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Elevated uric acid level decreases glycated hemoglobin in type 2 diabetes mellitus

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ABSTRACT

BACKGROUND
Type 2 diabetes mellitus is a heterogeneous disease which is characterized by variable degrees of insulin resistance and impaired insulin secretion. Uric acid has been identified as a marker for a number of metabolic and hemodynamic abnormalities. In diabetic patients, there is biochemical interaction between serum glucose and purine metabolism, with increased excretion of uric acid during hyperglycemia and glycosuria. The objective of this study was to evaluate the correlation of serum uric acid levels with glycated hemoglobin (HbA1c) and blood glucose levels in type 2 diabetes patients.

METHODS
A cross sectional study from May until July 2014 had been done in 82 type 2 diabetes patients. Serum was analyzed for uric acid, fasting and 2-hour post prandial blood glucose and lipid profile. Spearman correlation test was used to assess associations of HbA1c, fasting and post prandial blood glucose with serum uric acid levels.

RESULTS
There was a negative correlation of HbA1c with serum uric acid levels (r=-0.407; p=0.000) and of fasting and post prandial blood glucose with serum uric acid levels (r=-0.338; p=0.002 and r=-0.318; p=0.004, respectively).

CONCLUSIONS
Serum uric acid level was associated with HbA1c, fasting and post prandial blood glucose suggesting a significant role of serum uric acid in the deterioration of glucose toleration.

Keywords: Uric acid, HbA1c, type-2 DM

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Peningkatan kadar asam urat menurunkan hemoglobin terglikasi pada diabetes melitus tipe 2

ABSTRAK

LATAR BELAKANG

Diabetes melitus tipe 2 adalah penyakit heterogen dengan karakteristik derajat resistensi insulin dan gangguan sekresi insulin yang bervariasi. Asam urat telah diidentifikasi sebagai penanda pada sejumlah abnormalitas metabolik dan hemodinamik. Resistensi insulin dapat menyebabkan hiperinsulinemia yang meningkatkan reabsorpsi sodium dan air, termasuk asam urat dari ginjal. Pada pasien diabetes melitus, dijumpai interaksi biokimiawi antara glukosa serum dan metabolisme purin, dengan peningkatan ekskresi asam urat selama hiperglikemia dan glikosuria. Penelitian ini bertujuan untuk menetukan adanya hubungan antara kadar asam urat serum dengan HbA1c, glukosa puasa dan 2-jam post prandial pada pasien diabetes melitus tipe 2.

METODE

Penelitian potong lintang dilakukan pada 82 pasien diabetes tipe 2 antara bulan Mei dan Juli 2014. Serum diambil dan dilakukan pemeriksaan kadar asam urat, kadar glukosa darah puasa dan 2-jam post prandial dan profil lipid. Uji korelasi Spearman digunakan untuk menilai korelasi antara HbA1c, kadar glukosa darah puasa dan post prandial dengan kadar asam urat serum.

HASIL

Dijumpai korelasi negatif antara HbA1c dengan kadar asam urat (r=-0,407; p=0,000), kadar glukosa darah puasa dan post prandial dengan kadar asam urat serum (masing-masing, r=-0,338; p=0,002 dan -0,318; p=0,004).

KESIMPULAN

Kdar asam urat berhubungan dengan kadar HbA1c, glukosa darah puasa dan post prandial. Hal ini menunjukkan peran asam urat pada keadaan memburuknya toleransi glukosa.

Kata kunci: *Asam urat, HbA1c, DM tipe-2*

INTRODUCTION

According to the American Diabetes Association (ADA) diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.[1]

Uric acid has been identified as a marker for a number of metabolic and hemodynamic abnormalities. Insulin resistance can lead to hyperinsulinemia which increases reabsorption of sodium and water, including uric acid from the kidneys.[2,3] A meta-analysis showed that the risk of type 2 diabetes was increased by 6% per 1 mg/dL increment in serum uric acid level.[4] Choi et al.[5] and Kaur et al.[6] reported that the serum uric acid levels increased with moderately increasing levels of glycated hemoglobin (HbA1c) <7% and then decreased with further increasing levels of HbA1c >7% (a bell-shaped relation). Meanwhile Meera et al.[7] reported a negative correlation of serum uric acid with blood glucose in type 2 diabetes.

Previous studies reported that serum uric acid in type 2 diabetes was lower when compared with pre-diabetes and healthy population, especially in diabetes mellitus patients with blood glucose levels of >10 mmol/L (>180 mg/dL).

This probably reflects the biochemical interaction between serum glucose and purine metabolism, with increased excretion of uric acid during hyperglycemia and glycosuria.[8]

Rodriguez et al .[9] also reported that the incidence of gout among diabetes patients was lower, as compared with individuals with no diabetes and the inverse association was stronger with type 1 diabetes than with type 2 diabetes and was stronger among men than women. Nan et al.[10] found a linear correlation between serum uric acid with fasting and 2-hour post prandial blood glucose where serum uric acid concentration increased with increasing fasting blood glucose levels up to 7.0 mmol/L, but notably decreased when fasting blood glucose over 7.0 mmol/L, with an increasing trend in the uric acid concentration at 2-hour post prandial glucose <10.0 mmol/L and a decreasing trend at 2-hour post prandial glucose >10.0 mmol/L.

On the basis of the abovementioned information, considering that there are contrary results and only few studies that have analyzed the relationship between serum uric acid and HbA1c in type 2 diabetes, the objective of the present study was to determine the correlation of serum uric acid levels with HbA1c, fasting and 2-hour post prandial blood glucose in type 2 diabetes patients.

METHODS

Research design

A cross-sectional study was conducted at the Department of Internal Medicine of H. Adam Malik Hospital, Medan, from May 2014 to July 2014.

Research subjects

The study population comprised type 2 diabetes patients who were treated at the outpatient and inpatient clinics of the Department of Internal Medicine. The study sample consisted of individuals from the study population who met the inclusion criteria, which were: males or females ≥17 years of age, having type 2 diabetes, and willing to participate in the research. The exclusion criteria were: type 1 diabetes, anemia (males with Hb <12 g/dL or females with Hb <11 g/dL), gouty arthritis, and serum creatinine >1.5 mg/dL. The study subjects were selected by consecutive non-random sampling. We used the sample size calculation method to determine the minimum single sample using the coefficient of correlation.[11] To calculate the sample size, we used a previous study by Gill et al.[12] who reported a coefficient of correlation of approximately -0.532. The calculated sample size was 82, which was estimated to be adequate to detect a 30% difference between the two groups using a two-tailed test, an alpha of 0.05 and power of 80%.

Data collection

All study subjects were interviewed using a questionnaire for age, gender, history and duration of diabetes. Subjects were measured for height, weight and body mass index (BMI). The blood pressure was measured in a quiet room with the participant seated.

Laboratory analysis

Laboratory studies comprising routine blood parameters, serum uric acid, fasting and 2-hour post prandial blood glucose, HbA1c and lipid profile [total cholesterol, low density lipoprotein (LDL) cholesterol, and high density liprotein (HDL) cholesterol], were measured with the COBAS automated analyzer.

Statistical analysis

The Kolmogorov-Smirnov normality test was used to assess the normality of distribution of the data. The Pearson correlation test was used to assess correlations of HbA1c, fasting and post prandial blood glucose with serum uric acid for normally distributed data, and the Spearman correlation test for non-normally distributed data. Statistical analysis was performed with the SPSS statistical package for Windows, version 17.0, and a p-value of <0.05 was considered statistically significant.

Table 1. Baseline characteristics of diabetic type 2 subjects (n=82)

Variables	n
Gender	
Male	40 (48.80%)
Female	42 (51.20%)
Age (yrs)	59.10 ± 9.25
Body mass index (kg/m^2)	27.30 ± 3.69
Systolic blood pressure (mmHg)	127.80 ± 7.07
Diastolic blood pressure (mmHg)	78.00 ± 5.50
Haemoglobin (mg/dL)	13.50 ± 1.53
Glycated hemoglobin (%)	8.24 ± 1.83
Creatinine (mg/dL)	0.90 ± 0.27
Uric acid (mg/dL)	6.60 ± 2.12
Fasting blood glucose (mg/dL)	168.60 ± 74.30
2-hour post prandial blood glucose (mg/dL)	290.90 ± 103.89
Total cholesterol (mg/dL)	221.10 ± 43.73
Triglycerides (mg/dL)	166.10 ± 113.23
HDL cholesterol (mg/dL)	43.90 ± 11.12
LDL cholesterol (mg/dL)	131.10 ± 31.65

Ethical clearance

The study protocol was approved by the Health Research Ethical Committee, Faculty of Medicine, University of Sumatera Utara. All study subjects signed written informed consent after having been informed about the aims and benefits of the study.

RESULTS

During the study period 82 study subjects with diabetes mellitus type 2 were obtained consisting of 40 males (48.8%) and 42 females (51.2%), with mean age of 59.12 ± 9.25 years old and mean body mass index of 27.33 ± 3.69 kg/m^2. From measurement of serum uric acid we found mean uric acid levels of 6.69 ± 2.12 mg/dL. Mean HbA1c was approximately 8.24 ± 1.83%, while mean fasting blood glucose and 2-hour post prandial blood glucose were approximately 168.6 ± 74.3 mg/dL and 290.91 ± 103.89 mg/dL, respectively (Table 1).

Using the Spearman correlation test, we found a fairly significant negative correlation of HbA1c, fasting and post prandial blood glucose level with serum uric acid levels (r=-0.407; p=0.000, r=-0.338; p=0.002, and r=-0.318; p=0.004, respectively) (Table 2).

DISCUSSION

In this cross sectional study involving 82 type 2 diabetes mellitus subjects we found a fairly significant negative correlation between HbA1c and serum uric acid levels in type 2 diabetes patients, where with higher uric acid values the HbA1c levels actually decreased. Gill et al.[12] showed a contrary result, where HbA1c, serum insulin and serum uric acid parameters were found to be increased in patients with type

Table 2. Correlation of serum uric acid with glycated hemoglobin, fasting blood glucose, and 2-hour post prandial blood glucose in diabetic type 2 subjects

	Uric acid	p
Glycated hemoglobin	-0.407	0.000
Fasting blood glucose	-0.338	0.002
2-hour post prandial blood glucose	-0.318	0.004

2 diabetes mellitus as compared to their levels in controls. In newly diagnosed diabetic patients serum uric acid levels linearly increased with an increase in HbA1c levels. Previous studies showed that uric acid was found to be of prognostic value in patients with type 2 diabetes mellitus and confirmed coronary artery disease, where uric acid increased all-cause mortality and cardiac mortality risk by approximately 29% and 15%, respectively, for each standard deviation increase in the logarithmic scale of uric acid level.[13]

Choi et al.[5] and Kaur et al.[6] reported that serum uric acid levels increased with moderately increasing levels of glycated hemoglobin (HbA1c) <7% and then decreased with further increasing levels of HbA1c >7% (a bell-shaped relation). The study by Cervantes et al.[14] showed that the serum concentration of uric acid had a positive relationship with the total phase of insulin secretion, even in the state prior to hyperuricemia and thus uric acid can play an important role in the function of the beta cell in patients with type 2 diabetes. A study in diabetic patients found a negative and inverse relationship between serum uric acid and HbA1c. Hence, in that study uric acid was found to be a potential biomarker of the glucose metabolism. [15] Another study in Sarajevo showed there were no significant correlations between uric acid and both HbA1c levels and BMI in type 2 and type 1 DM.[16]

Our study also found a fairly significant negative correlation of serum uric acid with fasting blood glucose and 2-hour post prandial blood glucose, which agrees with the study by Meera et al.[7] who reported a negative correlation of serum uric acid with blood glucose in type 2 diabetes patients.

The study by Nan et al.[10] showed a linear correlation between serum uric acid with fasting and 2-hour post prandial blood glucose but only with increasing fasting blood glucose levels up to 7.0 mmol/L and post prandial blood glucose levels up to 10 mmol/L, and then serum uric acid notably decreased with fasting blood glucose over 7.0 mmol/L and post prandial blood glucose over 10 mmol/L. Fan et al.[17] reported that serum uric acid in individuals with impaired fasting glucose and/or impaired HbA1c was strongly associated with 2-hour post prandial blood glucose, independent of fasting plasma glucose and HbA1c and other established risk factors, where a 1.53 mg/dL increment of serum uric acid was significantly associated with a 36% higher risk for 2-hour newly diagnosed diabetes in multivariate logistic regression.

There are a number of hypotheses to explain the above negative correlation between uric acid and blood glucose. First, it probably reflects the biochemical interaction between serum glucose and purine metabolism, with increased excretion of uric acid (uricosuria) during hyperglycaemia and glycosuria.[8] Another hypothesis is that an increase in the inflammatory response in DM may have a direct protective effect on the incidence of gout and hyperuricemia that directly produces an intense inflammatory response against urate crystals which have anti-oxidant and free radical effects.[9] Moreover, there are conditions that interfere with purine catabolism or synthesis of uric acid due to a chronic inflammatory process.[18,19] Uric acid has been also known as an antioxidant. This antioxidant property might preserve or delay apoptosis and improve â-cell function in diabetics and augment insulin secretion.[20] Further studies are required on the role of uric acid as antioxidant in the diabetic state.

A limitation of this study was the absence of direct assessment of risk factors that may affect the outcomes of uric acid levels both in purine catabolism and chronic inflammatory systemic response and the presence of poor metabolic control, renal hyperfiltration and overt nephropathy necessitating further research of these factors in the future.

CONCLUSION

Serum uric acid level was associated with HbA1c, fasting and post prandial blood glucose,

suggesting a significant role of serum uric acid in the deterioration of glucose toleration.

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