

## Original Article

**HEMOGLOBIN A1C (HBA1C) IS STRONGLY CORRELATED WITH MEAN CORPUSCULAR VOLUME AMONG TYPE 2 DIABETES MELLITUS (T2DM) PATIENTS ADMITTED TO A TERTIARY HOSPITAL IN EAST JAVA, INDONESIA**Yusuf Salim<sup>1</sup>, Viskasari P. Kalanjati<sup>2</sup>, Jongky H. Prajitno<sup>3</sup>, Rezy R. Melbiarta<sup>1</sup><sup>1</sup>Medical Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.<sup>2</sup>Department of Anatomy, Histology, and Pharmacology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.<sup>3</sup>Endocrine and Metabolism Division, Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga-Dr. Soetomo General Academic Hospital Surabaya, Indonesia.**ABSTRACT**

*HbA1c showed the average level of blood sugar in the recent 2-3 months. This parameter can be used to help physicians to diagnose T2DM and to plan appropriate treatment. Meanwhile, the mean corpuscular volume (MCV) is established from the erythrocytes levels as one of the blood corpuscles, to which hemoglobin is bound. We hypothesized that MCV was correlated to the HbA1c levels and could be an indicator of blood sugar levels in adult T2DM patients. A retrospective cross-sectional study based on the medical record of patients admitted to the Outpatient Section of Department of Internal Medicine, Dr. Soetomo General Academic Hospital, Indonesia from January to December 2019 was done. Patients under 18-years old and incomplete medical record data were excluded. Adult patients diagnosed with T2DM and received initial treatment in this section were included (n=1.688). Data were analyzed using a correlation test in SPSS 17.0 (USA), a p-value less than 0.05 was considered significant. We found a significant negative correlation between HbA1c and MCV levels in these patients (r= -0.312; p<0.001). MCV levels showed a paradoxical pattern against the blood glucose levels in T2DM and could serve as the health indicator in these patients.*

**Keywords:** Diabetes; hemoglobin; HbA1c; MCV; health risk

**Correspondence:** Viskasari P. Kalanjati, Department of Anatomy, Histology, and Pharmacology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia. Email: viskasari-p-k@fk.unair.ac.id

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**Hii j ni j tu**

1. Moderate negative significant correlation between HbA1c and MCV levels in T2DM was yet reported widely.
2. MCV levels could mirror health indicator in adult T2DM patients.

**INTRODUCTION**

Type 2 diabetes mellitus (T2DM) is characterized by hyperglycemia caused by abnormalities in insulin secretion, insulin action, or both (PERKENI 2019). The prevalence is about 422 million amongst adult diabetes patients worldwide (World Health Organization 2021), while the prevalence of T2DM in 2018 in Indonesia was approximately 20.4 million (8.5%). This has increased from 2013 which was around 6.9%. A higher prevalence was reported in women than men (12.7% vs. 9.0%) (PERKENI 2019).

HbA1c is one of the laboratory tests to determine the diagnosis of T2DM, that is if the HbA1c level is >6.5%, someone is considered to have diabetes. Complications in T2DM are associated with increased risk factors for ischemic heart disease and impaired renal function, with abnormalities detected in complete blood cells laboratory results, including the hemoglobin and MCV levels (Alamri et al. 2019). It has been reported that HbA1c as the chronic indicator of blood glucose level in T2DM patients was closely correlated with the MCV levels (Rodriguez-Segade et al. 2016). Abnormality in MCV level is due to



hyperglycemia in T2DM patients resulting in relative depletion, hence affecting the oxygen transfer via hemoglobin in the red blood cells (Maner & Moosavi 2021, Wang et al. 2021). However, in our region, whether the MCV level reflects the HbA1c in T2DM has yet largely been determined, thus aimed in the current study. If MCV is related to the levels of HbA1c, this parameter can serve as the potential biomarker for detecting blood glucose levels, specifically in T2DM cases that would help physicians to be more aware of the health status and understand the success in T2DM patients' treatment.

## MATERIALS AND METHODS

This study has been granted ethical clearance by the health research ethics committee in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, No.:0195/LOE/301.4.2/XI/2020. We conducted a retrospective cross-sectional study from the medical record of adult patients aged more than 18 years old admitted to the Outpatient Section of the Department of Internal Medicine, Dr. Soetomo General Academic Hospital, from January to December 2019. Data recorded including diagnosis of T2DM, HbA1c level, MCV level, all taken after first treatment by the physician according to the protocols in this institution. All data were analyzed using normality and homogeneity test and Spearman correlation test to seek potential correlation between HbA1c and MCV levels in these patients; the p-values less than 0.05 were considered statistically significant. The correlation strength is defined as very strong if  $r > 0.75$ ; strong 0.5 to 0.75; moderate 0.25-0.5; and weak  $< 0.25$  (SPSS 17.0, USA).

## RESULTS

Of the 1.688 medical records, 717 (42.5%) were males and 971 (57.5%) were females. The mean of HbA1c levels of all patients was  $8.15\% \pm 1.89\%$ . The mean of MCV levels of all patients was  $84.39 \text{ fl} \pm 6.87 \text{ fl}$ . The mean HbA1c level in female patients was  $7.93\% \pm 1.82\%$ ; while in the male patients was  $8.30\% \pm 1.92\%$ . The mean MCV level in female patients was  $86.23 \text{ fl} \pm 6,09 \text{ fl}$ ; while in the male patients was  $90.09 \text{ fl} \pm 13.70 \text{ fl}$ .

There were significant differences between female and male patients in the HbA1c levels ( $p=0.002$ ). There were no significant differences between female and male patients in regards of the MCV levels ( $p=0.144$ ). There was a significant moderate correlation between HbA1c and MCV levels in all patients ( $r= -0.312$ ;  $p<0.001$ ) (Table 1).

## DISCUSSION

HbA1c mirrors the average level of blood sugar in approximately 2-3 months (Wang et al., 2021). This test can be used to help physicians to diagnose T2DM, thus planning the appropriate statement. It was reported that the HbA1c level in non-T2DM people is approximately 4-5.6%. Increased HbA1c level means pre-diabetic condition; higher than 6.5% is generally defined as diabetes. The management in diabetes patients targets HbA1c level to be less than 7%. Untreated diabetes patients in a while might be detected by increased HbA1c above 8%.

Combination of proper diet, exercise and meditation would bring HbA1c level into normal, the doctors usually ask the patient to test their HbA1c level every 3 months to make sure it is under controlled. However, if at least tested 2 times a year could be considered sufficient (Eyth & Naik 2021, PERKENI 2019). Several comorbidities, including anemia, could result in misinterpretation of HbA1c level. Supplements including vitamin C and E, kidney and liver diseases, dyslipidemia could also affect the hemoglobin levels thus misleading the result of HbA1c test (Eyth & Naik 2021).

HbA1c represents a glycosylated hemoglobin or glycosylated hemoglobin, where glucose is bound to the erythrocytes. In the erythrocytes, hemoglobin is the protein carrying the oxygen, whilst HbA1c levels reflect the percentage of all hemoglobin that are bound to the glucose. HbA1c showed the last 2-3 months blood glucose level average due to the erythrocyte life cycles in this period (Wang et al. 2021).

On the other hand, mean corpuscular volume (MCV) showed the average volume of red blood corpuscles, which mean multiplication of blood volume by the proportion of cellular components in the blood and divided by the number of erythrocytes in that volume. There are 3 types of corpuscles in human blood, which are erythrocytes, leukocytes and platelets. Abnormal MCV might indicate impaired corpuscle morphology and or count including the red blood cell. Impairment could lead to abnormal oxygen capacity and transfer into the tissue organs. The normal range of MCV in the adults is approximately between 80-100 fl. If a person has less than 80 fl, someone is likely suffering from the microcytic anemia. However, if the MCV levels are higher than 100 fl, the macrocytic anemia is determined (Maner & Moosavi 2021).

Certain conditions must be taken into consideration on interpreting the MCV levels. In patients with liver disease and folate deficiency, the MCV might be

Table 1. Statistical analysis between HbA1c and MCV levels in all included T2DM patients

	HbA1c level (%)				MCV level (fl)				#r	#p
	Male	Female	p (Mann-Whitney test)	Total	Male	Female	p (Mann-Whitney test)	Total		
Mean ( $\pm$ SD)	7.93 $\pm$ 1.82	8.30 $\pm$ 1.92	0.002	8.15 $\pm$ 1.90	90.09 $\pm$ 13.70	86.23 $\pm$ 6.09	0.144	84.39 $\pm$ 6.87	-0.312	<0.001*

#Spearman's correlation test  
\*: "correlation is significant at the 0,05 level (2-tailed)"

increasing. Increased MCV can also be used to monitor alcohol related disease, with macrocytosis detected. Macrocytosis itself generally asymptomatic, several drugs that may produce macrocytosis including methotrexate, antiretroviral agents, valproic acid, phenytoin, zidovudine, azathioprine, and hydroxyurea (Nagao & Hirokawa 2017). Previous study reported that stress can significantly increase the hemoglobin and MCV levels and impaired tissue oxygenation (Maes et al. 1998). However, this could be due to more serious reasons i.e. pernicious anemia; whilst another study reported that MCV more than 106 fl was correlated with the increased risk of esophageal squamous cell carcinoma amongst Japanese alcoholic man (Yokoyama 2003). On the other hand, in low MCV levels, the erythrocytes are found to be smaller than normal, this might be due to iron deficiency correlated with poor dietary intake of iron, or bleeding, including menstrual bleeding, and gastrointestinal bleeding. The treatment of microcytic anemia with low MCV level includes iron and vitamin C supplements. Other pathologies such as thalassemia and hypothyroidism might cause low MCV levels (Maner & Moosavi 2021).

In T2DM with very high glucose levels, increased MCV can be detected. The correction can be conducted by pre-dilution of the blood in isotonic medium, thus the hyperosmolar state produced by high glucose level in the cell might result in rapid diffusion of water intracellular in the counter. This process is temperature dependent and could be rapidly reversible (Morse et al. 1981). It was reported that HbA1c was significantly and independently associated with MCV levels among 50-year-old females (Simmons & Hlaing 2014). Another study by Rashed et al. (2020) found that HbA1c level of 202 patients measured by NycoCard reader II analyzer has significant negative correlation with the MCV level, the mean MCV was significantly higher in non-diabetic patient, when compared with pre-diabetic and diabetic patient. The red blood cell life span in hyperglycemia decreased compared with in the normoglycemia (Rio et al. 2016). The glycation synthesis of the terminal unit of the  $\beta$ -chain in hemoglobin is determined by the plasma glucose level and has been used to evaluate the level of metabolic

and has been used to evaluate the level of metabolic control and the development of complications in T2DM patients, thus the quality of diabetic management (Leow 2016).

### Strength and limitation

The study uses a large sample size of 1,688 patients, which increases the generalizability of the findings. The study focuses on a relevant topic, which has the potential to improve the diagnosis and treatment of T2DM. The study uses a retrospective cross-sectional design, which is appropriate for exploring associations between variables and can provide useful information for generating hypotheses. The study design is limited in that it can only establish associations between variables and cannot determine causality. The study only examines the correlation between MCV levels and HbA1c and does not consider other factors that may influence blood sugar levels in T2DM patients, such as diet, exercise, and medication.

### CONCLUSION

HbA1c and MCV levels are determined by blood glucose level. This study shows significant negative correlation between HbA1c and MCV level in adult T2DM patients admitted in our institution.

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### Conflict of interest

None0

### Funding disclosure

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### Author contribution

ÜÜT ÊRPÚÊ and ÝS contributed conceptual, study design, analysis data. ÝS was write the manuscript. XUS was final validation.

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