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THE RELATIONSHIP BETWEEN NITRIC OXIDE AND GLYCEMIC CONTROL IN CONTROLLED AND UNCONTROLLED TYPE 2 DIABETES MELLITUS PATIENTS IN THE ADAM MALIK HOSPITAL MEDAN

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ABSTRACT

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia. Hyperglycemia and other metabolic changes can cause Nitric oxide (NO) production disturbance. This study investigated the difference in the levels of NO and its relationship with HbA1c in controlled and uncontrolled diabetes mellitus type 2 patients in the Adam Malik Hospital. This study was a cross-sectional study, conducted in Outpatient Clinic and Inpatient Ward of Internal Medicine Section of Endocrinology in the Adam Malik Hospital on June through October 2016, involving 70 patients type 2 Diabetes Mellitus (DM) consisting of 35 controlled type 2 diabetes patients and 35 uncontrolled type 2 diabetes patients that fulfill this study's criteria. Nitric oxide examination conducted by using Chemwell analyzer with the principle of double-antibody sandwich using Enzyme-Linked Immunosorbent Assay (ELISA). There was no significant relationship between HbA1c and Nitric oxide in patients with controlled ($r = 0.264$) ($p = 0.125$) and uncontrolled ($r = 0.194$) ($p = 0.265$) type 2 diabetes mellitus. But there was a significant relationship between HbA1c and NO in patients with type 2 DM ($r = 0.636$) ($p = 0.0001$). In this study, there was no significant association between HbA1c and Nitric oxide levels in patients with controlled and uncontrolled type 2 diabetes mellitus. There is a statistically significant relationship between HbA1c and NO in patients with type 2 diabetes.

Key words: Type 2 diabetes mellitus, HbA1c, nitric oxide

INTRODUCTION

Diabetes mellitus is a metabolic disorder, which prevalences increases annually.¹ It is prevalence in Indonesia is in the seventh highest under China, India, United States, Brazil, Russia, and Mexico. World Health Organization predicts that the number of diabetes mellitus patients in Indonesia will increase from 8.4 million in 2000 to 21.3 million in 2030.²

Diabetes mellitus is the disease with the highest incidence in Medan in September-October 2009.³ Based on an initial survey from medical records done by researchers in the Adam Malik Hospital Medan, it stated that the number of patient visits with diabetes mellitus diagnosis in inpatient ward was 1,660 patients in 2013, 1,013 patients in 2014, and 1,014 patients in 2015. Meanwhile, the number of Diabetes mellitus patients visits were 8,567 patients in 2014, 13,802 patients in 2014 and 14,968 patients in 2015.

Diabetes mellitus patients are expected to undertake a medical examination and receive treatment routinely to monitor their metabolic

status. HbA1c nowadays is still considered as a single parameter that stands for the most prominent and independent to control metabolic condition, to evaluate the risk factors of diabetes complications and to monitor the treatment.⁴

Diabetes mellitus is a metabolic condition characterized by chronic hyperglycemia. The long-term effects of diabetes mellitus are cellular damage, inflammation and multiorgan failure. The diabetes complications are differentiated into two major parts, macrovascular complications (coronary artery disease, peripheral vascular disease, and stroke) and microvascular complications (diabetic nephropathy, retinopathy, and neuropathy).⁵ Endothelial dysfunction is the most common problem among the other complications. The endothelial cells secrete a different mediator such as vasodilator, i.e. nitric oxide and vasoconstrictor such as endothelin-1. The hyperglycemia and other metabolic disruption can cause disorder in NO production.⁶ Endothelial dysfunction in type 2 diabetes mellitus patients, can cause cardiovascular disease. Therefore, endothelial dysfunction is the

first feature of cardiovascular complication in type 2 diabetes mellitus.⁵

This research was aimed to know wheater there is a relationship between NO concentration with glycemic control (HbA1c) in controlled and also uncontrolled type 2 diabetes mellitus patients in the Adam Malik General Hospital Medan.

METHODS

This study was a cross-sectional study conducted in patients of Outpatient Clinic and Inpatient Ward of Endocrinology Section, Department of Internal Medicine Adam Malik General Hospital Medan in June-October 2016 the inclusion were male/female and type 2 diabetes mellitus patient. The exclusion criteria were pregnant, smoking, hypertension, dyslipidemia, and coronary heart disease. This study involved 70 type 2 diabetes mellitus patients that consisted of 35 controlled type 2 DM patient and 35 uncontrolled type 2 DM patients.

The patient's serum samples were used for nitric oxide examination. Nitric oxide was measured with Chemwell analyzer. The principle of this examination is a double antibody sandwich Enzyme-Linked Immunosorbent Assay (ELISA). Meanwhile, the HbA1c examination was measured from EDTA blood sample. Thermo Fischer Scientific Indiko automatic analyzer was used to measure the HbA1c. The principle of this device is turbidimetric immunoassay

using latex particles conjugated in monoclonal antibodies.

The statistical analysis was done to know the differences of NO concentration among controlled and uncontrolled type 2 diabetes mellitus patient. The independent t-test was used if the data were normally distributed; otherwise, Mann-Whitney test was used. The correlation between nitric oxide and HbA1c in controlled and uncontrolled type 2 diabetes mellitus was assessed with Pearson correlation test if the data were normally distributed and Spearman's rho test if the data were not normally distributed.

RESULT AND DISCUSSION

This study involved 70 patients diagnosed as type 2 diabetes mellitus with age ranged from 22-80 years old. The mean age was 54.64 years old. The number of female subjects (n=28) was higher than male (n=42).

As shown in Table 1, the mean age of controlled type 2 DM was 55.6 years old, older than the mean age of uncontrolled type 2 DM that was 53.69 years old. The mean age between the two groups was significantly different with p=0.008. However, there was no significant difference in the field of sex between the two groups with p=0.333.

As shown in Table 2, the median concentration of NO in uncontrolled type 2 diabetes mellitus was 1063.5 pg/mL. This concentration was higher than in

Table 1. Characteristics of the subject based on age and sex

Characteristics	Type 2 DM		p-value
	Controlled	Uncontrolled	
Sex, n (%)			
Male	23 (65.7)	19 (54.3)	0.333 ^
Female	12 (34.3)	16 (45.7)	
Age, Mean±SD	55.60±15.4	53.69±9.8	0.008*

Significantly different if p<0.05, the differential test used: * = independent t-test and ^ = Mann-Whitney U test

Table 2. Characteristics of the subjects based on laboratory examination results

	N	HbA1C(%) Median (Min-Max)	NO (pg/mL) Median (Min -Max)	P
Controlled type 2 DM	35	6.2 (4.2-6.9)	535.9 (279.3 - 4494.6)	<0.0001 ^
Uncontrolled type 2 DM	35	9.9 (7.0-17.4)	1063.5 (520.3 - 5725.7)	<0.0001 ^
Total	70			

Significantly different if p < 0.05. The differential test was Mann-Whitney U test

controlled type 2 DM patients which the median value was 535.9 pg/mL. Statistical analysis result showed significant differences in NO concentration between uncontrolled type 2 diabetes mellitus and controlled type 2 diabetes mellitus patients ($p < 0.0001$).

As shown in Figure 1, Spearman's rho test results showed that there was no correlation between HbA1c and NO concentration in controlled type 2 diabetes mellitus patients ($r = 0.264$) and the statistic analysis results also showed that there was no significant correlation between HbA1c and NO concentration in controlled type 2 diabetes mellitus

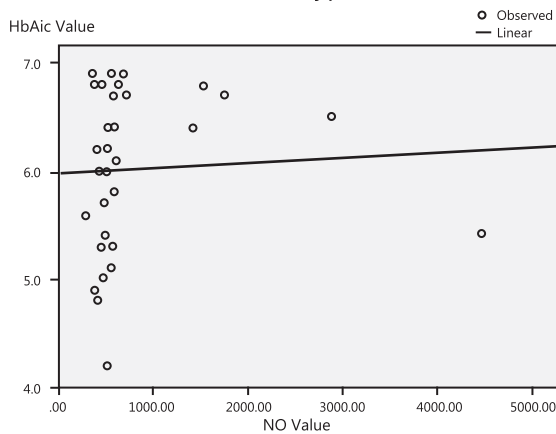


Figure 1. Correlation of HbA1c and NO in controlled type 2 diabetes mellitus patients

Figure 2 showed, the Spearman's rho test results there was no correlation between HbA1c and NO concentration in uncontrolled type 2 DM patients ($r = 0.194$) and the statistic analysis results also showed that there was no significant correlation between HbA1c and NO concentration in uncontrolled type 2 DM patients ($p = 0.265$).

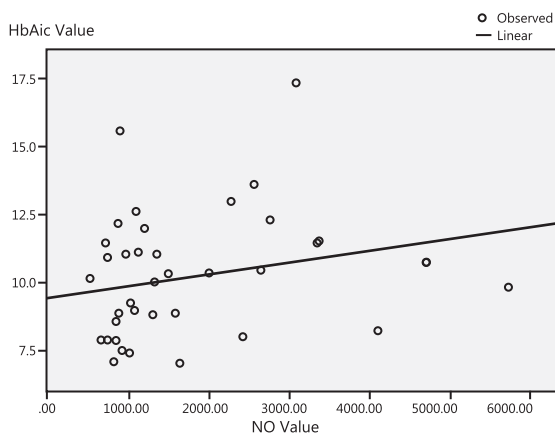


Figure 2. Correlation of HbA1c and NO in uncontrolled type 2 DM

Spearman's rho test result showed a strong positive correlation between HbA1c and NO

concentration in type 2 DM patients ($r = 0.636$). The statistic analysis results showed a significant correlation between HbA1c and NO level in type 2 DM patients ($p = 0.125$) (Figure 3).

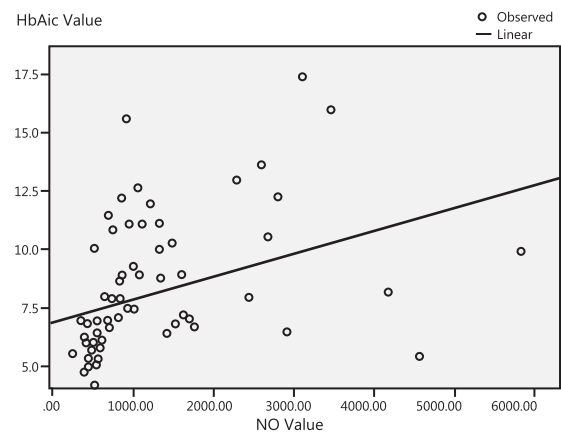


Figure 3. Correlation between HbA1c and NO concentration in type 2 DM

Free radical, the NO, has emerged as a primary signal that regulates every essential cellular function and acts as a potent mediator for cell damage in many conditions. Vascular injury in diabetes as a result of hyperglycemia has been related to oxidative stress which causes intracellular glutathione depletion by increasing extracellular superoxide dismutase in plasma which inhibits lipid peroxidation and causes complications in diabetes. The increase in superoxide dismutase concentration can cause endothelial nitric oxide synthase (eNOS) isoform dysfunction by trigger advanced glycation end product, and poly (ADP-ribose) polymerase take place. Nitric oxide is a gas molecule secreted by endothelial cells that act as the central regulator of endothelial function. Nitric oxide can be synthesized as conversion products from L-arginine precursor into L-citrulline. This reaction is catalyzed by nitric oxide synthases (NOSs), i.e. neuronal NOS (nNOS), endothelial NOS (eNOS) and inducible NOS (iNOS). Nitric oxide is the central molecule to regulate the process related to metabolic, vascular and cellular function.⁷

A study in coronary heart disease patients with and without diabetes mellitus by Widiastuti showed decreased production of anti thrombotic and vasodilator compound such as NO, thrombomodulin, and tissue plasminogen activator (tPA).⁸

The recent study found a strong positive correlation between HbA1c and NO concentration in type 2 DM patients ($r = 0.636$). Statistical test result found a significant correlation between HbA1c and

NO concentration in type 2 DM ($p=0.0001$). According to Naveen and Renuka study in 2014, they studied 55 diabetes and 25 non-diabetes patients. They found the NO concentrations were significantly higher in diabetes patients. That study also found a strong correlation between HbA1c and serum nitric oxide concentration with $r = 0.644$ and p -value <0.001 .⁹

Based on a study done in India that involved 87 patients in which 56 patients were typed 2 diabetes mellitus patients, while 31 patients were non-diabetics, the serum nitric oxide had a positive statistically significant correlation with HbA1c ($r = 0.35$ and $p = 0.0$).¹⁰

Nitric oxide plays roles in the endothelial dysfunction that cause atherosclerosis in coronary heart disease patients who suffered from diabetes mellitus. Nitric oxide is an important mediator that can act as free radicals and can be changed into peroxynitrite by neuronal cells. It can modulate neurotransmission in endothelial cells and stimulate vascular relaxation or dilatation. The decrease in nitric oxide concentration can be caused by a decrease in NO synthesis or an increase in its degradation so that the superoxide anion production will increase. Superoxide anion production enhancement has a consequence of a reduction in atherogenic and thrombogenic inhibition processes, also decrease in the coronary artery dilatation ability. Some experts state that nitric oxide concentration play a role as endothelial dysfunction marker rather than independent coronary risk factor.¹¹

CONCLUSION AND SUGGESTION

Recent studies found no significant correlation between HbA1c and NO concentration both in controlled and in uncontrolled type 2 diabetes mellitus patients. However, if the type 2 diabetes mellitus patient samples were analyzed, there was a significant correlation between HbA1c and NO concentration. There is a need to conduct further

studies with larger sample size and greater consideration in the effect of other variables that may influence endothelial dysfunction.

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