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A STUDY OF THE VARIATION OF SERUM URIC ACID IN PATIENTS WITH AND WITHOUT DIABETES MELLITUS WHO HAVE NORMAL RENAL FUNCTION

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ABSTRACT

1) Correlation of Serum Uric acid with Creatinine levels in male Diabetic population $r=-0.048$ and $p>0.05$ shows no significant correlation between serum uric acid and Creatinine levels. While in females $r=0.270$ and $p<0.05$ shows significant positive correlation between serum uric acid and Creatinine levels.

2) The correlation of Serum Uric acid with age in male Diabetic population $r=-0.0175$ and $p>0.05$ shows no significant correlation between serum uric acid and age. In female Diabetic population $r=-0.040$ and $p>0.05$ also shows no significant correlation between serum uric acid and age.

3) With duration of Diabetes in male population $r=0.388$ and $p<0.05$ shows significant positive correlation between serum uric acid and duration of Diabetes. Whereas in female Diabetic population $r=-0.159$ and $p>0.05$ shows no significant correlation between serum uric acid and duration of Diabetes.

4) This study aimed to investigate the level of uric acid in Type 2 Diabetes mellitus patients and in non Diabetic controls with normal kidney function. This study also included the correlation of serum uric acid with glucose, creatinine, age, gender and duration of Diabetes. Uric acid levels were measured by Uricase- PAP methodology, FBS and PPBS levels by GOD- PAP methodology and creatinine by modified Jaffe's kinetic method in 92 patients with Diabetes and 92 non Diabetic Controls and the uric acid levels were compared. The mean uric acid level showed no significant difference between Diabetic and non Diabetic population. The factors age, gender showed no significant correlation except in creatinine levels of female Diabetic population and duration of Diabetes in male diabetic population in which both showed a significant positive correlation with uric acid levels.

5) This study presents the pattern of relationship between serum uric acid, serum glucose and Diabetes mellitus of individuals with normal kidney function in a hospital based study.

- No significant difference is seen between the mean levels of Uric acid in Diabetic and non Diabetic individuals.
- No significant correlation is seen in the levels of uric acid with Glucose levels (FBS and PPBS), both in male and female Diabetic patients.
- Serum Creatinine levels show no correlation with serum Uric acid levels in male Diabetic population while in female Diabetics, there is a significant positive correlation.
- Pearson correlation shows no correlation with age and Uric acid levels in male and female Diabetic population.
- The study also shows no significant difference in levels of uric acid with gender.
- Duration of Diabetes in males show positive correlation with levels of uric acid, while no such correlation is observed in female diabetics. Since the cross sectional study show confounding data, the implication of uric acid levels in Diabetes and moreover in pre diabetes need to be investigated to a further extent.

INTRODUCTION

For some time, it has been recognized that serum uric acid is positively associated with serum glucose levels in healthy subjects. Recent studies have demonstrated that uric acid levels are higher in subjects with pre diabetes and early Type 2 Diabetes than in healthy controls. Furthermore, an elevated serum uric acid level was found to increase chances for developing Type2 Diabetes in individuals with impaired glucose tolerance. Hyperuricemia has been also added to the set of metabolic abnormalities associated with insulin resistance and/or hyperinsulinemia in metabolic syndrome. An elevated uric acid levels, as reported, often precedes the development of obesity, hyperinsulinemia and diabetes. In addition, uric acid has been implicated in the development of metabolic syndrome and hypertension. However, hyperuricemia is not always found in Diabetic individuals. Conflicting data exist about uric acid levels in type 2 Diabetes, as low levels were found in Diabetic patients, while elevated serum uric acid is a feature of hyperinsulinemia and impaired glucose tolerance. Although, several studies have implicated the role of uric acid in progression of pre diabetes to Diabetes, studies related to uric acid levels in Diabetes development are controversial and deserve further analysis. This study included the comparison of uric acid levels in Diabetic and non Diabetic populations with normal kidney function and the correlation of uric acid levels with Glucose, Creatinine, Age, Gender and Duration of Diabetes.

Objectives

To compare serum uric acid levels in patients with Type2 Diabetes and in non Diabetic population with normal kidney function.

MATERIALS AND METHODS

Study Design: Hospital based cross sectional study.

Study Period: Six months after getting ethical committee clearance.

Study Population

- Patients with Type 2 Diabetes attending Diabetic Clinic,
- Non Diabetic Patients attending Medicine Out Patient department with normal kidney functions.

Sampling

Sample Size Calculation

$$n = \frac{2\,(\,Z\alpha + Z\beta^2\,)\,\sigma^2}{\delta^2}$$

= Type 1 error (fixed at 5% level)

$1 -$ = Power (fixed at 80% level)

= $(\mu_1 - \mu_1)$ (Clinically meaningful difference)

From Literature,

$= 1.7 ,\quad = 0.7$

$$n = \frac{2\,(\,7.849\,)\,1.7^2}{0.7^2}$$

$=$ 93 per group

Inclusion Criteria

Type 2 Diabetes patients and non Diabetic patients without kidney diseases, both, age groups 35 – 65years.

Exclusion Criteria

Patients having serum creatinine greater than 1mg/dl

Those who have previous history of CVD (angina, myocardial infarction, ischaemic stroke, coronary vascularistion, etc).

Severe chronic obstructive pulmonary diseases, malignancies, gout, using hyperuricimic drugs, pregnancy, alcoholics,etc

Study Setting

Department of MLT, Govt. Medical College, Thiruvananthapuram. Department of Biochemistry, Govt. Medical College, Thiruvananthapuram. Department of Medicine and Diabetology, Govt. Medical College, Thiruvananthapuram.
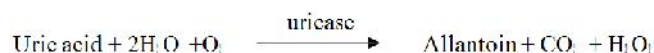
Methods

Uric acid assay is based on Uricase – PAP methodology
Mode of Action – End point

Principle

Enzymatic determination of uric acid according to the following reactions:

$$Uric\ acid + 2H_2O + O_2 \xrightarrow{uricase} Allantoin + CO_2 + H_2O_2$$

RESULTS

The present study was done on 92 patients with Diabetes mellitus and 92 patients without Diabetes mellitus attending Medicine Out Patient Department, Medical College, Thiruvananthapuram during the study period of six months and the results were obtained as below;

(1) **AGE:** Among Diabetics and non Diabetics, 40.2% were between age groups 35-45 years, 29.3% were between age groups 45-55 years and 30.4% were between age groups 55-65 years

(2) **Gender distribution among Diabetics and non Diabetics** Among Diabetics, 39.1% were males and 60.9% were females, In non Diabetic controls 41.3% were males and 58.7% were females.

(3) **Duration of Diabetes:** 51.1 % of patients were with Diabetes duration less than 5 years, 42.4% were between 5-10 years of Duration and 6.5% of patients were with more than 10 years duration.

Mean uric acid levels among males and females in Diabetic and non

Diabetic population

The mean value of uric acid in male Diabetic population was 4.9, whereas in non diabetic population it was 5.2, p value 0.234 showing no significant difference of uric acid levels in both the groups. The mean value of uric acid in female Diabetic population and female non Diabetic population was 4.1, with p value 0.890 which also shows no significant difference.

Correlation of Serum Uric acid with FBS levels in male Diabetic population: The Pearson correlation of Serum Uric acid with FBS levels in male Diabetic population r=-0.009 and p>0.05 shows no significant correlation between serum uric acid and FBS levels.

Correlation of serum uric acid and FBS in female diabetic population: The Pearson correlation of Serum Uric acid with FBS levels in female Diabetic population r=0.067 and p>0.05 shows no significant correlation between serum uric acid and FBS levels.

Correlation of Serum Uric acid and PPBS in male diabetic population: The Pearson correlation of Serum Uric acid with PPBS levels in male Diabetic population r=-0.083 and p>0.05 shows no significant correlation between serum uric acid and PPBS levels.

Correlation of Serum Uric acid and PPBS in female diabetic population: The Pearson correlation of Serum Uric acid with PPBS levels in female Diabetic population r=0.093 and p>0.05 shows no significant correlation between serum uric acid and PPBS levels.

Pearson correlation of serum Uric acid and Creatinine in male Diabetic population: The Pearson correlation of Serum Uric acid with Creatinine levels in male Diabetic population r=-0.048 and p>0.05 shows no significant correlation between serum uric acid and Creatinine levels.

Correlation of serum uric acid and creatinine in female Diabetic population: The Pearson correlation of Serum Uric acid with Creatinine levels in female Diabetic population r=0.270 and p<0.05 shows significant positive correlation between serum uric acid and Creatinine levels.

Correlation of serum Uric acid and Age in male Diabetic population: The Pearson correlation of Serum Uric acid with age in male Diabetic population r=-0.0175 and p>0.05 shows no significant correlation between serum uric acid and age.

Correlation of Serum Uric acid and age in female Diabetic population: The Pearson correlation of Serum Uric acid with age in female Diabetic population r=-0.040 and p>0.05 shows no significant correlation between serum uric acid and age

Correlation of serum Uric acid and duration of Diabetes in males: The Pearson correlation of Serum Uric acid with duration of Diabetes in male Diabetic population r=0.388 and p<0.05 shows significant positive correlation between serum uric acid and duration of Diabetes.

Correlation of serum Uric acid and duration of Diabetes in females: The Pearson correlation of Serum Uric acid with duration of Diabetes in female Diabetic population r=-0.159 and p>0.05 shows no significant correlation between serum uric acid and duration of Diabetes.

Statistical Methods

Mean and standard deviation of serum uric acid is computed. For comparison of values, t test is used. For data analysis SPSS solutions is used.

DISCUSSION

Previous studies examining the association between uric acid levels and Diabetes mellitus were restricted to specific racial/ethnic groups and gender were not consistent in their findings. Some studies reported that there is a positive association between uric acid and Diabetes whereas some other study reported no positive association between uric acid and Diabetes. Also, some studies reported that serum uric acid is inversely associated with Diabetes. The exact reason for why previous studies found with positive relation between uric acid and diabetes is not clear. Most of these studies were limited by small sample sizes, including either men or women and not both, not having data on confounding factors or were selected populations such as industrial workers as opposed to general population samples. In this study, 92 patients with Diabetes mellitus and 92 patients without Diabetes mellitus attending Medicine Out Patient Department, Medical College, Thiruvananthapuram during the study period of six months were taken. In that 64 % of Diabetic patients were taking oral hypoglycaemic drugs, 7% of patients were taking insulin, 23 %of patients were taking both Oral hypoglycemic drug and insulin and 6% of patients were on no medication. Blood pressure and Cholesterol levels were kept in control by taking antihypertensive drugs and lipid lowering drugs. Among Diabetics and non Diabetics, 40.2% were between age groups 35-45 years, 29.3% were between age groups 45-55 years and 30.4% were between age groups 55-65 years. Correlation of Serum Uric acid with Creatinine levels in male Diabetic population r=-0.048 and p>0.05 shows no significant correlation between serum uric acid and Creatinine levels. While in females r=0.270 and p<0.05 shows significant positive correlation between serum uric acid and Creatinine levels.

The correlation of Serum Uric acid with age in male Diabetic population r=-0.0175 and p>0.05 shows no significant correlation between serum uric acid and age. In female Diabetic population r=-0.040 and p>0.05 also shows no significant correlation between serum uric acid and age. While most of the earlier studies showed a significant elevation of uric acid with aging, a few studies did not show any consistent relationship with age. Experimental studies in rodents have suggested that uric acid may contribute to the development of the metabolic syndrome hypertension and kidney disease and recently clinical studies focusing on uric acid and the development and progression of diabetic kidney disease have been published. In the early report of Modification of Diet in Renal Disease study, uric acid was not found to be an independent predictor of renal disease. Other large epidemiologic studies have revealed conflicting results in this respect. While the majority of

these studies suggest an independent predictive role for uric acid in renal disease, others argue against it.

Summary

Identifying risk factors for the development of Type 2 Diabetes is essential for its early screening and prevention. It was shown in a prospective follow up study that high serum uric acid is associated with higher risk of Type 2 Diabetes independent of obesity, dyslipidemia and hypertension. Recent evidence suggests that uric acid plays a role in cytokinine secretion and has been identified as a mediator of endothelial dysfunction and systemic inflammation. It is quite conceivable, in the context of the complex cellular environment of metabolic syndrome which is clearly associated with oxidative stress, antioxidant properties of uric acid might convert to a pre oxidant state owing to reactive oxygen species accumulation. 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. This study aimed to investigate the level of uric acid in Type 2 Diabetes mellitus patients and in non Diabetic controls with normal kidney function. This study also included the correlation of serum uric acid with glucose , creatinine, age, gender and duration of Diabetes. Uric acid levels were measured by Uricase- PAP methodology, FBS and PPBS levels by GOD-PAP methodology and creatinine by modified Jaffe's kinetic method in 92 patients with Diabetes and 92 non Diabetic Controls and the uric acid levels were compared. The mean uric acid level showed no significant difference between Diabetic and non Diabetic population. The factors age, gender showed no significant correlation except in creatinine levels of female Diabetic population and duration of Diabetes in male diabetic population in which both showed a significant positive correlation with uric acid levels.

Conclusion

The prevalence of Diabetes and for that matter the associated complications have increased dramatically. Presently Diabetes is the leading cause of End Stage Renal Disease in the Western world. Although the progression of renal disease can be halted partially, Diabetic Nephropathy is still regarded as an irreversible and progressive disease. Therefore it has become increasingly essential to determine the pathophysiological mechanism underlying the development and progression of Diabetic associated diseases. Evidence is available of a complicated interaction between different contributors to the disease process. It is possible that genetic susceptibility, metabolic abnormalities, haemo dynamic changes, up regulated growth factors and cytokines may all play a part in the development of Diabetic Glomerulopathy. The strongest evidence of a role for uric acid in the development of the metabolic syndrome has been from study models showing that decreasing uric acid level can prevent or reverse features of the metabolic syndrome.

Two mechanisms have been suggested to explain how hyperuricemia might induce metabolic syndrome. The first mechanism is related to the fact that glucose uptake in skeletal muscle depend in part on increases in blood flow mediated by insulin stimulated release of nitric oxide from endothelial cells. Features of the metabolic syndrome develop in mice lacking endothelial nitric oxide synthase. The observations that hyperuricemia can induce endothelial dysfunction in rats and that treatment with allopurinol can improve endothelial function in patients with hyperuricemia would support this mechanism. The second mechanism concerns the inflammatory and oxidative changes uric acid induces in adipocytes, a process that is key in causing the metabolic syndrome in obese mice.

This study presents the pattern of relationship between serum uric acid, serum glucose and Diabetes mellitus of individuals with normal kidney function in a hospital based study.

- No significant difference is seen between the mean levels of Uric acid in Diabetic and non Diabetic individuals.
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REFERENCES

Amos, A.F., McCarty, D.J., Zimmet, P. 1997. The rising global burden of diabetes and its complications:estimates and projections to the year 2010. *Diabet Med.,* 14 (Suppl 5): S1-S85.

Bagust, A., Hopkinson, P.K., Maslove, L., Currie, C.J. 2002. The projected health care burden of Type 2 diabetes in the UK from 2000 to 2060. *Diabet Med.,* 19: 1-5.

Cryer, P.E. 1992. Glucose homeostasis and hypoglycaemia. In William's Textbook of Endocrinology. Wilson JD, Foster DW, Eds. Philadelphia, Pa., W.B. Saunders Company, p.1223 –1253

Farnkvist, L.M., Lundman, B.M. 2003. Outcomes of diabetes care: a population- based study. *Int J Qual Health Care.,* 15: 301-317.

Gerich, J.E. 1993. Control of glycaemia. Baillieres Best Pract *Res Clin Endocrinol Metab* 7:551 –586, 1993

Gerich, J.E., Schneider, V., Dippe, S.E., Langlois, M., Noacco, C., Karam, J., Forsham, P. 1974. Characterization of the glucagon response to hypoglycemia in man. *J Clin Endocrinol Metab* 38:77 –82.

Groop, L.C., Tuomi, T. 1997. Non-insulin-dependent diabetes mellitus- a collision between thrifty genes and an affluent society. *Ann Med.,* 29: 37-53.

Gu, D., Reynolds, K., Duan, X., *et al.* 2003.Prevalence of diabetes and impaired fasting glucose in the Chinese

adult population : International collaborative study of cardi-ovascular disease in Asia (InterASIA). *D iabetologia,* 46: 1190-1198.18

Harris, M.I., Flegal, K.M., Cowie, C.C., *et al.* 1988. Prevalence of diabetes, impaired fasting glucose, and impaired glu-cose tolerance in U.S. adults. The Third National Health and Nutrition Examination Survey, 1988-1994. *Diabetes Care.,* 21: 518-524.

Harris, M.I., Flegal, K.M., Cowie, C.C., *et al.* 1988. Prevalence of diabetes, impaired fasting glucose, and impaired glu-cose tolerance in U.S. adults. The Third National Health and Nutrition Examination Survey, 1988-1994. *Diabetes Care*, 21: 518-524.

Holst, J.J. 1994. Glucagon-like peptide 1: a newly discovered gastrointestinal hormone. Gastroenterology 107:1848 – 1855., 1994

International Diabetes Federation [IDF]. Diabetes e-Atlas. Retrieved June 20, 2005.

Kahn, C.R., Vicent, D., Doria, A. 1996. Genetic of non-insulin-dependant (Type-II) diabetes mellitus. *Ann Rev Med.,* 47: 509-531.

King, H., Aubert, R.E., Herman, W.H. 1998. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. *Diabetes Care,* 21: 1414-1431.

Lebovitz HE. Diagnosis, classification, and pathogenesis of diabetes mellitus. *J Clin Psychiatry* 2001; 62 (Suppl 27): 5-9.

Lefebvre PJ: Glucagon and its family revisited. Diabetes Care18: 715–730, 1995

Motala AA, Pirie FJ, Gouws E, Amod A, Omar MK. High incidence of Type 2 diabetes mellitus in South African Indians: a 10-year follow-up study. Diabet Med 2003; 20: 23-30.

Owen K, Hattersley AT. Maturity-onset diabetes of the young: from clinical description to molecular genetic characterization. *Best Pract Res Clin Endocrinol Metab* 2001; 15: 309-323.

Pozzilli P, Di Mario U. Autoimmune diabetes not requiring insulin at diagnosis (latent autoimmune diabe-tes of the adult): definition, characterization, and poten-tial prevention. *Diabetes Care* 2001; 24: 1460-1467.

Sicree R, Shaw J, Zimmet P. The global burden of diabetes, Diabetes and impaired glucose tolerance: preva-lence and projections. In: Gan D eds. Diabetes Atlas. 2nd ed. International Diabetes Federation, Brussels 2003; pp 15-71.

The Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) Study Group. Will new diagnostic criteria for diabetes mellitus change phenotype of patients with diabetes? Reanalysis of European epidemiological data. BMJ 1998; 317: 371-375.

Tuomi T, Carlsson AL, Li H, *et al*. Clinical and genetic characteristics of type 2 diabetes with and without GAD antibodies. Diabetes 1999; 48: 150-157.

Wallum BJ, Kahn SE, McCulloch DK, Porte D: Insulin secretion in the normal and diabetic human. In International Textbook of Diabetes Mellitus. Alberti KGMM, DeFronzo RA, Keen H, Zimmet P, Eds. Chichester, U.K., John Wiley and Sons, 1992, p.285 –301

Weyer C, Bogardus C, Mott DM, *et al*. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest* 1999; 104: 787-794.

Wild S, Roglic G, Green A, *et al*. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004; 27: 1047-1053.

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