Original Research Article

A study to determine the association of serum uric acid and urine uric acid with different levels of glucose

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Abstract

Introduction: Uric acid is end product of purine metabolism in human beings, possesses both antioxidant and pro-oxidant properties. Uric acid has proven emerging roles in various diseases such as gout, renal dysfunction, hypertension, hyperlipidemia, diabetes and obesity. **Material and Methods:** This was anobservational and Cross-Sectional Study conducted at ESIC Medical college and hospital, Kalaburagi, Karnataka from April 2019 to September 2019 with a Sample Size of 100 Subjects, which includes 50 cases and 50 controls. Individuals in the age group 30-70 years suffering from type 2 diabetes mellitus, which is defined as fasting serum glucose ≥ 126mg/dl were included. **Result:** The fasting blood sugars (FBS) of the subjects had mean of 83.9±13.43 mg/dl in control group, in Group I cases had 170.71±19.80 mg/dl and in Group II cases had 307.54±203.68 mg/dl. Uric acid in control group had level of 3.85±1.41 mg/dl, in Group I cases had 7.27±0.35 mg/dl and in Group II cases had 4.9±3.89 mg/dl. The urinary uric acid level 578±82.02 mg/day in control group, in Group I cases had 364.31±40.31 mg/day and in Group II cases had 999.13±899.44md/day. There is statistical significant difference between control and group I cases ($p<0.0001$). **Conclusion:** Initial increase in Serum Uric acid and decrease in Urinary Uric acid with hyperglycaemia can be due to hyperinsulinemia, urate redox shuttle, microvascular injury and/or increase generation and activity of Xanthine oxidase. Decrease in Serum Uric acid and increase in Urinary Uric acid with advancing hyperglycaemia can be due to glycosuria causing uricosuria and decrease in sodium reabsorption.

Keywords: Hyperuricemia, Diabetes, Serum uric acid, Urine uric acid, Blood glucose.

Introduction

Hyperuricemia was defined as the circulating uric acid levels of more than 6.0 mg/dl for women and 7.2 mg/dl for men [1]. The prevalence of hyperuricemia in the general population is estimated at about 10–25%. When the blood uric acid concentration exceeds the norm, the human body fluid becomes acidic, which affects the normal function of the human cells, subsequently leading to metabolic disease in the long term. Uric acid is end product of purine metabolism in human beings, possesses both antioxidant and pro-oxidant properties. The levels of serum uric acid (SUA) are determined by a balance of production, reabsorption and secretion [2].

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. [3] Kidney also plays an important role in the regulation of blood uric acid levels. 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 and the remaining excreted 10% is responsible for 60–70% of total body uric acid excretion [4]. A small amount of uric acid secreted in the intestine is responsible for 30–40% [5]. Changes in the uric acid content in body fluids can reflect the state of metabolism, immunity, and other functions of the human body. If the body produces more uric acid or the excretion mechanism is degraded, the body will retain excessive uric acid.

Uric acid has proven emerging roles in various diseases such as gout, renal dysfunction, hypertension, hyperlipidemia, diabetes and obesity. Hyperuricemia occurs as a result of the abnormal increased uric acid production and/or the impaired renal uric acid excretion [6]. As a concomitant of metabolic syndrome, hyperuricemia is an independent risk factor of impaired fasting glucose and type 2 diabetes [7]. On the other hand, serum UA was an important predictor of risk of metabolic syndrome, diabetes, and hypertension in adult males [8]. However, the relationship between blood UA and decreased insulin sensitivity in patients with type 1 diabetes mellitus is weaker than in healthy subjects [9]. Clarifying the association between plasma glucose and SUA levels in population with normal glucose tolerance benefits the screening and prevention of diabetes.

A noticeable relationship has been observed between plasma glucose and SUA levels. Interestingly, the relationship between the two factors does not show a simple linear correlation. Studies conducted in diverse ethnic groups showed similar results that blood glucose (FPG) and SUA exhibited a curvilinear correlation, both in general population and diabetic subjects [10]. Multivariate linear regression analysis showed that SUA had an independent effect on insulin

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secretion in female patients; the islet *β*-cell function of male was also affected by SUA, age, body mass index (BMI), and blood lipids; SUA correlated positively with insulin secretion and the insulin resistance index in male patients [11].

This study was carried out to evaluate the level of serum uric acid and urinary uric acid levels and to correlate it with different levels of glucose in type 2 Diabetes mellitus patients.

Material and Methods

This is anobservational and Cross-Sectional Study was conducted at ESIC Medical College and hospital, Kalaburagi, Karnataka from April 2019 to September 2019 with a Sample Size was of 100 Subjects, which includes 50 cases and 50 controls.

Inclusion Criteria

1. Individuals in the age group 30-70 years suffering from type 2 diabetes mellitus, which is defined as fasting serum glucose ≥ 126 mg/dl.
2. Includes both men and women.
3. Diagnosed type 2 diabetes mellitus patients taking oral hypoglycaemic medications or insulin for treatment.

Exclusion Criteria

Individuals having type 1 diabetes mellitus, diagnosed hypertensive, cardiovascular disease, stroke, pre-existing renal disease, dyslipidaemia, gout, drugs which alter serum uric acid levels were excluded.

The nature of study was explained to the subjects and written informed consent was taken. Subjects were instructed to have overnight 10-12 hours fast. Under aseptic conditions 4 ml of venous blood sample was collected from anticubital vein of which 2ml was collected in fluoride tubes for fasting serum glucose estimation and 2ml in plain tube for serum uric acid estimation. 24 hours urine was collected for urinary uric acid estimation.

Grouping of Cases

Based on fasting serum glucose level, 50 cases were arbitrary divided into 2-groups i.e., Group-I comprising of patients having FBS 126-220 mg/dL and Group-II having FBS >220 mg/dL. Estimation of Fasting Serum Glucose was done byHexokinase method [12] and Serum & Urinary Uric Acid by Uricasemethod[13].

Statistical analysis

Statistical analysis of data was done by applying independent t test, chi square test and z test. Statistical software SPSS 17 was used.

Result

The fasting blood sugars (FBS) of the subjects had mean of 83.9±13.43 mg/dl in control group and in Group I cases had elevated fasting blood sugar levels 170.71±19.80 mg/dl. Moreover, the uric acid of in control group had level of 3.85±1.41 mg/dl and in Group I cases 7.27±0.35 mg/dl. The urinary uric acid level 578±82.02 mg/day in control group and in Group I cases had 364.31±40.31 mg/day. There is statistical significant difference between control and group I cases (p<0.0001) in table 1.

Table 1: Serum Uric acid, Urinary Uric acid and Fasting Serum Glucose levels in controls and Group I cases (i.e., FBS range – 126-220mg/dl)

Parameters	Controls (Mean±SD)	Group I cases (Mean±SD)	p-value
Fasting Serum Glucose (mg/dl)	83.9±13.43	170.71±19.80	<0.0001
Serum Uric acid (mg/dl)	3.85±1.41	7.27±0.35	<0.0001
Urinary Uric acid (mg/day)	578±82.02	364.31±40.31	<0.0001

The fasting blood sugars (FBS) of the subjects had mean of 83.9±13.43 mg/dl in control group and in Group II cases had elevated fasting blood sugar levels 307.54±203.68 mg/dl. Moreover, the uric acid of in control group had level of 3.85±1.41 mg/dl and in Group II cases 4.9±3.89 mg/dl. The urinary uric acid level 578±82.02 mg/day in control group and in Group II cases had 999.13±899.44 mg/day. Fasting serum glucose and urinary uric acid shows statistical significant difference between control and group II cases in table 2.

Table 2: Serum Uric acid, Urinary Uric acid and Fasting Serum Glucose levels in controls and Group II cases (i.e., FBS range – ≥220mg/dl)

Parameters	Controls (Mean±SD)	Group II cases (Mean±SD)	p-value
Fasting Serum Glucose (mg/dl)	83.9±13.43	307.54±203.68	<0.0001
Serum Uric acid (mg/dl)	3.85±1.41	4.9±3.89	0.0964
Urinary Uric acid (mg/day)	578±82.02	999.13±899.44	0.0015

The fasting blood sugars (FBS) of the subjects had mean of 170.71±19.80 mg/dl in Group I cases and in Group II cases had elevated fasting blood sugar levels 307.54±203.68 mg/dl. Moreover, the uric acid of in Group I cases had level of 7.27±0.35 mg/dl and in Group II cases 4.9±3.89 mg/dl. The urinary uric acid level 364.31±40.31 mg/day in Group I cases and in Group II cases had 999.13±899.44 mg/day. There is statistical significant difference between Group I and Group II cases in table 3.

Table 3: Serum Uric acid and Urinary Uric acid levels in cases at different levels of Fasting Serum Glucose

Parameters	Group I cases (Mean±SD)	Group II cases (Mean±SD)	p-value
Fasting Serum Glucose (mg/dl)	170.71±19.80	307.54±203.68	0.0017
Serum Uric acid (mg/dl)	7.27±0.35	4.9±3.89	0.0040
Urinary Uric acid (mg/day)	364.31±40.31	999.13±899.44	0.0010

Graph 1 depicts Serum Uric acid is positively correlated with Fasting blood sugar in Group I cases with r value +0.73. Graph 2 depicts Serum Uric acid is negatively correlated with Urinary Uric acid in Group I cases with r value -0.1234. Graph 3 depicts Serum Uric acid is negatively correlated with Fasting blood sugar in Group II cases with r value -0.8025. Graph 4 depicts Serum Uric acid is negatively correlated with Urinary Uric acid in Group II cases with r value -0.9459.

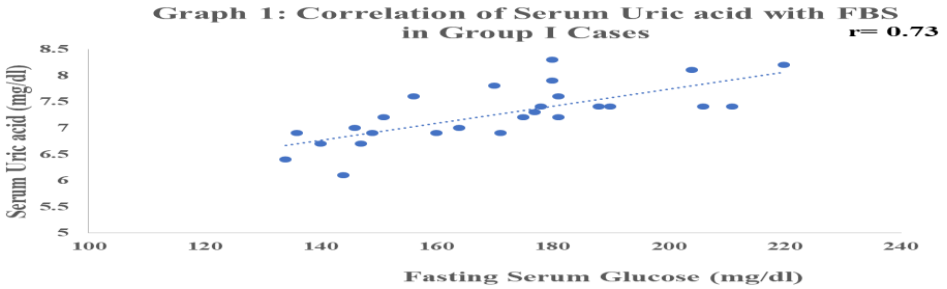

Fig 1:Correlation of serum uric acid with FBS in Group I cases

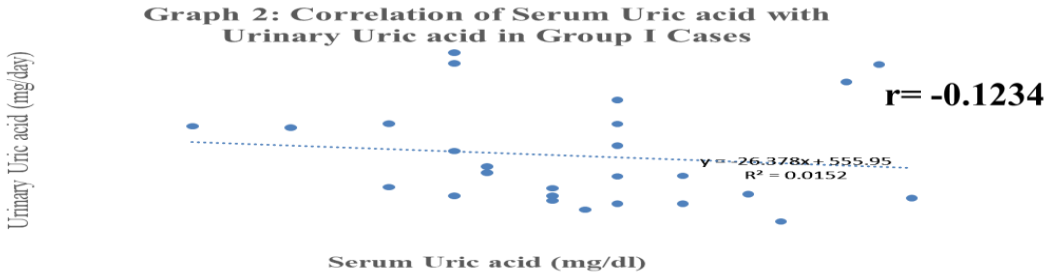

Fig 2:Correlation of serum uric acid with urinary uric acid in Group I cases

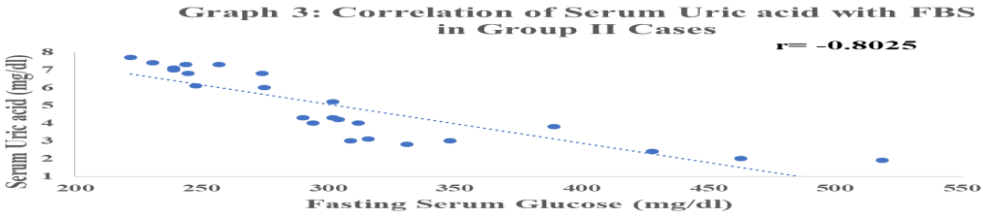

Fig 3:Correlation of serum uric acid with FBS in Group II cases

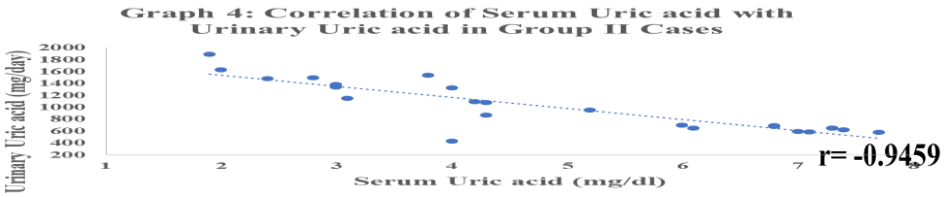

Fig 4:Correlation of serum uric acid with urinary uric acid in Group I cases

Discussion

In recent decades, the prevalence of hyperuricemia has increased substantially in the world with a rising trend both in the developed and developing nations [14]. High concentration of uric acid in the blood can lead to gout and are associated with several medical conditions, including diabetes and renal dysfunction [15]. However, the putative association between SUA and diabetes is not clear and the findings are controversial, and there may be sex and ethnic differences in the relationships. Previously, some studies reported a positive association between elevated SUA and diabetes [16], whereas, other studies reported no correlation [17], or an inverse relationship [18]. In healthy individuals, SUA has been reported to be positively correlated with blood glucose [19]. So, it is important to know the actual trend of SUA in diabetic individuals, as hyperuricemia is increasingly found to be associated with a number of modifiable risk factors contributing to cardiovascular diseases. Although there are some reports on the relationship between SUA and diabetes from different parts of the world, still there is a lack of such information for the Karnataka population. In this context, we aimed to assess the relationship between SUA and fasting blood glucose (FBG) levels in non-diabetic healthy and diabetic individuals in Kalaburagi.In our study we found that the serum uric acid levels

increased with increasing levels of FBS (126-220 mg/dl) and then decreased with further increasing levels of FBS. We found that the urinary uric acid levels decreased with increasing levels of FBS (126-220 mg/dl) and then increased with further increasing levels of FBS. Initial increase in Serum Uric acid level and decrease in Urinary uric acid level in Type 2 Diabetes Mellitus can be explained by following hypothesis: Insulin may enhance renal urate reabsorption by stimulating the urate-anion exchanger URAT1 and/or the Na^+-dependent anion co-transporter in the brush border membranes of the renal proximal tubule. [20] Hyperglycemia induces both an oxidative stress and a reductive stress through pseudohypoxia with the accumulation of NADH and NAD(P)H in the vascular intima. This redox stress consumes the natural occurring local antioxidants such as: Superoxide dismutase, Glutathione peroxidase and catalase. Once these local intimal antioxidants are depleted uric acid can undergo the paradoxical antioxidant – prooxidant switch or the urate redox shuttle. [21] Type 2 DM is associated with microvascular injuries resulting in local tissue ischemia. Ischemia with associated increased lactate production that blocks urate secretion in the proximal tubule and increased uric acid synthesis due to increased RNA-DNA (purine) breakdown, which increases uric acid and ROS through the effect of xanthine oxidase (XO). Ischemia itself causes increased generation of XO. [22,23] Decrease in Serum Uric acid level and increase in Urinary Uric acid level with advancing hyperglycemia in Type 2 Diabetes Mellitus can be explained by following hypothesis: The increased insulin levels in individuals with insulin resistance syndrome could conceivably contribute to their elevated serum uric acid levels to the point where the effect is offset by subsequent development of glycosuria in diabetic patients leading to uricosuria and lower uric acid levels. [23,24] Glycosuria causes osmotic diuresis leading to holding of water in tubules. There is a limit to the concentration gradient against which sodium can be pumped out of the proximal tubules. Sodium concentration in the fluid falls resulting in limitation of sodium reabsorption in proximal tubules. This leads to further decrease in the Serum Uric acid levels due to decreased in proximal reabsorption of sodium and urate.

Conclusion

Serum Uric acid initially increased with increase in Fasting Blood Sugar from 126mg/dl to 220mg/dl range and thereafter decreased with further increase in Fasting Blood Sugar. Urinary Uric acid initially decreased with increase in Fasting Blood Sugar from 126mg/dl to 220mg/dl range and thereafter increased with further increase in Fasting Blood Sugar. Initial increase in Serum Uric acid and decrease in Urinary Uric acid with hyperglycaemia can be due to hyperinsulinemia, urate redox shuttle, microvascular injury and/or increase generation and activity of Xanthine oxidase. Decrease in Serum Uric acid and increase in Urinary Uric acid with advancing hyperglycaemia can be due to glycosuria causing uricosuria and decrease in sodium reabsorption.

References

1. Carl A Burtis, Edward R Ashwood. Teitz Textbook of Fundamentals of clinical chemistry. 5th edition; Elsevier publications, 2003.
2. Modi AS, Sahi N. Serum uric acid levels in type 2 diabetes mellitus. Indian J Basic Appl Med Res. 2018;7:459–63.
3. 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.
4. van der Schaft N, Brahimaj A, Wen K-X, Franco OH, Dehghan A. The association between serum uric acid and the incidence of predia-betes and type 2 diabetes mellitus: the Rotterdam Study. PLoS ONE. 2017;12:e0179482.
5. Pavani CH, Mohanty S, Dharwadkar AA. Hypouricemia in type 2 diabetes mellitus without nephropathy: a case control study. Int J ClinBiochem Res. 2018;5:201–5.
6. Ali N, Mahmood S, Manirujjaman M, Perveen R, Al Nahid A, Ahmed S et al. Hypertension prevalence and infuence of basal metabolic rate on blood pressure among adult students in Bangladesh. BMC Public Health. 2017;18:58.
7. Arévalo-Lorido JC, Carretero-Gómez J, Robles Pérez-Monteoliva NR. Association between serum uricacid and carotid disease in patients with atherosclerotic acue ischemic stroke. Vascular. 2019;27:19-26.
8. Zuo T *et al*. Hyperuricemia and coronary heart disease mortality: a meta-analysis of prospective cohort studies. BMC Cardiovasc. Disord. 2016;16:207.
9. Li M *et al*. Hyperuricemia and the risk for coronary heart disease morbidity and mortality: a systematic review and dose-response meta-analysis. Sci. Rep. 2016; 6:19520.
10. Kamei K *et al*. Serum uric acid levels and mortality in the Japanese population: the Yamagata (Takahata) study. Clin. Exp. Nephrol. 2016;20:904-909.
11. Cho SK, Chang Y, Kim I, RyuS. U-Shaped Association Between Serum Uric Acid Level and Risk of Mortality: A Cohort Study. Arthritis. Rheumatol. 2018;70:1122-1132.
12. Tietz NW. Clinical guide to laboratory tests. 3rd edition Philadelphia: WB Saunders, 1995, 268-273.
13. Trivedi R, Berta E, Rebar L. Enzymatic uric acid determination at 500nm by Trinder method. Clin. Chem. 1976; 22:1223.
14. Zhang W *et al*. Serum Uric Acid and Mortality From Cardiovascular Disease: EPOCH-JAPAN Study. J. Atheroscler. Thromb. 2016;23:692-703.
15. Kamei K, Konta T, Hirayama A, Watanabe T. Associations between serum uric acid levels and the incidence of nonfatal stroke: a nationwide community-based cohort study. Clin. Exp. Nephrol. 2107;21:497–503.
16. Iseki K *et al*. Dipstick proteinuria and all-cause mortality among the general population. Clin. Exp. Nephrol. 2018; 22:1331–1340.
17. AkshayShirsath, Virendra C Patil, Makarand Mane, ShilpaPatil. A study of serum uric acid levels in type 2 diabetes mellitus subjects: a cross sectional study. International Journal of Contemporary Medical Research. 2019;6(1):A21-A24.
18. Akhtar SN, Dhillon P. Prevalence of diagnosed diabetes and associated risk factors: Evidence from the largescale surveys in India. Journal of Social Health and Diabetes. 2017;5(1):28.
19. Prashanthkumar G, Nagendra S, Kashinath RT. Plasma Uric Acid Levels in Relation to Plasma Cholesterol Levels in Type-2 Diabetes Mellitus. Global Journal of Medical Research. 2015;14:123-28.
20. Talwar T, L Tanwar, M Gupta. Study of serum uric acid levels in type-2 diabetes mellitus patients. Journal of Dental and Medical Sciences. 2017; 32:83-89.
21. Suryawanshi KS, Jagtap PE, Belwalkar GJ, Dhonde SP, Nagane NS, Joshi VS. To study serum uric acid and urine microalbumin in type-2 diabetes mellitus. Int J Med Sci. 2015;2:24-9
22. Goyal B, Goyal J, Sinha M, Fiza B, Sharma P, Bandhari S, Sharma P. Association of glycosylated hemoglobin with microalbuminuria in patients with type 2 diabetes mellitus. International Journal of Biotechnology and Biochemistry. 2017;13:311-23.
23. KhajaMoinuddin, SM Awanti. Evaluation of the relationship between glycemic parameters and serum uric acid level in type 2 diabetes mellitus patients. International journal of clinical biochemistry and research. 2016;3(4):395-401.
24. Avula NR,Shenoy D.Evaluation of association of hyper-uricaemia with metabolic syndrome and insulin resistance. Journal of clinical and diagnostic research: JCDR. 2016;10:32-53.

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