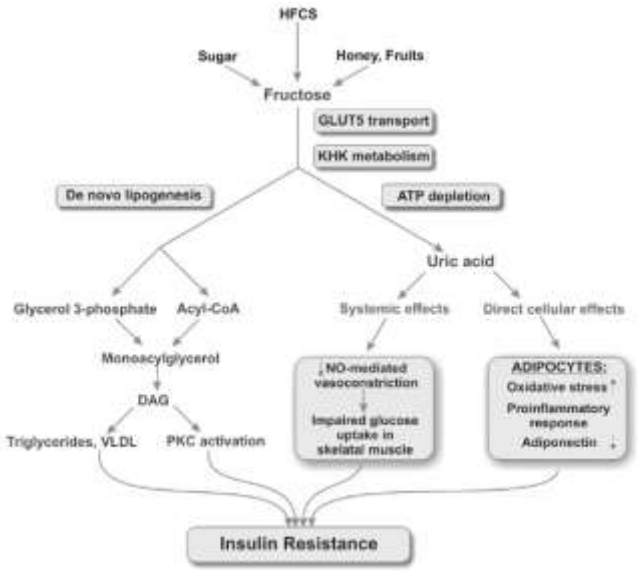

Fig. 4: Role of uric acid in generating free radicals

Discussion

The increasing incidence of Type 2 Diabetes Mellitus in younger age group and the upcoming debate about hyperuricemia preceding T2DM, demands further insight into the current topic. The present study was designed to prove the association of uric acid in newly diagnosed T2DM patients. As many patients experience a phase of impaired glucose tolerance before disease progression, it is not clear if hyperuricemia predicts the risk of T2DM.

In the present study Serum C-peptide levels were significantly higher in patients as compared to controls ($p<0.001$). This indicates high levels of insulin production in response to raised blood glucose levels which couldn't be utilized due to insulin resistance. C-peptide estimation is also useful to evaluate a patient with metabolic syndrome, a set of risk factors which include obesity, increased blood glucose and insulin resistance. These results were in agreement with those reported by Yuji tajiri et al. (2009)[14]

Glycated hemoglobin which gives integrated sugar levels of last 6-8 weeks was significantly higher in patients of Diabetes as compared to controls ($p<0.001$). Uric acid levels were also observed to be higher in group B as compared to group A (p, 0.001). Pearsons correlation coefficient serum uric acid was positive when compared to both C-peptides and HBA1c, and respectively although not significant. This is in accordance with the fact that the elevation in serum uric acid levels is consistent with insulin resistance. Many theories have been put forward to correlate the same. Uric acid being a product of purine metabolism has many reactions linked with it utilizing molecular oxygen as electron acceptor, thus generating superoxide and other free radicals. The final two reactions of its production catalyzing the conversion of hypoxanthine to xanthine and the latter to uric acid are catalysed by the enzyme xanthine oxidoreductase.[15] Serum uric acid levels have been shown to be associated with the generation of free radicals and Tumor necrosis Factor α, both of which are associated with pathogenesis of

diabetes.(Fig. 3) Other possible mechanisms for the observed results may be association of hyperuricemia with obesity which precedes diabetes.[16] Also any interference with glycolysis would divert the metabolite flow through the hexose monophosphate pathway may cause an increase in uric acid production.[17] The resulting accumulation of citric acid inhibits enzyme phosphofructokinase which diverts the cycle to the formation of 6 phosphogluconate and formation of purine nucleotides thus increasing uric acid levels during the development of diabetes.(Fig. 4) In dings are in accordance with Karam JH et al and many others.[18] The meticulous analysis of all parameters in both groups and the adjustment for all possible confounders, less likely makes this finding a chance.

According to other authors, in long term diabetes without nephropathy, uric acid levels start decreasing. The mechanism behind the Bell shaped association between diabetes and uric acid may be accounted to uricosuric effect of of glycosuria which occurs at blood glucose levels > 11 mmols/l.[19]

Strengths of the study

This study was population based in nature. Moreover the data was collected after rigorous methodology following a standard study protocol with both internal and external quality checks.

Limitations

1. The patients in the study should be followed over some years to see the variations in serum uric acid with the progression of the disease and treatment.
2. Even though we are able to detect the positive correlation of uric acid with early stages of diabetes mellitus, the study was not able to establish which one is the cause and which is the effect of the disease.

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