

## ORIGINAL ARTICLE

# Relationship between HbA1c Levels with eGFR and Blood Pressure in Type 2 Diabetes Mellitus Patients at General Hospital in Surabaya

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## ABSTRACT

**Introduction:** Diabetes mellitus is ranked seventh as the cause of death in the world, around 95% in the world is type 2 diabetes mellitus (T2DM). According to Riset Kesehatan Dasar (Riskesdas) in 2013, the prevalence of diabetes mellitus in Indonesia is 6,9%. Type 2 diabetes mellitus that is not well controlled will increase the risk of chronic complications, both microangiopathies such as nephropathy, and macroangiopathy such as hypertension. The aim of the study was to determine correlation between HbA1c levels with eGFR (Estimated Glomerulus Filtration Rate) and blood pressure (systolic and diastolic).

**Methods:** An analytic observational cross-sectional study, collecting the data from 94 patients with T2DM. The variables were collected from patient's medical records. Analysis using Spearman's Rank Correlation test.

**Results:** From total 232 patients, 134 (57.8%) were females, 203 (87.5%) >45 years old with average age 55.57. There was no significant correlation between HbA1c and systolic blood pressure and there was no significant correlation between HbA1c and diastolic blood pressure. There was no significant correlation between HbA1c and systolic blood pressure ( $r=-0.127$ ;  $p=0.054$ ). Also no significant correlation between HbA1c and diastolic blood pressure ( $r=-0.111$ ;  $p=0.093$ ). Analysis on other factor showed a significant correlation between HbA1c and eGFR ( $r=0.341$ ;  $p=0.000$ ).

**Conclusion:** No significant correlation between HbA1c and systolic blood pressure, and between HbA1c and diastolic blood pressure. Significant correlation between HbA1c and eGFR.

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## Introduction

CDiabetes mellitus is a global scale concern non-communicable disease.<sup>1</sup> There are several types of diabetes mellitus, type 1, type 2, gestational type and other types of diabetes mellitus. T2DM is a disease with metabolic disorders due to damage in insulin secretion or disorders of pancreatic beta cells and / or impaired insulin function. The prevalence of diabetes mellitus in the world according to the International Diabetes Federation (IDF) is 1.9% and diabetes mellitus is ranked seventh as the cause of death in the world, around 95% in the world is T2DM.<sup>2</sup> According to Riset Kesehatan Dasar (Riskesdas) in 2013, the prevalence of diabetes mellitus in Indonesia is 6,9%. Several unmodifiable risk factors, including gender,

genetic factors, and age could increase T2DM prevalence. While people can work on modifiable risk factor that are related to physical condition and social life, Body Mass Index (BMI), waist circumference, alcohol consumption, work and physical activity, education level, and smoking habits.<sup>3</sup>

T2DM that is un-controlled will increase the risk of chronic complications, both microangiopathies such as nephropathy, and macroangiopathy such as hypertension.<sup>4</sup> Theoretically, every person with type 2 diabetes mellitus is at risk of experiencing chronic complications. It depends on uncontrolled sugar levels, a history of hypertension, kidney damage, and long-standing diabetes mellitus. People with T2DM and hypertension will increase the risk of getting

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coronary heart disease higher. In addition, poor control of diabetes mellitus, characterized by hyperglycemia, will progressively lead to a decrease in the Glomerular Filtration Rate (GFR) and the destruction of the glomeruli, leading to chronic kidney disease.<sup>5</sup> In this study, uncontrolled diabetes mellitus seen from its HbA1c values. HbA1c is the component of hemoglobin that binds to blood sugar. In cardiovascular complications, diabetes mellitus can interfere with the function of diastole and systole. Patients with diabetes mellitus usually have diastolic dysfunction before experiencing systolic dysfunction.<sup>6</sup> Macrovascular complications can be in the form of heart disease, stroke, and peripheral blood vessels where peripheral artery disease can cause wounds that are difficult to heal, gangrene, and can even be amputated. Other complications cause a decrease in infection resistance, pneumonia, macrosomia, and complications during childbirth.<sup>7</sup> These complications lead to kidney failure, gangrene, vision problems, and cardiovascular disorders such as arteriosclerosis, myocardial infarction, stroke, and lower extremity artery obstruction. Patients with uncontrolled blood sugar levels and have diabetes for a long time as mentioned above are directly proportional to the incidence of microvascular complications.<sup>5,8</sup> Unfortunately, there have been few researches to evaluate diastolic dysfunction in patients with diabetes mellitus.<sup>9</sup> In addition, the main complication of patients with diabetes mellitus is diabetic nephropathy and is a major cause of terminal stage of kidney failure.<sup>10</sup> As many as 40% of diabetic patients can result in advanced stage of kidney disease. study aims to find correlations between HbA1c levels with eGFR and blood pressure.

## Methods

This analytic observational cross sectional study was conducted at Dr. Soetomo General Hospital, from June 2017 to October 2018. The population were all patients with T2DM in Dr. Soetomo General Hospital, Surabaya. there were 232 patients with 98 men and 134 women in range January to May 2018. The sampling technique in this research is conducted by purposive sampling.

The inclusion criteria in this study were patients with T2DM with or without its complications who had laboratory results including HbA1c levels and serum creatinine, and had blood pressure test results. The exclusion criteria were patients with other type of diabetes mellitus. Type of data collected is the secondary data that obtained from medical records of patients with T2DM who hospitalized in Dr. Soetomo General Hospital. The values of eGFR were obtained by using the MDRD (Modification of Diet in Renal Disease) formula by entering serum creatinine, sex, and age of the patient in the formula.

To test the correlation between HbA1c levels and eGFR, and the correlation between HbA1c levels and systolic blood pressure and diastolic blood pressure, we used the Spearman's Rank Correlation test and to test the normality of data we used the Kolmogorov-smirnov test. Data will be analyzed by Statistical Product and Service Solution (SPSS) for windows ver. 24 (IBM Corp.) with  $p=0.05$  and  $\alpha=0.05$  considered as significant.

## Results

There were more female (57,8%) than male with type 2

diabetes mellitus in this study. According to Indonesian Endocrinology Association, high risk groups are patients over the age of 45 years.<sup>12</sup> The group  $> 45$  years has a much higher number than the group  $\leq 45$  years. We found more women than men in the group of subjects under the age of 45 years, as well as the other group.

HbA1c values were found to be higher in women than men. The eGFR in men is slightly better than in women. Whereas the blood pressure did not get much difference. Data presented with mean and standard deviation (table 1).

Table 1. Gender and age groups of people with type 2 diabetes mellitus

Characteristic	Gender(mean±SD)	
	Male (n=98)	Female (n=134)
Age groups (years)		
<45	13(39±4.42)	16(37.06±5.88)
≥45	85(59.07±9.3)	118(57.38±7.2)
HbA1c	(8.14±2.39)	(8.28±2.56)
eGFR	(56.66±47.15)	(54.78±47.66)
SBP	(130.72±19.38)	(130.72±18.88)
DBP	(80.78±10.24)	(82.07±9.93)

The data obtained is not normally distributed with  $\alpha=0.05$ . The Spearman Rank's correlation test showed that there was no significant correlation between HbA1c and systolic blood pressure. Also there was no significant correlation between HbA1c and diastolic blood pressure. But, there was a significant correlation between HbA1c and eGFR with a weak positive correlation. The results can be seen in table 2.

Table 2. Correlation between HbA1c with eGFR and blood pressure

HbA1c with	r	p
eGFR	0,341	0,000*
SBP	-0,127	0,054
DBP	-0,111	0,093

\*: shows significant correlation with  $p<0,05$

## Discussion

Our study shows that number of female patients was 134 (57.8%) patients, more numbers in female patients compared to male patients. Two previous studies at Arifin Achmad Hospital with higher proportion of female than male.<sup>13</sup> A higher percentage in women is caused by several factors, such as premenstrual syndrome, an increase in the Body Mass Index (BMI), and menopause. After menopause, there are changes in hormone levels, especially estrogen and progesterone hormones that influence blood sugar levels and increase abdominal fat and total body fat.<sup>14</sup> Excess body fat is associated with an increased risk of metabolic diseases.<sup>15</sup>

The results of this study corroborate the statement issued by Indonesian Endocrinology Association, that people  $\geq 45$  years should be tested for DM, because the risk of suffering from glucose intolerance will begin to increase with age.<sup>12</sup> The study conducted by Fitri Nurmaya Sirait in 2018 with a total of 167 people T2DM, showed that patients aged  $\geq 45$

years tended to experience various complications compared to the age of <45 years. Various complications from patients  $\geq 45$  years were acute complications of 66.7%, chronic complications of 93.9%, mixed complications of 93.9% compared with patients <45 years. This may be caused by an unhealthy lifestyle, including consumption of foods high in fat and carbohydrates and lack of physical activity. In this age group there has not been a decline in body function as experienced in the age group  $\geq 45$  years, which is a decrease in the function of the pancreas to produce insulin, thus increasing the risk of glucose intolerance.<sup>13</sup>

Some research says that there is no relationship between blood sugar levels and systolic hypertension.<sup>16</sup> Different results stating that there was a relationship between HbA1c levels and macrovascular complications, with the incidence of complications occurring most often being hypertension as much as 35.4% of all samples of patients with T2DM.<sup>17</sup> In the global DISCOVER study programme with 3 years prospective observational studies involving 15,992 T2DM patients, microvascular and macrovascular complications were reported in 18.9% (ARR: 14.5–23.5%) and 12.7% (ARR: 5.0–26.6%) of patients.<sup>18</sup>

About the correlation between HbA1c and diastolic blood pressure, the same test results were conclude that there was no association between hyperglycemia and diastolic hypertension.<sup>16</sup> Another study has revealed that there is a relationship between HbA1c and hypertension which leads to diastolic dysfunction due to right ventricular stiffness. Patients with impaired glucose metabolism tend to have an interfere with relaxation and increase stiffness of the heart muscle.<sup>19</sup> AT2-receptor is increasingly shown to have potential cardioprotective effects. ACE inhibition reduces left ventricular (LV) volumes, retards the progression of LV dilatation and hypertrophy and increases systolic function in systolic dysfunction.<sup>20</sup> Methylglyoxal-derived Advanced Glycation End products (MG-AGEs) are produced post-myocardial infarction (MI) and identifies a causative role for their accumulation in the cellular changes, adverse remodelling and functional loss of the heart after MI.<sup>21</sup> In patients with diabetes mellitus, diastolic pressure is used to determine the risk of nephropathy.

High blood sugar levels can cause interactions between hemodynamic and metabolic factors. In metabolic factors, abnormalities of glucose metabolism occur, such as the process of protein glycation, increase in the polyol pathway, and activation of the protein kinase C (PKC) enzyme. Whereas in hemodynamic factors, the vasoactive hormone is angiotensin II which reacts. Both factors cause the cascade to activate intracellular cytokines such as the Transforming Growth Factor-Beta (TGF- $\beta$ ) and end with increased vascular permeability. Activation of TGF- $\beta$  will stimulate protein expression, cause glomerular mesangium expansion and generate Reactive Oxygen Species (ROS). These things will trigger the activation of PKC and the Mitogen-Activated Protein Kinase (MAPK) pathway. These two things will cause activation of proslclerotic cytokines, the Connective Tissue Growth Factor (CTGF), which stimulates the formation of fibronectin and collagen, leading to an increase in intrarenal pressure, increase in vascular permeability, proteinuria, decrease in EGFR.<sup>19</sup> Other research showed a significant relationship between HbA1c and GFR with the strength of a positive

correlation, an increase in HbA1c and an increase in GFR are probably caused by glomerular hyperfiltration in the early stages of type 2 diabetes mellitus. In addition, it has also been reported that after receiving therapy within a few months, a decrease in HbA1c levels is associated with a decrease in GFR levels.<sup>22</sup> Chronic kidney disease can be associated with anemia. Anemia will be more severe if kidney function deteriorates, this is due to reduced erythropoietin production and poor food intake.<sup>23</sup> So, HbA1c levels will decrease if anemia occurs due to reduced hemoglobin levels in the blood and short lifespan of erythrocyte cells.<sup>24</sup>

This result occurred because this study did not consider the use of drugs used by the subjects.<sup>25</sup>

## Conclusion

Type 2 diabetes mellitus patients age  $\geq 45$  years old are much more than < 45 years old with the ratio of 7 : 1. There are more female than male with type 2 diabetes mellitus. This can occur due to menopausal factors in women which cause changes in hormone levels, increased BMI, and increased total fat in the body. There was a significant correlation between HbA1c and eGFR.

## Conflict of Interest

The author stated there is no conflict of interest

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