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RESEARCH

COMPARISON OF GLYCEMIC STATE IN PATIENTS WITH AND WITHOUT HYPERURICEMIA

(Perbedaan Status Glikemia pada Pasien dengan dan tanpa Hiperurisemia)

Corrie Abednego, Banundari Rachmawati, Muji Rahayu

ABSTRAK

Hiperurisemia merupakan keadaan asam urat yang meningkat dalam serum. Beberapa penelitian melaporkan hiperurisemia menyebabkan kerusakan sel beta pankreas dengan mekanisme apoptosis melalui jalur NF-kB serta berhubungan dengan komplikasi mikrovaskular dan makrovaskular pada pasien diabetes. Perbedaan status glikemia (glukosa darah puasa/GDP dan glukosa darah 2 jam post-prandial/GD2PP dan HbA1c) pada pasien dengan dan tanpa hiperurisemia belum banyak diketahui. Tujuan penelitian untuk membuktikan perbedaan status glikemia pada pasien dengan dan tanpa hiperurisemia. Penelitian retrospektif, 110 pasien yang dibagi menjadi kelompok hiperurisemia dan tanpa hiperurisemia. Glukosa darah puasa dan 2 jam PP diperiksa menggunakan metode heksokinase, asam urat dengan metode urikase, HbA1c dengan metode elektroforesis kapiler. Data diuji normalitas data dan perbedaan antara variabel, dianalisis dengan uji Mann-Whitney. Subjek 58 laki-laki dan 52 perempuan, nilai rerata umur pasien 56,36 ± 8,7 tahun. Pasien laki-laki, terdapat perbedaan bermakna status glikemia (GDP, GD2PP, HbA1c) terhadap kelompok hiperurisemia dan tanpa hiperurisemia, p< 0,05. Pasien perempuan, terdapat perbedaan bermakna status glikemia (GDP dan GD2PP), p< 0,05 serta HbA1c tidak terdapat perbedaan bermakna pada pasien hiperurisemia dan tanpa hiperurisemia dengan p=0,084. Terdapat perbedaan bermakna pada status glikemia pasien laki-laki dan perempuan terhadap kelompok hiperurisemia dan tanpa hiperurisemia, kecuali $HbA1_C$ pada perempuan. Dibutuhkan penilaian terhadap diet pasien yang dapat mempengaruhi kadar asam urat.

***Kata kunci**: HbA1c, kadar glukosa darah puasa, glukosa darah 2 jam post-prandial, hiperurisemia, status glikemia*

ABSTRACT

The condition of increasing uric acid level in serum is hyperuricemia. Several studies have shown that apoptotic β cell pancreas is caused by hyperuricemia via the NF-kB pathway and a positive relation between hyperuricemia and macro-micro complication of diabetic patients. Little is known, however, regarding the comparison of glycemic states (fasting plasma glucose/FPG and 2-hour postprandial blood glucose/2-hour PPBG, HbA1c) in a patient with and without hyperuricemia. The purpose of this study is to evaluate the comparison of glycemic states in patients with and without hyperuricemia. Data were collected from 110 patients with and without hyperuricemia. The fasting plasma glucose level and 2-hour postprandial blood glucose level was analyzed with hexokinase method, the serum uric acid level was analyzed with uricase method, HbA1c with capillary electrophoresis method, while the comparison of the variables was examined by Mann Whitney U test. The mean value for age was 56.36 ± 8.7 years. Subjects consisted of 58 males and 52 females. In males, there was a significant difference of glycemic state (FPG, 2-hPPBG, HbA1c) in patients with and without hyperuricemia, $p < 0.05$. In females, there was significant difference of glycemic state (FPG, 2-hour PPBG levels, $p<0.05$) but not for HbA1c ($p=0.084$) in patients with and without hyperuricemia. There was a significant difference glycemic state of males and females in patients with and without hyperuricemia. Some dietary factors should be evaluated, which are known for their interference with uric acid values.

Key word: HbA1c, fasting plasma glucose, 2-hour postprandial blood glucose, hyperuricemia, glycemic statue

INTRODUCTION

Hyperuricemia (HU) occurs when blood uric acid level is more than two standard deviations, above the average laboratory result of patients with normal uric acid level. Normal uric acid level ranges from 3.4 to 7.0 mg/dL for males and 2.4 to 5.7 mg/dL for females before menopause.[1]

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Based on data of Riskesdas in 2013, the prevalence of hyperuricemia increased. The prevalence of hyperuricemia in Indonesia was 11.9%. The highest prevalence of hyperuricemia was found in Bali at 19.3%, then Aceh at 18.3%, West Java at 17.5% and Papua at 15.4%. The prevalence rate of hyperuricemia at age of ≥15 years in Lampung Province even was equal to 11.5%.[2]

Uric acid can lead to the formation of cytokines derived from leukocytes and chemokine in vascular smooth muscles, triggering granulocyte adhesion to the endothelium, platelet adhesion, free radical release (peroxide and superoxide), as well as oxidative stress. Uric acid or a xanthine oxidase is also capable of causing endothelial dysfunction and considered as mediators of the systemic inflammatory response, resulting in insulin resistance as well as cardiovascular system diseases. Xanthine oxidase can lead to the formation of Reactive Oxygen Species (ROS) as well as uric acid, triggering oxidative stress and inflammatory response.[3] Various researches even have shown that hyperuricemia can trigger various complications and potentially lead to hyperinsulinemia and obesity due to disruption of endothelial function stimulated by uric acid through Nitric Oxide (NO) production.[3-9]

Insulin, furthermore, is actually generated by the viability of pancreatic beta cells. Pancreatic beta cell damage triggered by the condition of hyperuricemia can occur through NF-kB, then lead to apoptosis.[3] A research conducted by Wali[10] explained that a metabolite of purines is strongly related to microvascular and macrovascular complications.[10] Uric acid as the final product of purine metabolism is a pro-oxidant used as a marker of oxidative stress.[3] Superoxide in patients with diabetes can lead to microvascular dysfunction and tissue damage that can cause lipid and protein peroxidation. In addition, a research conducted by Nagahama stated that hyperuricemia was associated with metabolic abnormalities that can lead to insulin resistance and/or hyperinsulinemia in metabolic syndrome.[6]

High uric acid exacerbates insulin resistance by disrupting insulin-stimulated glucose uptake, thus, there is a positive correlation between uric acid level and diabetes progression.[11] Similarly, some researches also have correlated uric acid to microvascular complications, such as nephropathy, retinopathy and neuropathy in diabetic condition. Nevertheless, there is a poor number of researches on the effects of hyperuricemia on pancreatic beta cell destruction, leading to insulin resistance, which can increase blood sugar levels. Consequently, this research also tried to examine HbA1c level in patients with and without a history of diabetes since some diabetic patients still have high HbA1c level although those have been treated for their glycemia.

As a result, this research aimed to analyze whether there was a difference in glycemic status (fasting blood glucose level, 2-hour postprandial blood glucose level and HbA1c level in patients with and without hyperuricemia. The significances of this research are to inform clinicians about serum uric acid and glycemic status as well as to improve hyperuricemia treatment in order to minimize complications emerged in treated patients.

METHODS

This research was a retrospective study with a cross-sectional approach to data of patients with and without hyperuricemia at the Dr Kariadi Hospital in Semarang from January to August 2016. Subjects of this research were patients with and without hyperuricemia, aged more than 40-80 years. Those subjects also had been examined their fasting blood glucose, 2-hour post prandial blood glucose and HbA1c levels. In addition, the subjects of this research were patients with and without type 2 diabetes. Meanwhile, patients with incomplete examination results, having chemotherapy, or after surgery were excluded. Hyperuricemia result can be considered to be positive in males when serum uric acid level exceeds 7.2 mg/dL, while in females, serum uric acid level exceeds 6.0 mg/dL. Besides, normal fasting blood glucose level was set into <126 mg/dL, while normal 2-hour postprandial blood glucose level was <180 mg/dL.

Next, collected data were analyzed descriptively. The normality of data distribution was tested with Saphiro Wilk test. The mean values of fasting blood glucose level, 2-hour postprandial serum and HbA1C levels in each group then were analyzed. Afterwards, difference test was performed on normal distributed variables by using Independent t-test. Meanwhile, difference test on non-distributed variables was carried out by using Mann Whitney statistical test.

RESULTS AND DISCUSSION

A total of 110 subjects who met the inclusion criteria were divided into two groups, namely 55 patients with hyperuricemia and 55 patients without hyperuricemia. The mean age of those subjects was 56.36 ± 8.71 years. Results of the Kolmogorov-Smirnov test showed that the data were normally distributed ($p > 0.05$).

Table 1. Characteristics of age and sex of all patients

	Total of patients (n=110)
Age (years)	56.36 ± 8.71
	57(31-79)
Sex	
Male	58(52.7)
Female	52(47.3)

n: Total

Moreover, results of the glycemic status examination, ie HbA1c, fasting blood glucose and 2-hour postprandial blood glucose levels, along with uric acid level are listed in Table 2.

Furthermore, results of the Mann Whitney test performed to indicate the difference in glycemic status of males and females with or without hyperuricemia were illustrated in Table 3 and Table 4.

The statistical test results indicated that there was a significant difference in glycemic status of males in the group without hyperuricemia and those in the group with hyperuricemia. Similarly, there was also a significant difference in glycemic status of females in the group without hyperuricemia and those in the group with hyperuricemia. However, the glycemic status of females were higher than in males. Unfortunately, there is no reason why HbA1c levels in females were more elevated than males. Inoue's research stated the effects of gender, age and erythrocyte index on HbA1c level also showed that $HbA1_C$ level in females at older age were increased more than in males. A similar result was also found in Zhao's research stating that HbA1c level in females was higher than in males. According to Becky's research, HbA1c level in diabetic patients was, also elevated in females, while that in males did not increase. The elevating HbA1c then can lead to a high risk of stroke incidence in females. Several previous researches even also have shown that hyperuricemia is more common in postmenopausal females than in premenopause ones.[21,22]

Moreover, this research also found that blood glucose levels, both fasting blood glucose and 2-hour postprandial blood glucose levels, were significantly different between the group with hyperuricemia and the group without hyperuricemia. Similarly, some previous researches showed that there was a positive correlation of fasting blood glucose and 2-hour postprandial blood glucose levels to hyperuricemia.[23,24] It was because hyperglycemic condition can be caused by insulin resistance so that the cells become less sensitive to insulin effects.[11] Consequently, the pancreas tries to restore the balance by producing more insulin to compensate for insulin resistance and to keep blood glucose levels, resulting in hyperinsulinemia and insulin resistance, which if continued, may damage the pancreatic beta cells.[28,33]

Table 2. Glycemic status and uric acid level examinations in 2 groups

Parameters	Without hyperuricemia		With hyperuricemia	
	Mean (x ± SD)	Median (min-max)	Mean (x ± SD)	Median (min-max)
$HbA1_C$ (%)	6.99 ± 2.08	6.2(3.9-14.5)	8.77 ± 2.50	8.40(5-16.3)
FBG (mg/dL)	112.05 ± 44.65	101(57-291)	184.56 ± 101.29	153(74-578)
2-hour PPBG (mg/dL)	156.47 ± 64.65	152(76-391)	233.89 ± 110.17	217(78-575)
Uric acid (mg/dL)	5.2 ± 1.16	5.1(2.7-7.2)	9.02 ± 2.02	8.7(6.1-16.1)

HbA1c: hemoglobin A1c, FBG: Fasting Blood Glucose Level; 2-hour PPBG: 2-hour postprandial blood glucose

Table 3. Results of glycemic status in males

Glycemic status		Males		p
		Non-HU (n = 34)	Hyperuricemia (n = 24)	
FBG (mg/dL)	[mean ± SD]	105.29 ± 50.79	160.33 ± 101.39	0.000
	[median (min-max)]	90.5 (57-291)	132 (84-578)	
2-hour PPBG (mg/dL)	[mean ± SD]	144.47 ± 68.49	202.04 ± 93.75	0.040
	[median (min-max)]	120.50 (76-391)	196 (78-528)	
HbA1c (mg/dL)	[mean ± SD]	6.46 ± 1.65	8.26 ± 2.11	0.000
	[median (min-max)]	5.90 (5.1-11.1)	8.00 (5.5-12.2)	

HU: Hyperuricemia; FBG: Fasting Blood Glucose Level; 2-hour PPBG: 2-hour postprandial blood glucose; HbA1c: hemoglobin A1c, $p < 0.05$: statistically significant

Table 4. Result of glycemic status in females

Glycemic status		Females		p
		Non-HU (n = 21)	Hyperuricemia (n = 31)	
FBG (mg/dL)	[mean ± SD]	123.00 ± 30.38	203.32 ± 98.76	0.001
	[median (min-max)]	116.00 (74-208)	177 (74-440)	
2-hour PPBG (mg/dL)	[mean ± SD]	175.90 ± 53.58	258.55 ± 116.92	0.002
	[median (min-max)]	164 (89-334)	228 (78-575)	
HbA1c (mg/dL)	[mean ± SD]	7.85 ± 2.44	9.16 ± 2.73	0.084
	[median (min-max)]	7.5 (3.9-14.5)	9.00 (5.0-16.3)	

HU: Hyperuricemia; FBG: Fasting Blood Glucose Level; 2-hour PPBG: 2-hour postprandial blood glucose; HbA1c: hemoglobin A1c; $p < 0.05$: statistically significant

Furthermore, the correlation between HbA_{1C} level and hyperuricemia, according to a research conducted by Munilakshmi[25], indicated that HbA1c had an affinity for oxygen concentration or indirect tissue anoxia occurrence, triggered by hyperuricemia, as well as leading to micro and macroangiopathy.[25] HbA1c level was also associated with pancreatic beta cell function.[26] Like the previous researches, the results of this research also showed that there was a difference in HbA1c level in the male groups, but not in the female groups.

In addition, hyperuricemia can make a patient's illness deteriorate due to complications of the disease. Many previous researches even had linked hyperuricemia with metabolic abnormalities, insulin resistance, as well as complications of both micro and macrovascular diabetic. Therefore, glycemic status in this research was analyzed using HbA1c, fasting blood glucose and 2-hour postprandial blood glucose parameters as a representative of the insulin viability produced by the pancreatic beta cells. In other words, the viability of pancreatic beta cells played a role in the production of adequate insulin for the body. Damage to the pancreatic beta cells by hyperuricemia may occur via the NF-kB pathway, resulting in apoptosis. Thus, damage to the pancreatic beta cells greatly affected the performance of insulin in up taking glucose in the blood.[3]

NF-kB (nuclear factor kappa light chain enhancer activated B cell or nuclear factor kappa B) is a complex protein that controls DNA transcription processes playing an important role in the regulation of gene expression associated with immune and inflammation responses, cell growth, cell proliferation, as well as cell defense against stress. Several previous researches even have shown that NF-kB also induced Nitric Oxide Synthase (iNOS), which can cause damage and death of pancreatic beta cells.[3,10]

Several theories actually underlie the correlation of hyperuricemia to worsening diabetes. First, hyperuricemia induces endothelial dysfunction and increases the production of NO. The increased production of NO caused by immunological and inflammatory stimulation processes can trigger apoptosis of pancreatic beta cells. Thus, an increase in nitric oxide can lead to a decrease in the intake of glucose by insulin in skeletal muscle, resulting in insulin resistance and diabetes. Hyperuricemia induces iNOS via the NF-kB pathway. The transcriptional activation process of iNOS by NF-kB can also make the production of NO increased, then the result is apoptosis that exacerbate the viability of pancreatic beta cells.[3,10] Second, hyperuricaemia is also associated with oxidative stress, playing an important role in the pathogenesis of type 2 diabetes.

Biosynthesis and insulin secretion by pancreatic beta cells, moreover, are governed by essential transcription factors, including MafA, PDX-1 and NeuroD. Mafa suppression can lead to a decrease in insulin production. Recent researches even suggest that Mafa dysfunction in transcription and translation can lead to a decrease in insulin production. As a result, uric acid can impair insulin secretion and pancreatic beta cell presence by increasing the activity of NF-kB and decreasing the activity of Mafa, leading to apoptosis of pancreatic beta cells. In other words, the activation of NF-kB - iNOS - NO is cytotoxic, which can trigger apoptosis in type 1 and 2 diabetes.[3,10]

The increased serum uric acid can also trigger endothelial dysfunction by inhibiting the production of NO and preventing the formation of ROS (reactive oxygen species), excessive synthesis of mitochondrial Na (+)/Ca (2+) exchanger-mediated mitochondrial

calcium, activate the renin-angiotensin system as well as generating inflammation to stimulate monocyte chemo-attractant protein-1, vascular smooth muscle cell proliferation and platelet aggregation. It can also stimulate endothelial dysfunction by increasing endothelin, contributing to vascular complications.[17]

Similarly, a research conducted by Krishnan et al[11], also found a positive correlation in which the increased serum uric acid level (0.1 mmol/L) can accelerate risks of both vascular complications (28%) in patients with type 2 diabetes and mortality (9%).[11] The meta-analysis research also stated that serum uric acid could be considered as an essential predictor of macrovascular complications, such as stroke and heart disease, as well as trigger a greater risk for microvascular complications.[11] Unfortunately, this research did not observe other risk factors that affect uric acid levels, e.g. dietary factors. This research also did not involve the same number of males and females due to the exclusion factor.

CONCLUSION AND SUGGESTION

In conclusion, there was a significant difference in glycemic status of male and female patients with and without hyperuricemia. Nevertheless, further researches should better determine the correlation of increased uric acid level on insulin production to pancreatic beta cells.

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