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The Relationship Between Carotid Artery Intima-Media Thickness and Duration and Glycemic Control in Type 2 Diabetes Mellitus Patients with Peripheral Artery Disease (PAD)

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Thickness of carotid media; Type 2 diabetes mellitus; Peripheral artery disease; glycemic control; length of disease

Abstract
Type 2 Diabetes Mellitus (DMT2) is associated with several complications, including Peripheral Artery Disease (PAD). Carotid Intima-Media Thickness (CIMT) has been recognized as an early marker of subclinical atherosclerosis, reflecting vascular changes in DMT2 patients. The relationship between disease duration and glycemic control with CIMT in PAD patients is still not fully understood, especially in Indonesia. A cross-sectional study was conducted with 40 DMT2 patients diagnosed with PAD. CIMT was measured using high-resolution Doppler ultrasound. Glycemic control was assessed based on HbA1c levels, with patients categorized based on a threshold of 7%. Data were analyzed using chi-square tests and multivariate logistic regression. A significant relationship was found between DMT2 duration and glycemic control with CIMT thickness ($p<0.05$). Patients with a disease duration of more than 2 years have a higher chance of experiencing an increase in CIMT. Similarly, poor glycemic control (HbA1c ≥7%) is strongly associated with an increase in CIMT. Long-term DMT2 and poor glycemic control are major contributors to increased CIMT, reflecting a greater burden of atherosclerosis in PAD patients. Early intervention and optimal glycemic control are essential in preventing cardiovascular complications in this population

INTRODUCTION

Type 2 diabetes mellitus (DMT2) is one of the chronic diseases with increasing prevalence globally and is a huge burden on the health system (Centers for Disease Control and Prevention, 2024). DMT2 has macrovascular complications, one of which is peripheral artery disease (PAD) which can be observed from the early stages through the examination of the intima-media thickness (IMT) of the carotid artery. PAD itself has a prevalence of about 113 million worldwide, and its prevalence in DMT2 sufferers is on an increasing trend. BMI thickness has been shown to correlate with subclinical atherosclerosis and an increased risk of cardiovascular events (Kozakova & Palombo, 2016). One of the important aspects of the course of DMT2 disease is the length of the disease and poor glycemic control, especially if glycated hemoglobin (HbA1c) levels remain chronically high.

Diabetes Mellitus (DM) is a group of metabolic disorders characterized by chronic hyperglycemia due to abnormal insulin secretion, insulin action, or both. This condition can cause various long-term complications in the body's organs such as the eyes, kidneys, nerves, and blood vessels. According to the American Diabetes Association (ADA) and the World Health Organization (WHO), a diagnosis of DM is established when fasting plasma glucose levels reach ≥126 mg/dL, HbA1c levels ≥7%, or plasma glucose levels at ≥200 mg/dL accompanied by classic symptoms of hyperglycemia, such as polyuria, polydipsia, and

unexplained weight loss (American Diabetes Association Professional Practice Committee, 2024; World Health Organization, 2020).

The length of time a person has been diagnosed with type 2 diabetes mellitus (DMT2) is one of the important factors that significantly affects the progression of the disease as well as the risk of various complications, both microvascular and macrosculular (Ojo et al., 2023). Several longitudinal studies show that the risk of complications such as diabetic retinopathy, nephropathy, peripheral neuropathy, to coronary heart disease and stroke increases significantly as the disease progresses (Sone et al., 2025). For example, a study by the UK Prospective Diabetes Study (UKPDS) found that after 10 years of DMT2, more than 50% of patients experienced one or more microvascular complications.

Glycemic control is a key aspect in the management of type 2 diabetes mellitus (DMT2), as it is directly related to the risk of long-term complications both microvascular and macroascular (Antoniou et al., 2021). The most commonly used parameters to assess glycemic control include glycated hemoglobin levels (HbA1c), fasting blood glucose (GDP), and postprandial 2-hour blood glucose (GD2PP). HbA1c reflects the average blood glucose level over the past 2–3 months and is considered a key indicator in long-term evaluation. The standard of practice from the ADA and the Indonesian Endocrinological Association (PERKENI) stipulate that the ideal HbA1c target is <7% for most adult patients, although this target can be adjusted to be looser (e.g. <8%) in elderly patients, with severe comorbidities, or a high risk of hypoglycemia (PB PERKENI, 2021). Glycemic control is based on the results of the examination of glucose levels, HbA1c levels and lipid profiles. The 2023 Indonesian Health Survey (SKI) shows that only 27.2% of people with diabetes mellitus undergoing treatment have fasting blood glucose levels of <140 mg/dL—an indirect indicator of good glycemic control (Kementerian Kesehatan Republik Indonesia, 2023).

The relationship between disease length and glycemic control in patients with type 2 diabetes mellitus (DMT2) has been a major focus of various clinical and epidemiological studies as they are both determinant factors in the development of chronic complications. As a person has diabetes for longer, the tendency for a decrease in glycemic control becomes higher. This is largely caused by a phenomenon known as glucotoxicity, which is a chronic hyperglycemia condition that is toxic to β pancreatic cells. Long-term exposure to high glucose leads to oxidative stress, mitochondrial dysfunction, and subclinical inflammation that impair β cell function and survival, thereby lowering endogenous insulin secretion (Berbudi et al., 2025; Schwartz et al., 2013). The landmark ADVANCE study conducted by Holman et al. showed that every 1% increase in HbA1c was associated with an 18% increased risk of cardiovascular events, confirming the importance of strict glycemic control in preventing macrovascular complications.

CIMT specifically refers to the thickness of the intima layer and the media of the walls of the communist carotid artery, which is usually measured using high-resolution B-mode ultrasound. Carotid Artery Intima-Media Thickness Measurement (CIMT) has long been recognized as one of the most valuable non-invasive diagnostic tools in cardiovascular disease screening and risk assessment (Kozakova & Palombo, 2016). The intima layer is the innermost layer of blood vessels that come into direct contact with the blood flow, while the media layer is the smooth muscular layer responsible for the regulation of the diameter of the blood vessels. An increase in thickness in these two layers, even in the subclinical stage without obvious

symptoms, is an early indicator of the atherosclerosis process. In addition to being an early marker, CIMT also serves as an independent predictor of long-term cardiovascular risk. Various epidemiological and clinical studies have consistently shown that increased CIMT values are strongly correlated with an increased risk of cardiovascular events such as stroke, coronary artery disease (CAD), and overall cardiovascular mortality (Shimoda et al., 2020).

The increase in CIMT in DMT2 patients is mainly due to complex interactions between chronic hyperglycemia, insulin resistance, atherogenic dyslipidemia, oxidative stress, as well as long-term systemic inflammation that collectively impair endothelial function and accelerate vascular remodeling (Christen et al., 2010). Persistent hyperglycemia leads to the formation of advanced glycation end-products (AGEs) that trigger the activation of RAGE receptors (receptors for AGEs), induce the expression of vascular adhesion molecules, pro-inflammatory cytokines, and oxidative stress reactions in the endothelial, thereby facilitating the accumulation of smooth muscle cells and collagen in the intima layer and carotid artery media. In addition, insulin resistance to DMT2 disrupts the NO-endothelial pathway, worsens vasodilation, and decreases protection against healthy shear pressure, accelerating the process of thickening of the arterial walls (Abdul-Ghani & DeFronzo, 2010).

Longevity of type 2 diabetes mellitus (DMT2) has long been identified as an important determinant in the progression of atherosclerosis, specifically an increase in the thickness of the intima-media carotid artery (CIMT). A large meta-analysis of 57 studies involving 8,254 DMT2 patients showed that the mean CIMT in diabetic patients was significantly higher than in non-diabetic (SMD 1.01; 95% CI 0.75–1.26; $p < 0.00001$) and was consistently closely related to disease duration, along with other factors such as age, hypertension, and body mass index (Antoniou et al., 2021). Its pathophysiological mechanisms involve exposure to chronic hyperglycemia (glucotoxicity) that impairs endothelial function, increases oxidative stress, as well as the expression of adhesion molecules (ICAM, VCAM) that trigger inflammatory cell infiltration, vascular media remodeling, and atherosclerotic plaque progression. In fact, each 1-year increase increases the odds of CIMT thickening by ~33% after adjusting for other confounder variables.

Glycemic control parameters such as HbA1c levels, fasting blood glucose, and postprandial glucose showed a consistent and meaningful association with increased carotid intima-media thickness (CIMT). A large population study in Japan (Tohoku Medical Megabank, N=13,366) found that after adjusting for cardiovascular risk factors, any increase in HbA1c was significantly associated with an increase in mean CIMT (β positive; $p < 0.05$) (Sone et al., 2025).

Peripheral artery disease (PAD) is a pathological condition characterized by obstruction of blood flow in the peripheral arteries, especially in the lower extremities, due to the process of atherosclerosis. Atherosclerosis itself is a chronic degenerative process that involves the formation of atheromal plaques consisting of lipids, inflammatory cells, and fibrotic tissue on the walls of the arteries, thus causing a progressive narrowing of the lumen of blood vessels. In PAD, these plaques interfere with the perfusion of peripheral tissues that require adequate oxygen and nutrient supply, which can ultimately lead to typical clinical symptoms (Ojo et al., 2023).

In patients with DMT2, the pathophysiological process of PAD involves a complex interaction between metabolic dysfunction, chronic inflammation, and disorders of the vascular

system. Uncontrolled chronic hyperglycemia plays a major role in endothelial damage of blood vessels through increased oxidative stress and the formation of advanced glycation end-products (AGEs) (Berbudi et al., 2025). AGEs trigger the activation of various inflammatory pathways and worsen endothelial function by decreasing the bioavailability of nitric oxide, which is important in vasodilation and hemodynamic regulation.

Carotid Intima-Media Thickness (CIMT) has long been used as a non-invasive parameter to assess the degree of subclinical atherosclerosis in the vascular system. PAD and CIMT are closely related because they both reflect the systemic atherosclerosis process. Prospective studies show that increased CIMT values are positively correlated with the presence of PAD and can be used as an early indicator of the risk of peripheral vascular disorders (Shimoda et al., 2020). Physiologically, an increase in CIMT indicates a thickening of the inner lining of the carotid artery due to lipid infiltration and activation of vascular smooth muscle cells, reflecting the degree of vascular damage that occurs throughout the major arterial system, including the lower extremities (Christen et al., 2010).

The urgency of this research is driven by several critical factors. First, Indonesia has one of the fastest-growing diabetes epidemics in Asia, with the 2023 Indonesian Health Survey (SKI) showing that only 27.2% of people with diabetes mellitus undergoing treatment have fasting blood glucose levels <140 mg/dL, indicating poor glycemic control in the majority of patients (Kementerian Kesehatan Republik Indonesia, 2023). Second, PAD in diabetic patients is often underdiagnosed due to atypical or silent presentations, yet it carries a high risk of lower extremity amputation and cardiovascular mortality. Third, early detection of subclinical atherosclerosis through CIMT measurement could enable risk stratification and targeted preventive interventions, but normative data and risk factor relationships in Indonesian T2DM patients with PAD are lacking. Fourth, without local evidence, clinicians must rely on Western guidelines that may not account for Indonesia's unique genetic, lifestyle, and healthcare system characteristics. The novelty of this study lies in its specific focus on T2DM patients with established PAD, its use of both disease duration and glycemic control (HbA1c) as independent variables, its multivariate analysis adjusting for confounders (age, gender, BMI, lipid profile, hypertension, smoking), and its contribution of primary data from an Indonesian tertiary hospital (Cipto Mangunkusumo Hospital, Jakarta).

Based on this rationale, this study aims to evaluate the relationship between disease duration and glycemic control with carotid intima-media thickness in type 2 diabetes mellitus patients with peripheral artery disease. The specific objectives are: (1) to analyze the relationship between T2DM duration and CIMT thickness in PAD patients; (2) to analyze the relationship between glycemic control (HbA1c) and CIMT thickness in PAD patients; (3) to identify the strongest predictor (disease duration vs. glycemic control) of CIMT thickening using multivariate logistic regression; and (4) to quantify the magnitude of risk (adjusted odds ratio) for each factor. This research is expected to provide theoretical benefits by contributing to the understanding of atherosclerosis pathophysiology in diabetic patients with PAD and to offer practical benefits for clinicians in identifying high-risk patients who require more aggressive glycemic control and cardiovascular risk factor management. The findings will also inform screening protocols for subclinical atherosclerosis in Indonesian T2DM patients.

RESEARCH METHOD

This study is a prospective study using primary data from carotid Doppler ultrasound examination and laboratory results of HbA1c, blood glucose, lipid profile; secondary data from medical records and patient interviews with a large sample of 40 patients who were treated in DKI Jakarta, Cipto Mangunkusumo Hospital, Polyclinic and Vascular Surgery inpatient room during October - November 2025. This study used a cross-sectional, analytical design to evaluate the relationship between long profile and glycemic control (HbA1c) with carotid BMI thickness in DMT2 patients with PAD. Bivariate analysis was carried out first. Furthermore, to evaluate the influence of each variable simultaneously on the thickness of CIMT, a multivariate logistic regression analysis was performed.

RESULT AND DISCUSSION

Basic Characteristics of Research Subjects

This study involved 40 subjects who met the inclusion criteria and did not include the exclusion criteria (Table 4.1), Here it was found that there was no significant relationship between the duration of diabetes and glycemic control in the subjects who were active smokers or not.

Table 1 Data on the characteristics of the research subjects.

Variabel	Long DM		P-Value	Control Glichemia		P-value
	> 2 years	< 2 years		HbA1C <7 %	HbA1C ≥7 %	
Age						
< 60 years old	15	6	0,626	9	12	0,395
≥ 60 years old	14	5		4	15	
Gender						
Male	16	8	0,628	9	15	0,474
Women	13	3		4	12	
Body mass index						
< 23.0 kg/m2	11	7	0,280	7	11	0,621
≥ 23.0 kg/m2	18	4		6	16	
HDL						
≥ 50 mg/dl	5	5	0,838	2	8	0,720
< 50 mg/ dl	24	6		11	19	
LDL						
< 100 mg/dl	19	7	0,148	8	17	0,080
≥ 100 mg/dl	10	4		5	10	
Trigliseride						
< 150 mg/dl	20	11	0,702	10	22	0,193
≥ 150 mg/dl	7	2		3	5	
Total cholesterol						
< 200 mg/dl	25	10	0,237	11	24	0,067
≥ 200 mg/dl	5	0		2	3	
Hypertension Status						
Ya	18	8	0,562	7	19	0,454
No	11	3		6	8	
Active Smokers						
Ya	7	2	0,573	3	6	0,360
No	22	9		10	21	

The Long-Standing Relationship of DMT2 with CIMT Values

Based on the analysis of the relationship between the length of suffering from diabetes mellitus and the thickness of CIMT (Table 4.2.), it was found that the proportion of CIMT

thickening (≥0.71 mm) was higher in the group with DM duration ≥2 years, which was 22 people (75.9%), compared to the group with DM duration <2 years which was only 3 people (27.3%). Statistical tests showed a significant relationship between DM length and CIMT thickness (p = 0.005). The odds ratio calculation showed that patients with a duration of DM ≥2 years had an 8.38 times greater chance of experiencing a thickening of CIMT than those with a DM duration of <2 years. These findings indicate that the longer a person suffers from DM, the more likely it is that structural changes will occur in the walls of the carotid artery.

Table 2. Relationship between DM lama with CIMT thickness

Long DM	CIMT <0,71mm	CIMT ≥0,71mm	p-value
<2 years	8	3	0,005
≥2 years	7	22	

Relationship of Glycemic Control (HbA1c) to CIMT value

Analysis of the relationship between glycemic control and CIMT thickness showed that the group with poor glycemic control (HbA1c ≥7%) had a much higher prevalence of CIMT thickening, which was 23 people (79.3%), compared to the group with HbA1c <7% which was only 2 people (18.2%). Statistical tests showed a significant association between glycemic control and CIMT thickness (p < 0.001). The odds ratio of the manual calculation showed that patients with HbA1c ≥7% had a 17.25 times greater chance of experiencing CIMT thickening than patients with controlled HbA1c. This confirms that poor glycemic control is an important factor contributing to the increase in the thickness of the carotid artery-intima-media.

Table 3. Relationship between glycemic control (HbA1c) with a CIMT value.

Control Glibone	CIMT <0,71mm	CIMT ≥0,71mm	p-value
<7.0%	9	2	<0.001
≥7,0%	6	23	

Multivariate Logistic Regression Analysis

Bivariate analysis was performed to look for factors related to CIMT. The results can be seen in Table 4.

Table 4. Factors related to CIMT value based on bivariate analysis

Variabel	CIMT <0,71	CIMT ≥0,71	OR (95%CI)	p-value
Age				
<Mean	11	10	4,13 (1,02-16,67)	0,041
≥Mean	4	15		
Gender				
Male	9	15	1,00 (0,27-3,69)	1,000
Women	6	10		
IMT				
<23.0 kg/m2	9	9	2,67 (0,71-9,95)	0,140
≥23.0 kg/m2	6	16		
Long DM				
<2 years	8	3	8,03 (1,73-40,53)	0,005
≥2 years	7	22		
HbA1c				
<7.0%	9	2	17,25 (2,92-101,90)	<0.001

≥7,0%	6	23		
HDL				
≥50mg/dL	5	9	0,89 (0,23-3,42)	0,864
<50mg/dL	10	16		
LDL				
<100mg/dL	8	18	0,44 (0,12-1,69)	0,231
≥100mg/dL	7	7		
TG				
<150mg/dL	12	19	1,26 (0,26-6,03)	0,769
≥150mg/dL	3	6		
Total Cholesterol				
<200mg/dL	13	22	0,89 (0,13-6,02)	0,902
≥200mg/dL	2	3		
Hypertension Status				
Ya	5	9	0,89 (0,23-3,42)	0,864
No	10	16		
Active Smokers				
Ya	13	18	2,53 (0,45-14,20)	0,282
No	2	7		

Based on bivariate analysis, a meaningful relationship was found between the duration of DM, and glycemic control on CIMT values. It was found that patients with a history of DM for more than 2 years, and the last HbA1c value in 3 months was still above 7.0% tended to find a CIMT value above normal (0.71 mm). Other confounding factors such as gender, body mass index (BMI), lipid profile (HDL/LDL/TG/Total Cholesterol), comorbidities of hypertension, and active smokers did not have a statistically significant relationship with CIMT values.

From the above bivariate analysis, the variables that have a p<value of 0.20 are eligible for inclusion in the logistic regression model are age, BMI, DM duration, and DM/HbA1c control (Table 5).

Table 5. Multivariate logistic regression analysis after Enter eligible variables

Variabel	Category	Risk AOR (95%CI)	p-value
Long DM	≥2 years	12,50 (1,28-122,26)	0,030
HbA1c	≥7,0%	25,58 (2,36-277,77)	0,008

In multivariate logistic regression analysis, two variables showed a meaningful relationship with increased CIMT thickness. First-time diabetes ≥2 years was also significantly associated with CIMT thickness, with an AOR of 12.50 (95% CI: 1.28–122.26; p = 0.030). Thus, patients who have had diabetes for ≥2 years have about 12 times greater chance of developing CIMT thickening than patients with a diabetes duration of <2 years.

Second, poor glycemic control (HbA1c ≥7%) was the strongest predictor in the model, with an AOR of 25.58 (95% CI: 2.36–277.77; p = 0.008). This means that patients with HbA1c ≥7% have about 25 times greater chance of thickening CIMT than those with HbA1c <7%. These results confirm the important role of glycemic control against the progression of atherosclerosis. This regression model suggests that poor glycemic control, and longer duration of diabetes are independent predictors that contribute to increased carotid intima-media thickness in patients with type 2 diabetes mellitus with PAD.

The results showed that the length of suffering from diabetes had a meaningful relationship with the thickening of CIMT (p=0.005). Subjects with DM ≥2 years had an 8.38 times greater risk of developing abnormal CIMT. This is in accordance with the theory that exposure to chronic hyperglycemia leads to the accumulation of endothelial damage, increased formation of AGEs (advanced glycation end-products), as well as activation of inflammatory pathways that accelerate atherosclerosis (Christen et al., 2010; Berbudi et al., 2025). From the study we found a statistically significant relationship between glycemic control and CIMT thickness ($p < 0.001$). Subjects with an HbA1c ≥7% had a 17.25 times greater chance of thickening CIMT than those with an HbA1c <7%. This makes glycemic control the strongest predictor of CIMT increase in this study (Antoniou et al., 2021).

Recent research shows that HbA1c variability (glycemic control fluctuations) is associated with arterial stiffness and CIMT thickening even though the average HbA1c is not very high. This means that unstable glycemic control also contributes to vascular damage (Kozakova & Palombo, 2016). This study is consistent with the meta-analysis of Lorenz et al. which showed a strong association between HbA1c and CIMT, as well as a Japanese study (Tohoku Megabank Project) which showed that HbA1c is an early predictor of CIMT changes in DMT2 patients (Sone et al., 2025). Multivariate logistic regression analysis was performed to identify variables that were independently related to CIMT thickening. From the final model, there were two variables that were significantly related, namely: HbA1c ≥7% (AOR 25.58; 95% CI 2.36–277.77; p = 0.008), and DM Duration ≥2 years (AOR 12.50; 95% CI 1.28–122.26; p = 0.030) Meanwhile, the other variables did not show a significant association after controlling for other variables in the model.

These results suggest that the thickening of CIMT is affected by a combination of chronic exposure (duration of DM) and metabolic severity (glycemic control). These findings are consistent with large studies such as ARIC and MESA that show that glycemic control, and disease duration are independent predictors of CIMT (Antoniou et al., 2021; Shimoda et al., 2020).

CONCLUSION

Based on the results of this study conducted at Cipto Mangunkusumo Hospital, Jakarta, involving 40 type 2 diabetes mellitus patients with peripheral artery disease, it can be concluded that there is a significant relationship between disease duration and carotid intima-media thickness (p=0.005), as well as between glycemic control (HbA1c) and carotid intima-media thickness (p<0.001). Multivariate logistic regression analysis revealed that poor glycemic control (HbA1c ≥7%) is the strongest independent predictor of CIMT thickening (AOR 25.58; 95% CI 2.36-277.77; p=0.008), followed by disease duration ≥2 years (AOR 12.50; 95% CI 1.28-122.26; p=0.030). Patients with T2DM duration ≥2 years have approximately 12 times higher odds, and those with HbA1c ≥7% have approximately 25 times higher odds, of experiencing abnormal CIMT thickening compared to patients with shorter duration or better glycemic control. These findings confirm that both chronic exposure to diabetes (duration) and the severity of metabolic derangement (glycemic control) contribute independently to subclinical atherosclerosis in PAD patients, with glycemic control playing a dominant role.

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