ORIGINAL ARTICLE

ASSOCIATION OF URIC ACID AND ATHEROGENIC INDEX OF PLASMA IN DIABETES MELLITUS

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ABSTRACT

Diabetes mellitus (DM) is a chronic disease characterized by insulin deficiency or peripheral resistance resulting in hyperglycemia. Diabetic patients have increased rates of coronary heart disease, cerebrovascular disease and peripheral vascular disease, and are two to three times more likely to develop cardiovascular disease (CVD). Serum uric acid (SUA) has been known to be associated with cardiovascular diseases. "Atherogenic index of plasma" (AIP) is considered to be a very sensitive predictor of future cardiovascular events. The study was done to evaluate the association of serum uric acid and atherogenic index of plasma in diabetic patients. A total of 315 diabetic patients were selected as study subjects based on predefined enrollment criteria. The patients were separated into groups according to their serum uric acid levels. Serum uric acid levels under 6 mg/dL were considered as normal. AIP was calculated as the logarithmically transformed ratio of triglyceride to high density lipoprotein cholesterol. The study found that AIP levels were significantly high in high SUA group compared to normal SUA group. The study showed a positive significant correlation between AIP and SUA ($r=0.347$, $P<0.001$) in diabetes patients. Additionally, in binary logistic regression analysis, AIP was found to be independently associated with high UA levels. Present study reveals that SUA and AIP are closely related.

Key Words: Diabetes mellitus, Serum uric acid, Atherogenic index of plasma.

Introduction

Diabetes mellitus (DM) was the 6th leading cause of death under the age of 70 in 2015. Approximately 2.8% (1.59 million) of total deaths were caused by type 2 diabetes mellitus. WHO reveals that the global prevalence of diabetes among adults (>18 years) has risen from 4.7% to 8.5%, from 1980 to 2014[1]. The disease is caused by absolute or relative deficiency of insulin or by an inability of the body to respond appropriately to insulin. These result in chronically elevated blood glucose levels, excessive excretion of glucose in the urine, and accumulation of certain acidic substances in the blood. Diabetes mellitus is also responsible for increased risks of heart disease, stroke, kidney failure, accounting for another 2.2 million deaths worldwide[2].

Individuals with diabetes are two to three times more likely to develop cardiovascular disease (CVD) than the general population. So diabetes is a risk factor to develop CVD. Again CVD is the

leading cause of early death among people with diabetes. About 65% of the people with diabetes die from heart disease and stroke[3]. Several other factors, including smoking, hypertension and dyslipidemia have been shown to accelerate the progression of cardiovascular events[4]. On the other hand, elevated serum uric acid has also been shown to be a major risk for the development of CVD[5].

Dyslipidemia, an important risk factor for CVD, can be determined by the measurement of plasma lipid and lipoprotein levels. In the last two decades, studies have demonstrated that a mathematical relationship between plasma triglyceride (TG) and high density lipoprotein cholesterol (HDL-C) levels can be effectively used as an additional index for evaluation of CVD risk[6]. In this respect, Dobiasova and Frohlich proposed the term Atherogenic Index of Plasma (AIP), defined as log (TG/HDL-C), to assess the cardiovascular risk. People with high AIP will have a higher risk for CHD than those with low AIP. TG and HDL-C in AIP reflect the balance between the atherogenic and anti-atherogenic lipoproteins. It has been suggested that AIP values of -0.3 to 0.1 are associated with low CVD risk, >0.1 to 0.24 are associated with medium CVD risk and above 0.24 are associated with high CVD risk[6].

Elevated serum uric acid (SUA) concentration has been reported in patients with CVD[7,8]. Again some investigators have suggested that uric acid plays a causal role in the development of CVD[9] whereas others have concluded that uric acid merely reflects other concomitant risk factors, such as hypertension, insulin resistance or dyslipidemia[10].

Some studies have shown the association between hyperuricemia and raised AIP in hypertensive patients[11] and in the general population[12], but there has not been much study of the same relationship in diabetic patients in our country. So this study was under taken to determine the association between SUA concentration and AIP in diabetic patients.

Material and Method

It was a cross-sectional study carried out in the Department of Internal Medicine, Bangladesh Medical College, Dhaka during the period of 26 February to 7 December 2016. A total of 315 study subjects of both sexes with age range between 40 to 50 years were selected from type 2 DM patients. Patients taking medications for hypertension, hyperuricemia, and dyslipidemia were excluded. After taking informed written consent from the study subjects, personal data and history of co-existing medical conditions were recorded in a data sheet. With necessary aseptic precautions, fasting blood samples were collected from each study subject. Laboratory investigations of all patients were subsequently performed to determine their serum lipid profiles including total cholesterol (TC), HDL-C, TG, calculated low density lipoprotein cholesterol (LDL-C), SUA and Hemoglobin A_{1c} (HbA_{1c}). Serum TC was estimated by enzymatic end point (CHOD-PAP) method. Serum TG was estimated by enzymatic (GPO-PAD) method. Serum HDL-C was estimated by homogenous assay method. LDL-C was calculated by Friedewald's formula (TC=LDL+HDL+TG/5). AIP was calculated as log (TG/HDL-C) using the Czech online calculator of atherogenic risk. SUA concentration was measured by enzymatic method (uricase-peroxidase). Estimation of percentage of HbA_{1c} was done by high performance liquid chromatography method by a variant hemoglobin testing system.

The study subjects were divided into two groups according to SUA level (SUA<6 being normal and SUA>6 as hyperurecemia). For categorical variables, differences between the groups in relation to the level of significance were determined by chi-square test. For continuous variables, both nonparametric (Mann-Whitney U test) and parametric test (t test) were used as appropriate. Pearson's correlation coefficient test was done to correlate between SUA and AIP.

Binary logistic regression analysis was also performed to show the association of AIP with SUA and expressed in 95% confidence interval. P value <0.05 was regarded as significant. All statistical analyses were carried out using the SPSS program (version 22.0; SPSS Inc., Chicago, Illinois, USA).

Results

Table-I: Demographic features of the subjects according to uric acid levels (n=315)

Parameters	Uric Acid (mg/dl)		p value
	Diabetic patients with normal uric acid values (Uric Acid < 6 mg/dl)	Diabetic patients with high uric acid values (Uric Acid ⩾ 6 mg/dl)	
Gender [n(%)]*			
Male	93 (53.8%)	78 (54.9%)	0.835
Female	80 (46.2%)	64 (45.1%)	
Age (years)**	46.79 ± 4.55	47.10 ± 4.36	0.537

**Chi-square test, **Independent sample t test was done to find out level of significance*

Table-II: Laboratory features of the subjects according to uric acid levels (n=315)

Parameters	Uric Acid (mg/dl)		p value
	Diabetic patients with normal uric acid values (Uric Acid <6 mg/dl)	Diabetic patients with high uric acid values (Uric Acid ⩾ 6 mg/dl)	
HbA1c (%)*	6.60 (4.00-15.20)	6.70 (3.10-22.30)	0.184
Total cholesterol (mg/dl)*	183 (142 - 330)	191 (141 - 349)	0.021
LDL (mg/dl)*	118 (87 - 216)	110 (87 - 206)	0.077
Triglyceride (mg/dl)*	146 (80 - 456)	210 (91 - 440)	<0.001
HDL (mg/dl)*	39 (20 - 61)	36 (10 - 67)	<0.001
AIP*	0.60 (0.23 - 1.20)	0.78 (0.17 - 1.18)	<0.001

**median/ IQR (in case of nonparametric data) whereas *Mann whitney U test was done to find out level of significance.*

Table-III: Association of high serum uric acid with AIP

Parameters	Odds Ratio	95%CI		p value
		Lower	Upper	
AIP	11.871	4.295	32.814	<0.001

Binary logistic regression was performed.

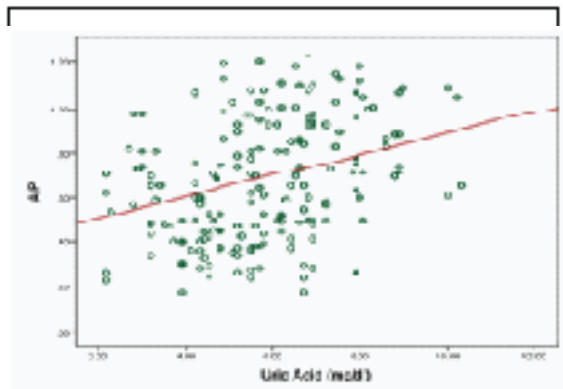

Figure-1: Correlation between Uric Acid and Atherogenic Index of plasma (AIP). Pearson correlation is +0.347 with a p-value of <0.001.

Baseline characteristics and laboratory data of patients grouped according to SUA levels are given in Table I and II. It can be observed that there were no significant differences between groups in relation to sex, age, HbA_{1c} and LDLC levels. There were statistically significant differences in SUA level with respect to the TC, TG, HDL-C and AIP levels. It can also be seen that between the two groups (normal and high SUA level), TC, TG, AIP, levels are higher and HDL-C level lower for the high-SUA level group.

The correlation between SUA and AIP were tested using Pearson Correlation analysis (Figure1). The study showed a positive significant correlation between AIP and SUA ($r = 0.347$, $P<0.001$) in diabetes patients.

Binary logistic regression analysis was also performed to define the variables associated with SUA (Table III). AIP levels were found to be independently associated with SUA levels.

Discussion

The study population mostly belonged to the 40 to 50 years age group. The mean (±SD) age of diabetic patients were 47.10±4.36 years in hyperuricemic group and 46.79±4.55 years in normo uricaemic group. No significant age differences were found in between hyperurecemic and normo urecemic groups. This is consistant with previous studies, where no significant relationship was found between SUA level and age[13]. Neupane *et al*. observed significant positive correlation between these two variables in DM patients[14].

There was also no significant sex difference between two groups (p- value 0.835). This finding is consistent with the findings of Woyesa *et al*. who studied hyperuricemia in DM patients in South West Ethiopia[15]. But hyperuricemia was reported high among female study subjects in China by Wang *et al*. which is not consistent with our study[16]. But reason behind this is may be due to the fact, they have taken post menopausal women as their study subject whose mean age was also higher than of men.

Though in this present study HbA_{1c} was found to be slightly higher in hyper uricemic group than those of normo uricemic group but no significant difference was found between groups regarding HbA_{1c}. Studies by Akbas *et al*. also found no significant relationship between SUA level and HbA_{1c}[13]. But studies by Wang *et al*. presented different results and noted that the risk of hyperuricemia decreased 0.928-fold for every 1% increase in HbA_{1c}[16].

Present study found that TC and TG are significantly higher and HDL-C is significantly lower in hyperuricemic group. Several other studies also found that TC and TG to be positively associated with serum uric acid[17-19]. Similarly, HDL-C was reported to be negatively correlated with serum uric acid by Mikkelsen *et al*. and Wingrove *et al*.[20,21].

In the present study a positive significant correlation between AIP and SUA ($r=0.347$, $P<0.001$) in diabetic patients was observed. AIP levels were found to be independently associated with SUA levels not alowed logistic regression analysis. Baliarsingh *et al*. reported such positive relationship between SUA and AIP in healthy, middle aged men[12] while Ahmed *et al*. noted the same pattern of the relationship in hypertensive patients[11]. The present study found the same association in DM patients which corroborates with the findings of Akbas *et al*.[22].

From this study it can be concluded than hyperuricemia and raised AIP is associated in DM patients. From an applied perspective, physicians should be conscious that patients with concomitant hyperuricemia and high AIP are at an increased risk of CVD. These factors are the combination of independent risk factors which contribute to the development of CVD.

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