Glycemic Gap, Clinical, Angiographic Characteristics and In-hospital Outcomes of Diabetic Patients Presenting with Acute Coronary Syndrome undergoing Primary Percutaneous Coronary Intervention

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Abstract

Background and objectives: a number of severe illnesses have been linked to the glycemic gap which is the difference between estimated average glucose and blood glucose at admission as a potential prognostic indicator, it's function in individuals with acute coronary syndrome is still unclear, nevertheless, this study aims to evaluate the glycemic gap in acute coronary syndrome patients as well as its correlation with clinical outcomes, including length of hospital stay and occurrence of complications.

Methods: Between January 1st and April 1st, 2023, we performed a prospective cohort study with 100 patients who were admitted with acute coronary syndrome at Surgical Specialty Hospital, Erbil Cardiac Center, a glycemic gap calculation was made, the clinical outcomes were evaluated and the prognostic importance of the glycemic gap was ascertained by multivariate analysis.

Results: Mean age was 61.77 ± 10.44 years, with 55% being male and 45% female, the mean admission blood glucose level was 256.47 ± 63.90 mg/dL, mean glycemic gap was 77 ± 61 mg/dl, and the mean HbA1c level was $7.8\% \pm 0.82\%$, there was no significant difference between the two groups admission random blood glucose levels ($p = 0.789$), but diabetic patients who encountered major adverse cardiac events had a substantially higher glycemic gap than those who did not ($p < 0.001$).

Conclusion: Based on our research, patients with acute coronary syndrome may benefit from using the glycemic gap as a useful prognostic indicator, in the regular treatment of acute coronary syndrome patients.

Keywords: Acute coronary syndrome, Diabetes, Glycemic gap, Hyperglycemia, Major adverse cardiac events

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Introduction

Coronary heart disease is the leading cause of death worldwide, acute coronary syndrome encompasses a range of clinical conditions from ST-elevation myocardial infarction to non-ST-elevation myocardial infarction and unstable angina.[1,2] Coronary artery disease has several well-established risk factors, including smoking, family history, hypertension, obesity, diabetes, lack of exercise, stress, and hyperlipidemia.[3,4] Acute hyperglycemia is frequently observed in both diabetic and non-diabetic patients presenting to the emergency department with acute coronary syndrome. While the prognostic significance of hyperglycemia in non-diabetic patients with acute coronary syndrome is well established, it remains controversial in diabetic patients, particularly in the short term.[5,6] In diabetic patients, hyperglycemia is a primary characteristic that may be observed independently of stressful events due to various causes such as poor glycemic control.[7] Chronic hyperglycemias is linked to long-term dysfunction, damage, and failure of several organs, particularly the nerves, kidneys, eyes, heart, and blood vessels.[8] Hyperglycemia is a common finding in patients presenting with acute coronary syndrome, even among those without pre-existing diabetes. This acute hyperglycemic response, often termed stress hyperglycemia, results from the release of counter-regulatory hormones such as catecholamine, cortisol, and growth hormone during the acute stress of myocardial infarction. These hormones enhance gluconeogenesis and glycogenolysis while impairing insulin secretion and sensitivity, leading to elevated blood glucose levels.[9,10] Importantly, stress hyperglycemia has been associated with worse outcomes in acute coronary syndrome, including increased mortality, larger infarct size, and a higher incidence of heart failure and arrhythmias.[11] Managing patients with acute coronary syndrome often involves addressing various risk factors, including blood glucose levels, hyperglycemia on admission is a common finding in acute coronary syndrome patients and has been associated with poorer outcomes, regardless of diabetic status.[12] The glycemic gap, defined as the difference between admission blood glucose levels and estimated average glucose (derived from glycated hemoglobin, HbA1c), has emerged as a potential marker for stress hyperglycemia, unlike simple hyperglycemia.[13] The prognostic significance of admission hyperglycemia in acute coronary syndrome has been emphasized by several studies. However, the glycemic gap may offer superior prognostic accuracy by differentiating between chronic hyperglycemia and acute, stress-induced hyperglycemia, this distinction is crucial as stress hyperglycemia has been linked to adverse outcomes such as increased infarct size, arrhythmias, and mortality, understanding the role of the glycemic gap could thus refine risk stratification and guide more personalized management strategies in acute coronary syndrome patients.[14] This study aims to evaluate the glycemic gap in patients with acute coronary syndrome and investigate any possible associations with clinical outcomes. In particular, we aim to ascertain whether longer hospital admissions, and other unfavorable outcomes are linked to a higher glycemic gap.

Patients and methods

This prospective cohort study was conducted at emergency department of Surgical Specialty Hospital, Erbil Cardiac Center, spanning from January 1st to April 1st, 2023. The study was approved by Kurdistan Higher Council of Medical Specialties (No. 1856 on November 1, 2023) after meeting ethical requirements., and the need for informed consent was waived due to the prospective nature of the analysis. Inclusion criteria included adults aged 18 years and older, admitted with a diagnosis of acute coronary

syndrome, including unstable angina, non-ST elevation myocardial infarction, or ST-elevation myocardial infarction, admission blood glucose and HbA1c levels were measured within the first 24 hours of hospital admission. Exclusion criteria were known history of type 1 diabetes, non-diabetic, pregnant women, those with hemodynamic instability, and those with hemoglobinopathies were excluded from the study, and incomplete medical records or missing data necessary for calculating the glycemic gap. Demographic information age, sex, BMI, history of diabetes, hypertension, dyslipidemia, smoking status, previous cardiovascular events, type of acute coronary syndrome, presenting symptoms, initial treatment strategies, laboratory values admission blood glucose, HbA1c, lipid profile, renal function tests. The glycemic gap was calculated as the difference between admission blood glucose levels and the estimated A1c-Derived Average glucose level (ADAG). The ADAG was calculated using the following formula based on HbA1c levels.[15] ADAG (mg/dL) $=28.7 \times$ HbA1c (%) -46.7. Glycemic Gap (mg/dL) = Estimated Blood Glucose (mg/dL) − ADAG (mg/dL). The outcome was Length of hospital stay, incidence of major adverse cardiovascular events, such as recurrent myocardial infarction, heart failure, arrhythmias, and stroke, the characteristics and results of the patients were summed together using descriptive statistics. When applicable, the means ± standard deviations or medians with interquartile ranges were used to display continuous variables. Comparisons between groups (e.g., high vs. low glycemic gap) were performed using the chi-square test for categorical variables and the t-test or Mann-Whitney U test for continuous variables, multivariate logistic regression analysis was conducted to identify independent predictors of occurrence of complications and in hospital stays, all statistical analyses were performed using [statistical software, e.g., SPSS, S 26], with a p-value of <0.05 considered statistically significant. The ethics committee of the Kurdistan Higher Council Board for Medical Specialization approved the study (No. 1856 on November 1, 2023), the investigator approached each patient separately, written informed consent was obtained from the patients after they had been told about the nature of the study, confidentiality was assured.

Results

A total of 100 diabetic patients with acute coronary syndrome were included in the study, the mean age was 61.77 ± 10.44 years, with 55% being male and 45% female, the mean admission blood glucose level was 256.47 ± 63.90 mg/dL, and the mean HbA1c level was $7.8\% \pm 0.82\%$, the mean glycemic gap was 77 ± 61 mg/dL, patients were stratified into two groups based on the median glycemic gap value high glycemic gap >77 mg/dL and low glycemic gap ≤77 mg/dL, patients with a high glycemic gap had a longer median hospital stay compared to those with a low glycemic gap 7 days vs. 4 days, p < 0.01, the incidence of major adverse cardiac events was higher in the high glycemic gap group compared to the low glycemic gap group 18% vs. 8%, p < 0.01, this included recurrent myocardial infarction 6% vs. 2%, p < 0.05, heart failure 12% vs.6%, p < 0.05, and arrhythmias 5% vs.3%, p < 0.05,Table(2)and(3),Figure(1).According to Table (1), there was no significant difference between the two groups admission random blood glucose levels (p = 0.789), but diabetic patients who encountered major adverse cardiovascular events had a substantially higher glycemic gap than those who did not (p < 0.001).

Table (1): Relationship between MACE and different glycemic measures (n = 100)

Variable	With MACE (n:28)	Without MACE (n:72)	p value
RBS mg/dl Mean ± SD	288.65 ± 58.19	282.76 ± 54.43	0.789
Glycemic gap (mg/dl) Mean ± SD	102.38 ± 44.36	56.45 ± 33.28	<0.001

Table (2): The glycemic gap value and the incidence of MACE with ACS showed a strong positive correlation

Correlations		glycemic gap
glycemic gap	Pearson Correlation	1
	Sig. (2-tailed)	
	N	100
MACE	Pearson Correlation	-.909-**
	Sig. (2-tailed)	.000
	N	100
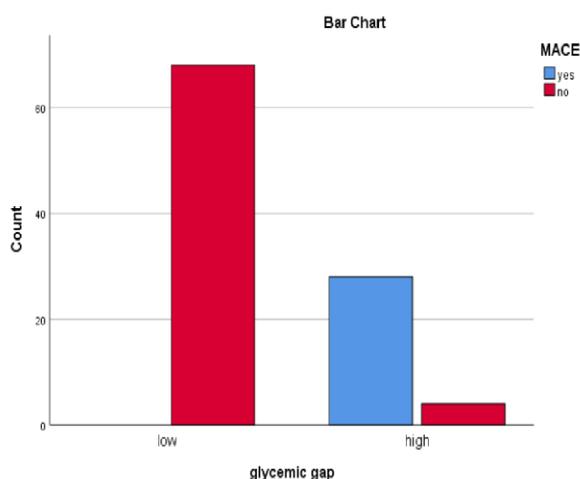
Figure (1): Correlation is significant at the 0.01 level (2-tailed).

Table (3): In diabetic patients with ACS, there was a significantly negative relationship between HbA1c levels and the incidence of MACE

Correlations		HbA1c	MACE
HbA1C	Pearson Correlation	1	-.138-
	Sig. (2-tailed)		.170
	N	100	100
MACE	Pearson Correlation	-.138-	1
	Sig. (2-tailed)	.170	
	N	100	100

Discussion

Our study demonstrates that a higher glycemic gap is significantly associated with increased incidence of major adverse cardiovascular events and a longer hospital stays with acute coronary syndrome, these findings underscore the prognostic value of the glycemic gap, a marker that reflects acute stress hyperglycemia, in the acute management of ACS. The association between admission hyperglycemia and adverse outcomes in ACS has been well-documented, conducted a systematic review highlighting that hyperglycemia on admission is a predictor of increased mortality and complications in both diabetic and non-diabetic patients with myocardial infarction.[16] Similarly, Kosiborod et al. found that elevated blood glucose levels at the time of admission were independently associated with a higher risk of mortality and heart failure in ACS patients.[17] The glycemic gap, which explains both acute and chronic glycemic regulation, is the focus of our study, this approach allows for a more precise evaluation of hyperglycemia's impact. Marfella et al. demonstrated that stress-induced hyperglycemia, rather than chronic hyperglycemia alone, is a critical determinant of adverse outcomes in ACS, the glycemic gap helps to differentiate between these two states, providing a more accurate risk

stratification tool acute hyperglycemias also enhances platelet aggregation and thrombosis, contributing to the progression of ischemic events in ACS, understanding these mechanisms reinforces the importance of managing acute glycemic fluctuations in ACS patients.[18] The pathophysiological mechanisms underlying the adverse effects of a high glycemic gap include increased oxidative stress, endothelial dysfunction, and a pro-inflammatory state, all of which can exacerbate myocardial injury and impair recovery.[19] Similarly, a prospective observational study by Yahiya et al. found that an elevated glycemic gap was associated with adverse outcomes and longer hospital stays in diabetic patients with acute coronary syndrome.[20] The majority of previous research on the relationship between HbA1c and ACS outcomes either found no relationship at all or identified a relationship but only over an extended period of time.[21-24] Very few research discovered a connection between short-term ACS results and HbA1c level. The current study discovered a statistically significant inverse relationship between the measured values of HbA1c and the incidence of MACE and prolonged hospital stays. With the exception of one study which found that greater levels of HbA1c were linked to a lower risk of myocardial damage following PCI in diabetic patients due to improved energy supply, the results were inconsistent with the majority of previously conducted studies. This could explain the confounding element in the short-term prognosis, as all ACS patients in the current study had primary PCI.[25] Our findings suggest that the glycemic gap should be considered in the routine risk assessment of ACS patients, identifying patients with a high glycemic gap on admission can prompt more aggressive glycemic management and closer monitoring during hospitalization. In this study evaluated that acute glycemic control is equally crucial in improving outcomes for ACS patients, regardless of their diabetic status. Targeted interventions to manage the glycemic gap in ACS patients should be explored in future research, this could include protocols for rapid normalization of blood glucose levels in the acute phase, tailored to the severity of the glycemic gap. Further studies are needed to determine the optimal glucose targets and the safest and most effective strategies for achieving them without increasing the risk of hypoglycemia. For instance, Umpierrez et al. showed that intensive insulin therapy in critically ill patients with hyperglycemia could reduce mortality, but the balance between strict glucose control and the risk of hypoglycemia needs careful consideration.[26]

Conclusion

In conclusion, the glycemic gap is a valuable prognostic marker in patients with ACS, reflecting acute hyperglycemic stress and its impact on clinical outcomes, incorporating the glycemic gap into risk assessment and management strategies could improve the care of ACS patients. Further research is warranted to validate these findings in larger, multicenter cohorts and to develop effective interventions for mitigating the adverse effects of acute glycemic dysregulation.

Limitations

Our study has several limitations. First, its prospective design may introduce selection and information biases. Second, we relied on single measurements of admission blood glucose and HbA1c, which may not capture the full dynamic range of glycemic fluctuations during hospitalization. Third, our findings may not be generalizable to all populations, as our study was conducted in a single center. Finally, we did not assess long-term outcomes beyond the hospital stay, which would provide a more comprehensive understanding of the glycemic gap's prognostic value.

Acknowledgments

Conflict of Interest

The writers declare that they have no competing interests.

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