ASSOCIATION BETWEEN SERUM URIC ACID AND BLOOD GLUCOSE LEVEL IN DIABETIC AND NON-DIABETIC PATIENTS

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ABSTRACT

Uric acid increases insulin resistance; likewise, hyperinsulinemia increases uric acid concentration, and both are global health problems. This study is conducted to find the association between serum uric acid and blood glucose level. This was a cross-sectional study conducted in the Department of Biochemistry and Internal Medicine at Dhulikhel Hospital, Nepal, for a duration of six months (September 2021 - February 2022). A total of 130 diabetic patients who consented were compared with 130 non-diabetics by using non-probability convenient sampling technique. Ethical clearance was taken from the Institutional Review Committee-Kathmandu University School of Medical Sciences. Venous blood was collected and fasting blood glucose, post-prandial blood glucose, and serum uric acid were measured. Data were analyzed in the Statistical Package for Social version 16.0. Analytical data were compared using Mann Whitney U test, and Spearman correlation was performed to correlate numerical parameters. Statistical significance was defined as a two-sided p-value of less than 0.05. The median of serum uric acid level was significantly higher in diabetics than non-diabetics; the level of fasting and post-prandial blood glucose positively correlated with serum uric acid ($p<0.05$). Hyperuricemia was more in diabetics than non-diabetics ($p<0.05$). Serum uric acid level increased with the increase in age and duration of diabetes.

KEYWORDS

Association, blood glucose, diabetes, uric acid

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INTRODUCTION

Diabetes is a significant public health problem worldwide with a prevalence of 8.5% in Nepal itself.[1,2] Increased intake of high refined sugar leads to increase in serum uric acid (SUA).[3] Hyperuricemia is closely related to cardiovascular diseases, metabolic syndrome, insulin resistance, and diabetes.[4] Hyperinsulinemia causes an increase in SUA concentration by both reducing renal uric acid (UA) secretion and accumulating substrates for UA production.[5]

The level of SUA has been suggested to be independently associated with the risk of type 2 diabetes.[6] On the other hand, some studies have reported that there is no co-relation between SUA and diabetes[7] while some suggest an inverse relationship.[8,9] A study from Nepal stated SUA was higher in patients with diabetes than in without diabetes.[10]

Since the association of UA in patients without diabetes and with diabetes is not consistent, studies are required to know the actual trend of SUA in healthy and diabetic individuals. Although, there are some studies on the relationship between SUA and diabetes from different parts of the world, there are very few studies in Nepal. Therefore, this study is aimed to assess the level of SUA in non-diabetic healthy and diabetic individuals and also the relationship between SUA and serum glucose level in Nepalese population.

MATERIALS AND METHODS

This was a cross-sectional study conducted in the Department of Biochemistry and Internal Medicine of Dhulikhel Hospital, Nepal, for a duration of six months (September 2021 - February 2022) after IRC / KUSMS approval (108/2021). A total of 260 individuals who gave their written consent were included in the study by using non-probability convenient sampling technique. One hundred and thirty patients with diabetes were compared with equal number of non-diabetic individuals. Patients were included regardless of the duration of the disease. Patients who had any kind of disease conditions such as hypertension, cardiovascular disease, renal diseases, pregnancy, or any conditions which can derange the UA level and who were unwilling to take part in the study were excluded. Two ml of venous blood was collected into a vial with clot activator gel. Blood samples were allowed to clot and centrifuged at 3000 rpm for five minutes to separate the serum. The samples were tested for SUA, fasting blood glucose (FBG), and post-prandial blood glucose (PPBG). The reference ranges for the tests used were SUA: 2-7mg/dl male, 2-6 mg/dl female[11] FBG: 60-100 mg/dl; and PPBG: 80-140 mg/dl.[12] The laboratory method for the measurements of SUA, FBG, and PPBG was done by the enzymatic spectrophotometry method using a commercial kit from BioSystems (BA 400, Biosystems S.A. Spain). Body mass index (BMI) was measured from all participants. The WHO classification of obesity was considered and only normal and overweight participants were taken to eliminate bias since uric acid is associated with obesity.[13] History of duration of diabetes (DOD) was also noted.

Data were entered in MS Excel 2010 and analysed in Statistical Package for Social Sciences (SPSS Inc., Chicago, USA) version 16.0. The analytical study continued with the test for normality of numerical continuous variables, the Kolmogorov-Smirnov test as the normality test for the continuous variables (SUA, FBG and PPBG) was performed. Continuous variables were described as medians with interquartile range (IQR). Continuous data were compared using Mann Whitney U test. Spearman correlation was performed to correlate FBG and PPBG with age, SUA, and BMI; and SUA with age, BMI, and duration of diabetes. Statistical significance was defined as a two-sided p-value of less than 0.05.

RESULTS

A total of 260 participants (130 patients with diabetes and 130 without diabetes) were recruited into the study. Among them 100 were males and 160 were females.

Table 1: Biochemical parameters in males and females

	Male (IQR)	Female (IQR)	P value+
Age (years)	48.0 (18-84)	49.0 (19-81)	0.27
Fasting blood glucose (mg/dl)	100.0 (58-442)	100.0 (70-435)	0.74
Post prandial blood glucose (mg/dl)	140.0 (86-617)	126.5 (77-484)	0.13
Serum uric acid (mg/dl)	5.5 (2.9-10.7)	4.8 (1.5-9.4)	<0.001*
Body mass Index (kg/m^2)	23.05 (18.5-29.9)	21.4 (18.5-29.0)	<0.001*

+ Man-Whitney U test, *statistically significant

Table 2: Comparison of age and biochemical parameters among diabetics and non-diabetics			
	Diabetics (IQR)	**Non-diabetics (IQR)**	**P-value+**
Age (years)	57.0 (27-84)	35.0 (18-78)	<0.001*
Serum uric acid (mg/dl)	5.5 (2.7-10.7)	4.7 (1.5-10.7)	0.004*
Body mass Index (kg/m^2)	22.0 (18.5-29.5)	22.0 (18.5-29.9)	0.110

+Mann-Whitney U test, *Statistically significant

Table 3: Association between hyperuricemia and diabetes.			
Hyperuricemia	**Diabetics N (%)**	**Non-diabetics N (%)**	**P-value (Fischer's Exact)**
Present	32 (24.6)	18 (13.8)	0.040*
Absent	98 (75.4)	112 (86.2)	

*statistically significant at p<0.05 (fischer's exact test)

In our study, among non-diabetics, 35.4% were male and 64.6% were female and among diabetics, 41.5% were males and 58.5% were females. Among diabetics, 26.2% were of overweight and 73.8% normal weight, and among non-diabetics, 20.8% were overweight and 79.2% normal weight.

The medians of age, FBG, PPBG, SUA, and BMI were 49.0 (18-84) years, 100.0 (58-442) mg/dl, 131.0 (77-617) mg/dl, 5.0 (1.5-10.7) mg/dl, and 22.0 (18.5-29.9) kg/m^2, respectively. The differences in the levels of these parameters between male and female patients were calculated and were significant for SUA and BMI (Table 1).

The medians of age, SUA and BMI were calculated and compared between diabetics and non-diabetics and were significant for ageand SUA (p<0.05) (Table 2).

Among diabetics, the proportion of participants with hyperuricemia was 24.6% and among non-diabetics 13.8% had hyperuricemia in the study population (Table 3).

Table 5: Correlation of serum uric acid with age, BMI, and DOD.#		
SUA/ Spearman correlation	**r_s**	**P value**
Age	0.114	0.064
BMI	0.207*	0.001
DOD	0.183*	0.003

Spearman correlation, *statistically significant at p<0.05.

Table 4: Correlation of FBG and PPBG with age, SUA, and BMI.#						
Blood glucose	**Age (r_s value)**	**Age (p value)**	**SUA (r_s value)**	**SUA (p value)**	**BMI (r_s value)**	**BMI (p value)**
Fasting	0.421*	<0.001	0.170*	0.006	0.128	0.039
Post prandial	0.426*	<0.001	0.253*	<0.001	0.112	0.070

Spearman correlation, *statistically significant at p<0.05.

The level of FBG was significantly correlated with age and SUA level, while PPBG was significantly correlated with age, SUA and BMI (Table 4). The level of SUA had a significant positive correlation with BMI and DOD (Table 5).

In our study population, median of SUA was 6.2 (2.9-10.7), 5.0 (2.7-6.5), and 6.2 (3.7-9.4) years for DOD of 1-4 years, 5-8 years, and 9-12 years,

respectively and was lower in DOD of more than 12 years i.e. 3.5 (3.5-8.2) years.

DISCUSSION

After observing the strong association between SUA levels and the occurrence of coronary atherosclerosis in patients with type 2 diabetes mellitus, this study has been undertaken to compare the SUA levels with blood glucose level in patients with diabetes and without diabetes. In our study, older participants were seen more in the diabetic group than without diabetics, which is consistent with the meta-analysis by Shrestha *et al.*[14] in which diabetes increased with increasing age.

The SUA level was found to be higher in diabetics than in non-diabetics in our study, also the percentage of participants having hyperuricemia was higher in diabetics than in non-diabetics. Along with this, the level of SUA had positive correlation with FBG and PPBG. A similar finding was also shown in the study by Rao and Vanukiri,[15] where there was not a single case of hyperuricemia in the non-diabetic category. In a review article, Katsiki *et al.*[16] have shown a strong association between SUA levels and diabetes. Men with a high cardiovascular risk profile with gout had a higher future risk of type 2 diabetes independent of other known risk factors, as shown in a study by Choi *et al.*[17] These study findings suggest a strong association of diabetes, SUA and diabetes-related complications. These findings are supported by a meta-analysis by Kodama *et al.*[6] which summarized that each increase of 1 mg/dl in SUA resulted in an increase of 17% in the risk of type 2 diabetes. This is by far the strongest association shown by any study.

This finding is suggested by the fact that in recent years, our intake of foods such as those with umami flavor (rich in purines), high added sugar (sucrose), and high fructose corn syrup have increased[18] causing mitochondrial oxidative stress leading to intracellular ATP depletion and nucleotide turnover, leading to a significant increase in SUA.[3]

Since unhealthy food choices and sedentary lifestyle with high calorie intake and various metabolic profiles such as BMI and hypertension are shown to be associated with elevated SUA concentration,[19] all participants were excluded from having hypertension or any cardiovascular disease and BMI was also measured to establish whether the observed positive association between SUA level and blood glucose level is not causal as far as possible. In our study, the participants were either of normal BMI or overweight and there was no significant difference in the BMI between diabetics and non-diabetics and there was no significant correlation between BMI and FBG whereas there was a correlation between BMI and PPBG. Our analysis indicated that a significant association was observed in SUA with diabetes even if some metabolic confounders, such as hypertension and BMI, were adjusted. Therefore, these findings suggest that there was a good association between SUA and diabetes. Similar observation was seen in the meta-analysis by Kodoma *et al.*[6] where they adjusted alcohol intake along with more than three metabolic confounders such as BMI, high density lipoprotein, low density lipoprotein, and triglycerides etc.

In our study, the level of SUA increased with the duration of diabetes, which is similar to the study by Rao and Vanukiri[15] and Kramer *et al.*[20] But among diabetics, the level of median of SUA was similar with the duration of diabetes of 1-4 years, 5-8 years, and 9-12 years but decreased in more than 12 years. These findings suggest that there is a strong relationship between the SUA level and the DOD. And for the type of relation, our finding suggests SUA could be contributing factor for diabetes since high level of SUA was found in the patients with less DOD and SUA level was lesser in patients with DOD more than 12 years. The attributing reasons could be increased oxidative stress and production of tumor necrosis factor alpha by increased SUA contributing to the development of diabetes.[21]

Limitation: Since this is a hospital-based study, it cannot represent the entire Nepalese population. The role of diet has also not been studied in this study.

The level of SUA was more in diabetics than non -diabetics and so was hyperuricemia. SUA increased with increase in age, FBG, PPBG, and DOD. However, a lower level of SUA was observed in older cases of diabetes than in newer cases suggesting the development of diabetes due to higher SUA.

This study suggests a routine annual estimate of uric acid among diabetics. Furthermore, more longitudinal studies are needed in a large population from onset of diabetes to establish the fact.

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