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HbA1c Levels Relate to the Severity of Atherosclerotic Lesions in Coronary Heart Disease Patients with Type 2 Diabetes Mellitus

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Abstract: Cardiovascular disease is one of the main causes of death in the world. In diabetes mellitus patients who experience hyperglycemia, the risk of coronary heart disease increases 2-4 times. Diabetes mellitus can be diagnosed using HbA1c examination. Coronary heart disease can be diagnosed using a coronary angiography examination, and the results are assessed using the vessel disease score. The design of this research is observational analytic with a cross-sectional approach. The research was conducted in October-December 2023 at RSU. Medan Hajj. The sample for this study was patients with coronary heart disease who had type 2 diabetes mellitus and underwent HbA1c examination and coronary angiography. Data analysis used the Mann-Whitney test. Based on data from RSU. Haji Medan obtained 23 samples, after 18 samples of multi-vessel disease were found with uncontrolled HbA1c levels, and then analysed with a result of 0.027 (p-value <0.05), which means there is a relationship between HbA1c levels and the severity of atherosclerotic lesions in disease patients. Coronary heart disease patients who have type 2 diabetes mellitus. There is a relationship between HbA1c levels and the severity of atherosclerotic lesions in coronary heart disease patients who have type 2 diabetes mellitus.

Keywords: Coronary heart disease, diabetes mellitus type 2, HbA1c, angiography

INTRODUCTION

Cardiovascular disease is one of the leading causes of death in the world. Coronary Heart Disease (CHD) is a disorder of heart function due to a lack of blood in the heart muscle, due to blockage or narrowing of the coronary blood vessels due to damage to the lining of the blood vessel walls.[1] According to the American Heart Association (AHA), Coronary Heart Disease (CHD) is a heart attack that occurs due to plaque buildup in the heart arteries.[2] The World Health Organisation (WHO) in 2021 stated that cardiovascular disease is estimated to claim the lives of 17.9 million people, as much as 32% of global deaths.[3] This number is expected to continue to increase to 23.3 million in 2030. In 2019, the Global Burden of Disease reported that

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the number of deaths in the world due to cardiovascular disease was 18.5 million (32.84%), and the number of deaths in Indonesia was 651,481 (38.19%).[4] According to the 2014 Sample Registration System survey, 12.9% of deaths were due to coronary heart disease. Based on the 2018 National Basic Health Research, the prevalence of coronary heart disease in North Sumatra Province was 1.4%.[1]

Coronary heart disease is caused by plaque buildup (atherosclerosis). Atherosclerosis can occur due to abnormally high cholesterol levels, resulting in the accumulation of cholesterol in the walls of blood vessels. This accumulated cholesterol then forms a blockage called plaque, which can gradually damage blood vessels. When plaque forms in the arteries, it can harden and narrow the lumen of the arteries, reducing blood flow to the heart muscle and leading to coronary heart disease.[5]

Coronary heart disease has risk factors that consist of non-modifiable and modifiable risk factors. Non-modifiable risk factors include age, gender, race, genetics, family history, and previous history of cardiovascular disease. Modifiable risk factors include smoking, diet, hyperglycemia, dyslipidemia, hypertension, excessive alcohol intake, physical inactivity, obesity, and stress.[4,6]

In patients with diabetes mellitus who experience hyperglycemia, the risk of coronary heart disease increases 2-4 times. Hyperglycemia is caused by insulin resistance. Insulin resistance or insulin deficiency will cause lipid metabolism disorders, hypertension, inflammation, oxidative stress, and coagulation disorders.[7] Hyperglycemia can cause microthrombi through several processes, namely increased aggregation, increased vascular permeability, increased neovascularisation, increased total cholesterol as a factor in atherogenesis, and decreased fibrinolysis.[6] Diabetes mellitus can be diagnosed using glycosylated haemoglobin A1c (HbA1c) examination. Haemoglobin A1C (HbA1c) is one of the glycated and subfractionated haemoglobins formed by the attachment of various glucose molecules to the HbA molecule, which is formed in two stages by a non-enzymatic reaction of glucose with the N-terminal amino group of the beta chain of normal adult Hb (HbA). The HbA1c test is used for diagnosis or to determine DM risk factors in patients at risk for cardiovascular diseases, such as coronary heart disease.[7] Coronary heart disease can be diagnosed using invasive and non-invasive examinations. Invasive examinations include coronary angiography using a percutaneous catheter to determine the severity of the disease.[8] Angiography results in coronary heart disease patients are assessed using a vessel disease score. Vessel disease is measured based on the number of coronary arteries that have stenosis (narrowing of the lumen) of more than 50-70%. Single vessel disease (SVD) is defined as patients with stenosis in one coronary artery, double vessel disease (DVD) is defined as patients with stenosis in two coronary

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arteries, while multiple vessel disease (MVD) is defined as patients with stenosis in three coronary arteries.[9,10]

Patients with MVD are at a higher risk of death than those with SVD. The mortality rate is significantly increased in MVD patients.[11] Another study stated that the cardiovascular mortality rate in SVD patients was 2.6% and in MVD patients was 4.9%.[9] A study by Weissler-Snir et al. stated that the 3-year mortality rate in SVD patients was 5% and in MVD patients was 5.4%.[12]

Research conducted by Tavares et al. (2018) showed that uncontrolled HbA1c experienced increased stenosis in 1 vessel, 2 vessels, and 3 vessels compared to controlled HbA1c, so that HbA1c levels were related to the severity of coronary lesions in patients with coronary heart disease.[13] Another study conducted by Park et al. (2019) also stated that uncontrolled HbA1c levels were related to increased atherosclerotic lesions.[9]

Considering the high incidence of morbidity and mortality in coronary heart disease associated with diabetes mellitus, which is expected to continue, and the lack of research on the relationship between HbA1c levels and the degree of stenosis based on single vessel disease (SVD), double vessel disease (DVD), and multiple vessel disease (MVD) in North Sumatra, researchers are interested in researching the relationship between HbA1c levels and the severity of atherosclerotic lesions in coronary heart disease patients with type 2 diabetes mellitus.

METHOD

This study design is a non-experimental observational analytic with a cross-sectional approach, where the study is conducted only through observation, without any intervention on the research subjects. The cross-sectional approach is used to determine the relationship of HbA1c levels to the severity of atherosclerotic lesions in heart disease patients with type 2 diabetes mellitus. This study was conducted from October to December 2023, and this study will be implemented in the Medical Records Installation Room of Haji Medan General Hospital. The sample of this study is coronary heart disease patients with type 2 diabetes mellitus who underwent HbA1c examination and coronary angiography. Sampling used a consecutive sampling technique until the required number of samples was met. In determining the sample size in this study, the Slovin formula method was used, and the sample size in this study was obtained as many as 23 people. The data collection technique used in this study is secondary data obtained from patient medical records from Haji Medan General Hospital. Data taken from patient medical records include age, gender, HbA1C levels, and angiography examination. After data collection and processing, the data will be analysed using univariate and bivariate analysis. Univariate analysis is conducted to describe the characteristics of the research variables. The bivariate analysis of this study uses a comparative test between two variables, namely the chi-

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square test. If it is not met, it is analysed using the Mann-Whitney test. If the p-value <0.05, then H0 is rejected and Ha is accepted, so there is a relationship between the two variables, whereas if the p-value>0.05, then H0 is accepted and Ha is rejected, so there is no relationship between the two variables.

RESULTS

Table 4.1 Patient Distribution Based on Age

Age Characteristics (Years)	Frequency (n)	Percentage (%)
40-50	3	13
51-60	9	39,1
61-70	11	47,8
Total	23	100

Based on Table 4.1 it shows that the distribution of patient characteristics based on age was found in samples aged 40-50 years, namely 3 people (13%), samples aged 51-60 years, namely 9 people (39.1%), and samples aged 61-70 years, namely 11 people (47.8%).

Table 4.2 Distribution of Patients by Gender

Gender Characteristics	Frequency (n)	Percentage (%)
Man	15	65,2
Woman	8	34,8
Total	23	100

Based on Table 4.2 it shows that the distribution of patients based on gender shows that there were 15 male samples (65.2%) and 8 female samples (34.8%).

Table 4.3 Results of HbA1c Level Examination

	Mean (%) (Standard Deviation)	Minimum-Maximum (%)
HbA1c levels	8,85 (SD 1.902)	5,7 – 12,6

Table 4.4 Distribution of HbA1c4 Levels

	HbA1c levels	Frequency (n)	Percentage (%)
HbA1c Level Overview	Controlled (<7%)	5	21, 7
	Uncontrolled (≥7%)	18	78, 3
	Total	23	100

Based on Table 4.4 shows that the description of HbA1c levels was controlled, namely 5 samples (21.7%) and the HbA1c levels were uncontrolled, namely 18 samples (78.3%).

Table 4.5 Distribution of Atherosclerotic Lesion Images

	Atherosclerotic Lesion	**Frequency (n)**	**Percentage (%)**
Atherosclerotic Lesion	*Single vessel disease*	4	17,4
	Double vessel disease	7	30,4
	Multiple vessel disease	12	52,2

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Total	23	100

Based on Table 4.5 it shows that the picture of atherosclerotic lesions in the sample shows that atherosclerotic lesions in single samples were found. Vessel disease as many as 4 samples (17.4%), double vessel disease as many as 7 samples (30.4%), and multiple vessel disease as many as 12 samples (52.2%

Table 4.6 Relationship between HbA1c Levels and the Severity of Atherosclerotic Lesions

		Atherosclerotic Lesions						Total		*p-value*
		SVD		DVD		MVD				
		N	%	N	%	N	%	N	%	
HbA1c levels	Uncontrolled (<7%)	3	13,1	1	4,3	1	4,3	5	21,7	0,027
	Uncontrolled (≥7%)	1	4,3	6	26,1	11	47,9	18	78,3	
	Total	4	17,4	7	30,4	12	52,2	23	100	

Based on table 4.6 it shows that from 23 samples, it was found that patients with controlled HbA1c levels had stenosis in single vessel disease in 3 people (13.1%), double vessel disease in 1 person (4.3%) and multiple vessel disease in 1 person (4.3%), while in patients with uncontrolled HbA1c levels, stenosis was found in single vessel disease in 1 person, (4.3%) double vessel disease in 6 people (26.1%) and multiple vessel disease in 11 people (47.9%).

Based on Table 4.6, the Mann-Whitney statistical test results show an Asymp. Sig (2-tailed) of 0.027 (p-value <0.05), which means there is a significant relationship between HbA1c levels and the severity of atherosclerosis lesions.

DISCUSSION

From the results of a study conducted on 23 samples of coronary heart disease patients at RSU. Haji Medan, the results obtained based on Table 4.1 found that the most patients experiencing coronary heart disease were aged 61-70 years, namely 11 people (47.8%) and the fewest were aged 40-50 years, namely 3 people (13%). This is in accordance with the 2018 RISKESDAS statistical data showing that coronary heart disease patients are more common in the age of 61-70 years, namely 4.6% while in the age of 40-50 years, namely 2.4%.[1] This study is in line with the study of Rahayu et al. (2021) that the most coronary heart disease patients were aged 61-70 years, namely 29 people (59.2%), aged 51-60 years, namely 13 people (26.5%) and aged 40-50, namely 7 people (14.3%).[13]

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Research conducted by Suciana et al. (2021) also showed that most coronary heart disease patients were aged ≥ 60 years, namely, there were 37 patients, while 13 were under 60 years old. This indicates that age is a risk factor for coronary heart disease.[14]

A study by Ruiz et al. (2020) stated that the development of atherosclerosis accelerates with age. This study explains that ageing results in a significant increase in plaque and necrotic core, indicating an effect associated with the development of atherosclerosis. The impact of ageing on patients is twofold more severe. This is explained by changes in vascular endothelial function and thrombogenesis. Impaired thrombogenesis disrupts fibrinolytic activity and the coronary vasodilation response. Therefore, in old age, there is an increase in circulating fibrinogen, which leads to reduced blood flow within the blood vessels.[15]

Table 4.2 shows that most coronary heart disease patients were men (15 patients (65.2%), compared to women (8 patients (34.8%). This is in line with research conducted by Bachtiar et al.). (2023) also showed that coronary heart disease was more common in men, namely 54 people (58.1%), compared to women, namely 39 people (41.9%).[6] Another study conducted by Amisi et al. (2021) showed that there were more male patients, namely 75 people (75%), while women were 25 people (25%).[16] This shows that the percentage of coronary heart disease sufferers in men is higher than in women. In addition, other literature also states that men have a risk of coronary heart disease 2 times greater than women at the age of 55-64 years. Before menopause, women's chances of developing coronary heart disease are smaller than men's because women's blood vessels are protected by the protective hormone estrogen. The hormone estrogen can reduce oxidative stress by increasing superoxide dismutase expression and inhibiting NADPH oxidase activity. Furthermore, the hormone estrogen increases the ratio of high-density lipoprotein (HDL), which is a protective factor in preventing atherosclerosis [17]

Table 4.4 shows that the distribution of uncontrolled HbA1c levels is most commonly found in coronary heart disease patients with type 2 diabetes mellitus. This is consistent with research conducted by Mhlaba et al. (2023), which showed that uncontrolled HbA1c levels were more common in 196 patients (74.8%) compared to controlled HbA1c levels in 66 patients (25.2%).[18] Furthermore, research conducted by Chen et al. (2021) also showed that uncontrolled HbA1c levels were more common than controlled HbA1c levels in coronary heart disease cases.[19] Table 4.5 shows that stenosis in multi-vessel disease is more common than stenosis in single or double vessel disease. This is consistent with previous research that found stenosis is more common in multi-vessel disease.[9,12]

Based on the statistical analysis in Table 4.6 using the Mann-Whitney test, a significant result was obtained with a p-value of 0.027. This indicates a significant

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relationship between HbA1c levels and the severity of atherosclerotic lesions in coronary heart disease patients with type 2 diabetes mellitus. This study found that the majority of multi-vessel disease cases occurred with uncontrolled HbA1c levels. This is consistent with research conducted by Tavares et al. (2018), which showed that 10 patients with uncontrolled HbA1c levels experienced stenosis in three vessels, while 6 patients with controlled HbA1c levels experienced stenosis in three vessels. This study indicates that uncontrolled HbA1c levels increase the degree of stenosis in atherosclerotic lesions.[12] Furthermore, another study conducted by Park et al. (2019) also showed that uncontrolled HbA1c levels experienced stenosis in 63 individuals with single-vessel disease and 21 individuals with multi-vessel disease, while controlled HbA1c levels experienced stenosis in 54 individuals with single-vessel disease and 20 individuals with multi-vessel disease.[9] Furthermore, this table also shows that uncontrolled HbA1c levels experienced stenosis in 1 individual with single-vessel disease, while controlled HbA1c levels experienced stenosis in 3 individuals with single-vessel disease. This indicates that controlled HbA1c levels experience minimal stenosis in atherosclerotic lesions.

Endothelial dysfunction plays a crucial role in the development of atherosclerosis. There is a significant relationship between diabetes mellitus, oxidative stress, and endothelial dysfunction. In uncontrolled diabetes mellitus, oxidative stress increases due to chronic hyperglycemia. Increased oxidative stress can affect vascular endothelial cells, including membrane lipid peroxidation, transcription factor activation (NF-κB), and the formation of glycation products. Activation of the receptor for advanced glycation end products (RAGE) in blood vessels increases. This condition is a product of the reaction of glucose binding to proteins and lipids. The interaction between AGEs and their receptors can trigger inflammatory and thrombolytic reactions, which play a crucial role and are considered mediators of atherogenesis. Furthermore, selective insulin resistance in endothelial cells leads to decreased nitric oxide (NO) production and increased endothelin-1 production from the endothelium, resulting in endothelial dysfunction. Endothelial dysfunction is caused by the inability of endothelial cells to maintain vascular homeostasis due to a disruption in the balance between endothelial-derived proatherosclerotic factors and anti-atherosclerotic factors that support proatherosclerotic factors, leading to the initiation and progression of atherosclerosis. Nitric oxide released from the endothelium has various antiatherosclerotic effects, such as vasodilation, inhibition of vascular smooth muscle cell proliferation, inhibition of leukocyte adhesion, and inhibition of platelet adhesion and aggregation. Therefore, endothelial dysfunction is influenced by decreased

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nitric oxide, which results in reduced nitric oxide bioavailability which resulting in increased atherosclerotic lesions. [20,21]

Uncontrolled diabetes mellitus can lead to an increased incidence of multivessel disease. This is because hyperglycemia causes changes in blood vessel tissue that can potentially accelerate atherosclerosis, including non-enzymatic protein and lipid glycosylation, oxidative stress, and activation of protein C-kinase. Furthermore, endothelial dysfunction, platelets, lipoproteins (especially LDL), and coagulation are major contributors to the increase in multivessel disease in diabetic patients. Uncontrolled diabetes mellitus will result in an increase in pro-inflammatory CRP (C-Reactive Protein) levels in patients with coronary heart disease. CRP activates macrophages and T lymphocytes, fixes, and modulates platelet activation. Furthermore, hyperglycemia causes excessive proinflammatory phospholipid synthesis and coagulation activation, leading to multivessel disease in uncontrolled diabetic patients [22,23]

CONCLUSION

Based on the results of research conducted at RSU Haji Medan regarding the relationship between HbA1c levels and the severity of atherosclerotic lesions in coronary heart disease patients with type 2 diabetes mellitus. There is a significant relationship between HbA1c levels and the severity of atherosclerotic lesions in coronary heart disease patients with type 2 diabetes mellitus with a p-value of 0.027.

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