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The Compatibility Of Hba1c And Glycated Albumin Levels As Markers For Blood Glucose Follow-Up In Type 2 Diabetes Mellitus

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ABSTRACT: BACKGROUND: Diabetes mellitus (DM) is a group of metabolic diseases, characterized by hyperglycaemia that occurs due to abnormalities in insulin secretion. Uncontrolled diabetes will lead to the development of further complications. HbA1c level measurement is the current gold standard for monitoring glucose levels in DM patients. Glycated albumin (GA) is a fructosamine formed through a non-enzymatic glycation process. There are still few studies on the correlation between HbA1c and GA levels in T2DM patients. Therefore, we decided to investigate the correlation between HbA1c and GA levels in T2DM patients.

OBJECTIVE: To determine the correlation between HbA1c and GA levels in T2DM patients.

METHODS: This study was an observational study with a cross-sectional design conducted on 69 T2DM patients at Diponegoro National Hospital from June to August 2020. We collected data consisting of age, weight, blood pressure, waist circumference, HbA1c and GA levels. We measured HbA1c levels using I-chroma Boditech tool with the enzyme-linked fluorescent assay (ELFA) method, and GA levels using the Architect C8000 tool with an enzymatic method. Finally, we performed statistical analysis using Spearman's correlation test.

RESULTS: The median ± SE values of HbA1c and GA levels were (7.1 ± 0.19%) and (21.2 ± 0.85%), respectively. The Spearman's correlation test results between HbA1c and GA levels were p <0.001; r = 0.775.

DISCUSSION: Maintenance of blood glucose levels in the body is essential for T2DM patients. HbA1c and GA levels can be used for clinical evaluation of T2DM patients.

CONCLUSION: There was a strong significant correlation between HbA1c and GA levels in T2DM patients. HbA1c and GA levels can be used for clinical evaluation of DM patients according to the patient's condition.

Keywords: HbA1c, Glycated Albumin, type 2 DM

1. BACKGROUND

Diabetes mellitus (DM) is a group of metabolic diseases, characterized by hyperglycemia, which occurs due to abnormalities in insulin secretion, insulin action, or both. Classic complaints of DM include polyuria, polydipsia, polyphagia, and unexplained weight loss. Furthermore, there might be other complaints, such as weakness, tingling, itching, blurred vision and erectile dysfunction in men, as well as vulvar pruritus in women [1].

Type 2 Diabetes Mellitus (T2DM) is common and accounts for about 90% of all DM cases worldwide [2]. In 2017, the Center for Disease Control and Prevention (CDC) stated that 30.3 million people in the United States suffered from DM [3]. A report from the International Diabetes Federation (IDF) in 2017 predicted an increase in the number of DM patients worldwide, from 425 million to 629 million in 2045. Meanwhile, in Southeast Asia, they predicted that there was going to be an increase, from 82 million to 151 million in 2045. Indonesia was ranked 7th out of 10 countries that were estimated to have 5.4 million diabetic patients in 2045, and have a low blood glucose control rate [4]. The Basic Health Research (Riskesdas) Report by the Ministry of Health of the Republic of Indonesia in 2013 showed that the average prevalence of DM in each province in Indonesia based on physician diagnosis for people aged ≥15 years was 1.5%, and would increase in 2018, reaching 2% [5].

Uncontrolled DM will lead to the development of further complications, such as nephropathy, retinopathy, neuropathy, and cardiovascular disease. Glycaemic status can be monitored by measuring blood glucose levels, but results may vary depending on diet, occupation, and antidiabetic drug [6]. Glycated haemoglobin (HbA1c) is an approximate index of mean blood glucose over the previous three months, which provides an estimate of long-term glycaemic status. The value can be used for diagnosis and monitoring of blood glucose in DM patients. However, HbA1c is not recommended clinically in patients with haemoglobin metabolism disorders, such as haemolytic disorders, secondary anaemia or iron deficiency anaemia, hemoglobinopathy, pregnancy, and uraemia [7].

Apart from the measurement of HbA1c levels, glycated albumin (GA) has received attention as an indicator in several physiological and pathological conditions because it provides more information than the HbA1c does. Glycated albumin is a reliable biomarker for diabetes diagnosis and monitoring the hypoglycaemic treatment. In patients with good glycaemic control, GA levels will decrease compared to HbA1c levels at the initial treatment. This condition indicates that the GA level has a higher sensitivity than the HbA1c level in detecting changes in glycaemic control. The GA measurement at day 14 is the strongest predictor compared to the measurement of HbA1c levels at day 90, which suggests that GA can detect glycaemic levels more quickly than the HbA1c does, thus providing earlier treatment to DM patients [8].

The proper selection of examinations to diagnose and monitor blood glucose levels is necessary by considering the clinical condition of the DM patient. The selection of appropriate examination in T2DM patients is beneficial for the prognosis of the disease. The correlation between HbA1c and GA levels needs to be investigated to ensure that both are equivalent in their use for the clinical evaluation of DM patients.

2. METHOD

This study was an analytic observational study with a cross-sectional design. This study was conducted from June to August 2020 at the Diponegoro National Hospital (RSND), Semarang, Central Java, Indonesia.

The subjects of the study were 69 patients, which were taken by calculating the sample size formula. They are type 2 diabetes mellitus (T2DM) patients who underwent routine follow-up examinations at Diponegoro National Hospital, Semarang. The inclusion criteria of this study included patients aged 30-55 years, male and female, normal body temperature (± 36.5^{o} C), and willing to participate in the study. Meanwhile, the exclusion criteria included patients with a history of or were suffering from anaemia, bone disorders, liver disease, renal disease, cardiac disease and vascular disease.

We interviewed the subjects who were willing to participate in the study for data collection, including the duration of diabetes mellitus, blood pressure, and anthropometric measurements. We subsequently took blood samples from the subjects. We used 3 CCs of EDTA blood sample to measure the HbA1c levels, while another 3 CCs of a blood sample without anticoagulant was used for GA measurement. We measured HbA1c level using the I-chroma Boditech tool, with the enzyme-linked fluorescent assay (ELFA) method and measured GA level using the Architect C8000 tool, with an enzymatic method.

We analyzed the data using SPSS version 21. The correlation test was performed using the Spearman's correlation test and was considered significant if the p-value was <0.05. This study received ethical approval from the Ethics Committee of the Faculty of Medicine, Diponegoro University, Semarang and each subject gave written informed consent.

3. RESULTS AND DISCUSSION

The number of patients involved in this study was 69 subjects, which were obtained based on the exclusion and inclusion criteria in T2DM patients. Table 1 shows that most of the patients were female, with 46 (66.7%) female patients and 23 (33.3%) male patients. The mean minimum and maximum age of patients was 36-61 years.

Table 1. The characteristics of subjects of the study

Variable	**n**	**%**	**Median ± SE**	**min – max value**
Age			55 ± 0,746	36 – 61
Sex				
Male	23	33,3		
Female	46	66,7		
Height (cm)			156 ± 1,03	140 – 181
Weight (kg)			62 ± 1,52	41,3 – 89,5
Body Mass Index (kg/m^2)			24,3 ± 0,51	18 – 35,4
Waist circumference (cm)			91 ± 1,28	70 – 118
Systolic pressure (mmHg)			150 ± 2,69	110 – 222

Diastolic pressure (mmHg)			90 ± 2,43	65 – 195
The duration of diabetes mellitus (year)			4 ± 0,58	0,08 – 22

Notes: SE: Standard Error; min: minimum value; max: maximum value.

The correlation between HbA1c and GA levels in T2DM patients can be seen in Table 2. There was a strong significant correlation between HbA1c and GA levels in T2DM patients ($p < 0.001$; $r = 0.775$).

Table 2. The result of correlation test between HbA1c and GA levels in type 2 diabetes mellitus

Variable	**Median ± SE**	***p***	**r**
HbA1c (%)	7,1 ± 0,19	<0,001	0,775
Glycated albumin (%)	21,2 ± 0,85		

Notes: SE: standard Error; min: minimum value; max: maximum value.

4. DISCUSSION

Maintenance of blood glucose levels in the body is important for patients with type 2 diabetes. Proper maintenance of blood glucose levels can reduce the incidence of micro and macrovascular complications in diabetic patients. The maintenance of blood glucose levels can be monitored according to the patient's current condition, either monthly, using HbA1c level, or weekly, using GA level.

HbA1c is the percentage of circulating glycated haemoglobin. Glycation is a non-enzymatic process and is a measure of blood glucose levels over time. This marker reflects the mean plasma glucose over the previous 8-12 weeks. It is currently used for the diagnosis and management of diabetes and is recommended as the gold standard in the assessment of diabetes-related outcomes. The measurement is uncomplicated to perform, cost-effective, and relatively inexpensive [9].

Historically, elevated HbA1c levels in diabetic patients were first reported by Rahbar et al. in 1968, which later became an important indicator for blood glucose control. The World Health Organization (WHO) and the American Diabetes Association (ADA) used HbA1c levels as a diagnostic parameter and defined an HbA1c level above 6.5% as diabetes and a level of 5.7-6.4% as prediabetes [7].

HbA1c measurement is recommended in monitoring blood glucose control in prediabetic patients, and patients with previous increased blood glucose levels. The advantage of this measurement is that it is comfortable for patients, because it does not require any special preparations, such as fasting, and can be done at any time. The sample is relatively more stable at room temperature after collection, and the variability in levels is less than that of fasting blood glucose [7].

The drawbacks of using the HbA1c parameter are the presence of abnormal haemoglobin, interference with red blood cell synthesis, impaired red blood cell destruction, and in certain circumstances, such as hyperbilirubinemia, alcoholism, and the use of large-dose aspirin, which can increase HbA1c levels. Furthermore, a decrease in HbA1c levels can occur in

hypertriglyceridemia. HbA1c levels also decrease in the second trimester of normal pregnancy [7].

Albumin makes up 60% of all protein in serum at a concentration of 30-50 g/L. The molecular weight of albumin is 66.7 kDa, which consists of a single polypeptide chain, with 585 amino acids and 17 disulphide chains. Albumin is involved in the maintenance of biological homeostasis, including osmotic pressure and blood pH. Albumin also binds free radicals, acts as an antioxidant and transports several solutes, such as hormones, fatty acids, and certain drugs [10]

The measurement of glycated albumin has been one of the important laboratory tests in monitoring glycaemic control in diabetic patients for the last decade. Glycated albumin is a fructosamine formed through a non-enzymatic glycation process, which has the advantage of being not affected by the concentration of other serum proteins. GA measurements do not require the patient to fast before the examination. This examination reflects short-term levels of glycaemic level because the half-life of albumin is approximately three weeks. Glycated albumin is the ratio between glycated albumin levels and total serum albumin [1],[11].

GA levels were not affected by changes in erythrocyte age. Furthermore, GA measurements were not affected by conditions, such as haemolytic anaemia or bleeding episodes. The GA measurement was also useful for patients at high risk of developing hypoglycaemia or with chronic kidney disease [11].

The results of this study showed that there was a strong significant correlation between HbA1c and GA levels ($p < 0.001$). The results of this study contrasted to the study by Nazki et al. on 408 patients at the Owaisi hospital and research centre, from November 2015 to June 2017, which showed that there was no significant correlation between albumin and HbA1c levels [12].

Several previous studies have reported GA reference values. Tominaga et al. (1999) stated that the GA reference value in the Japanese population was 12.3 - 16.9%. On the other hand, a study by Kohjum et al. (2011) obtained GA reference values in the American population of 11.9 - 15.8%. Meanwhile, the validation test by Ma et al. (2010) in the Chinese population showed that the cut-off point of GA was 17.1%, with a sensitivity value of 76.82% (CI: 73.64-79.79%) and a specificity value of 76.89% (CI: 74.42-79.23). Finally, Roohk and Zaidi (2008) stated that the target of glycaemic control, as measured by the GA parameter, was <20%, with a normal value of 11-16% [13].

A Study by Felyn (2020) concluded that there was a significant correlation between HbA1c and albumin levels in DM patients with a p-value of 0.002 [14]. Widyadi et al. (2016) conducted a study on 89 patients and showed that there was a significant correlation similar to the results of the present study. The study of Widyadi et al. used glycated albumin, while this study used plasma albumin levels as a comparison to HbA1c levels [15]

5. CONCLUSION

There was a strong significant correlation between HbA1c and GA levels in T2DM patients. HbA1c and GA levels could be used clinically for the evaluation of type 2 diabetes mellitus based on the patient's condition.

Conflict of Interest

No conflict of interest

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