

# ASSOCIATION OF GLYCATED HAEMOGLOBIN LEVELS, LDL LEVELS, SYSTOLIC BLOOD PRESSURE, AND BMI WITH CAROTID ARTERY INTIMA-MEDIA THICKNESS (CIMT) IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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## ABSTRACT

**Background:** Hyperglycemia in type 2 Diabetes Mellitus patients causes glycated haemoglobin (HbA1C) transformed into AGEs, increasing oxidative stress and reduce nitric oxide activity. It lead to inflammation and endothelial dysfunction that triggers atherosclerosis. Changes in the vascular wall indicating atherosclerosis can be detected non-invasively using B-mode ultrasound.

**Objective:** To analyze the relationship between HbA1C levels, LDL levels, blood pressure, and BMI with the carotid artery intima-media thickness (CIMT) score in type 2 diabetes mellitus patients.

**Methods:** This was an observational analytic study consisted of 30 subjects with type 2 Diabetes Mellitus at the Endocrine Clinic Saiful Anwar Hospital, Malang, Indonesia from September 2018 to December 2019. Primary data were collected by CIMT examination using B mode ultrasound and measurement of other variables. Statistical analysis was done using SPSS 20.

**Results:** Statistical analysis showed a significant corellation between CIMT and HbA1C levels ( $P < 0.05$ ) with correlation coefficient  $P -0.441$  and  $R 0.183$ , while the blood pressure, LDL levels, and BMI had a positive relationship to CIMT although they were not significant ( $P > 0.05$ ).

**Conclusion:** There was a significant corellation between HbA1C levels and CIMT with an inverse relationship. The effectiveness of HbA1C predictor variable for CIMT was 18.3%.

**Keywords:** CIMT, type 2 diabetes mellitus, HbA1C, dyslipidemia, hypertension, obesity

## INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease characterized by an increased blood glucose levels (hyperglycemia) caused by insulin inadequacy. The most common cases in DM is type 2 diabetes.<sup>1</sup> According to data from the International Diabetes Federation (IDF) in 2015, the number of people with diabetes worldwide is around 415 million.

Indonesia is the 6th country with highest number of diabetes patients in the world which is about 10.3 million people<sup>2</sup>. Diabetes with complications is the third leading cause of death after stroke and coronary heart disease, the percentage of deaths due to diabetes in Indonesia reaches 6.7%.

In type 2 diabetes mellitus, chronic hyperglycemia may transformed glycated

haemoglobin (HbA1c) into advanced glycation end products (AGEs), increase oxidative stress and reduce nitric oxide (NO) activity, then cause inflammation and endothelial dysfunction lead to atherosclerosis. Atherosclerotic plaque formation is a complex process involving many factors that play a role in the inflammatory response. This process takes a long time, progressively, slowly, and making it difficult to find the disease before the clinical symptoms occur<sup>3</sup>.

Atherosclerosis commonly occurs in arterial branches, especially the common carotid artery which makes this artery as a sentinel vessel that describes the entire vascular condition. It is located in superficial and relatively easier to be examined than the aorta and femoral arteries. The carotid arteries are also being recognized as a valuable indicator for the status of coronary arteries. Atherosclerosis in the common carotid artery can be identified by measuring the intima-media thickness of the common carotid artery using carotid ultrasound examination. Sonographically, atherosclerotic plaque initially appears as an increased thickness of the intima and media layer then followed by ecogenic material lining the arterial lumen. B-mode ultrasound is a sensitive, noninvasive method for evaluating arterial walls and allows measurement of the carotid intima-media tunica thickness (CIMT) for the presence of stenosis and plaque. A thickening of the intima-media of the carotid artery by 0.1 mm is associated with an increased risk of developing myocardial infarction (10-15%) and stroke (13-18%). Carotid ultrasound is noninvasive, without ionizing radiation, is relatively inexpensive, and widely distributed so that it is easier to be reached<sup>4</sup>.

A cross-sectional study that determines the correlation between levels of HbA1C and the thickness of intima-media tunica of the common carotid artery in 15 subjects with type 2 diabetes mellitus and 15 subjects with hypertension in India, resulted a positive correlation between HbA1C levels and CIMT of the common carotid arteries ( $r = 0.44$ ;  $p = 0.009$ ). A study with the same method by Perumal, et al., (2015) on 35 subjects with type 2 diabetes mellitus and 20 healthy subjects also described similar results. In a study at the Faculty of Pharmacy, Brawijaya University Malang with 54 children: 27 came from parents with ischemic

stroke as a case group and 27 came from healthy parents as a control group, resulted a genetic variation in the osteopontin promoter T-443C and G- 156GG that increases the thickness of the carotid intima-media<sup>5</sup>.

At the Saiful Anwar Hospital, Malang, Indonesia there were recorded as 9,567 patients with diabetes mellitus, which was the second most frequent outpatient visit in 2014. The study aimed to determine the relationship of HbA1C levels, LDL levels, blood pressure, and BMI with the CIMT score in patients with type 2 diabetes mellitus in Saiful Anwar Hospital, Malang, Indonesia which has never been done before.

## METHOD

### Population and Sample

The study population was type 2 diabetes mellitus patient in the endocrine clinic in Saiful Anwar hospital, Malang, Indonesia from September 2018 to December 2019. The inclusion criteria were patients with third or more visit to endocrine clinic with Type 2 DM with glycated hemoglobin (HbA1c) levels which is greater than or equal to 6.5%, age ranging from 30-75 and were agreed to participate in the study. Meanwhile, the exclusion criteria were non-cooperative patients or had involuntary movement disorders so that carotid ultrasound examination was difficult to performed. Based on Indonesian basic health research, the prevalence of diabetes mellitus in Indonesia was estimated 8.5% of total population in 2018 (Riskasdas, 2018). Based on these data, it is possible to calculate the number of research samples using the Cochran's formula ( $n = (Z^2 * P * (P-1) / D^2)$  where Z is a standard normal deviation set of 95% confidence level P is a prevalence rate, and D is confidence interval. Then we got the calculation become  $n = (1.96^2 * 0.085 * (1-0.085) / 0.1^2) = 0.298 / 0.01 = 30$  participants.

### Method

This study was an observational analytic design with a cross-sectional approach, to determine the relationship between glycated Hb levels, LDL levels, blood pressure, and BMI to CIMT score in type 2 DM patients. This study was conducted in the USG room, Radiology Unit, Saiful Anwar Hospital, Malang, Indonesia. This study used a primary data. The first primary data was the ultrasound results of

four ultrasound machines, two Philips Epiq 5 machines and two GE Logiq S8 using a linear probe (5-12 Mhz). IMT (Intimal-Media Thickness) sampling was carried out according to the Manneheim protocol on the proximal segment of the right-left common carotid artery manually or automatically using IMT auto measurement software. The data obtained from the measurements of the right and left carotid arteries were sampled and then calculated on its average <sup>6</sup>. Around 3 cc of peripheral blood was drawn from patient to obtain the HbA1C and LDL levels. Body height and weight and blood pressure also measured from every patient.

### Statistical Analysis

Descriptive data were analyzed using descriptive statistics and presented in distribution frequency

tables. After the data were grouped, statistical analysis was carried out using SPSS version 20 with Kolmogorov-smirnov test and Pearson correlation test. If a significant correlation is obtained, then followed by the analysis to determine which risk factor has the biggest role in increasing the thickness of carotid intimal media, a linear regression analysis regression was also obtained. CI 95%.

### RESULTS

#### Subject characteristics

The study sample was limited to the first 30 people who were collected in this study, the sample consisted of 13 men and 17 women, along with the characteristics of samples (Table 1).

**Table 1.** Subject clinical characteristics

Variable	Means and Standard Deviation	Score Range
HbA1C levels	9,827 ± 2,629	6,6-16,0 %
Systolic blood pressure	144,33 ± 21,121	100 – 180 mmHg
Diastolic blood pressure	80,67 ± 11,121	60 – 110 mmHg
LDL levels	147,167 ± 44,693	48 – 225 mg dL
BMI	26,83 ± 6,482	16,61 – 47,91
CIMT	0,729 ± 0,212	0,455 – 1,200
Age	57,27 ± 11,453	33 – 75 years

**Table 2.** Age and sex characteristics based on CIMT score

Variable	CIMT < 0,9	CIMT > 0,9	p-value
Age (means and standard deviation)	57.78 ± 10.929	55.57 ± 13.843	0.663
Sex			
Male	11 (36.7%)	2 (6.7%)	0.368
Female	12 (40%)	5 (16.7%)	

The age and gender characteristic of samples in this study were grouped based CIMT score category with a cut off score of 0.9. In the group with CIMT score below 0.9 was with a mean age of 57.78. In the different test for the age variable using the Independent T-Test, it was obtained a value of 0.663, which indicates that there was no significant difference in the age variable in the CIMT score group below 0.9 or scores above 0.9. Meanwhile, sex variable showed that both men and women were more likely to have a CIMT score below 0.9. Whereas the chi square test showed no significant

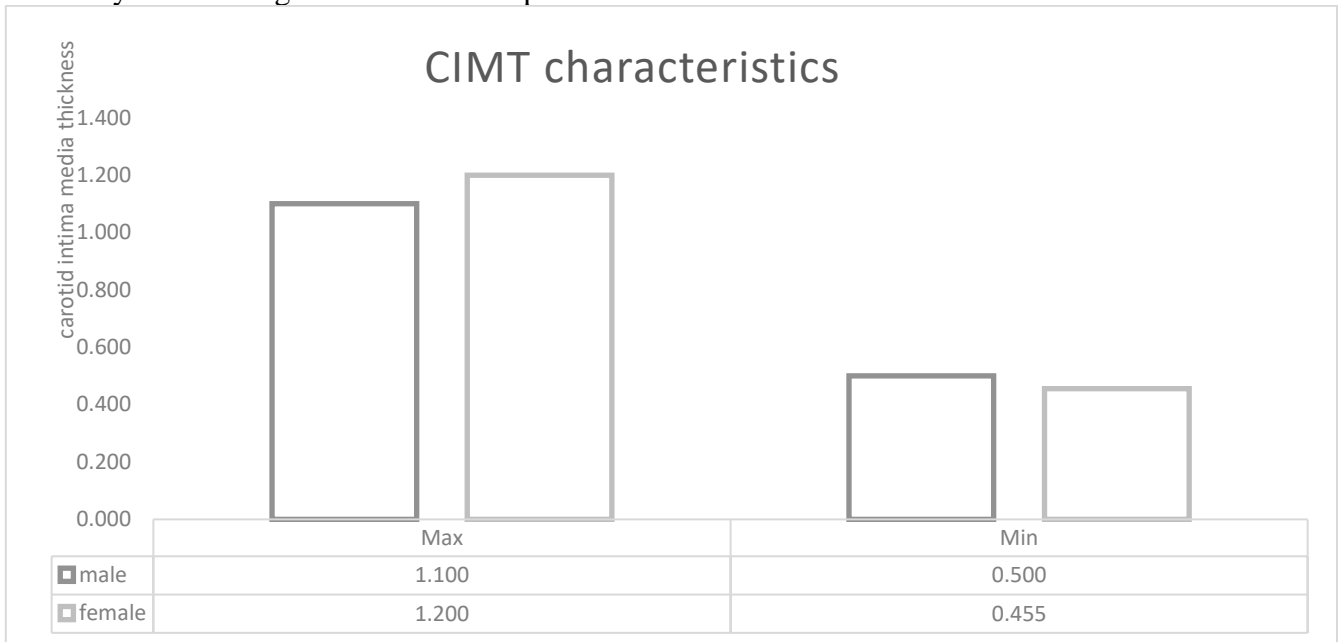
difference in CIMT scores based on sex variables (p value = 0.368) and the odds ratio score showed that female sex had a risk of 2.292 times higher than male sex to have a CIMT score of more than 0.9.

#### CIMT characteristics

The results after measuring the common carotid artery wall, from the CIMT characteristic chart below, we obtained the highest CIMT reaches 1.1 mm in men and 1.2 mm in women. Meanwhile, the lowest CIMT was at 0.5 mm for men and 0.45 mm for women. It can be concluded that the thickness of

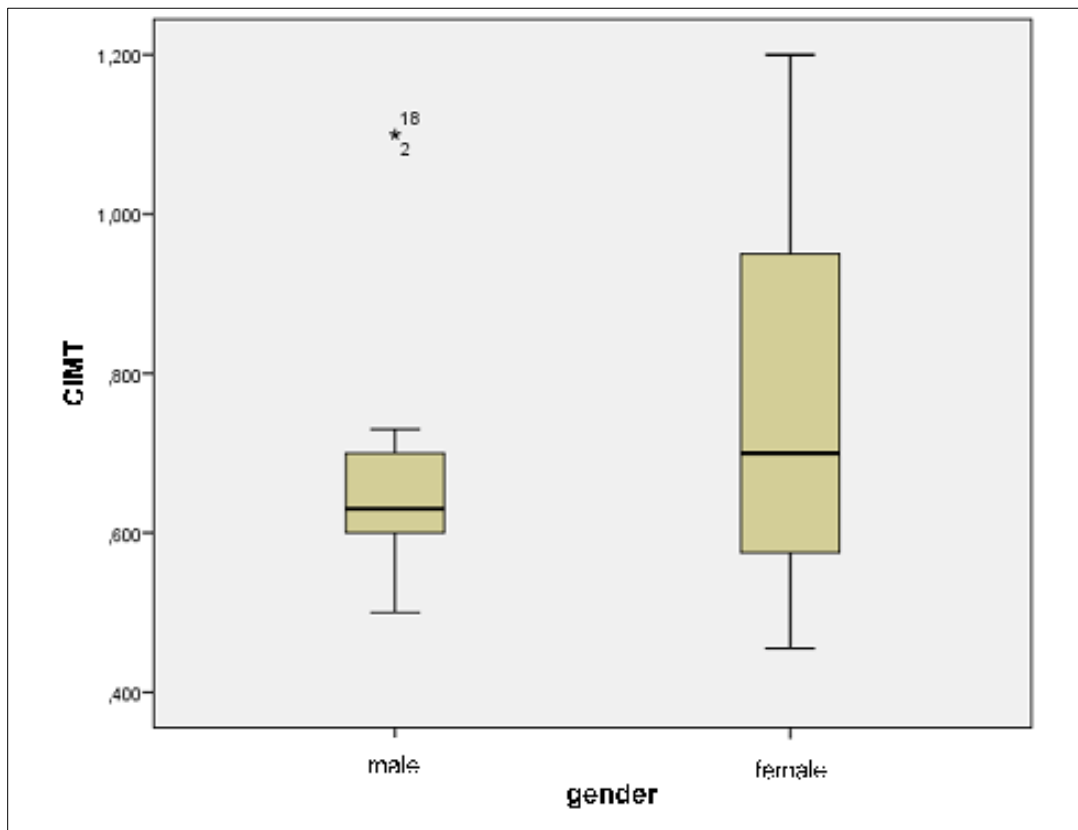
carotid vessel walls on type 2 diabetes patients varies widely. Thickening indicates that the patient

has subclinical atherosclerosis if CIMT score > 0.9 mm.



**Figure 1.** Diagram of CIMT characteristic based on sex

Deviation that occurs in the boxplot also shows the condition than most patients do not experience atherosclerosis, especially in men. Meanwhile in women there is a tendency to experience atherosclerosis even though the proportion of atherosclerosis from the collected is low.



**Figure 2.** Boxplot of carotid characteristics based on sex

**Correlation between Carotid Artery Intima-Media Thickness with Glycated Hb Levels, LDL Levels, Blood Pressure, and BMI**

**Table 3.** The Correlation between Carotid Artery Intima-Media Thickness and Glycated Hb Levels, LDL Levels, Blood Pressure, and BMI

<b>Correlation CIMT and Glycated Hb Levels</b>	
<i>p-value</i>	0.015
<i>Coefficient correlation</i>	-0.441
<b>Correlation CIMT and LDL Levels</b>	
<i>p-value</i>	0.696
<i>Coefficient correlation</i>	+0.074
<b>Correlation CIMT and Systolic Blood Pressure</b>	
<i>p-value</i>	0.350
<i>Coefficient correlation</i>	+0.177
<b>Correlation CIMT and BMI</b>	
<i>p-value</i>	0.831
<i>Coefficient correlation</i>	+0.041

Table 3 shows there was a significant relationship between the Glycated Hb Level and the Carotid Artery Intima-Media Tunica Thickness with the calculation of the correlation coefficient of -0.441 which indicates that the relationship that occurs has the opposite direction, namely the higher the Hb content, the lower the thickness of the arterial wall. carotid. In addition, it also shows that there was no significant relationship between the variables of LDL

levels, blood pressure, and BMI with the carotid artery intima-media thickness.

**Multivariate Analysis**

To determine the form of the relationship that occurs in each predictor variable in this study, a linear regression test was carried out with the prerequisite that a linearity test was carried out to determine whether the variable has a linear relationship so that a regression test can be carried out.

**Table 4.** Data Linearity Analysis

Independent Variable	Dependent Variable	Df	F Score	F Table*	Note
BMI	CIMT	1:28	102,417	249	Linear
LDL		1:28	3,080	249	Linear
HbA1C		6:23	1,486	3,87	Linear
Systolic Blood Pressure		21:8	0,859	2,42	Linear

\*. F Table at the 0,05 level

It can be interpreted from table 4 that all independent variables have a linear relationship to the dependent variable, so that these variables can be continued in the next regression test. After that, linear regression tests were carried out at a significance level of 0.05 as follows:

**Table 5. Data Linearity Analysis**

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	R Square Change
	B	Std. Error	Beta			
1 (Constant)	1,516	,316		4,796	,000	0,183
HbA1C	-,805	,321	-,428	-2,506	,018	

a. Dependent Variable: CIMT

The form of the relationship obtained on the variable this time is:

$$Y = a + bX$$

$$Y = 1,52 - 0,81 X$$

Table 5 shows the R Square between variable HbA1C and CIMT is 0.183 and it can be interpreted that the effectiveness of the relationship between HbA1C and CIMT is 18.3%. In all predictor variables (HbA1C, LDL, BMI, and systolic blood pressure) the effectiveness was 18.3% contributed by the HbA1C predictor variable.

## DISCUSSION

In this study, there was a significant correlation between the glycated Hb levels and CIMT with negative weak relationship. It is different from the previous researches where the higher of HbA1C levels will be followed by an increase in the thickening of the intima-media tunica wall of the carotid artery. These antithetical results may occur due to a different duration of increased HbA1C levels in the study subjects. Carotid intima media wall thickening takes a long time and high HbA1C levels are one of its risk factors. Some of study subjects that had lower HbA1C levels but had higher CIMT scores, could have been experienced type 2 diabetes for a long time and had received treatment already, so that when data was obtained the subjects had a lower HbA1C levels than before. The opposite results can also occur in subjects with higher HbA1C levels and lower CIMT scores, could be due to recent increase of HbA1C levels. Singh et al. (2013) revealed that this type of cross-sectional study could not determine the relationship between HbA1C levels and the occurrence of ischemic stroke, without knowing the duration of the increase in HbA1C<sup>7</sup>. The importance of including the duration of DM disease was supported by the study of Kota et al. (2013) showed that the prevalence of CIMT in DM patients with a duration of more than 10 years was higher than DM patients with a duration of less than

10 years<sup>8</sup>. The limitation of this research is this is done in cross sectional not cohort study so the length of HbA1C increase cannot be evaluated. Patient also do not have previous HbA1C result.

Metabolic factors, such as hyperglycemia, obesity, insulin resistance, hypertension, hyperlipidemia, and increased inflammatory states have all been shown to contribute to the development of CIMT in diabetics. Variable LDL levels that indicate hyperlipidemia in DM patients, this study showed results ranging from 48-225 mg / dL with a mean value of 147.167 mg / dL and a normal threshold value of 100 mg / dL. There was no correlation between LDL levels and CIMT score in this study (p = 0.696). This finding was in contrary to previous research by Bulut (2019) which stated that there was a relationship between LDL levels and CIMT (p = 0.001). LDL plays an important role in the pathogenesis of atherosclerosis and the evolution of atherosclerotic plaque in studies worldwide<sup>13</sup>. The development of atherogenesis is associated with an abnormally high accumulation of low density lipoproteins in the intima. LDL is responsible for the transport of cholesterol from the liver to all tissues of the human body. Due to its role as a precursor to atherosclerosis the problem of transporting LDL molecules in the arterial walls<sup>14</sup>. Another factor is that VEGF can mediate the transport of LDL across the endothelial barrier via specific signaling



pathways that have recently been demonstrated. Studies show that LDL, by binding to LDLR, induces the autophosphorylation of VEGFR1 and internalizes it together with LDL and LDLR, thus providing an additional mechanical route for LDL transport and leading to increased CIMT<sup>9</sup>.

There was no significant relationship between blood pressure and CIMT in this study. This can be influenced by a wide range of blood pressure level obtained in this study. Previous study by Kota (2013) found higher CIMT score in diabetes patients with hypertension in compare to those without hypertension<sup>8</sup>. In addition, the study of Kong et al. (2000) stated there was no association between CIMT and fasting glucose level in normotensive individuals with type 2 diabetes mellitus<sup>15</sup>.

In another study, measurement of the right carotid artery intima-media tunica in 394 healthy individuals, 327 uncontrolled hypertension, and 528 uncontrolled hypertension showed that the thickness in both patient groups, who are not taking any treatment, was higher than in the healthy group. In another study in 6975 people aged 19-90 years resulted the mean progression of the CIMT was significantly higher, especially having a significant association with arterial risk factors such as age, sex, hypertension, diabetes, and smoking habits<sup>16</sup>.

The BMI data for the sample of this study resulted with a range from 16.61 to 47.91 and a mean value of 26.83. This study showed there was no significant relationship between BMI and CIMT ( $p = 0.831$ ).

Several recent studies also found an activation of the cytokine resistin that secreted by adipocytes has been associated with obesity, insulin resistance, and atherosclerosis and has been specifically shown to increase endothelial permeability and thickness<sup>19</sup>. Body mass index and visceral fat accumulation in Human subjects are associated, inter alia, with elevated serum VEGF levels that exacerbate the thickness of the tunica in the carotid arteries<sup>20</sup>. However according to Jin et al. (2018), to examine the risk of obesity against CIMT, it is also necessary to measure the total fat mass or body fat distribution, because a high BMI value does not always indicate a person's high fat content, which refers to dyslipidemia conditions<sup>12</sup>.

Besides that, several other factors that can affect a person's CIMT condition are drugs consumption, albumin levels, smoking habits, alcohol consumption habits, physical activity levels, and diet. A meta-analysis study by Ji et al. (2019) revealed that several cohort studies examining types of drugs such as antihypertensives, lowering fat levels drugs, and antidiabetics showed protective characteristics against CIMT process<sup>21</sup>. Research by Bots et al. (2009) and Herder et al. (2013) showed that the long-term use of lipid-lowering drugs was more effective in preventing CIMT than short-term use<sup>22,23</sup>. Therefore, in this study were not in line with other similar studies, it could be due to the consumption of drugs by the research subjects that can affect the condition of CIMT.

Smoking habits can increase macrophage infiltration and plaque thrombogenicity that lead to the risk of atherosclerosis<sup>24</sup>. Longitudinal study by Ji et al. (2017) stated that smoking habits can be associated with extracranial carotid atherosclerosis but not intracranial arteries<sup>25</sup>. Alcohol consumption habits can increase LDL oxidation and oxidative stress to increase the risk of atherosclerosis in men who consume alcohol more than 40 g / day<sup>21</sup>. revealed by Gao et al. (2017) patients with type 2 diabetes have a higher risk factor for experiencing CIMT if they have a habit of consuming alcohol<sup>26</sup>.

Physical activity and diet also play an important role on the CIMT score. Study by Park et al. (2017) who provided aerobic exercise intervention and endurance for 24 weeks resulted in a significant reduction in CIMT and an increase in the ratio of carotid flow velocity wall shear in a sample of overweight and obese elderly women<sup>27</sup>. Blekkenhorst et al. al. (2018) stated that the intervention of a Mediterranean diet which is rich in vegetables and fish show an oxidative stress inhibition and has a long-term prevention of the development of carotid atherosclerosis in patients newly diagnosed with type 2 diabetes<sup>28</sup>.

## CONCLUSION

There was a negative relationship between HbA1C level and CIMT in type 2 diabetes mellitus patients and no relationship of LDL levels, systolic blood

pressure, BMI towards CIMT in type 2 diabetes mellitus patients

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