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By Andi Renny Amita

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Andi Renny Amita[1,2], Husaini Umar[1,2], Pendrik Tandean[1,2], Syakib Bakri[1,2], Wasis Udaya[1,2], Andi Alfian Zainuddin[2,3]

[1]Department of Internal Medicine, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

[2]"Dr. Wahidin Sudirohusodo" General Teaching Hospital, Makassar, Indonesia

[3]Department of Public Health and Community Medicine, Faculty of Medicine, Hasanuddin University Makassar, Indonesia

Andi Renny Amita **ORCID ID:** 0009-0009-5095-1385

Corresponding author:
Andi Renny Amita
Email: rennyamita88@gmail.com

ABSTRACT

Background and aim. Patients with type 2 diabetes mellitus (DM) have a higher chance of acquiring cardiovascular illnesses, particularly Acute Coronary Syndrome (ACS), than those without DM. For people with type 2 diabetes, cardiovascular problems are the main cause of morbidity and death. This study aims to explore the relationship between patients with type 2 DM and ACS during therapy and their blood glucose levels and HbA1c at admission.

Methods. This is a retrospective cohort study of type 2 DM and ACS patients. Data was obtained from patient's medical records at the Central General Hospital (RSUP) "|Dr. Wahidin Sudirohusodo" Makassar from January 2023 until the sample size was fulfilled.

Results. Patients with type 2 DM and ACS had their blood glucose levels and HbA1c upon admission correlated with arrhythmias, according to a statistical test. The blood glucose level (BGL) of the patient with arrhythmia had a p-value of 0.370 ($p>0.05$) at admission, while the HbA1c had a p-value of 0.390 ($p > 0.05$) at the same time. When the patient with CHF was admitted, the p-value for BGL was 0.423 ($p>0.05$), and the p-value

for HbA1c was 0.763 ($p > 0.05$). In patients who had died, the p-value of HbA1c upon admission was 0.037 ($p < 0.05$), whereas the p-value of BGL was 0.513 ($p > 0.05$).

Conclusions: In patients with T2DM and ACS, there is a correlation between HbA1c and death; however, there is no correlation between blood glucose levels at admission and arrhythmia, CHF, or mortality.

Keywords: diabetes mellitus, glucose levels, HbA1c, ACS

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic illnesses that lead to hyperglycemia due to decreased insulin production, insulin action, or both, and includes type 1 DM, type 2 DM, and additional kinds of DM. Type 1 diabetes mellitus is defined by absolute insulin deficiency, whereas type 2 diabetes mellitus is the most common type, and it is produced by a variety of processes including abnormalities in insulin action and function, as well as other chronic hyperglycemic variables. Meanwhile, gestational diabetes is hyperglycemia which arises during pregnancy [1].

Diabetes mellitus affects 537 million persons globally, with 95% having type 2 diabetes. In 2019, Indonesia has the seventh-highest diabetes prevalence in the world, with 10.7 million people affected. Diabetes mellitus was among the top three causes of death in Indonesia in 2017 [2].

Type 2 DM is caused by eleven underlying pathomechanisms known as "The Egregious Eleven" concept, with the two main mechanisms being insulin resistance in muscle and adipose tissue, as well as impaired insulin production due to pancreatic beta cell defects as a negative impact of beta cell compensation for prolonged insulin resistance. Other pathomechanisms that play a role in decreased incretin effect include pancreatic alpha cell defect, increased hepatic glucose production, increased brain dopamine and appetite, abnormalities in gut GLP-1 secretion due to microbiome imbalance, chronic inflammation, increased gastrointestinal glucose absorption, and increased renal glucose absorption [3].

Type 2 diabetes was diagnosed using blood glucose and HbA1c tests on venous blood [4]. The American Diabetes Association's (ADA) diagnostic criteria for diabetes mellitus [5]:

1. Patients with classic symptoms of polydipsia, polyuria, or polyphagia with a blood glucose ≥ 200 mg/dl (11.1 mmol/L), or
2. HbA1C ≥ 6.5% or

3. Fasting blood glucose (GDP) ≥126 mg/dl (7 mmol/L) in the absence of caloric intake for at least about 8 hours, or
4. Oral glucose tolerance (TTGO) or 2-hour post prandial blood glucose (GD2PP) ≥ 200 mg/dl (11.1 mmol/L) (test is performed by giving 75 g of glucose dissolved in water).

Diabetes management consists of a healthy lifestyle and pharmaceutical therapies using oral (OHO) and/or injectable anti-hyperglycemic medications, either alone or in combination. Biguanide and thiazolidinedione increase insulin sensitivity; sulfonylurea and glinide increase pancreatic insulin secretion; GLP-1 analogs and DPP-4 inhibitors increase insulin secretion while reducing glucagon secretion; alpha glucoside inhibitors inhibit intestinal glucose absorption; and SGLT-2 inhibitors excrete glucose through urine [6].

Insulin injection is recommended for HbA1c >9% or <7.5% after using one or two anti-diabetic drugs, rapid weight loss, severe hyperglycemia with ketosis, hyperglycemia crisis, failure with optimal doses of combination, severe stress such as systemic infection, major surgery, acute coronary syndrome, pregnancy with uncontrolled DM, severe renal or hepatic impairment [7].

Persistent hyperglycemia in DM can lead to a variety of acute and chronic complications. Furthermore, type 2 diabetes can result in a number of chronic microvascular problems, including nephropathy, neuropathy, and retinopathy, as well as chronic macrovascular complications such cardiovascular disease, peripheral artery disease, and cerebrovascular disease. It is estimated that 1.4-1.7% of diabetic adults experience cardiovascular disease every year, and 75% of death in type 2 DM patients are caused by cardiovascular disease [8,9].

The aim of this study is to investigate into the association between patients with type 2 DM and ACS during treatment and their blood glucose levels and HbA1c at admission.

MATERIALS AND METHODS

This research includes patients with type 2 DM and ACS and uses an observational, retrospective cohort methodology. From January 2023 until the sample size was met, information was obtained from patient medical records at the Central General Hospital (RSUP) by "Dr. Wahidin Sudirohusodo" Makassar. All patients receiving treatment at the hospital and diagnosed with ACS comprised the target population. Patients with ACS and type 2 diabetes who are 40 years of age or older and who have

completed blood glucose and HbA1c testing at the time of admission considered the inclusion criteria. Individuals having a history of long-term steroid usage, individuals with a history of malignancy diagnosis, and patients with missing data from their medical records on independent and outcome factors are all considered exclusion criteria. Consecutive sampling was used in this study for obtaining secondary data; subjects who met the selection criteria and were enrolled in the study in the appropriate order were included until the requisite number of subjects was reached. Predetermined criteria were used to choose the study's subjects.

RESULTS

Characteristics of the study population

The study involved 136 subjects that fulfilled the inclusion criteria. 93 subjects were male (68.38%) and 43 were female (31.62%). Subject characteristics are shown in Table 1.

Table. 1 Characteristics of the study

Variable	N	Result
Age, mean ± SD	136	60.16 ± 8.90
Weight, mean ± SD	112	64.50 ± 10.61
Height, mean ± SD	112	160.88 ± 6.74
IMT, mean ± SD	110	24.72 ± 3.34
Admission blood glucose, mean ± SD	136	249.76 ± 89.85
GDP, mean ± SD	132	192.93 ± 72.99
HbA1C, mean ± SD	133	9.16 ± 2.16
EF, mean ± SD	132	42.10 ± 9.26
Sex, n (%)	136	
male		93 (68.38%)
female		43 (31.62%)
Arrhthmia, n (%)	136	
yes		53 (38.97%)
no		83 (62.03%
CHF, n (%)	136	
yes		115 (84.6%)
no		21 (15.4%)
Mortality, n (%)	136	
yes		7 (5.14%)
no		129 (94.86%)

Association between blood glucose and HbA1c levels at admission with arrhythmia

This study analyses the association between BGL and HbA1c at admission with arrhythmia in patients with ACS. The proportion of arrhythmia occurrence based on BGL

at admission and HbA1c were follows: BGL admission ≤140 mg/dl (7 subjects, 13.2%), and ≥140 mg/dl (77 subjects, 92.8%); HbA1c ≤7.0% (9 subjects, 9%), and ≥7% (44 subjects, 87%) which is not significant statistically (p>0.05).

Table. 2 Association between Blood Glucose and HbA1c Levels at Admission with Arrhythmia

Variable	Arrhythmia				p*
	yes		tno		
	n	%	n	%	
BGL Admission					
≤140 mg/dl	7	13.2%	6	7.2%	0.370
≥140 mg/dl	77	92.8%	46	86.8%	
HbA1c					
≤7.0%	9	17.0%	20	24.1%	0.390
≥7.0%	44	83%	63	75.9%	

*Chi Square test

Association between Blood Glucose Level and HbA1c at admission with CHF

This study analyses the association between BGL and HbA1c at admission with CHF incidence in ACS patient. The proportions of CHF incidence based on BGL and HbA1c at admission were follows: BGL admission ≤140 mg/dl (10 subjects, 8.7%), and ≥140 mg/dl (105 subjects, 91.3%); HbA1c of patients with CHF had HbA1c levels ≤7.0% (15 subjects, 20.3%), and ≥7% (59 subjects, 79.7%), which is not significant statistically (p>0.05).

Tabel. 3 Association between Blood Glucose Level and HbA1c at admission with CHF

Variable	CHF				p*
	yes		no		
	n	%	n	%	
BGL Admission					
≤140 mg/dl	10	8.7%	3	14.3%	0.423
≥140 mg/dl	105	91.3%	18	85.7.%	
HbA1c					
≤7.0%	23	20.4%	3	15.0%	0.763
≥7.0%	90	79.6%	17	85.0%	

Association between blood glucose level and HbA1c at admission with patient's mortality

This study analyses the association between BGL and HbA1c at admission with mortality in patients with ACS. The proportion of mortality based on admission BGL and

HbA1c is admission BGL ≤140 mg/dl 1 person (14.3%) and ≥140 mg/dl 6 (85.7%), HbA1c ≤7.0% as many as 4 people (57.1%), and HbA1c ≥7% as many as 3 people (42.9%) where statistically significant HbA1c value (p<0.05).

Table. 4 Association between Blood Glucose Level at Admission and HbA1c with Patient's Mortality

Variabel	Mortality				p*
	yes		no		
	n	%	n	%	
BGL Admission					
≤140 mg/dl	1	14.3%	12	9.3%	0.513
≥140 mg/dl	6	85.7%	117	90.7%	
HbA1c					
≤7.0%	4	57.1%	25	19.4%	**0.037**
≥7.0%	3	42.9%	104	80.6%	

DISCUSSION

Characteristics of the study population

This study investigates the relationship between admission blood glucose levels and clinical outcomes such as mortality, arrhythmia, and CHF in DM patients with ACS. Since January 2023, 136 DM patients with ACS have been hospitalized at "Dr. Wahidin Sudirohusodo" Hospital.

The mean age of the subjects in this study was 60.16 ± 8.90 years. The majority of the samples in this study were male as many as 93 samples (68%). The study found that the average HbA1c level was 9.16 ± 2.16, indicating uncontrolled diabetes mellitus.

Furthermore, the mean admission blood glucose profile level was 249.76 ± 89.85 mg/dl. The results of sample characteristics based on clinical outcomes are the presence of arrhythmias in 53 samples (38.97%), CHF in 74 samples (54.41%) with a mean EF of 42.10 ± 9.26. While for the incidence of mortality in this study there were 7 samples (5.14%).

Association between blood glucose level and HbA1c at admission with arrhythmia

In the statistical analyses evaluating the correlation between blood glucose level and HbA1c at admission with the incidence of arrhythmias in type 2 diabetes mellitus patients hospitalized with acute coronary syndrome, The results revealed that the p-value of BGL upon admission was 0.370 > 0.05, while the p-value of HbA1c at admission was 0.390 >

0.05, so it can be concluded that there is no association between blood glucose at admission and HbA1c with the incidence of arrhythmias.

Clinically, blood glucose levels >140 mg/dl upon admission were linked to a high incidence of arrhythmia at 92.8%, or 46 respondents, despite not being statistically significant. In contrast, among respondents with glucose levels <140 mg/dl, only 13.2%, or 7 respondents, suffered arrhythmia.

This investigation is consistent with a study in 2020 by Sally et al., that reported at 110 ACS samples that had arrhythmias and hyperglycemia. The study's conclusions showed that among ACS patients, there was no discernible relationship between the incidence of arrhythmias and acute hyperglycemia [10]. However, the findings of this inquiry do not align with those of earlier research, such as a study by Mohaved et al. (2005) on a large sample that found that DM is a separate risk factor for the incidence of flutter and atrial fibrillation [11].

In addition, a different study by Hoang V et al. (2018) revealed that, in comparison to patients with normoglycemia, patients with high blood glucose levels onto hospital admission had a considerably higher risk of VT during hospitalization [11,12].

There are multiple explanations for the correlation between arrhythmias and hyperglycemia. Ventricular arrhythmias can arise from hyperglycemia due to poor ventricular repolarization, which prolongs the QT interval. Cardiac arrhythmias like atrial fibrillation can also be brought on by the oxidative stress that leads to the generation of inflammatory cytokines in hyperglycemia. In certain forms of ACS, hyperglycemia is also linked to bigger infarct sizes, which increases the risk of arrhythmias and worse outcomes. Furthermore, the hyperosmolar condition associated with hyperglycemia might modify myocytes' electrical activity, which can result in arrhythmias [13].

Levels of glycosylated hemoglobin (HbA1c) have also been examined as an alternative prognostic indicator for patients with ACS. Contrary to admission blood glucose levels, investigations on HbA1c have yielded inconsistent findings. In a study published in 2022, Chan et al. examined individuals with diabetes and ACS and found no correlation between HbA1c levels and arrhythmias or other short-term (up to six months) outcomes in ACS patients [14].

Association between blood glucose level and HbA1c at admission with CHF

As a result of the statistical analyses conducted on type 2 DM patients hospitalized with ACS, it was determined that there was no correlation between the incidence of heart failure and the levels of blood glucose and HbA1c at admission. Specifically, the p-value

of BGL at admission was 0.370 > 0.05, while the p-value of HbA1c at admission was 0.390 > 0.05.

Clinically, blood glucose levels >140 mg/dl at admission were linked to a higher incidence of heart failure (91.3% or 105 respondents) even though the association was not significant statistically. In contrast, blood glucose levels <140 mg/dl were linked to 85.7% or 18 respondents having heart failure. According to earlier research, a patient's blood glucose level upon hospital admission is thought to be a reliable indicator of heart failure due to a variety of biomechanisms. Barsheset et al. (2006) emphasized on how hyperglycemia can worsen heart failure through multiple distinct routes in a different study. First, hyperglycemia causes endothelium and vascular smooth muscle cells to create reactive oxygen species and diminish nitric oxide, compromising endothelial function. Secondly, elevated blood sugar levels may indicate an insulin shortage, which is linked to heightened lipolysis and increased free fatty acids. This can cause toxicity inside the damaged myocardium and could result in myocyte membrane damage, calcium excess, and arrhythmias. Finally, hyperglycemia alters the extracellular matrix of the heart, impairing relaxation and increasing ventricular stiffness. These effects worsen diastolic dysfunction independently of left ventricular systolic dysfunction. Sarcoplasmic reticulum calcium-adenosine triphosphatase (SERCA) expression and function are also compromised by hyperglycemia. Finally, hyperglycemia may hasten atherosclerosis and encourage platelet-dependent thrombosis [15].

Association between blood glucose level and HbA1c at admission with mortality

The results of the statistical analyses examining the association between admission BGL and HbA1c with mortality in patients with type 2 DM who were admitted with ACS revealed that admission BGL had a p-value of 0.513 > 0.05 and admission HbA1c had a p-value of 0.037 < 0.05. Based on these findings, it can be concluded that admission blood glucose has no correlation with mortality, but admission HbA1c occurs.

The results of this study have been validated by some studies, one of which was conducted by Benamer et al. (2015) that found no statistically significant difference in mortality between patients whose blood glucose levels at hospital admission were less than 140 mg/dL and those whose blood glucose levels were more than that. The lack of an association between blood glucose level and mortality in our study can be explained by some factors. Firstly, fasting blood glucose samples rather than the present blood glucose level were utilized as a predictor of death based on many previous studies. Second, this lack of effect could be attributed to the fact that there were fewer patients

with blood glucose levels less than 140 mg/dL (n=29) than patients with blood glucose levels greater than that (n=91). Although this study found that blood glucose before admission and average blood glucose during hospitalization were related with greater complication rates both before and after hospitalization [16].

Hyperglycemia may worsen cardiac injury and impair prognosis in people with ACS through a number of pathways. First, by producing free radicals, hyperglycemia causes oxidative stress that damages the cells of the heart. Moreover, hyperglycemia has been proven to affect cardiac contractility, decrease shock and end-diastolic volume, and increase osmotic diuresis and circulating volume, all of which may lead to a rise in mortality [16].

A different study by Rina et al. (2012) found no connection between blood glucose levels and mortality in patients who had both diabetes mellitus and acute coronary syndrome. Furthermore, the study discovered that in individuals with ACS and DM, blood glucose levels cannot be used as a predictor of mortality [17].

CONCLUSION

It was established that there was an association between HbA1c and mortality in patients with Type 2 diabetes and Acute Coronary Syndrome (ACS). Hyperglycemia causes oxidative stress by creating free radicals, which leads to cardiac cellular damage and increases the chance of death in ACS patients. Otherwise, there was no correlation between current blood glucose at admission and arrhythmia, CHF, or death in patients with Type 2 diabetes and Acute Coronary Syndrome (ACS).

Conflict of interest:

The authors certify that they have no financial relationships (such as stock ownership, consulting, equity interests, patent/licensing arrangements, etc.) that could present a conflict of interest with the work that was turned in.

Author's contributions:

AR implies idea, design, sources, materials, preparation and collection of data, interpretation and analysis, literature search, and manuscript writing. HU: Idea, Planning, Guidance, and Literature Review. Principle, Theory, Supervision, Literature Review). SB stands for Concept, Design, Supervision, Interpretation and Analysis, and Literature Search. WU (Idea, Planning, Assessment). AZ (Idea, Planning, Study and Interpretation, Evaluation).

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