ИЗУЧЕНИЕ ВЛИЯНИЯ ПОВЫШЕННОГО СОДЕРЖАНИЯ МОЧЕВОЙ КИСЛОТЫ В СЫВОРОТКЕ КРОВИ НА ВЕРОЯТНОСТЬ ВОЗНИКНОВЕНИЯ ДИАБЕТИЧЕСКОЙ ПЕРИФЕРИЧЕСКОЙ НЕЙРОПАТИИ У ПАЦИЕНТОВ С САХАРНЫМ ДИАБЕТОМ 2 ТИПА В ГОСПИТАЛЕ SOETOMO

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АКТУАЛЬНОСТЬ. Повышенное содержание мочевой кислоты (МК) в сыворотке крови при сахарном диабете 2 типа ассоциировано с высокой вероятностью макрососудистых осложнений. Однако зависимость между уровнем МК в сыворотке и риском развития диабетической периферической нейропатиии до сих пор полностью не изучена.

ЦЕЛЬ. Целью данного исследования было изучение корреляции между повышенной концентрацией МК в сыворотке и диабетической периферической нейропатией.

МЕТОДЫ. В данное исследование, спланированное по типу «случай-контроль», включались последовательные пациенты в соответствии с принятыми критериями включения/исключения. Диагностику диабетической периферической нейропатии проводили с помощью электронейромиографии (ЭНМГ). Также выполняли определение уровня МК в сыворотке крови. Для оценки корреляции использовали критерий χ2 Пирсона.

РЕЗУЛЬТАТЫ. В исследование были включены 30 пациентов, 15 из которых вошли в экспериментальную группу, а остальные 15 составили контрольную группу. Достоверной зависимости между повышенной концентрацией МК в сыворотке и диабетической периферической нейропатией выявлено не было (отношение шансов (ОШ) = 3,143; 95% доверительный интервал (ДИ) 0,681–14,503; p=0,136).

ЗАКЛЮЧЕНИЕ. Нами не было установлено корреляции между высоким уровнем МК в сыворотке и диабетической периферической нейропатией.

КЛЮЧЕВЫЕ СЛОВА: мочевая кислота; диабетическая периферическая нейропатия; сахарный диабет 2 типа

CORRELATION BETWEEN HIGH SERUM URIC ACID LEVELS WITH OCCURRENCE OF DIABETIC PERIPHERAL NEUROPATHY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS IN SOETOMO GENERAL HOSPITAL

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BACKGROUND: The increased serum uric acid (SUA) levels have been linked to macro vascular disease in Type 2 Diabetes Melitus. The correlation between serum uric acid levels and diabetic peripheral neuropathy has not been addressed properly.

OBJECTIVE: The aim of this study was to determine the correlation between high serum uric acid levels and diabetic peripheral neuropathy.

METHODS: This was a case-control design study and the sampling was done consecutively by following the inclusion and the exclusion criteria. The diabetic peripheral neuropathy was evaluated using Electroneuromyography (EMNG) and the serum were taken for uric acid level examination. Chi square test was used for the correlation analysis.

RESULT: Thirty subjects were enrolled and divided into an experimental group of 15 subjects and a control group of 15 subjects as well. We found that the diabetic peripheral neuropathy did not show a significant correlation with high serum uric acid levels, p=0,136 and OR 3,143 (CI 95% 0,681-14,503).

CONCLUSIONS: There was no correlation between high serum uric acid levels with diabetic peripheral neuropathy.

KEYWORDS: uric acid; diabetic peripheral neuropathy; diabetes mellitus type 2

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Diabetes mellitus (DM) is a clinical syndrome characterized by hyperglycemia that occurs due to insulin secretion abnormalities, insulin performance, or both.[1, 2] Type 2 Dibetes Mellitus (T2DM) is an increasing health problem of incidence and prevalence so it becomes a worldwide concern. [1-4] Diabetic Peripheral Neuropathy (DPN) is one of the most frequent chronic microvascular complications in T2DM.[3-5] Finger or foot infections and amputations are common risks faced by DPN. This causes an increase in morbidity and mortality resulting in increased medical costs of patients with DPN.[4-6] Prevalence of neuropathy in DM patients over 50% for 25 years.[7] The overall prevalence of neuropathy was estimated at 30%.[4, 8, 9] In the EURODIAB IDDM Complication Study, DPN is associated with blood glucose control and DM duration. Microvascular complications still occur, despite controlling of blood glucose levels was performed well (HbA_{1c} 5.4% to 7%), so it is suspected other factors involved besides blood glucose control and duration of DM [10].

High serum uric acid (SUA) levels were associated with the incidence of macrovascular and microvascular complications in patients with DM.[11] Increased levels of SUA have been associated with endothelial dysfunction, ischemic heart disease, stroke, peripheral artery disease and death from cardiovascular disease.[3, 12, 13] In T2DM, the increasing levels of SUA were associated with metabolic syndrome and insulin resistance. The association of high SUA levels with DM was reported in several studies.[13-17] The association of hyperuricemia with DPN is still controversial. The study by Ito et al (2011) showed a significant difference between the proportion of DPN in hyperuricemia and normosemia (p=0.19).[11] But another study showed that DPN had a moderate significance (p <0.001) with a positive correlation (r=0.509) towards high SUA levels.[18]

Therefore, the purpose of this study was to determine the correlation between high serum uric acid levels and diabetic peripheral neuropathy.

METHODS

Research design

This study used a case control design with the population of all T2DM patients who visited to the endocrinology outpatient unit of Soetomo General Hospital and fulfilled the inclusion and the exclusion criteria during the period of August to December 2016.

Conformity criteria

The inclusion criteria were 40-60 years old, EMNG results supported the DPN and agreed to join the research.

While the exclusion criteria were chronic renal impairment, chronic liver disorder, history of malignancy, history of drug use and radiotherapy, history of alcohol consumption.

Group analysis

We used consecutive sampling as the sampling technique because it was the best non-probability sampling and easy to do. The sample size was determined using the formula of unpaired categorical analytic research. The value of the effect proportion on the control (P2) was determined based on the preliminary study and the calculation of the required minimum sample size was 15 people in each group.

The samples were divided into two groups; 15 subjects with EMNG results that did not support the diabetic neuropathy referred to as a control group and 15 subjects with EMNG results that supported the diabetic neuropathy, hereinafter referred to as case/experimental group. The sampling conducted for 5 (five) months.

Additionally, the T2DM patients who fulfilled the inclusion and the exclusion criteria will be performed anamnesis, physical examination and then performed the blood tests for serum uric acid levels and other confounding factors.

Ethical review

This study has been approved by the ethical committee of Soetomo General Hospital with ID 658/Panke.KKE/XI/2016 on 17 November 2015.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, N.Y., USA). Collected categorical data (hypertension, dyslipidemia, disease duration, DPN) were analyzed using Chi-Square test while numerical data were analyzed by T-test. Because from the analysis of normality was normal (p=0,20). We used P value level < 0,05 as statistically significant.

RESULTS

Research sample (participants/respondents)

The total subjects were 30 patients consisting of 15 subjects with EMNG results that did not support the DPN that referred to as a control group and 15 subjects with EMNG results that supported the DPN, referred to as case/experimental group. The basic characteristics of research subjects consisting of demographic and clinical data were showed in table 1.

Primary findings

While the correlation between high serum uric acid levels and the incidence of diabetic peripheral neuropathy was shown in table 2. Subjects in case group who had high serum uric acid levels as many as 8 people (53.3%) more than subjects in the control group with high serum uric acid level of 4 people (26.7%). However, there was no statistically significant difference (P = 0.136).

In this study, the glycemic control and disease duration analyzed as cofounding factors. There was no significant difference in glycemic control (HbA_{1c}) between two groups with P = 0,682, while the duration of disease was significant with P<0,001.

DISCUSSIONS

This was an observational analytic study to determine the correlation between high serum uric acid levels and the incidence of diabetic peripheral neuropathy in patients with T2DM.

Case control was used in this study. This design was chosen because it was considered in accordance with the purpose of the research to assess the role of risk factors for high serum uric acid levels in the occurrence of diabetic peripheral neuropathy (cause-effect relationship).[19, 20]

In this study, there were no significant differences in basic variables consisting of demographic data. In addition, we obtained that there were no significant differences in clini-

Table 1. The Basic Characteristics of Subjects

Characteristics		DPN Incidence				OR
		Experimental	Control	Total	p	(CI 95%)
Sex						
-	Male	5 (33.3 %)	5 (33.3 %)	10 (33.3 %)	1,000	1,000
-	Female	10 (66.7 %)	10 (66.7 %)	20 (66.7 %)		(0.219-4.564)
Age		51.60+6,52	53.53+4.72		0.25	
Body Mass Index (BMI)						
-	Normal	9 (60.0 %)	9 (60.0 %)	18 (60.0 %)	1,000	1,000
-	Obesity	6 (40.0 %)	6 (40.0 %)	12 (40.0%)		(0.232-4.310)
Dyslipidemia						
-	Dyslipidemia	10 (66.7 %)	13 (867 %)	23 (76.7 %)	0.270	0.213888889
-	Normal	5 (33.3 %)	2 (13.3 %)	7 (23.3 %)		(0.049-1.928)
Hypertension						
-	Hypertension	4 (26.7 %)	6 (40.0 %)	10 (33.3 %)	0.305	0.378472222
-	Normal	11 (73.3 %)	9 (60.0 %)	20 (66.7 %)		(0.117-2.549)
Smoking						
-	Yes	1 (6.7 %)	1 (6.7 %)	2 (6.7 %)	1,000	1,000
-	No	14 (93.3 %)	14 (93.3 %)	28 (93.3 %)		(0.057-17.621)
Duration of Disease						
Type 2 Diabetes Mellitus						
-	≥ 5 years	12 (80.0 %)	2 (1.3 %)	14 (46.7 %)	0.001	0.038
-	< 5 years	3 (20.0 %)	13 (86.7%)	16 (53.3 %)		(0.005-0.271)
Serum HbA_{1c} Levels						
-	High	12 (80.0 %)	10 (66.7 %)	22 (73.3 %)	0.473	0.347222222
-	Normal	3 (20.0 %)	5 (33.3 %)	8 (26.7 %)		(0.117-2.549)

Table 2. The Correlation between High Serum Uric Acid Levels and the Incidence of Diabetic Peripheral Neuropathy

		DPN Cases				OR
		Experimental	Control	Total	p*)	(CI 95%)
Serum Uric Acid Levels						
-	High	8 (53.3%)	4 (26.7%)	12 (40 %)	0.094	3,143
-	Normal	7 (46.7%)	11 (73.3 %)	18 (60 %)		(0.681-14.503)
Total		15 (100%)	15 (100%)	30 (100%)		

cal data except the T2DM duration (P<0,001). Demographic data included age and sex while clinical data included BMI, dyslipidemia, hypertension, smoking, serum HbA_{1c} levels and T2DM duration.

In this study, among the total 30 subjects, there were 10 (33,3%) male and 20 (66,7%) women. This was consistent with T2DM epidemiologic data suggesting that women were more likely to have diabetes mellitus than men. Women were at higher risk for T2DM because women have a greater chance of increasing body mass index than men.[21] The prevalence of DPN by sex was in accordance with the other developing countries such as Sri Lanka, India, North Africa, and Iran.[22] Some studies also suggested that men were fewer than women.[22-24] Bansal et al reported that women had a DPN risk of three times higher than men (OR 3.15, 95% CI 1.57-6.31, p <0.001).[24] However, this study found that there were no statistically significant difference in sex proportion between the experimental and control groups.

The mean age of the experimental group (51.60±6.52 years) was slightly younger than the control group (53.53±4.72 years), but this difference was not statistically significant with p=0.360. This result was in accordance with a study by Guirrero et al that the mean age of samples that has suffering from DPN was 56.9±9.6 years.[25] But the mean age in this study was relatively young compared to the research that conducted by Lu et al that the mean age of samples suffering DPN was 68.27±10.66 and the mean age that did not suffer DPN was 62.26±10.05.[26] Multicenter studies conducted in the United Kingdom reported that the prevalence of diabetic peripheral neuropathy increases with age, from 5% (3.1-6.9%) in the 20-29 years age group to 44.2% (41.1-47.3%) in the 70-79 years age group.[27] However, the

samples over the age of 60 were not included in this study, because the age affects other types of neuropathy such as neuropathy due to vitamin deficiency, malnutrition, and others.

Characteristics of the subjects based on body mass index (BMI) in the experimental group were the subjects with normal BMI that was 9 patients (60.0%) meanwhile the subject of obesity in 6 patients (40.0%). However, this difference was not statistically significant with p=1,000. This was in accordance with a study that conducted by Kiani et al., reported that there was also no significant difference between BMI and diabetic neuropathy (p=0.056) in 84 subjects[22]. Obesity or combination with metabolic syndrome was a risk factor for neuropathy complications. Obesity and triglycerides were associated with the loss of small axon nerves that were unveiled myelin. Obesity was associated with edema that precedes the occurrence of clamp phenomena that disrupt the barrier so that nutritional deficiencies in susceptible nerve tissue. Obesity along with other metabolic syndromes leads to an increase in insulin resistance.[28, 29] T2DM and obesity have a complex relationship. Obesity was a precursor of T2DM via insulin resistance mechanism.[30, 31]

Characteristics of the subjects based on the risk factor of dyslipidemia in the experimental group were found in 10 patients (66.7%) that less than the control group as many as 13 patients (86.7%). However, this difference was not statistically significant with p = 0.390. This was consistent with a study conducted by Basal et al who found that dyslipidemia in the diabetic neuropathy group was 8% while in the diabetic neuropathy group was 44% with p=0.075 (p <0.001).[24] The study of dyslipidemia as a risk factor for neuropathy was still controversial. There was no significant difference between total cholesterol, HDL, LDL and triglyceride levels in people with type 2 DM who had somatic neuropathy with or without neuropathy.[32] Patients with type 2 DM who were treated intensively with statins reduce the risk of autonomic neuropathy, but not DPN.[33] The different studies found that dyslipidemia was an independent risk factor for macro vascular disease in type 2 diabetes mellitus patients. In the preliminary study, decreased lipid levels with both fibrates and statins within 5 years prevented the incidence of new sensory neuropathy. The decrease in lipid levels was performed using fibrate therapy (HR= 0.52; 95%; CI 0.27-0.98) and the use of statins therapy (HR = 0.65; 95% CI 0.46-0.93; p <0.042).[32] The results was consistent with the in vitro studies and animal studies that showed the levels of lipid-lowering therapy had the neuroprotective effects by improving the Schwann cells, polyol pathway, and the repair of nerve blood flow.[33]

The characteristics of subjects based on hypertension in the experimental group found 4 patients (26.7%) with hypertension, then fewer than the control group that was 10 patients (40.0%). But in this study there was no statistically significant difference between the experimental and control group (p=0.439). This was consistent with a study that conducted by Papanas et al., stated that there was also no statistically significant difference between the case and the control group in 130 subjects (p=0.999).[3] Kiani et al.'s study also found that there was no significant difference between the history of hypertension (p=0.124), systolic blood pressure (p=0.373), and diastolic blood pressure (p=0.640) with diabetic neuropathy.[22] Hypertension was an independent factor in macro vascular disease, retinopathy, and nephropathy. Hypertension was a complication of blood vessels due to hyperinsulinemia. Insulin resistance increases sodium reabsorption in the proximal tubules of the kidney.[28]

The characteristics of subjects based on smoking were 1 person (6.7%) who smoked in the experiment group while in the control group there were 14 people who did not (93.3%). But in this study there was no statistically significant difference between the experiment and control group (p=1.000). This was according to the research conducted by Kiani et al., who found that there was no significant difference between smoking and diabetic neuropathy in 84 subjects.[22] The study by Mitchel et al examined the association between smoking and diabetic neuropathy that resulted in a strong relationship between the number of cigarettes smoked during their lifetime and the presence of neuropathy. Patients who smoked >30 pack/year had a 3.32 times increased risk of neuropathy compared with those who smoked <30 pack/year.[34] In recent years, there was a potential role of vascular factors in the pathogenesis of diabetic neuropathy. It was speculated that smoking could lead to tissue hypoxia which might further injure the microvascular.[34]

Additionally, the characteristics of subjects based on long-term T2DM ≥5 years in the case group were 12 people (80.0%) it was more than the control group that only 2 people (13.3%). While the subjects who suffer from DM <5 years in the case group was 5 people (20.0%), less than the control group that was 13 people (86.7%). The correlation test results showed that there was a correlation between the duration of DMT2 and the incidence of diabetic peripheral neuropathy (P<0,001; odds ratio 0.038; 95% CI 0.005-0.271). This was consistent with some studies obtained a correlation between the duration of DM and diabetic neuropathy.[24, 35] Research conducted by Fatkhur et al stated that the longer the patient suffering from DM, the risk of diabetic neuropathy was 16.7787 times greater in DM ≥5 years (P<0,001).[35] In addition to hyperglycemia, the duration of DM was a risk factor for DPN in Diabetes Control and Complications Trial. [10] DPN was a microangiopathic complication in patients with type 2 DM which increases its prevalence in accordance with the duration of DM.[24] DPN complications could occur in patients with DM through various mechanisms. Hyperglycemia that has a long period, genetic and other mechanisms such as immune will increase oxidative stress and stimulate other pathways that caused damage of nerve, vascular endothelial, glomerular, mesangial, and retinal cells.[36] Examination using electrophysiology can detect subclinical DPN as indicated by the decrease in both sensory and motor neuronal conductivity in patients with DM after 5-10 years.[37]

Moreover, characteristics of the subjects by high serum levels of HbA_{1c} as many as 12 people in the experimental group (80.0%) was more than the control group as many as 10 people (66.7%). However, this difference was not statistically significant with p=0.682. This was consistent with research conducted by Kiani et al. who stated that there was no significant correlation between serum HbA_{1c} levels and the incidence of diabetic neuropathy.[22] Research by Kamran et al showed HbA_{1c} levels associated with neuropathy in patients with DM. HbA_{1c} levels greater than 10 mg/dL were associated with neuropathy.[38] HbA_{1c} levels were associated with micro vascular complications.[38, 39]

Based on the risk factor of serum uric acid level in the group of the incidence of peripheral diabetic neuropathy was obtained 8 people (53.3%) with high serum uric acid level, it was more than in the group without peripheral paralytic neuropathy that found 4 people with high serum uric acid level (26.7%). However, there was no statistically significant difference with p=0.136 and odds ratio by 3.143 (95% CI 0.681-14.503) in this study. The result of odds ratio (OR) was more than 1, so then it was concluded that high serum uric acid levels had no correlation with the incidence of diabetic peripheral neuropathy in type 2 diabetes mellitus. It was not in accordance with this research that conducted by Rafie et al against 132 patients with T2DM aged 45-80 years who suggested there was a correlation between high serum uric acid and diabetic peripheral neuropathy in DM patients (p <0.0001) [40].

Next, the difference could be caused by the age of research. The subjects in this study was 40-60 years while the subjects by Rafie et al up to 80 years. In general, the older age also affects the incidence of peripheral diabetic neuropathy. The multicenter study conducted in the UK, the prevalence of diabetic peripheral neuropathy increased with age, from 5% (3.1- 6.9%) in the 20-29 year age group to 44.2% (41.1-47.3%) In the 70-79 age group [27].

Lastly, in this study, the risk factor that affected the DPN was the duration of T2DM.. In the experimental group with T2DM duration ≥5 years more than the control group and statistically significant with P<0,001

7. In addition, the previous studies suggested that there was an inadequate correlation between high serum uric acid levels and diabetic peripheral neuropathy with r=0.509.[18] This research strength was 30% statistically, in other word, there was a 70% chance to not find a significant correlation between high serum uric acid levels with the incidence of DPN.

CONCLUSIONS

There was no correlation between the high serum uric acid levels and the incidence of diabetic peripheral neuropathy in patients with T2DM.

ADDITIONAL INFORMATION

Conflict of interests. Authors declare no explicit and potential conflicts of interests associated with the publication of this article.

Authors involvement. DPS initiated, drafted the manuscript, and analyzed the data; MB designed and revised the manuscript; MH, Fi and Fa contributed to interpretation of data.

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