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ORIGINAL RESEARCH ARTICLE

EVALUATION OF SERUM URIC ACID, GLUCOSE AND OTHER GLYCEMIC PARAMETER IN TYPE II DIABETIC INDIVIDUALS

Arun Dhungana[1,*], Arun Pandeya[1], Subash Pant[2], Babu Ram Pokharel[3]
[1]Department of Biochemistry, Kathmandu Medical College Teaching Hospital, Bhaktapur, Nepal
[2]Department of Internal Medicine, Kathmandu Medical College Teaching Hospital, Kathmandu, Nepal
[3]Department of neuro-medicine, Nepal Mediciti Hospital, Bhaisepati, Lalitpur, Nepal

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***Correspondence to:** Arun Dhungana, Department of Biochemistry, Kathmandu Medical College Teaching Hospital, Bhaktapur, Nepal.*
Email: a_dhungana1@yahoo.com
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ABSTRACT

Background: In spite of antioxidant property serum uric acid (SUA) has a positive association with blood glucose. SUA is considered as a strong and an independent risk factor for diabetes but low serum level of uric acid has been reported in the hyperglycemic state. Diabetes mellitus is a metabolic disorder of multiple etiologies resulting from defect in insulin action. So, aim of this study is to assess whether there is any change in SUA level and to establish whether there is any association with type II diabetes mellitus (DM) or not.

Methods: A cross sectional study was conducted in 264 cases of DM. SUA, fasting blood glucose (FBG), post-prandial blood glucose (PPBG) and glycated hemoglobin (HbA1c) level were measured. Pearson's correlation was employed to calculate the 'r' value by using SPSS version 15.

Results: In our study prevalence of hyperuricemia was 18.5%. Mean SUA in male and female was 5.95 mg/dl and 5.54 mg/dl respectively in DM. HbA1c has positive correlation with FBG and PPBG (r value = 0.720 and 0.775, respectively p=<0.001), while SUA has negative correlation with HbA1c, FBG and PPBG (r value= -0.179, p =0.004, -0.070, p=0.257 and -0.078, p=-0.204 respectively.).

Conclusions: SUA level is increased in DM. SUA was high among male and SUA initially increased when FBS and HbA1c increases then decreases as FBG and HbA1c level were further increased. SUA has negative correlation with FBG, PPBG and HbA1c, while HbA1c has a positive correlation with FBG and PPBG.

INTRODUCTION

Uric acid is the final breakdown product of purine nucleotide catabolism.[1, 2] It is a weak diprotic acid acting as a pro-oxidant. The action is dependent upon the surrounding environment such as onset of disease, location and the oxidant environment in tissues.[3, 4] Prevalence of hyperuricemia is increased in both developed and developing nation,[5] and high levels of uric acid have potentially a toxic effect, which favors precipitation of uric acid crystals in joints and tissues, leading to complications such as gout, nephrolithiasis and chronic nephropathy.[4]

A positive association between elevated Serum Uric Acid (SUA) and diabetes has been reported,[6-8] while, other has reported no correlation,[9, 10] or an inverse relationship.[11-13] SUA has positive association with serum glucose in healthy subjects.[14] However, this association is not consistent between healthy and diabetic individuals.[10, 15] SUA is considered as a strong and an independent risk factor for diabetes,[7] however, a study has shown low serum level of uric acid in hyperglycemic state.[12] Since most individuals experience a phase of impaired glucose tolerance before progression to diabetes and during the time, a prediction to risk of type II Diabetes mellitus (DM) with raised level of SUA is unclear. [10, 15]

Therefore, aim of this study was to assess whether there is any change in SUA level. Hence a study is needed to find out the significance of SUA in DM by evaluating the relationship between glycemic parameters and serum uric acid levels at different glucose tolerance status.

METHODS

A present cross sectional study was conducted in Kathmandu Medical College from September 2021- February 2022 after obtaining ethical approval from institutional review committee (IRC), reference (0504202106). Medicine in and out patient department is chosen as the study site where patient with DM most frequently visits when their blood glucose is not controlled. This present study included 264 patients ranging from 35 to 75 years of age of both sexes by non-probability sampling methods using consecutive sampling technique. Our study objective matched, based on selection criteria, patient were informed regarding the nature of the study. Subjects,

who wished to participate in this study, written consent was obtained from all the participants. On their next visit instruction was given to perform the biochemical test regarding fasting blood glucose (FBG), post prandial blood glucose (PPBG), glycated hemoglobin (HbA1c) and SUA level following the procedure. Under aseptic conditions, venous blood sample was obtained by venipuncture from cubital vein and collected in fluoride tubes. Blood sample was collected for estimation of FBG after the overnight fast and for PPBG sample was collected two hours after meal. Two ml of blood sample was collected in a plain tube for SUA estimation. Serum was separated after centrifugation then the specific tests; FBG, PPBG and SUA level was estimated by Selectra pro S fully automated analyzer using Elitech reagents and 2 ml of blood was collected in EDTA tubes for HbA1c estimation which was done by High Performance Liquid Chromatography (HPLC) methods. Those patients were only enrolled who came in next follow up and study was continued until desired participant number was not obtained. FBG = level below 110 mg/dl, PPBG = level lesser than 140mg/dl, HbA1c = 4.0-5.6 and SUA = 3.5-7.2 mg/dl for male and 2.6-6 mg/dl for female was considered normal.[16-18]

Grouping of cases: Based on fasting blood glucose level, 264 cases were arbitrary divided into 5-groups i.e., Group- I comprising of patients having FBG ≤125, Group- II having FBG 126-175 mg/dL, Group- III having FBG 176-225 mg/dL, Group-IV having FBG 226-275 mg/dL and Group-V having FBG ≥276 mg/dL. Similarly based on HbA1c level, cases were arbitrary divided into 3-groups i.e., Group-A comprising of patients having HbA1c 6.0-7.9%, Group-B having HbA1c 8.0-9.9%, Group-C having HbA1c ≥10%.

In this study already diagnosed cases of DM who were taking oral hypoglycemic medications or insulin for treatment were included, and individual patients having type I diabetes mellitus and diagnosed as hypertensive, cardiovascular disease, stroke, pre-existing renal disease, dyslipidemia, gout, and patient prescribed with drugs (e.g.: thiazide diuretics, probenecid, allopurinol, etc.) which alter serum uric acid levels were excluded.

Sample size was determined from the study conducted by Arersa et al[19] and the prevalence of hyperuricemia was 22% observed in type II diabetes patient. The sample size was calculated using following information.

$n=Z^2pq/e^2$

Where,

Z= statistic for a level of confidence. (For the level of confidence of 95%, which is conventional, Z value is 1.96).

p= expected proportion in population

q= (1-p)

e= absolute error or precision.(e is considered 0.05)

$n= (1.96)^2X0.22 X 0.78/(0.05)^2$

= 263.68

= 264

We did not account for non-response rate in sample size calculation because only those who gave consent and participate in our study were enrolled and study was continued until desired participant number was not obtained. So, in this study 264 samples will be taken.

Statistical analysis was done by SPSS (Statistical package for social science) version 15. Descriptive statistics was represented as Mean ± Standard deviation (S.D) with 95% confidence intervals for continuous data (age, height, weight, body mass index (BMI), FBG, PPBG, HbA1c and Uric Acid) and categorical data (gender, hyperuricemia, FBG group and HbA1c group) was depicted as frequency number. For measuring the correlation between two variables, pearson's coefficient of correlation 'r' was used to assess relation between HbA1c and FBG, PPBG and uric acid, as well as relation between uric acid and FBG and PPBG was observed. Statistical significance was assumed at $p<0.05$.

RESULTS

In our study mean age of cases was 54.79 years and 55.85 years for male and female respectively. Around 10.2% of male and 8.3% female were hyperuricemic in DM. A mean BMI of 25.41 kg/m2, FBG level of 155.95mg/dl, PPBG level of 228.17 mg/dl and HbA1C level of 8.20% was found to be increased in female participant while males have increased mean SUA level of 5.95 mg/dl was observed (Table 1).

Table 1: Baseline characteristics of clinicodemographic profile and biochemical parameters of patient

Parameter	Type II Diabetes Mellitus (Mean ± SD, %)	
	Male (n=150)	Female (n=114)
Age (years)	54.79 ± 10.19	55.85 ± 10.03
Gender	56.8%	43.2%
Hyperuricemia	27(10.2%)	22(8.3%)
Height (cm)	163.37 ± 5.56	158.01 ± 5.91
Weight (kg)	67.20 ± 6.12	63.48 ± 5.38
BMI (kg/m^2)	25.14 ± 1.46	25.41 ± 1.55
FBG (mg/dl)	151.72 ± 42.22	155.95 ± 38.44
PPBG (mg/dl)	224.30 ± 69.13	228.17 ± 73.32
HbA1C (%)	7.86 ± 1.42	8.20 ± 1.81
Uric Acid (mg/dl)	5.95 ± 1.89	5.54 ± 1.71

Cases were divided according to the fasting blood glucose into different groups as depicted in table 2. We observed that serum uric acid level and HbA1c varies in different level of fasting blood glucose. Our finding shows that fasting blood glucose level and serum uric acid level has some association that is when blood glucose level rises SUA level also rises but when further increase in blood glucose level results to decreased in SUA level. However, HbA1c level increases with increase in fasting blood glucose (Table 2).

Table 2: Serum uric acid level in cases at different level of fasting blood glucose and HbA1c

Group	Fasting blood Glucose range (mg/dl)	Fasting blood Glucose (mg/dl)	Serum Uric acid (mg/dl)	HbA1c (%)
I	≤125 (n=62)	118.32 ± 3.79	5.59 ± 1.55	6.87 ± 0.36
II	126-175 (n=148)	144.90 ± 14.21	5.97 ± 1.90	7.75 ±1.25
III	176-225 (n=40)	197.47 ± 14.00	5.56 ± 1.95	9.75 ± 1.58
IV	226-275 (n=8)	243.75 ± 14.92	5.46 ± 1.93	10.71 ± 1.67
V	≥276 (n=6)	317.66 ± 20.87	4.75 ± 1.04	10.78 ± 1.54

Table 3: Serum uric acid, FBG and PPBG level in case at different level of HbA1c

Group	HbA1c Range (%)	HbA1c (%)	Serum Uric acid (mg/dl)	FBG (mg/dl)	PPBG (mg/dl)
		Mean ± S.D	Mean ± S.D	Mean ± S.D	Mean ± S.D
A	6-7.9 (174)	7.07±0.39	5.80 ± 1.76	133.86 ± 17.00	189.14 ±33.61
B	8-9.9 (55)	8.80±0.56	6.83 ± 1.74	177.50 ± 33.04	273.78 ± 58.99
C	10 and above (35)	11.42±1.17	4.01 ± 0.50	213.74 ± 53.97	333.97 ± 70.15

HbA1C was grouped in different level which is depicted in table 3, an interesting finding can be obtained that is when HbA1C is increased, SUA and FBG both are increased. A further increase in HbA1C above 10%, lowers SUA but increases FBG.

Table 4: Correlation of fasting, post prandial glucose and uric acid with HbA1c

Parameter	Correlation coefficient (r value)	p value
HbA1c v/s FBG	0.720	<0.001
HbA1c v/s PPBG	0.775	<0.001
HbA1c v/s Uric Acid	-0.179	0.004

This study found the positive correlation of HbA1c with fasting and post prandial blood glucose (r value = 0.720 and 0.775, respectively p=<0.001), but there was a negative correlation of serum uric acid with HbA1c (r value= -0.179, p =0.004) which is depicted in table 4.

Table 5: Correlation of fasting, postprandial glucose with uric acid

Parameter	Correlation coefficient (r value)	p value
Uric acid v/s FBG	-0.070	0.257
Uric acid v/s PPBG	-0.078	0.204

In this study there was negative correlation of Uric acid with fasting and post prandial blood glucose (r value = -0.070, p=0.257 and -0.078, p=-0.204 respectively) which is shown in table 5.

DISCUSSION

Diabetes mellitus is one of major health problem in the developing as well as in developed countries; it is a heterogeneous group of disease that is characterized by hyperglycemia and is associated with various complications. In our study 264 cases of DM patient were enrolled. The prevalence of hyperuricemia in the our study group was 18.5% which is comparable with the results obtained in the study conducted by Wei F et al.[20] reported the prevalence rate to be 17.25%. In another study conducted in Nepal reported the prevalence rate to be 28%.[21] Similarly a study conducted in Nigeria reported the prevalence rate to be 25%. Likewise, hyperuricemia in DM is also shown by other various studies.[6,22-24]

Blood levels of Uric acid is also influenced by several factors such as overproduction, decreased glomerular filtration or renal hypoperfusion, enhanced tubular reabsorption or diminished elimination.[25] In our study raised level of SUA could be due to presence of high glucose concentration in blood resulting in tissue injury, which in turn leads to increased non protein substances that may accounts for increase uric acid levels. Hyperuricemia may also be caused by muscle wasting or due to weight loss. Hyperuricemia has been found to be associated with obesity and insulin resistance, and consequently with Type II diabetes.[26, 27]

Various mechanisms have been postulated that are responsible for the association between type II diabetes mellitus and uric acid level. Increased fructose level can cause hyperuricemia which can play a significant role in the pathogenesis of metabolic syndrome.[28] Another possible mechanism is due to induction of endothelial dysfunction by high uric acid level which would lead to the reduction of nitric oxide level.[29, 30] Nitric oxide has a crucial role in glucose intake, therefore, its reduction will lead eventually to less intake of glucose in skeletal muscles. The result of all these reactions is increased insulin resistance and the development of DM. Additionally, in patients who have higher levels of uric acid in their serum were noticed to have increased oxidative stress[31, 32] that can affect tissues and aid in the development of DM.

Serum uric acid has been shown to be associated with oxidative stress and production of tumor necrosis factor-alpha,[31] which are both related to the development of diabetes. Since, research

findings support high serum uric acid as a predisposing factor for type II diabetes, therefore, we need to re think about Uric acid, as it no more looks to be a waste product but seems to have some more roles to play in the pathology of the disease.[33] We observed a higher levels of serum uric acid in male than in female and similar type of finding was observed in a study conducted by Yeasmin R et al.[34] It could be due to gender related factors as there is higher renal clearance of urate in women, possibly due to their higher plasma estrogen levels. Estrogen is known to possess the effect of promoting excretion of uric acid.[35]

In our study females were having increased BMI when compared to males as it could be due to sex-based differences in fat storage location as males have great visceral and hepatic fat compared to women.

In our study from table 4, both FBG and PPBG correlated significantly with HbA1c values (r value 0.720 and 0.775 respectively, p<0.001). Similar type of finding was obtained in a study conducted by Shrestha L et al.[36] In another study conducted by Chauhan et al.[37] found a positive correlation of FBG and HbA1c level. Similarly Dave M et al.[38] observed that the level of HbA1c in diabetic patient is linearly correlated with FBG. While in another study conducted by Soonthornpun S et al.[39] found PPBG correlated more strongly with HbA1c in comparison with FBG. As depicted in table 5, there was negative correlation of Uric acid with fasting and post prandial blood glucose r value = -0.070, p=0.257 and -0.078, p=-0.204 respectively was observed which was statistical insignificant. A study conducted by Nair SP et al, also reported negative correlation of SUA with FBG. So, this negative correlation of SUA and FBG indicates uric acid as a potential biomarker to find deterioration in glucose metabolism.[40] In our study from table 3, SUA, FBG and PPBG level in case at different level of HbA1c shows very interesting finding; when mean HbA1c (7.07%) level there is a rise in mean SUA and FBG levels. A further rise in HbA1c(8.8%) result to further increase in mean uric acid and FBG level but when mean HbA1c (>10%) there is decrease in mean uric acid but increase in FBG level is observed. From the Table 4, HbA1c shows negative correlation with serum uric acid and similar type of findings were observed in a study conducted by Sushilendu V et al.[41] and Cui Y et al.[42] SUA initially increases with increase in HbA1c from 6% to 9.9% range in cases and thereafter decreases with further increase in HbA1c levels could be due to the effect of insulin on the metabolism of uric acid and glucose. Hyperinsulinemia could increase the activation of the hexose phosphate shunt, which would promote the biosynthesis and transformation of purine, thus increasing the rate of uricogenesis.[24] At the same time, insulin may increase reabsorption of uric acid from the kidneys by stimulating the urate anion transporter and/or Na^+ dependent anion co-transporter on the brush border membrane in the proximal tubules.[2]

However, at higher levels of HbA1c (≥10%), the serum levels of uric acid decreases which may be due to subsequent development of glycosuria in diabetic patients leading to uricosuria and lower uric acid levels.[43] Also glycosuria causes sodium concentration in the fluid to fall resulting in limitation of sodium reabsorption in proximal tubules. This leads to further decrease in the SUA levels due to a decrease in proximal reabsorption of sodium and urate.[24]

There are some limitations like measurement of waist and hip circumference to find waist-to-hip ratio was not included. Patient blood pressure, lipid profile and duration of diabetes and its relation to uric acid, HbA1c was not assessed.

CONCLUSION

From this present study, it can be concluded that serum uric acid is increased in DM. In spite of antioxidant effect the level can rise due to oxidative stress in the body so regular monitoring of uric acid could be beneficial. Moreover, hyperuricemia causes insulin resistance leading to development of DM. SUA has negative correlation with FBG, PPBG and HbA1c. But, HbA1c had a positive correlation with FBG and PPBG. SUA increases with moderate degree of rise in blood glucose level and thereafter decreases in presence of higher degree of blood glucose level. Although there are some controversial issues regarding effective treatment of hyperuricemia in diabetes, proper steps can be taken to manage and provide the productive life of the diabetic patients is required to be established. Hence, timely diagnosis and management of diabetes patient is one the basis necessity for the better and effective care of patient. Hyperuricemia, should be identify timely in diabetic patients for the better and effective treatment of the patient so that they can be benefited from this endocrine disorder.

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CONFLICT OF INTEREST: None

FINANCIAL DISCLOSURE: None

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