International Journal Of

Recent Scientific Research

ISSN: 0976-3031

Volume: 7(1) January -2016

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THE OFFICIAL PUBLICATION OF
INTERNATIONAL JOURNAL OF RECENT SCIENTIFIC RESEARCH (IJRSR)
http://www.recentscientific.com/ recentscientific@gmail.com

ISSN: 0976-3031

Available Online at http://www.recentscientific.com

International Journal of Recent Scientific Research
Vol. 7, Issue, 1, pp. 8430-8436, January, 2016

International Journal of Recent Scientific Research

RESEARCH ARTICLE

ASSOCIATION BETWEEN SERUM AND URINE URIC ACID LEVELS IN PATIENT WITH DIABETES MELLITUS

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ARTICLE INFO

Article History:

Received 06th October, 2015
Received in revised form 14th November, 2015
Accepted 23rd December, 2015
Published online 28st January, 2016

Key words:

Uric acid, glucose, diabetes mellitus, insulin resistance, Oxidative stress

ABSTRACT

In India diabetes mellitus prevalence ranges from 0.4 to 3.9% in rural areas and from 9.3 to 16.6% in urban areas. Serum uric acid has been shown to be associated with oxidative stress and production of tumor necrosis factor-α [2], which are both related to the development of diabetes. Uric acid levels were measured in both, serum and urine samples, and then urine/serum ratio of uric acid levels was calculated and compared between Type 2 diabetic patients and control subjects. Our results demonstrated a profound increase in uric acid urine/serum ratios in Type 2 diabetic patients as compared to healthy controls.Our data demonstrated significant positive correlation between Urine and serum uric acidand serum glucose levels in patients diagnosed with Type 2 diabetes. Our results demonstrated no effect of sex on uric acid levels in serum and urine in both control and diabetic patients. Body mass index had a significant and independent impact on plasma uric acid levels both in non-diabetic and diabetic men and women.
This prospective study suggests a positive association between the plasma concentration of uric acid and the incidence of type 2 diabetes. The uric acid may serve as a potential biomarker of deterioration of glucose metabolism.

INTRODUCTION

The tide of type 2 diabetes is rising in all over the world, thereby becoming an Increasingly powerful threat to global health. International Diabetic Federation data shows that world Diabetes & Pre-diabetes prevalence in 2007 is 5.7% and7.5% respectively. In India Diabetes mellitus prevalence ranges from 0.4 to 3.9% in rural areas and from 9.3 to 16.6%in urban areas. Diabetes causes long term dysfunction of various organs like heart, kidneys, eyes, nerves and blood vessels (K Park *et al*, 2009). Age adjusted mortality rates among diabetic is1.5 to 2.5 times higher than general population. Much of this excessive mortality is attributable to cardiovascular (K Park *et al*, 2009) disease.

Recent studies have introduced serum uric acid (UA) as a potential risk factor for developing diabetes, hypertension, stroke, and cardiovascular diseases.Recognition of high serum uric acid as a risk factor for diabetes has been a matter of debate for a few decades, since hyperuricemia has been presumed to be a consequence of insulin resistance rather than its precursor. Serum uric acid has been shown to be associated with oxidative stress and production of tumor necrosis factor-α (Butler R *et al*, 2000), which are both related to the development of diabetes. Serum uric acid (or more correctly, its monoanion uric acid at physiological pH values) has been thought to be in humans a metabolically inert end product of purine metabolism without physiological significance (except gouty diathesis). However, serum uric acid has been recently associated with obesity & insulin resistance, and consequently with type 2 diabetes (Modan M *et al*, 1987, Facchini F *et al* 1991). Further potentially important biological effects of uric acid relate to endothelial dysfunction by inducing antiproliferative effects on endothelium and impairing nitric oxide production and inflammation, e.g., through increased C-reactive protein expression.Furthermore, in nondiabetic subjects an elevated level of uric acid has been shown to be an independent predictor of coronary heart disease and total mortality (Brand FN *et al*, 1985, Bengtsson C *et al*, 1988, Levine W*et al*, 1989, Zavaroni I *et al*, 1989).

Uric acid is one of the major endogenous water-soluble antioxidants of the body (Feingold KR *et al*, 1992).

There is accumulating evidence that increased oxidative stress is closely related to diabetesand its vascular complications (Baynes JW *et al*, 1991). Uric acid can act as a

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prooxidant and may thus be a marker of oxidative stress, but it may also have a therapeutic role as an antioxidant (Patterson RA *et al*,2003). Urate, the soluble form of uric acid, can scavenge the superoxide and the hydroxyl radicals and it can chelate the transition metals (Ames BN *et al, 1981*). Hyperuricaemia hasbeen also added to the set of metabolic abnormalities which are associated with insulin resistance and/or hyperinsulinaemia in the metabolic syndrome (Nakagawa T *et al*, 2005).

Thus, high circulating uric acid levels may be an indicator that the body is trying to protect itself from the deleterious effects of free radicals by increasing the products of endogenous antioxidants, eg, uric acid. Finally, uric acid may play a role in immune activation with subsequent increased chemokine and cytokine expression (Gersch MS *et al*, 2006, Lozada LG *et al*, 2006).

Thus, although there are plausible mechanisms to suggest uric acid as a potential direct mediator of cardiometabolic and other chronic diseases (except for gout), this is still a controversial area. Metabolic syndrome, type 2 diabetes, and atherosclerotic vascular disease are characterized by various established but also emerging risk factors, and interestingly, these three disorders have several risk factors in common. uric acid presents one of the candidates that may be involved in these three cardiometabolic disorders.

Although several studies have implicated the role of UA in progression of prediabetes to diabetes, studies related to UA levels in diabetes development are controversial and deserve further analysis. Therefore, in this study we have analyzed and examined potential role of UA as a biomarker for impaired glucose metabolism and diabetes progression by analyzing serum and urine levels of UA in Type 2 diabetic patients.

MATERIALS AND METHODS

A case control study was conducted on 50 patients with known type 2 diabetes mellitus and on 50 healthy controls who were in the age group of 30 -60 years. The patients were randomly selected from the Outpatients Medicine Department of SreeNarayana Institute of Medical Sciences, Ernakulam. This study was approved by the Institutional Ethics Committee. All subjects gave their informed consent for participation in the study.

All research involving human subjects and material derived from human subjects in this study will be in accordance with the ethical recommendations. Clinical diagnosis of Type 2 Diabetes Mellitus was clinically diagnosed by standardized clinical examination conducted by specialist of Internal Medicine. All the data were collected in a prescribed proforma and they were compiled. The questionnaire contained questions regarding the duration of diabetes, the family history of diabetes, the dietary history and the history of hypertension, smoking, alcohol drinking, etc. A criterion for the selection of the patients which was included in the study, was that all the individuals who gave a history of diabetes and were under treatment with either oral antidiabetic drugs or insulin were considered to have diabetes. The patients with a history of gout and cardiovascular or renal diseases or liver diseases and those who were on drugs (other than antidiabetics) that could alter the blood glucose levels were excluded from the study. The controls were non-diabetic, non-hypertensives, non-smokers and non-alcoholics with normal plasma glucose levels.

The patients who gave a history of hypertension and were on antihypertensive treatment or whose blood pressure was more than 140/90 mm of Hg were considered to have hypertension. The height and the weight of patients and the controls were measured. The body mass index (BMI) was calculated by dividing the weight (Kg) by the height (m) squared. By measuring the waist circumference at the level of the iliac crest and the hip circumference at the maximal horizontal girth between the waist and the thigh, the waist/hip ratio (W/H ratio) was calculated.

Blood samples was taken for the analysis from patients and subjects in fasting conditions from antecubital vein into plain vacutainer. Blood analyses was carried out in fresh samples.24 hours urine sample was collected for uric acid analysis. In our study UA levels were measured in both, serum and urine samples, and then urine/serum ratio of uric acid levels was calculated and compared between Type 2 diabetic patients and control subjects.Analysis of UA in serum and urine were performed using uricase/peroxidase method while the analysis of plasma glucose was done by the glucose oxidase method. Endpoint method was used to measure the concentration of uric acid in serum. Uric acid is oxidized by uricase to produce allantoin and hydrogen peroxide. The hydrogen peroxide reacts with 4-aminoantipyrine (4-AAP) and 3,5-dichloro-2-hydroxybenzene sulfonate (DCHBS) in a reaction catalyzed by peroxidase to produce a colored product. The system monitors the change in absorbance at 520 nm at a fixed time interval. The change in absorbance is directly proportional to the concentration of uric acid in the sample. These tests were performed on Coralyzer 200, fully automated random access Clinical Chemistry analyser (Tulip Diagnostics (P) Ltd.).

Statistical Analysis

Statistical analysis of the results from this study was done using SPSS 10.0 for Windows. Data are presented as mean ± SEM. Statistical significance was set as $p<0.05$. Statistical analysis of the results from this study will be analyze by student's t- test for unpaired data using SPSS .

RESULTS

Table 1 Demographic Data

Variables	Controls	Diabetes	P value
Age (yrs)	52.9± 4.5	52.8± 4.8	NS
BMI (kg/m2)	22.8± 0.8	26.9±0.9	< 0.0001
waist circumference (cm)	78.9 ±7.6	83.4 ±7.1	< 0.0001
Fasting plasma Glu (mmol/l)	4.4± 0.16	9.2 ± 0.85	< 0.0001
Serum Uric acid (µmol/l)	294.1 ± 10.84	349.8 ± 14.24	< 0.004
Urine uric acid (µmol/l)	3200 ± 150	4800 ± 200	< 0.004
Systolic blood pressure (mm/Hg)	110.6±16.2	124.0 ± 18.4	< 0.0001
Diastolic blood pressure (mm/ Hg)	70.2 ± 10.2	79.4±11.9	< 0.0001

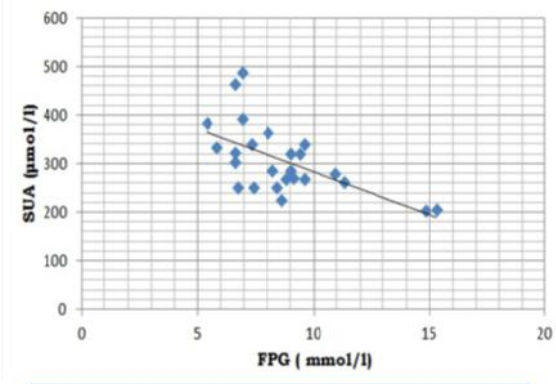

Fig.1 Correlation between serum uric acid and fasting plasma glucose levels in patients with type 2 diabetes mellitus

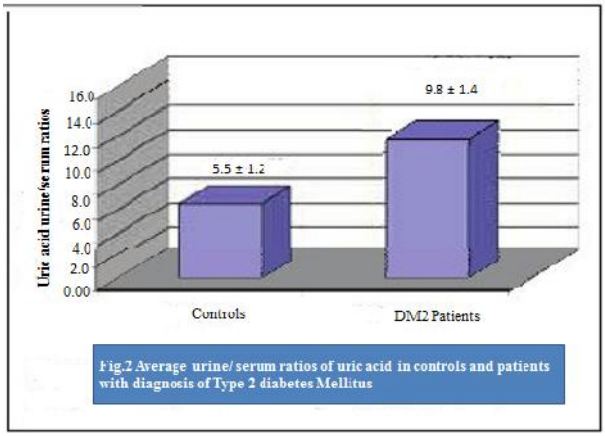

Fig.2 Average urine/ serum ratios of uric acid in controls and patients with diagnosis of Type 2 diabetes Mellitus

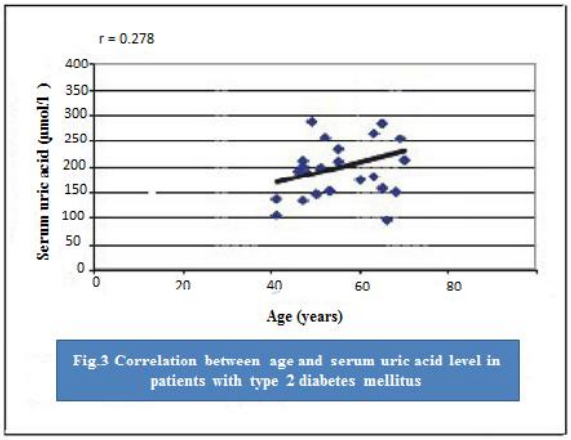

Fig.3 Correlation between age and serum uric acid level in patients with type 2 diabetes mellitus

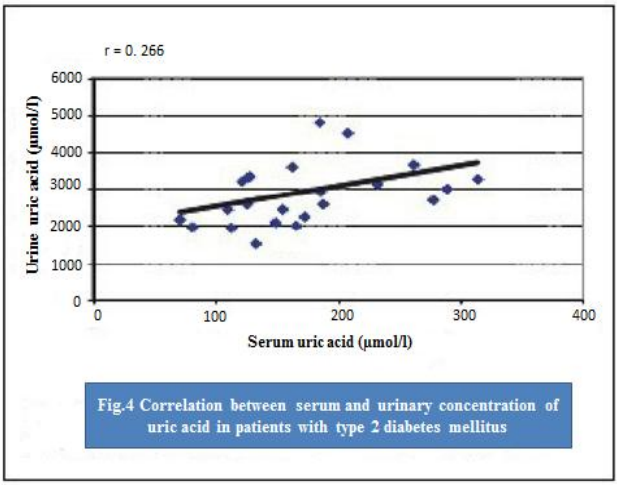

Fig.4 Correlation between serum and urinary concentration of uric acid in patients with type 2 diabetes mellitus

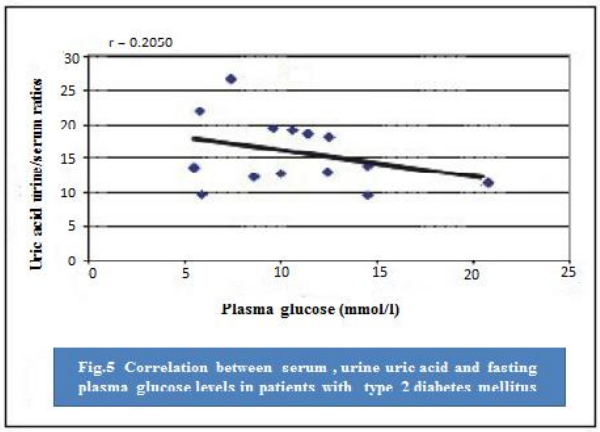

Fig.5 Correlation between serum , urine uric acid and fasting plasma glucose levels in patients with type 2 diabetes mellitus

Table 2 Basal data

Current smoker %	13.8
Everyday drinker %	13.2
Antihypertensive medication %	76.4
Hypoglycemic medication %	82.5
Antihyperlipidemic medication %	54.8

Of the 50 diabetic subjects studied, 28 were males while 22 were females. Demographic data are shown in Table 1.The mean ages (in years) of diabetic patients were 52.8± 4.8 against 52.9± 4.5 in the controls. The BMI, the W/H ratio, the fasting were higher in the diabetics as compared to the controls.
The serum uric acid levels in the diabetic males and females were higher as compared to those in the controls, this was statistically significant. Uric acid positively correlated with BMI, waist circumference.

A negative correlation was observed between the fasting plasma glucose and the serum uric acid levels [r = −0.60] in diabetic patients [Table/Fig-1]. The serum uric acid levels increased with an increased duration of diabetes, although it was not statistically significant [Fig-3].

Figure - 2 the Urine &Serum uric acid values for diabetic patients were about 2 fold higher than in control subjects. Our data also demonstrated a trend in correlation of Urine and Serum Uric acid values with the blood glucose levels in diabetic patients, which was more prominent in male than in female patients [Fig -5].

As shown in Figure - 4, there was a correlation between serum and urinary uric acid levels in diabetic patients. Interestingly, with aging, levels of uric acid increased in serum of diabetic patients. As demonstrated in Figure -3, there was a correlation between diabetic patients' age and uric acid levels in serum.

Factors which might have an association with serum uric acid or glucose concentration have been examined (Table 2). Uric acid concentration is positively associated with alcohol intake, with a 14% increase in those drinking more than 6 drinks daily compared with occasional drinkers. The 76% patients currently on anti-hypertensive treatment showed a 15% higher mean uric acid concentration than all subjects in the study.

Systolic and diastolic BP, and hypertension was found to have significant direct correlation with Uric acid. Adjustment for BP

or a history of hypertension did not alter the observed relationship.

The percentage of the diabetics who gave a positive family history of diabetes and a history of hypertension was more among the females than among the males, while smoking and alcohol drinking were predominantly seen in the males.

DISCUSSION

In India Diabetes mellitus prevalence ranges from 0.4 to 3.9% in rural areas and from 9.3 to 16.6% in urban areas. Diabetes causes long term dysfunction of various organs like heart, kidneys, eyes, nerves and blood vessels (K Park *et al*, 2009). Uric acid is formed by the breakdown of purines and by direct synthesis from 5-phosphoribosyl pyrophosphate and glutamine. Serum urate levels vary with age and sex. Several epidemiologic studies have reported that high serum levels of uric acid are strongly associated with prevalent health conditions such as obesity, insulin resistance, metabolic syndrome, diabetes, essential hypertension, and renal disease (Stephen Waring, *et al*, 2006) and cardiovascular disease (Zoppini G *et al*,2009). In Type 2 diabetes, hyperuricemia seems to be associated with the insulin-resistance syndrome, impaired glucose tolerance, and an early onset of nephropathy,nephropathy, while hypouricemia is associated with nonadequate metabolic control, hyperfiltration, and a late onset of overt nephropathy (Bo S *et al*,2001).

The positive association between uric acid concentration and diabetes may be explained by at least 3 potential mechanisms. First, metabolic syndrome, as a precursor of diabetes, induces high oxidative stress,which is worsened by the accompanying hyperuricemia (Hansel B *et al*,2004). Uric acid usually has an antioxidative effect; however, uric acid becomes a strong oxidant in the environment of metabolic syndrome (Hayden MR *et al*, 2004). This phenomenon of the urate redox shuttle may explain the paradoxical effects of uric acid on oxidative stress (Patterson RA *et al*, 2003). Inflammation and oxidative stress induced by metabolic syndrome and hyperuricemia may predispose individuals to a higher risk for diabetes.

Second, uric acid stimulates vascular smooth muscle proliferation and induces endothelial dysfunction (Johnson RJ *et al*, 2003). Uric acid has been shown to decrease endothelial nitric oxide production and to lead to endothelial dysfunction and insulin resistance (Nakagawa T *et al*, 2006, Feig DI *et al*, 2006) Consequently, uric acid induces vascular inflammation and artery damage (Johnson RJ *et al*, 2003, Heinig M *et al*, 2006) which in turn leads to an increased risk of diabetes and atherosclerosis (Sundstrom J *et al*, 2005, Mellen PB *et al*, 2005).

Third, uric acid is associated with increased renal glomerular pressure and increased renal sodium reabsorption, and these renal reactions are greatly enhanced by high insulin concentrations (Quinones Galvan A *et al*, 1995). Among diabetic patients, hyperuricemia has been associated with microalbuminuria (Bo S *et al*, 2001). The combined effects of insulin resistance and hyperuricemia on renal functions may lead to increased glucose intolerance, hypertension, and diabetes risk.

This hospital based cross sectional study shows that serum uric acid level increased in diabetic subjects than controls.In our study UA levels were measured in both, serum and urine samples, and then urine/serum ratio of uric acid levels was calculated and compared between Type 2 diabetic patients and control subjects. Patients receiving drugs known to influence UA levels were excluded from the analysis.

Our results demonstrated a profound increase in uric acid urine/serum ratios in Type 2 diabetic patients as compared to healthy controls. This finding is concurrent with data published in previous studies in which hyperuricemia has been associated with the higher risk for developing impaired glucose tolerance and Type 2 diabetes (Nakanishi N *et al*, 2003, Boyko EJ *et al*,2000, Dehghan A *et al*,2008)

Here we also show a positive correlation between serum and urine UA levels in diabetic patients. Interestingly, our data suggest a trend of negative correlation betweenurine/serum ratio of UA levels (USRUA) values and serum glucose levels, which was more profound in male than in female diabetic patients. Here we demonstrated an effect of aging on serum UA in diabetic patients, and there was a positive correlation between diabetic patients' age and UA levels in serum. Serum UA levels were significantly higher in older diabetic patients, while similar correlation was not observed in regards to urinary UA levels. Thus, our data suggest that with aging UA levels are increasing in serum of diabetic patients, probably due to impaired UA clearance in these patients. The serum uric acid level was consistently related to kidney function--the higher the uric acid, the lower the kidney function. "The serum concentration of uric acid in these patients varied in a manner consistent with its having played a role in this early loss of kidney function," If higher uric acid levels do contribute to loss of kidney function, then the findings may offer a new approach to treating diabetic kidney disease, "The serum uric acid concentration is modifiable by drugs or by decreasing the intake of dietary protein, the main source of uric acid,"

In this respect, it is important to emphasize that the progressive decline in kidney function, which frequently occurs with aging and the course of type 2 diabetes, is also generally paralleled by progressive increases in serum uric acid levels (Nakagawa T *et al*, 2006).

Previous studies reported that hyperglicemia was a risk factor for hyperuricemia (Yoo T.W *et al*, 2005, Becker M.A *et al*, 2006) and that an elevation of serum UA concentration increased the risk of Type 2 diabetes (Nakanishi N *et al*, 2003). This is was complemented with our results, which demonstrated that the USRUA values were higher in diabetic patients than in controls.

our data demonstrated significant positive correlation between USRUA and serum glucose levels in patients diagnosed with Type 2 diabetes. Our results demonstrated no effect of sex on uric acid levels in serum and urine in both control and diabetic

patients. Although there was a trend of increased UA levels in males as compared to females, this difference was not significant.

The findings of the BMI, and the waist hip ratio in the diabetic males and females in our study were in accordance with the findings of others (Schmidt MI *et al*, 1992, Matsuura F*et al*, 1998). High serum UA was significantly associated with several metabolic factors such as a large waist circumference (or BMI), dyslipidemia, high BP. In obese individuals, high serum UA is due to an overproduction of UA and impairment in renal clearance of UA owing to the influence of hyperinsulinemia secondary to IR (Quinones Galvan A*et al*,1995, Matsuura F*et al*,1998). Waist hip ratio is a potential risk on elevated serum uric acid more than overall obesity.

Aging and sex hormones (estrogen and androgen) may contribute to gender difference, but the mechanism is uncertain. In addition, the difference in smoking and diet between men and women may be involve, since smoking and drinking alcohol were more popular for men than women . This can not be investigated, however, because the detailed dieting information (e.g. meat and seafood) was not collected.

Treatment with thiazide diuretics in hypertensive subjects may induce both hyperuricaemia and hyperglycaemia. Although men on hypertensive therapy had higher glucose and uric acid levels than those not on treatment. Diuretics increase the net reabsorption of uric acid in the proximal tubule of the nephron and thereby reduce urinary excretion and increase the risk of hyperuricaemia (Choi HK *et al*,1979, Reyes AJ *et al*,2003) and gout*(*Choi HK *et al*,2005). Although not as impressive as the hyperuricaemic property of diuretics, β blockers, including propranolol, atenolol, metoprolol, timolol, and alprenolol, also have been shown to increase serum uric acid levels (Reyes AJ*et al*, 2003, Report of Medical Research Council Working Party on Mild to Moderate Hypertension. Lancet1981)

Several factors are known to alter the serum uric acid levels in T2DM. From the present study, it appears that uric acid alone cannot act as an independent risk marker for type 2 diabetes mellitus. Our study had several potential limitations. First, this observational study did not clarify the time sequence of hyperuricemia and metabolic syndrome. Second, because baseline serum uric acid concentrations were measured only once, our results may be prone to intraindividual variations that might have attenuated our results. Finally, we were unable to obtain detailed information on antihypertensive medications and the intake of foods that might have affected plasma uric acid concentrations.

The limitations of the present study include being a hospital based study; a community based study would yield better information. The number of participants is small for subgroup analysis. The Uric acid level is subjected to vary based on other co morbidities.

This study showed significantly elevated Urine &Serum UA levels in patients with Type 2 diabetes, a negative Urine & Serum UA correlation with the blood glucose levels in diabetic patients, and an effect of sex and age on the uric acid levels. Since literature data suggest a strong genetic effect on UA levels, it would be pertinent to perform further, possibly genetic studies, in order to clarify gender and ethnic differences in UA concentrations.

CONCLUSION

In conclusion, the uric acid may serve as a potential biomarker of deterioration of glucose metabolism. Diabetics may be at higher risk of developing uric acid related complications like gout and nephropathy. A large community based prospective study in Indian population is needed to verify the findings. Both uric acid and glucose concentrations were strongly associated with the body mass index.

This prospective study suggests a positive association between the plasma concentration of uric acid and the incidence of type 2 diabetes. The uric acid may serve as a potential biomarker of deterioration of glucose metabolism.

This study showed significantly elevated Urine &Serum UA levels in patients with Type 2 diabetes, a negative Urine & Serum UA correlation with the blood glucose levels in diabetic patients, and an effect of sex and age on the uric acid levels. Since literature data suggest a strong genetic effect on UA levels, it would be pertinent to perform further, possibly genetic studies, in order to clarify gender and ethnic differences in UA concentrations.

Acknowledgement

We would like to express our deep sense of gratitude to Indian Council of Medical Research for funding this student project. We would also like to thank SreeNarayanaInstitute of Medical Sciences, Ernakulam, Kerala for providing the resources andfacilities.

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How to cite this article:

Seema L Jawalekar *et al*.2016, Association Between Serum And Urine Uric Acid Levels In Patient With Diabetes Mellitus. *Int J Recent Sci Res.* 7(1), pp. 8430-8436.

TSSN 0976-3031