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CORRELATION BETWEEN HBA1C LEVELS AND SEVERAL METHODS OF ESTIMATED GLOMERULAR FILTRATION RATE CALCULATION STUDY IN TYPE-2 DIABETES MELLITUS PATIENTS

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ABSTRACT

Background: Diabetes mellitus is a long-term chronic disease characterized by an enhancement blood glucose levels (hyperglycemia). Diabetes is closely related to hyperglycemia. Prolonged hyperglycemic conditions can initiate abnormal interactions of metabolic and hemodynamic factors and stimulate the establishment of fibronectin and collagen, including affecting eGFR values. This study analyzed the correlation between HbA1c level and several methods of calculating eGFR in patients with type-2 diabetes mellitus. **Objective:** Analyzing the correlation between HbA1c levels and several methods of calculating eGFR (CKD-EPI, MDRD, and CG) in patients with type-2 diabetes mellitus. **Method:** This study was a cross-sectional observational study on 85 research subjects aged over 18 in February to November 2021. The data were taken from medical records of type-2 diabetes mellitus patients at RSND Semarang. The statistical analysis used the Pearson test. **Results:** The Pearson results showed that there was a significant correlation between HbA1c levels (8.14 ± 1,98%)and several methods of calculating eGFR in patients with type-2 diabetes mellitus (p=0,000; r=0,430 in the CKD-EPI method, p=0,000; r=0,384 in the MDRD method, p=0,001; r=0,361 in the CG method). **Conclusion:** There was a significant positive correlation between HbA1c levels and eGFR CG, MDRD, and CKD-EPI methods in patients with type-2 diabetes mellitus, characterized by increased HbA1c levels and still high eGFR values.
Keywords: Diabetes mellitus, HbA1c, eGFR, CKD-EPI, MDRD, CG

INTRODUCTION

Diabetes mellitus (DM) is a long-term chronic disease characterized by blood glucose level enhancement (hyperglycemia). Diabetes mellitus could occur due to insulin secretion or work mechanism disruption.[1] Type-2 diabetes mellitus happens when insulin secretion in β-cells of the pancreas is disrupted, or the patient is resistant to insulin due to the interaction between genetic and environmental factors.[2]

The International Diabetes Federation (IDF) stated that one out of every 11 adults aged 20-79 has diabetes mellitus.[3] IDF also stated that in 2017, the number of diabetes mellitus patients worldwide was estimated to be approximately 426 million, and its prevalence increases yearly.[4] Generally, around 90-95% of diabetes mellitus incidence falls into type-2 DM, with a higher prevalence in females.[5,6]

Diabetes mellitus is closely related to hyperglycemia conditions. Various methods to diagnose hyperglycemia, such as glycated hemoglobin levels inspection (HbA1c). HbA1c inspection is considered better than other methods due to its stability and ability not to be influenced by physical activities and daily glucose variability.[7]

HbA1c gives information regarding mean plasma glucose levels in the past 2-3 months, making this inspection suitable for diagnosing DM and evaluating ongoing treatment.[8] Inadequate patient therapy causes chronic hyperglycemia and causes microvascular glomerulus, namely diabetic nephropathy. When this complication occurs, the glomerular filtration rate (GFR) will be disrupted by showing a decrease that can end up in end-stage renal disease.[9]

Glomerular filtration rate (GFR) is the plasma volume that can quickly be cleared perfectly from certain substances by the kidney. GFR is mostly estimated by measuring inulin or serum creatinine clearance levels as an index to evaluate renal function. Currently, there is three formulation model to estimate GFR, which are Cockcroft-Gault (CG), Modification of Diet in Renal Disease (MDRD), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).[10,11]

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Hyperglycemia in type-2 DM patients may cause interaction abnormalities from metabolic and hemodynamic factors. This abnormality would induce PKC and *Mitogen-Activated Protein Kinase* (MAPK) activation, which would, in turn, activate pro-sclerotic cytokines, such as Connective Tissue Growth Factor (CTGF). Activation of CTGF would stimulate collagen and fibronectin formation, increase intrarenal pressure, and affect eGFR values.[12]

This research was conducted because of result differences in previous research and to determine whether there is a correlation between HbA1c levels and some eGFR calculation methods often used in type-2 DM patients.

METHODS

This observational analytic research with a cross-sectional approach was conducted at Diponegoro National Hospital in February-November 2021. The research subjects used were 85 type-2 diabetes mellitus patients who met the criteria for inclusion and exclusion with consecutive sampling methods.

The inclusion criteria for this study were patients aged > 18 years, previously diagnosed with DM, average body temperature, creatinine, and HbA1c data.

Exclusion criteria included patients with a history of autoimmune disease, cardiovascular disease, nephrotic syndrome, urinary tract infections/urinary stones, other degenerative diseases, and anemia. Patient identity, including name, sex, weight, height, diagnosis, body temperature, and HbA1c and creatinine test results obtained from the medical record.

The independent variable in this research was HbA1c levels, while the dependent variable was the estimated Glomerulus Filtration Rate (eGFR) based on several calculation methods. HbA1c levels were the mean glycated glucose levels in hemoglobin for the past 2-3 months measured using the HPLC method. The average value for HbA1c was 4.5-6.5%. The eGFR in this research was the estimated glomerular filtration rate value based on formula-based calculations. Based on literature from Oman Medical Journal, methods that could be used were CKD-EPI, MDRD, and CG.[11] Normal reference value for eGFR was ≥90 mL/min/1.73m^2.

Data analysis was done using a computer statistics program. Hypothesis test of the correlation between HbA1c levels with several methods of eGFR used Pearson test because data obtained were normally distributed.

RESULTS
Characteristics of Research Subjects

The distribution of research subjects was 42 male patients (49.4%) and 43 female patients (50.6%). Table 1 showed the characteristics of research subjects that covered age, blood pressure, duration of DM, type of therapy received by research subjects, body mass index and its components, history of smoking, and physical activity. The majority of type-2 DM patients that became research subjects (64.7%) had hypertension. The majority of subjects were also categorized as obese (60%).

Table 2 showed that the HbA1c levels of research subjects ranged between 5-14.1%. The characteristic hbA1c levels of study subjects were obtained 25 subjects (31.2%) had HbA1c levels <7% and 60 subjects (68.8%) had HbA1c levels ≥7%. Based on Table 3, research subjects who had normal eGFR based on the CKD-EPI method were 20 subjects (23.5%), 12 subjects (14.1%) based on the MDRD method, and 15 subjects (17.6) based on the CG method. Research subjects that had low eGFR (15-29 mL/min/1.73m^2) based on the CKD-EPI and MDRD methods were 3 subjects (3.6%) each while using the CG method were 7 subjects (8.3%).

Table 1. Characteristics of Research Subjects

Variable	F	%	Mean ± SD	Median (min-max)
Age (years)			58.56 ± 10.87	60 (34-84)
Blood Pressure (mmHg)				
Systole			134.15 ± 13.94	132 (110-184)
Diastole			83.68 ± 7.19	81 (65-104)
Weight (Kg)			64.23 ± 12.59	63.3(35.8-101.8)
Height (cm)			157.04 ± 7.81	157 (140-173)
BMI (Kg/m^2)			25.96 ± 4.46	25.6 (16.4-39.7)
Duration of DM				
≥ 6 Months	79	92.9		
< 6 Months	6	7.1		
Type of Therapy				
Oral Therapy	60	70.6		
Insulin Therapy	13	15.3		
Combination Therapy	12	14.1		
History of Smoking				
Active Smoker	4	4.7		
Had Smoked	12	14.1		
Never Smoked	69	81.2		

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Physical Activity

Active	26	30.6
Not Active	59	69.4

Table 2. HbA1c and eGFR Levels

Parameter	Mean ± SD	Median (Min-Max)
HbA1c (%)	8.14 ± 1.98	7.9 (5-14.1)
eGFR (mL/min/1,73m^2)		
CKD-EPI	69.45 ± 22.99	69 (25-123)
MDRD	69.45 ± 22.99	63.4 (242-176.7)
CG	67.79 ± 28.86	66.15 (21.3-167.9)

Note: eGFR = estimated Glomerulus Filtration Rate; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; MDRD = Modification of Diet in Renal Disease; CG = Cockcroft- Gault.

Table 3. Amount of Research Subjects According to Staging

	n (%)		
	CKD-EPI	**MDRD**	**CG**
Stage 1: ≥90 mL/min/1,73m^2	20 (23.5)	12 (14.1)	15 (17.6)
Stage 2: 60-89 mL/min/1,73m^2	33 (38.8)	33 (38.8)	33 (38.8)
Stage 3: 30-59 mL/min/1,73m^2	29 (34.1)	37 (43.5)	30 (35.3)
Stage 4: 15-29 mL/min/1,73m^2	3 (3.6)	3 (3.6)	7 (83)

Note: n = Amount of Research Subject

Correlation Test

HbA1c levels data were normally distributed (p=0.070), and eGFR data based on several calculations were also normally distributed (p=0.200 on CKD-EPI, p=0.054 on MDRD, and p=0.200 on CG), hence the usage of the Pearson correlation test. Table 4 shows that the CKD-EPI method had p=0.000 and r=0.430, the MDRD method had p=0.000 and r=0.384, and the CG method had p=0.001 and r=0.361. This meant a significantly positive correlation between HbA1c levels and several methods of eGFR calculation in type-2 DM patients.

Table 4. Results of the Pearson Correlation Test

Parameter	r	*p*
HbA1c (%)		
eGFR (mL/min/1.73m^2)		
CKD-EPI	0.430	0.000*
MDRD	0.384	0.000*
CG	0.361	0.001*

Note: * = Significant; *p* = Significance value; r = Correlation coefficient value

DISCUSSION
Characteristics of Research Subjects

The majority of the research subjects' distribution was female, with 43 out of 85 patients (50.6%). The age distribution ranged between 34-84 years old, adjusted for inclusion criteria of >18 years old. Blood pressure data showed a general increase with a mean blood pressure of 134/84 mmHg, which fell into stage 1 hypertension according to the American College of Cardiology (ACC)/American Heart Association (AHA).[13] Type-2 DM and hypertension have some of the same pathophysiologies and can cause abnormalities of blood vessel function, which then becomes one of the risk factors for hypertension.[14] Type-2 DM patients with hypertension were not excluded from this research.

HbA1c levels distribution in this research ranged between 5-14.1%. The target criteria for diabetes control, according to the Indonesian Society of Endocrinology(2015), is HbA1c levels of <7%.[7] Research study results obtained 60 subjects (68.8%) with HbA1c levels ≥7% (poor glycemic control).

The eGFR value distribution of the CKD-EPI method ranges from 25-123 mL/min/1.73m^2, the MDRD method eGFR ranges from 24.2-176.7 mL/min/1.73m^2, and the eGFR CG method ranges from 21.3-167.9 mL/min/1.73m^2. Normal criteria for eGFR based on the National Kidney Foundation is ≥90 mL/min/1,73m^2.[15] Based on the calculation data, 20 subjects have a normal eGFR based on the CKD-EPI method, 12 subjects based on the MDRD method, and 15 subjects based on the CG method.

Correlation of HbA1c Levels with Several Methods of Estimated Glomerular Filtration Rate Calculations in Type-2 Diabetes Mellitus Patients

The result of the correlation test between HbA1c levels and several eGFR calculation methods showed a significant positive relationship. This result was in line with Susanti's (2020) research, which concluded a correlation between HbA1c and glomerulus filtration rate in type-2 DM patients (p=0.035, r=0.655).[16] This research is also consistent with a study held by Damara (2018) that found a meaningful correlation between HbA1c and GFR (p=0.000, r=0.784).[17]

This result, however, contradicts a study conducted by Gahung (2016) that found no significant correlation between HbA1c and the glomerulus filtration rate of type-2 DM patients (p=0.462, r=0.093). Such results were obtained because of the discovery of normal HbA1c values in

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type-2 DM patients with chronic kidney disease. This normal HbA1c condition is caused by a high degree of the eGFR stage of the patient, resulting in a decrease in sugar and hemoglobin levels in the blood.[18] Another cause could be the low number of samples used in the study, which risked involving type-2 DM patients with a high degree of eGFR stadium that were admitted to the Renal Hypertension Polyclinic.

A larger r value in the CKD-EPI method showed a clinically significant relationship. This was similar to the research held by Wieneke *et al.* (2010), which explained that in regards to accuracy, out of three models of eGFR calculation, CKD-EPI came out as the candidate for a better estimator.[10]

The positive correlation in the value of r has a directly proportional meaning, namely that the higher the HbA1c level, the higher the eGFR value. A positive correlation is shown by HbA1c, which increased by almost 60% and obtained a still high eGFR value with evidence of still many eGFR classified in stadiums 1 and 2. High levels of HbA1c proved that there is more hemoglobin bonded with glucose and indicated an increase in plasma glucose levels (hyperglycemia).[19] An increase in eGFR often occurs in hyperglycemia conditions caused by glomerular hyperfiltration as an early stage of renal involvement in people with type-2 DM.[20]

Research data showed that 60 out of 85 subjects (70.6%) had terrible glycemic control (HbA1c ≥7%), with the majority being in the range of 40-59 years old. Prolonged hyperglycemia due to poor glycemic control may cause glomerulus hyperfiltration, which will create extracellular protein overdeposition, tissue expansion due to growth factors, and glomerulus sclerosis that eventually will lead to an eGFR decrease. The National Kidney Foundation explained that as the age increase, eGFR would gradually decrease since the age of 30 yet stay within the normal threshold, then experience a significant decline when entering the age of about 60 years.[15] Decreasing eGFR conditions support the data in this research, where 33 subjects (38.8%) experienced stage 2 decreased renal function.

The National Health and Nutrition Examination Survey III study results concluded that 30% of type-2 DM patients decreased their GFR. Several processes that could cause decreasing GFR were the hydrostatic pressure increase in Bowman's capsule, the colloid osmotic pressure increase in the glomerulus capillary, and sympathetic nervous system activities. In type-2 DM cases, it is recommended that HbA1c levels be maintained at <7% because good glycemic control could minimalize renal dysfunctions in type-2 DM patients.[21, 22]

Limitations of this research were the sole usage of one type of glycemic status observation parameter and the need for further research in the form of a prospective cohort to understand the change in eGFR in controlled and uncontrolled HbA1c.

CONCLUSION

There was a significant positive correlation between HbA1c levels and the eGFR method of CG, MDRD, and CKD-EPI in patients with type 2 DM. This study was a cross-sectional study that only took one-time specimen sampling during this research, so it is necessary to conduct a prospective cohort study to see changes in the eGFR value.

ETHICAL APPROVAL

This study has obtained ethical clearance from the Health Research Ethics Committee of the Faculty of Medicine of Diponegoro University with a certificate number of No. 319/EC/KEPK/FK-UNDIP/IV/2021. The privacy of the data of the research subjects used would be guaranteed.

CONFLICT OF INTEREST

There is no conflict of interest related to this research.

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