A Study of the Correlation between Altered Blood Glucose and Serum Uric Acid Levels in Diabetic Patients

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ABSTRACT

BACKGROUND

The prevalence of diabetes mellitus ranges from 0.4 - 3.9% in rural areas to 9.3 - 16.6% in urban areas, in India. Diabetes causes long term dysfunction of various organs like heart, kidneys, eyes, nerves, and blood vessels. Hyperuricemia is defined as serum uric acid concentration in excess of urate solubility. In non-diabetic subjects, an elevated level of uric acid has been shown to be an independent predictor of coronary heart disease and total mortality. Also elevated levels of uric acid is a risk factor for peripheral arterial disease.

METHODS

This is a cross sectional study conducted over a period of 1 year. 565 individuals visiting the routine health check-up were included in the study. Serum uric acid, glycated haemoglobin (HbA1c) and glucose were estimated on Siemens Dimension auto analyser. Descriptive statistics was applied for frequency and Mean ± SD were derived for all the parameters. One-way Anova, unpaired two sample 't' test was applied for gender - specific and age - specific group comparisons for all the markers. Correlation analysis was performed using the Pearson's correlation method. p values <0.05 were considered statistically significant.

RESULTS

This study comprised of 565 individuals, of which there were 267 cases and 298 controls. Levels of HbA1c were significantly increased in patients with diabetes mellitus (8.3 ± 1.5 mg/dL) as compared to control group. (5.9 ± 0.3 mg/dL; p <0.001). Furthermore, Uric acid levels were also significantly increased in patients with diabetes mellitus (8.1 ± 1.2 mg/dL) as compared to control group. (4.6 ± 1.0 mg/dL; p <0.001). There was a significant correlation between uric acid and HbA1c levels (r = 0.132, p =0.031) and also between uric acid and FBS level (r = 0.155, p = 0.011) in patients with diabetes mellitus.

CONCLUSIONS

Our data suggested a positive correlation between altered blood glucose and serum uric acid levels and between serum uric acid and HbA1c levels. From our study we deciphered that high serum uric acid levels were associated with diabetes mellitus. Thus, serum uric acid may serve as a potential biomarker of the deterioration of glucose metabolism.

KEYWORDS

Uric Acid, HbA1c, Glucose

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BACKGROUND

Diabetes mellitus is a group of disorders characterized by chronic hyperglycaemia associated with disturbances in carbohydrate, fat and protein metabolism, due to absolute or relative deficiency of insulin secretion or its action.[1] The prevalence of diabetes in adults aged 20 years or older in India increased from 5·5% (4·9-6·1) in 1990 to 7·7% (6·9-8·4) in 2016.[2] Diabetes causes long term dysfunction of various organs like heart, kidneys, eyes, nerves and blood vessels.[3] Hyperuricemia is defined as serum uric acid concentration in excess of urate solubility. Uric acid (UA)[2] trihydroxy purine, C5H4N4O3) is a purine derivative. UA metabolism is a type of nucleic acid metabolism metabolizing purine and its derivatives (adenine, and guanine). Phosphorus oxidation of adenine and guanine (resulting in ATP and GTP) and UA production are essential for many physiological functions. Serum Uric acid is formed by the breakdown of purines and by direct synthesis from 5-phosphoribosyl pyrophosphate and glutamine. High fructose consumption causes hyperuricemia.[4] People with elevated uric acid, but without the symptoms of gout, nephropathy, or kidney stones are classified as having asymptomatic hyperuricemia. If the gouty symptoms do not occur, people with asymptomatic hyperuricemia are usually unaware of their condition and the possible consequences such as hypertension, diabetes, renal disease and cardiovascular diseases. Patients with hyperuricemia are at a significant risk of progressing to type 2 diabetes. Furthermore, in non-diabetic subjects an elevated level of uric acid has been shown to be an independent predictor of coronary heart disease and total mortality. Serum uric acid has been shown to be associated with an increased risk of hypertension,[5,6] cardiovascular disease[7,8] and chronic kidney disease[9] in previous epidemiological studies. Also elevated levels of uric acid is a risk factor for peripheral arterial disease,[10] insulin resistance and components of the metabolic syndrome. There has been growing interest in the association of hyperuricaemia with hyperglycaemia.[11] Hence, the purpose of this study is to show the correlation between elevated blood glucose and serum uric acid levels in diabetic patients.

METHODS

This was a cross sectional study conducted in 2016 over a period of 1 year in a tertiary care hospital in Anand district, Gujarat. The study was done after getting a written approval from the ethics committee. 565 individuals visiting the routine health check-up were included in the study. Patients with renal failure, cardiovascular diseases, altered liver function tests and thyroid dysfunction were excluded from the study. Detailed history was taken with prior permission from the concerned authorities. During the course of study there was no change in the equipment, reagent, Calibration standards and controls. Before starting the analysis, the instrument was calibrated using standard calibrators. Fasting morning blood samples were collected from anterior cubital vein venipuncture and 2-4 ml of blood collected in plain, EDTA and fluoride vacutainers for separation of serum. The sample was placed aside for 15 minutes to clot. The specimens were centrifuged and serum uric acid & glucose were estimated. HbA1c was estimated from whole blood. Serum uric acid was measured by colorimetric method using uricase and peroxidase. HbA1c levels were measured by immunoturbidimetry method and glucose levels were measured by using Hexokinase method. All tests were performed on Siemens Dimension® RxL Max® auto analyzer.

Statistical Analysis

Analysis was performed using the commercially available statistical software Stata 14, SPSS- 14.0 version, MedCalc version 12.5 and Microsoft excel. For each analyte (serum uric acid, Glucose, HbA1c) Mean ± SD values were presented. One way Anova and unpaired two sample 't' test was applied for gender-specific and age - specific group comparisons for all the markers. Descriptive statistics was applied for frequency and Mean ± SD. Correlation analysis was performed using the Pearson's correlation method. p values <0.05 were considered statistically significant.

RESULTS

This study comprised of 565 individuals (291 men and 274 women) with mean age of 56 and 49 years respectively. Among 565 individuals 267 were cases and 298 were controls. Case group comprised of 180 male individuals and 117 female individuals while the control group comprised of 141 male individuals and 157 female individuals. Age and gender wise partitioning of subjects were done. (Table 1) The one way Anova showed t=-2.042, degree of freedom=118 and p=0.298 which showed that there was no significant difference between these age groups.

Age (year)	Total	Male	Female
20 - 30	30	14 (4.81%)	16 (5.84%)
31 - 40	82	44 (15.12%)	38 (13.87%)
41 - 50	100	54 (18.56%)	46 (16.79%)
51 - 60	170	83 (28.52%)	87 (31.75%)
61 - 70	183	96 (32.99%)	87 (31.75%)
Total	565	291 (100%)	274 (100%)

Table 1. Age and Gender Distribution

Variables	Case Group	Control Group
Sample size	267	298
Mean value (mg/dL)	187	99
95% Confidence interval	182 to 192	98 to 100
Standard Deviation	43.3	8.3
t value	-34.4	
Degree of Freedom	563	
P value	p <0.001	

Table 2. Comparison of FBS between Case and Control Groups

The FBS values for the control reference population were normally distributed. The unpaired t-test showed that FBS levels were significantly increased in patients with diabetes mellitus (187 ± 43.3 mg/dL) as compared to control group. (99 ± 8.3 mg/dL) p <0.001 (Table 2).

Variables	Case Group	Control Group
Sample size	267	298
Mean value (%)	8.3	5.9
95% Confidence interval	8.1 to 8.4	5.8 to 5.9
Standard Deviation	1.5	0.3
t value	-27.5	
Degree of Freedom	563	
p value	p <0.001	

Table 3. Comparison of HbA1c between Case and Control Groups

The HbA1c values for the control reference population were normally distributed. The unpaired t-test showed that HbA1c levels were significantly increased in patients with diabetes mellitus (8.3 ± 1.5 mg/dL) as compared to control group. (5.9 ± 0.3 mg/dL) p <0.001 (Table 3).

Variables	Case Group	Control Group
Sample size	267	298
Mean value (mg/dL)	8.1	4.6
95% Confidence interval	8 to 8.2	4.5 to 4.7
Standard Deviation	1.2	1.0
t Value	-37.7	
Degree of Freedom	563	
p value	p <0.001	

Table 4. Comparison of Uric Acid between Case and Control Groups

The uric acid values for the control reference population were normally distributed. The unpaired t-test showed that Uric acid level were significantly increased in patients with diabetes mellitus (8.1 ± 1.2 mg/dL) as compared to control group. (4.6 ± 1.0 mg/dL); p <0.001 (Table 4)

Variable	Pearson's Correlation Coefficient	P Value
Uric acid vs HbA1c	0.132	0.031
Uric acid vs FBS	0.155	0.011

Table 5. Correlation of Serum Uric acid with HbA1c and FBS

Table 5 shows that significant correlation exists between uric acid and HbA1c levels (r = 0.132, p =0.031) and also there was also a significant correlation found between uric acid and FBS levels (r = 0.155, p = 0.011) in patients with diabetes mellitus.

DISCUSSION

In the current study it was observed that the fasting blood sugar levels were significantly increased in cases (187 ± 43.3 mg/dL), p<0.001. As compared to control group (99 ± 8.3 mg/dL), p<0.001. The HbA1c levels were significantly increased in cases (8.3 ± 1.5 mg/dL) p<0.001, as compared to control group (5.9 ± 0.3 mg/dL), p<0.001 and Uric acid levels were significantly increased in cases (8.1 ± 1.2 mg/dL), p<0.001, as compared to control group (4.6 ± 1.0 mg/dL), p<0.001. Uric acid and HbA1c levels were found to be significantly correlated (r = 0.132, p = 0.031). There was also a significant correlation between Uric acid and Fasting blood sugar levels (r = 0.155, p = 0.011). At present, many studies have shown that the relevant pathological mechanisms that lead to increased uric acid levels. Increased uric acid levels in the blood promoted the expression of interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and CRP production. In human studies, serum UA was positively associated with TNF-α, interleukin-6 and C-reactive protein in healthy people.[12] Excessive uric acid will lead to an increase in reactive oxygen species (ROS) production, which leads to inflammation and dysfunction in the vessel. Uric acid is a powerful antioxidant that can remove superoxide and hydroxyl radicals in plasma, and it has prooxidant effects in vascular tissue by increasing ROS production, such as hydrogen peroxide. Uric acid mediated oxidative stress-induced lipid peroxidation, DNA damage, and activation of inflammatory factors finally lead to cellular damage.[13] Oxidative stress also can affect the expression of insulin gene, causing a decrease in insulin secretion. UA can react with Nitric oxide (NO) to form 6-amino uracil, uric acid-dependent ROS reacts with NO to form peroxynitrite, and UA can hold back L-arginine uptake and stimulate L-arginine degradation. As a result of the effects of hyperglycaemia and neurohormonal activation, uric acid levels are independently associated with endothelial dysfunction in animals and humans, thereby promoting hypertension.[14]

A study was conducted in Raysan village, Gandhinagar, Gujarat to find out prevalence of diabetes mellitus in rural area. It proved that uric acid was associated with insulin resistance. It also stated that in non-diabetic subjects an elevated level of uric acid is an independent predictor of coronary heart disease and total mortality.[15] Sudhindra Rao et al. in 2012 studied a total of 117 subjects. The mean serum uric acid levels were lower in control group 3.83 mg/dL (p-value 0.009) rise in pre diabetics 4.88 mg/dL (0.003) and again decreased in diabetics 3.78 mg/dL (0.982) this could be probably due to associated conditions or drug intake which can decrease uric acid level while our study included 565 individuals wherein the mean serum Uric acid levels in controls was 4.6 mg/dL and in diabetic patients was 8.1 mg/dL which was statistically significant (<0.001). More participant helps in establishing a better correlation of serum uric acid with diabetes mellitus. Pavani Bandaru and Anoop Shanker et al, in 2011 performed a study on the baseline characteristics of the study population by increasing quartiles of serum uric acid levels and the association between increasing serum uric acid levels and diabetes mellitus in the whole cohort observed an inverse association between serum uric acid levels and diabetes mellitus in both the age and sex adjusted and the multivariable adjusted models.[16] One more similar study was conducted by H.K Choi and E. S. Ford et al. in which the mean serum uric acid was 316.4 µmol/l (361.0 µmol/l among men and 276.6 µmol/l among women) and 18% were hyperuricemia (19% with serum uric acid >416 µmol/l among men and 17% with serum uric acid >339 µmol/l among women). The characteristics of the study population according to HbA1c levels are shown. The serum uric acid level increased with increasing serum HbA1c levels up to the category of 6 - 6.9% and there after decreased with further increasing HbA1c levels.[17] Abbas Dehghan et al in their study showed that one quarter of diabetes cases can be attributed to a high serum uric acid levels.[18]

CONCLUSIONS

High serum uric acid levels were associated with diabetes mellitus. Our data suggested a positive correlation between altered blood glucose and serum uric acid levels and also between serum uric acid and HbA1c levels. There was an increase in uric acid levels in diabetic patients with increased levels of HbA1c. Thus, serum uric acid may serve as a potential biomarker of the deterioration of glucose metabolism.

Limitations

Since the study was conducted in a tertiary hospital, it is necessary to conduct similar studies with more participants and in diverse geographical areas.

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