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Human Platelet Antigen-2b Gene Polymorphism in Type 2 Diabetes Mellitus Patients with Macrovascular Complications

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ABSTRACT

Background: *The prevalence of Type 2 Diabetes Mellitus continues to increase globally, with Indonesia ranking fifth worldwide, affecting an estimated 20.4 million adults as of 2024. Patients with T2DM often experience abnormal platelet activation leading to platelet hyperactivity, which contributes to macrovascular complications such as coronary heart disease, cerebrovascular disease, and peripheral arterial disease.*
Objective: *To analyze the differences in frequency and distribution of HPA gene polymorphisms between T2DM patients with macrovascular complications and those without macrovascular complications.*
Methods: *A case control study was conducted involving 100 T2DM patients, consisting of 50 patients with macrovascular complications and 50 without macrovascular complications. HPA gene polymorphisms were analyzed using the polymerase chain reaction method. Clinical and laboratory variables including age, sex, HbA1c level, hypertension, and dyslipidemia were evaluated. Statistical analyses were performed to determine the association between HPA polymorphisms and macrovascular complications.*

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Results: *HPA gene types 1–5 were detected, while HPA-15a and HPA-15b were absent. Most participants were male (53%), aged 18–65 years (84%), had uncontrolled HbA1c levels (93%), were not hypertensive (72%), and had no dyslipidemia (57%). Significant differences were observed in hypertension, dyslipidemia, and HPA-2b polymorphism between the macrovascular and non-macrovascular complication groups ($p < 0.05$). Multivariate analysis demonstrated that HPA-2b polymorphism was significantly associated with macrovascular complications in patients with Type 2 Diabetes Mellitus ($p < 0.001$).*
Conclusion: *HPA-2b gene polymorphism is more prevalent in T2DM patients with macrovascular complications and is significantly associated with the occurrence of these complications.*

Keywords: *Type 2 diabetes mellitus; human platelet antigen; gene polymorphism; macrovascular complications; platelet activation*

INTRODUCTION

Diabetes mellitus (DM) is a long-term metabolic disease characterized by impaired insulin production, ineffective insulin utilization, or both, resulting in elevated blood glucose levels. Insulin plays an essential role in maintaining glucose homeostasis within the body. Persistent hyperglycemia associated with uncontrolled diabetes can progressively damage various organs and tissues, especially the vascular and nervous systems.[1] The global burden of diabetes has escalated dramatically over recent decades. According to the World Health Organization (WHO), the prevalence of diabetes among adults aged 18 years and older reached 14% in 2022, doubling from approximately 7% in 1990. [2] According to the 11th edition of the International Diabetes Federation (IDF) Diabetes Atlas (2024), an estimated 589 million adults aged 20–79 years were living with diabetes globally, representing 11.1% of the adult population, and this number is projected to rise to 853 million by 2050. In 2024 alone, diabetes was responsible for approximately 3.4 million deaths worldwide.[3] In Indonesia, national data from the Indonesian Health Survey (Survei Kesehatan Indonesia/SKI) 2023 documented a diabetes prevalence of 11.7% among individuals aged 15 years and above, increasing from 10.9% in Riskesdas 2018 and from 5.7% in 2007.4 According to the IDF Diabetes Atlas 2024, Indonesia ranks fifth globally in the total number of adults living with diabetes, with an estimated 20.4 million affected individuals, underscoring the urgency of research into diabetes-related complications, including macrovascular disease.[3]

Type 2 Diabetes Mellitus (T2DM), formerly referred to as non–insulin-dependent diabetes, develops primarily due to the body's inability to effectively respond to insulin. More than 95% of diabetes cases worldwide are classified as T2DM. This condition is strongly associated with obesity, excess body weight, and limited physical activity. The disease is characterized by progressive

dysfunction of pancreatic β-cells, often accompanied by insulin resistance.[4] According to the IDF Diabetes Atlas, the number of adults globally living with diabetes increased from 537 million in 2021 to 589 million in 2024.Updated estimates from the IDF Diabetes Atlas 11th edition (2024) confirm Indonesia's position as the country with the fifth highest number of adults with diabetes globally, with an estimated 20.4 million cases and a national prevalence of 11.0% among adults aged 20-79 years, a figure projected to increase substantially in the coming decades. Diabetes prevalence affects both men and women relatively equally and is most common among individuals aged 75-79 years. The condition is also more frequently observed in urban populations than in rural communities and is more prevalent in high-income countries compared with low-income regions.[5]

Complications of diabetes mellitus are generally categorized into acute and chronic conditions. Acute complications include hypoglycemia and diabetic ketoacidosis, whereas chronic complications may affect multiple organs and body systems, including the eyes, kidneys, heart, skin, gastrointestinal tract, and nervous system. Chronic diabetic complications are further classified into microvascular and macrovascular disorders. Microvascular complications commonly involve diabetic neuropathy, nephropathy, and retinopathy, while macrovascular complications include coronary artery disease, cerebrovascular disease, and peripheral arterial disease (PAD).[6] PAD is recognized as one of the major vascular complications associated with diabetes and is characterized by atherosclerotic narrowing or obstruction of large peripheral arteries, leading to reduced blood circulation, particularly in the lower extremities. Atherothrombosis represents a significant contributor to morbidity and mortality among patients with diabetes mellitus. Individuals with diabetes have approximately a two- to four-fold greater risk of developing coronary heart disease, stroke, and peripheral arterial disease compared with the general population.[7] Accelerated atherosclerosis in diabetes promotes a prothrombotic environment, in which platelet hyperactivity plays a fundamental role. Increased platelet activation contributes substantially to thrombus formation, progression, and stabilization, thereby enhancing the risk of macrovascular complications in diabetic patients.[8]

Thrombosis is defined as the development of a blood clot inside a blood vessel and may occur in both arterial and venous circulation. The presence of a thrombus can impair or completely block blood flow, resulting in a variety of vascular disorders. Platelet adhesion to the damaged vascular wall is mediated by several platelet membrane receptors, including glycoprotein (GP) Ib/IIa collagen receptors and the von Willebrand factor receptor complex GPIb/IX. After adhesion occurs, platelets undergo activation and subsequently aggregate through fibrinogen interactions with the GPIIb/IIIa receptor. In patients with Type 2 Diabetes Mellitus (T2DM), abnormalities in platelet activation and function contribute to macrovascular disease and enhanced platelet reactivity. Several mechanisms underlying

platelet dysfunction in diabetes have been identified, including excessive production of larger and highly reactive immature platelets from the bone marrow, platelet stimulation induced by the diabetic metabolic milieu, and platelet activation triggered by vascular endothelial injury.[9]

Accelerated thrombopoiesis leads to increased platelet turnover and reduced platelet lifespan, resulting in larger and more reactive platelets with enhanced thrombogenic potential. Increased platelet adhesion, activation, and aggregation have been observed in patients with diabetes, and platelet counts are influenced by platelet lifespan, production rate, and turnover.[10] Human Platelet Antigen (HPA) represents alloantigens expressed on the platelet membrane. Each HPA corresponds to one of six platelet glycoproteins, including GPIIb, GPIIIa, GPIa, GPIbα, GPIbβ, and CD109. These glycoproteins are encoded by genetic sequences that may exhibit genetic variation known as polymorphisms. Genetic polymorphism refers to the presence of two or more alternative alleles within a population with a frequency greater than 1%, often resulting from amino acid substitutions. Although polymorphisms do not necessarily cause structural protein changes, they may alter protein function and influence susceptibility to disease.[11]

Environmental exposures and carcinogens can induce various alterations in deoxyribonucleic acid (DNA). One of the most common genetic variations is the single nucleotide polymorphism (SNP), which involves substitution of a single nucleotide in the DNA sequence and may lead to amino acid changes in platelet glycoproteins. Such polymorphisms can be identified using gene sequencing or molecular amplification techniques. Phenotypic manifestations can be detected through alloantigen identification or antigen antibody reaction assays, as well as platelet function tests. Genotypic detection of HPA polymorphisms can be performed using nucleic acid amplification methods. HPA gene polymorphisms significantly influence platelet function because they alter glycoprotein expression and platelet membrane antigenicity, thereby affecting platelet activation, adhesion, and aggregation processes that play a critical role in the pathogenesis of atherosclerosis.[12]

Accelerated thrombopoiesis contributes to increased platelet turnover and shortened platelet survival, producing larger platelets with greater thrombogenic activity. Enhanced platelet adhesion, activation, and aggregation are frequently observed in individuals with diabetes mellitus, while platelet count is influenced by platelet lifespan, production rate, and turnover dynamics. Human Platelet Antigens (HPAs) are alloantigenic determinants located on platelet membrane glycoproteins. Each HPA is associated with one of several platelet glycoproteins, including GPIIb, GPIIIa, GPIa, GPIbα, GPIbβ, and CD109. These glycoproteins are encoded by genes that may undergo polymorphic variations. Genetic polymorphism refers to the presence of two or more allelic variants within a population at a frequency greater than 1%, often arising from amino acid substitutions. Although such polymorphisms

do not always alter protein structure directly, they may influence protein function and contribute to disease susceptibility.[13]

METHODS

Study Design

This study employed an observational analytic design with a case control approach. The study aimed to analyze the genetic polymorphism of Human Platelet Antigen (HPA) and compare its distribution between patients with Type 2 Diabetes Mellitus who developed macrovascular complications and those without macrovascular complications. Genetic phenotype analysis of HPA polymorphisms was performed in patients diagnosed with T2DM who were treated either as inpatients or outpatients.

Study Setting and Period

The study was conducted at Dr. Wahidin Sudirohusodo General Hospital, Makassar, where patient recruitment and blood sample collection were performed. Genetic analysis was carried out at the Research Unit of the Faculty of Medicine, Hasanuddin University Teaching Hospital (RSP-UH), Makassar. The study was conducted from September to October 2022.

Study Population

The study population consisted of all patients diagnosed with T2DM who had either macrovascular complications or no macrovascular complications and received inpatient or outpatient care at Dr. Wahidin Sudirohusodo General Hospital and Hasanuddin University Hospital during the study period.

Sample and Sampling Technique

The study sample comprised eligible patients who met the inclusion criteria. Participants were divided into two groups: the case group, consisting of patients with Type 2 Diabetes Mellitus (T2DM) with macrovascular complications, and the control group, consisting of patients with T2DM without macrovascular complications, including patients with microvascular complications or without vascular complications. Sampling was conducted among accessible patients who fulfilled the study criteria during the research period. Participants were eligible for inclusion if they were adults aged ≥18 years, had been diagnosed with Type 2 Diabetes Mellitus with or without macrovascular complications, and

were willing to participate in the study by providing written informed consent. Participants were excluded if they had hemolyzed or lipemic blood samples, inability to repeat specimen collection, incomplete clinical data, a history of congenital vascular anomalies, congenital heart disease, congenital platelet dysfunction based on medical history and medical records, or were pregnant patients.

Ethical Considerations

All study procedures were conducted following ethical standards. Written informed consent was obtained from all participants prior to inclusion in the study. Ethical approval was granted by the Health Research Ethics Committee of the Faculty of Medicine, Hasanuddin University Hasanuddin University Teaching Hospital Dr. Wahidin Sudirohusodo General Hospital, Makassar (Ethical Clearance No. 508/UN4.6.4.5.31/PP36/2022; Protocol No. UH22480491; issued September 14, 2022).

Study Procedures

Participants who met the inclusion criteria and agreed to participate were enrolled in the study. Patient demographic and clinical data were recorded after providing a detailed explanation regarding the objectives and benefits of the study. Venous blood samples (2 mL) were collected using tubes containing ethylenediaminetetraacetic acid (EDTA) as an anticoagulant for genetic analysis of HPA. Blood samples were centrifuged to separate the buffy coat fraction. The buffy coat samples were subsequently stored at −80°C to preserve sample integrity prior to analysis. Genetic analysis of HPA polymorphisms was then performed using the sequence-specific primer polymerase chain reaction (SSP-PCR) method.

RESULTS

The study was conducted from September to October 2022 and involved a total of 100 research subjects. The participants consisted of 50 (50%) patients with macrovascular complications of Type 2 Diabetes Mellitus and 50 (50%) patients with non-macrovascular complications of Type 2 Diabetes Mellitus. The age of the subjects ranged from 36 to 82 years, with a mean age of 58.0 ± 9.5 years. Serum HbA1c levels ranged from 6.0 to 16.0, with a mean value of 9.9 ± 2.2.

Table 1. Characteristics of the Study Subjects in the Macrovascular Complication and Non-Macrovascular Complication Groups of Type 2 Diabetes Mellitus (mean±SD)

Criteria	Macrovascular Complications Type 2 DM (n %)	Non-Macrovascular Complications Type 2 DM (n %)
Sex		
Male	31 (62%)	22 (44%)
Female	19 (38%)	28 (56%)
Age*		
Adults (≥18–65 years)	41 (82%)	43 (86%)
Elderly (>65 years)	9 (18%)	7 (14%)
HbA1c Level		
Controlled	4 (8%)	3 (6%)
Uncontrolled	46 (92%)	47 (94%)
Dyslipidemia	29 (58%)	14 (28%)
Hypertension	21 (42%)	7 (14%)
HPA 1a	48 (96%)	47 (94%)
HPA 1b	33 (66%)	33 (66%)
HPA 2a	49 (98%)	49 (98%)
HPA 2b	38 (76%)	11 (22%)
HPA 3a	44 (88%)	45 (90%)
HPA 3b	32 (64%)	36 (72%)
HPA 4a	49 (98%)	50 (100%)
HPA 4b	37 (74%)	37 (74%)
HPA 5a	49 (98%)	44 (88%)
HPA 5b	26 (52%)	18 (36%)
HPA 15a	0 (0%)	0 (0%)
HPA 15b	0 (0%)	0 (0%)

*Age categories according to the Indonesian Ministry of Health (2019)

Based on Table 1, male subjects were more prevalent in the macrovascular complication group of Type 2 Diabetes Mellitus, with 31 individuals (62%), compared to 19 females (38%). In contrast, in the non-macrovascular complication group, females were more frequent with 28 subjects (56%) compared to males with 22 subjects (44%). Overall, males accounted for 53 subjects (53.0%), which was slightly higher than females with 47 subjects (47.0%) from the total population of both groups. Regarding age distribution, the majority of subjects were adults aged 18–65 years. In the macrovascular complication group, 41 individuals (82%) were within this age range, while 43 individuals (86%) were observed in the non-macrovascular complication group. Overall, 84 subjects (84%) were aged 18–65 years, while 16 subjects (16%) were older than 65 years.

The frequency of risk factors, including dyslipidemia, hypertension, and serum HbA1c levels, in the macrovascular complication group were 29 subjects (58%), 21 subjects (42%), and 46 subjects (92%), respectively. Overall, uncontrolled HbA1c levels were observed in 93 subjects (93.0%), which was considerably higher than controlled HbA1c levels found in 7 subjects (7.0%) across both groups. Subjects without hypertension accounted for 72 individuals (72.0%), which was higher than those with hypertension (28 individuals, 28.0%). Similarly, subjects without dyslipidemia were more common (57 individuals, 57.0%) compared with those with dyslipidemia (43 individuals, 43.0%) among the total study population.

Statistical analysis of the frequency and distribution of Human Platelet Antigen (HPA) gene polymorphisms in macrovascular and non-macrovascular complication groups showed that among the 12 HPA polymorphism types examined, HPA types 1–5 were detected as positive, while HPA-15a and HPA-15b were not detected. The most frequent HPA genes in the macrovascular complication group were HPA-2a, HPA-4a, and HPA-5a, each identified in 49 subjects (98%). In contrast, the most frequent HPA genes in the non-macrovascular complication group were HPA-2a and HPA-4a, identified in 49 subjects (98%) and 50 subjects (100%), respectively.

Table 2. Analysis of Differences in the Frequency Distribution of HPA Gene Polymorphisms Between the Macrovascular and Non-Macrovascular Complication Groups in Type 2 Diabetes Mellitus

Variable	Type 2 Diabetes Mellitus		p-value
	Macrovascular Complications (n %)	Non-Macrovascular Complications (n %)	
HPA 1a	Negative	2 (4)	3 (6)

Variable	Type 2 Diabetes Mellitus		p-value
	Positive	48 (96)	47 (94)
HPA 1b	Negative	17 (34)	17 (34)
	Positive	33 (66)	33 (66)
HPA 2a	Negative	1 (2)	1 (2)
	Positive	49 (98)	49 (98)
HPA 2b	Negative	12 (24)	11 (22)
	Positive	38 (76)	39 (78)
HPA 3a	Negative	6 (12)	5 (10)
	Positive	44 (88)	45 (90)
HPA 3b	Negative	18 (36)	14 (28)
	Positive	32 (64)	36 (72)
HPA 4a	Negative	1 (2)	0 (0)
	Positive	49 (98)	50 (100)
HPA 4b	Negative	13 (26)	13 (26)
	Positive	37 (74)	37 (74)
HPA 5a	Negative	1 (2)	6 (12)
	Positive	49 (98)	44 (88)
HPA 5b	Negative	24 (48)	32 (64)
	Positive	26 (52)	18 (36)
HPA 15a	Negative	50 (100)	50 (100)
	Positive	0 (0)	0 (0)
HPA 15b	Negative	50 (100)	50 (100)
	Positive	0 (0)	0 (0)

*Chi-square test, *Fisher's Exact test, NA = not applicable

Based on Table 2, statistical analysis using the Chi-square test and Fisher's Exact test demonstrated a significant difference in the distribution and frequency of the Human Platelet Antigen

(HPA)-2b gene between the macrovascular complication and non-macrovascular complication groups of Type 2 Diabetes Mellitus ($p < 0.001$). The positive HPA-2b gene polymorphism was significantly more frequent among subjects with macrovascular complications (77.6%) compared with those without macrovascular complications (22.4%). These findings indicate a significant association between the HPA-2b gene polymorphism and the occurrence of macrovascular complications in patients with Type 2 Diabetes Mellitus. In contrast, the distribution of other HPA gene polymorphisms did not show statistically significant differences between the macrovascular and non-macrovascular complication groups (all $p > 0.05$). Based on these results, the HPA-2b gene polymorphism was considered eligible for inclusion in the multivariate analysis.

Table 3. Analysis of Differences in the Frequency Distribution of Risk Factors Between Macrovascular and Non-Macrovascular Complication Groups in Type 2 Diabetes Mellitus

Variable	Type 2 Diabetes Mellitus		p-value
	Macrovascular Complications (n %)	Non-Macrovascular Complications (n %)	
Age	Adult	41 (82)	43 (86)
	Elderly	9 (18)	7 (14)
Sex	Male	31 (62)	22 (44)
	Female	19 (38)	28 (56)
HbA1c Level	Controlled	4 (8)	3 (6)
	Uncontrolled	46 (92)	47 (94)
Dyslipidemia	No	21 (42)	36 (72)
	Yes	29 (58)	14 (28)
Hypertension	No	29 (58)	43 (86)
	Yes	21 (42)	7 (14)

*Chi-square test

*Fisher's Exact test

Based on Table 3 the data presented in Table 6, the Chi-square test revealed that risk factors with a significant difference in frequency distribution between the macrovascular complication group and the non-macrovascular complication group in Type 2 Diabetes Mellitus were dyslipidemia and

hypertension, with p-values of 0.002 and 0.002, respectively ($p < 0.05$). Based on these findings, the variables hypertension and dyslipidemia were considered potential confounding factors and therefore were included and controlled for in the multivariate analysis. Meanwhile, the variables age, sex, and HbA1c level did not show statistically significant differences between the two groups, with p-values of 0.585, 0.071, and 1.000, respectively ($p > 0.05$). These results indicate that the two sample groups were homogeneous in terms of age, sex, and serum HbA1c levels, and therefore these variables were not included in the multivariate analysis.

Table 4. Results of Multivariate Multiple Logistic Regression Analysis

Variable	Coefficient	p-value	OR	95% CI for OR	
				Min	Max
HPA 2b	-3.022	<0.001	0.049	0.014	0.166
Dyslipidemia	-1.745	0.005	0.175	0.051	0.596
Hypertension	-1.381	0.032	0.251	0.071	0.890

Based on Table 4, the initial bivariate analysis using the Chi-square test and Fisher's Exact test showed that only several variables met the inclusion criteria for the multivariate logistic regression analysis ($p < 0.25$). These variables included HPA-2b, HPA-5a, HPA-5b, dyslipidemia, and hypertension. Further analysis using multiple logistic regression demonstrated that variables significantly associated with the occurrence of macrovascular complications in Type 2 Diabetes Mellitus were:

1. HPA-2b gene polymorphism ($p < 0.001$)
2. Dyslipidemia ($p = 0.005$)
3. Hypertension ($p = 0.032$)

Among these variables, hypertension showed the strongest association with macrovascular complications (OR = 0.251), followed by dyslipidemia (OR = 0.175) and the HPA-2b gene polymorphism (OR = 0.049). These findings indicate that both genetic factors and metabolic risk factors contribute to the development of macrovascular complications in patients with Type 2 Diabetes Mellitus.

DISCUSSION

Environmental factors and exposure to carcinogenic agents may trigger multiple alterations in deoxyribonucleic acid (DNA). One of the most frequently encountered genetic variations is the single nucleotide polymorphism (SNP), which involves substitution of a single nucleotide within the DNA sequence and may result in amino acid changes in platelet glycoproteins. These genetic variations can be identified through sequencing techniques or molecular amplification methods. Phenotypic expression of HPA polymorphisms may be evaluated through alloantigen detection, antigen–antibody reaction assays, and platelet function testing, whereas genotypic identification is commonly performed using nucleic acid amplification techniques. Variations in HPA genes are considered important determinants of platelet function because they can modify glycoprotein expression and alter platelet membrane antigenicity. Such changes may subsequently influence platelet adhesion, activation, and aggregation processes, all of which play essential roles in the development of atherosclerosis.[14]

Previous studies have suggested that certain HPA alleles may increase susceptibility to cardiovascular disorders. Several reports have linked specific HPA variants with myocardial infarction among individuals with diabetes mellitus. In addition, a retrospective observational study involving 306 patients with ischemic stroke demonstrated that polymorphisms in the GPIIb gene were associated with ischemic stroke in young and middle-aged populations. Other investigations have also indicated that the HPA-2b allele may contribute to a greater risk of coronary heart disease and cerebrovascular disorders. The cardiovascular genome contains numerous polymorphic genes that influence individual vulnerability to cardiovascular diseases, particularly coronary artery disease. Genes involved in platelet activation and aggregation are considered important contributors to inherited susceptibility to thrombotic and vascular complications. Alterations in platelet glycoproteins and membrane receptors may substantially modify platelet function and thrombogenic potential. Therefore, the present study was conducted to evaluate the frequency and distribution of HPA gene polymorphisms in patients with macrovascular complications of Type 2 Diabetes Mellitus using the sequence-specific primer polymerase chain reaction (SSP-PCR) technique.[15]

Based on the frequency distribution analysis of hypertension status, the number of subjects without hypertension was higher than those with hypertension in both groups. However, the analysis of differences in risk factor distribution revealed a significant difference between groups, where hypertensive subjects were more likely to develop macrovascular complications compared with non-hypertensive subjects. Therefore, hypertension was included as a confounding variable in the multivariate analysis. According to previous studies, patients with diabetes mellitus frequently develop hypertension.[16] Poorly controlled hypertension accelerates renal damage and cardiovascular disorders. Conversely, effective blood pressure control may protect against both macrovascular and microvascular

complications when accompanied by adequate glycemic control. The pathogenesis of hypertension in Type 2 Diabetes Mellitus is complex and involves multiple mechanisms, including insulin resistance, hyperglycemia, obesity, and dysregulation of blood pressure autoregulation systems, such as activation of the renin angiotensin aldosterone system (RAAS).[17]

This study employed an observational analytical design using a case–control approach. The investigation was conducted to evaluate Human Platelet Antigen (HPA) genetic polymorphisms and to compare their distribution between patients with Type 2 Diabetes Mellitus (T2DM) who developed macrovascular complications and those without macrovascular complications. Analysis of HPA phenotypes was performed in T2DM patients receiving either inpatient or outpatient treatment. The research was carried out at Dr. Wahidin Sudirohusodo General Hospital, Makassar, where participant recruitment and blood sample collection were undertaken. Molecular and genetic examinations were subsequently performed at the Research Unit of the Faculty of Medicine, Hasanuddin University Teaching Hospital (RSP-UH), Makassar. Data collection and laboratory analysis were conducted during the period from September to October 2022.[19]

The study population included all patients diagnosed with Type 2 Diabetes Mellitus (T2DM), either with or without macrovascular complications, who received inpatient or outpatient treatment at Dr. Wahidin Sudirohusodo General Hospital and Hasanuddin University Hospital during the study period. Eligible participants who fulfilled the inclusion criteria were recruited as study samples and categorized into two groups. The case group consisted of patients with T2DM accompanied by macrovascular complications, whereas the control group included patients with T2DM without macrovascular complications, including those with microvascular complications or no vascular complications.[20] Participant recruitment was carried out among accessible patients who met the study requirements throughout the research period. Individuals were considered eligible if they were aged 18 years or older, had been diagnosed with T2DM with or without macrovascular complications, and agreed to participate by signing written informed consent. Participants were excluded in cases of hemolyzed or lipemic blood specimens, inability to repeat sample collection, incomplete clinical information, a history of congenital vascular abnormalities, congenital heart disease, congenital platelet dysfunction identified through medical records, or pregnancy.[21]

Platelet abnormalities identified in patients with diabetes include elevated expression of platelet membrane proteins such as P-selectin, GPIb, and GPIIb/IIIa integrins, all of which are important in platelet adhesion and thrombus development. A case–control study conducted in Croatia evaluating platelet genetic polymorphisms in ischemic stroke demonstrated that variations in HPA-1, HPA-2, and

HPA-3 were associated with an increased risk of pediatric ischemic stroke, particularly among individuals carrying the HPA-1b, HPA-1a2a3b, HPA-1b2a3a, and HPA-1b2b3a alleles. In addition, homozygous HPA-1b/b and HPA-5b/b genotypes were reported to correlate significantly with greater neurological impairment and recurrent stroke episodes. These observations suggest that HPA-1b and HPA-5b polymorphisms may serve as important genetic determinants contributing to ischemic stroke susceptibility.[12]

Several previous investigations have produced inconsistent findings regarding the relationship between HPA polymorphisms and stroke risk. Some studies reported that polymorphisms in HPA-1, HPA-2, HPA-3, and HPA-5 were not significantly associated with an increased incidence of stroke, although the frequency of the HPA-1b genotype appeared to be higher among patients with cardiovascular disease compared with healthy individuals. Genetic polymorphism refers to variations occurring at the DNA level among individuals, including differences in nucleotide sequences or DNA fragment length caused by mutations or unequal recombination events. Such genetic variations may influence phenotypic expression and increase susceptibility to specific diseases. In the present study, HPA polymorphisms involving types 1–5 were identified using the sequence-specific primer polymerase chain reaction restriction fragment length polymorphism (SSP-PCR) technique. Polymerase chain reaction (PCR) is based on the principle of exponential in vitro amplification of specific nucleotide sequences, enabling highly sensitive and specific detection of genetic polymorphisms.[21]

CONCLUSION

This study demonstrated that there was a significant difference in the frequency distribution of the HPA-2b gene polymorphism between patients with macrovascular complications and those without macrovascular complications among individuals with Type 2 Diabetes Mellitus. The frequency of the HPA-2b polymorphism was found to be higher in the group with macrovascular complications compared with the non-complication group, suggesting a potential genetic predisposition contributing to vascular complications in diabetic patients. The results of statistical analysis revealed a significant association between the HPA-2b gene polymorphism and the incidence of macrovascular complications in patients with Type 2 Diabetes Mellitus. These findings suggest that genetic variation in platelet surface glycoproteins may contribute to platelet hyperreactivity and thrombotic processes that underlie macrovascular disease in diabetic individuals. The HPA-2b gene polymorphism was identified as having a strong association with the development of macrovascular complications in type 2 Diabetes Mellitus. This result highlights the potential importance of genetic factors, particularly platelet antigen polymorphisms, in the pathogenesis of vascular complications in diabetes. The identification of such genetic markers may contribute to improved risk stratification and may provide insights for future

research aimed at developing personalized preventive and therapeutic strategies for diabetic patients at risk of macrovascular disease.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this research.

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