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Effect of Glycated Hemoglobin A1C-Based Adjusted Glycemic Variables on the Outcome of Diabetic Patients Presenting with Acute Coronary Syndrome

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Abstract

Background: Acute hyperglycemia is frequently used as a marker for predicting ACS adverse outcome in diabetic patients. In this study we suggest the introduction of a more accurate biomarker which could anticipate adverse outcome and length of hospital stay in ACS diabetic patients, the glycemic gap.

Methods: The 100 diabetic patients who were presented to ER with ACS were prospectively followed during their hospital stay. Admission blood glucose was measured and glycemic gap was calculated using the equation (28.7 × HbA1c − 46.7). Glycemic gap then correlated with MACE and hospital stay length.

Results: There was a statistically significant relation between the glycemic gap value and MACE that the ACS patients with DM may witness during their hospital stay (p=0.001). Also there was a statistically significant relation between the glycemic gap value and the length of hospital stay of ACS patients with DM with p<0.001. In the analysis of the ROC curve for glycemic gap value to predict patient have complications, the optimal cutoff value of the glycemic gap was 55 mg/dL, with maximum AUROC of 0.796 (95% CI=0.702-0.891) (sensitivity 86.11% and specificity 56.25%) regarding complication occurrence.

Conclusion: Glycemic gap could be used as a biomarker for predicting MACE and duration of hospital length in diabetic patients with ACS. Glycemic gap is a better marker than admission blood glucose alone in diabetic patient presented with ACS.

Keywords: Hyperglycemia; Glycemic gap; Diabetes; Acute coronary syndrome; MACE

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Introduction

Acute hyperglycemia is a common finding in patients who attend the Emergency Department (ED) With Acute Coronary Syndrome (ACS) in both diabetic and non-diabetic patients. The prognostic role of hyperglycemia in non-diabetic patients with (ACS) may be more well-established, but that role in diabetic patients remains controversial at least on the short term basis [1,2].

In diabetic patients hyperglycemia is the cardinal feature which may be noticed regardless of a stressful event due to many causes as poor glycemic control. So it is necessary to consider pre-existing hyperglycemia in diabetic patients when investigating the association between blood glucose level and adverse outcomes in patients with (ACS) or in other words- if hyperglycemia in this patient group will be used as a biomarker for predicting the outcome [3].

The chronic effect of hyperglycemia is associated with long-term dysfunction, damage, and failure of various organs, especially the nerves, kidneys, eyes, heart, and blood vessels. In the development of diabetes, several pathogenic processes are involved. These may range from autoimmune destruction of the pancreatic β cells with consequent insulin deficiency to abnormalities that result in resistance to insulin action [4].

Stress hyperglycemia is defined as a transient increase in blood glucose concentration during acute illness. It represents two distinct populations of patients: Those with undiagnosed diabetes

or impaired glucose tolerance, and those who develop hyperglycemia as the result of hormonal surges responding to severe stress. Insulin resistance is common to both groups. Evidence shows that stress hyperglycemia involves increased insulin resistance in tissues and organs (in particular skeletal muscle), increased gluconeogenesis, decreased glycogenolysis and increased lipolysis. Elevated oxidative stress and increased serum levels of pro-inflammatory cytokines, cortisol, and glucagon promote these activities [5-7].

In patients with an (ACS), the concomitant occurrence of hyperglycemia enhances the risk of morbidity and mortality whether or not the patient has a prior diagnosis of diabetes. Stress hyperglycemia shares many properties with hyperglycemia associated with type 2 diabetes, including increased oxidative stress, inflammation, and activation of stress-responsive kinases. Infarcts are usually larger in patients with stress-related hyperglycemia. Increased sensitivity to ischemia-reperfusion injury and more severe infarction is one reason for the poor prognosis of ACS patients with stress hyperglycemia. Evidence from clinical and preclinical studies suggests that insulin resistance and glucose homeostasis play key roles by predisposing hyperglycemic myocardial tissue to injury during ischemia and reperfusion [8,9].

Materials and Methods

Study population

In this study, a total of 100 diabetic male and female patients aged between 40 years and 81 years were recruited from emergency department at Alexandria University Hospital, Egypt, and were followed in the cardiology department for MACE occurrence and for hospital stay length then glycemic gap values were correlated with the outcome.

Informed consent was obtained from all subjects prior to their participation in the study. Patients who are less than 18 years, pregnant females, and patients presented with hemodynamic instability and patients with hemoglobinopathies were excluded from this study. The study protocol was conducted in accordance with the principles laid down in the declaration of Helsinki and approved by the Alexandria Ethics Committee.

A complete medical history including; demographic details, characters and duration of the chest pain, risk factors for ACS and full clinical examination had been checked for all patients. 12-lead ECG had been done for all patients within 10 min of presentation. Random blood glucose was measured by finger stick sample with ACCU-CHEK device for capillary blood glucose measurement which was confirmed by serum blood glucose level in the central lab.

Biochemical analysis

Blood samples were collected from all patients for blood gases analysis and cardiac biomarkers of ischemia i.e. CK-MB and high sensitive Troponin. All samples were determined for glycated Hemoglobin (HbA1c) concentration using High Performance Liquid Chromatography (HPLC) method. Random blood glucose was measured by finger stick sample with ACCU-CHEK device for capillary blood glucose measurement which was confirmed by serum blood glucose level in the central lab.

A 12-lead ECG had been done for all patients within 10 min of presentation and all patients had a chest radiograph to exclude the risk of ACS mimics e.g. aortic dissection, pneumothorax and pneumonia.

The following formula was used to convert HbA1c levels to the estimated A1c-Derived Average Glucose (ADAG) levels: 28.7 × HbA1c − 46.7 [10]. The glycemic gap, which shows changes in blood glucose levels during the acute event, was calculated from the glucose level measured at ED minus the ADAG level [11]. The glycemic gap had been correlated with the patients' outcome which was assessed by the complications that occurred to the patient during his duration of stay and the length of that stay. Complications during hospitalization were considered in any patient that witnessed a sudden cardiac arrest, life threatening arrhythmias or acute pulmonary edema [12-14].

Statistical analysis

Continuous data are expressed as the mean standard deviation and were analyzed using the two-tailed student t-test. Categorical data are expressed as frequencies (%) and were evaluated using the chi-square test or Fisher's exact test. A one-way analysis of variance was used to assess the significance of various characteristics, laboratory data, and adverse outcomes. A post-hoc analysis was performed using the Bonferroni test. A Receiver Operator Characteristic (ROC) curve was plotted to analyze the discriminative power of the prediction tools, and the area under the ROC (AUROC) and the corresponding 95% Confidence Intervals (CI) were calculated.

Univariate and multivariate Cox hazard regression analyses were performed to identify the risk factors associated with MACEs. Variables with a $p<0.05$ in the univariate analysis were entered into the multivariate Cox hazard regression analysis. The correlation between glycemic gap and continuous variables was evaluated by the Pearson product-moment correlation. The correlation between the glycemic gap and ordinal variables was evaluated by the Spearman's rank-order correlation. The data were analyzed using Statistical Package for the Social Sciences statistical software (SPSS, Inc., Chicago, IL, USA), and differences with p values <0.05 were considered statistically significant.

Results

Baseline clinical characteristics and metabolic parameters of the study population are summarized (Table 1). In total, this study included 100 diabetic participants presented to us in ER with ACS. The sample includes 74 males (74%), 19 patients aged more than 50 years (19%) and 51 were above 60 (51%), with a median age of 60, a mean of 60.33 ± 10.06.

There were 36 patients who witnessed Major Adverse Cardiac Event (MACE) during their hospital stay representing 36% of our total sample as shown in Table 2. There glycemic gap values vary from 29.26 to 206.60 with a mean of 100.28 and a standard deviation

Table 1: Distribution of the studied cases according to demographic data (n=100).

	No.	%
Gender		
Male	74	74
Female	26	26
Age (years)		
<50	19	19
50-60	30	30
>60	51	51
Min. - Max.	40.0-85.0	
Mean ± SD.	60.3 ± 10.04	
Median (IQR)	61.0 (51.50-69.0)	

Table 2: Distribution of the studied cases according to complications (n=100).

Complications*	No.	%
Cardiac arrest	6	6
Pulmonary edema	24	24
Life threatening dysrhythmia	13	13

*note that the same patient may have had 2 or more complications during his hospital stay course

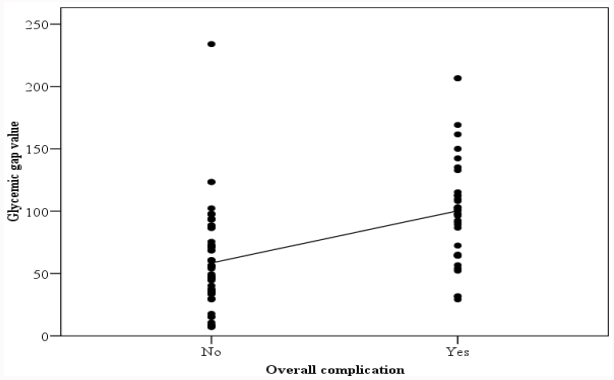

Figure 1: Correlation between MACE occurrence and Glycemic gap value (n=100).

of 43.25. There was a statistically significant relation between the glycemic gap value and MACE that the ACS patients with DM may witness during their hospital stay (p=0.001) as shown in Table 3.

Also there was a statistically significant relation between the glycemic gap value and the length of hospital stay of ACS patients with DM; either CCU, ward stay or both collectively with p<0.001. There was also a statistical inverse significant relation between HbA1c level and the total hospital stay (p=0.036) as shown in Figure 1, but there was no statistical significance between admission blood glucose and the length of hospital stay (p=0.064) as shown in Figure 2.

There was a statistically significant relation between age and MACE occurrence with increased rates as the age increases (p value <0.001). There was no statistical significance between overall complications and other demographics. There was no statistical

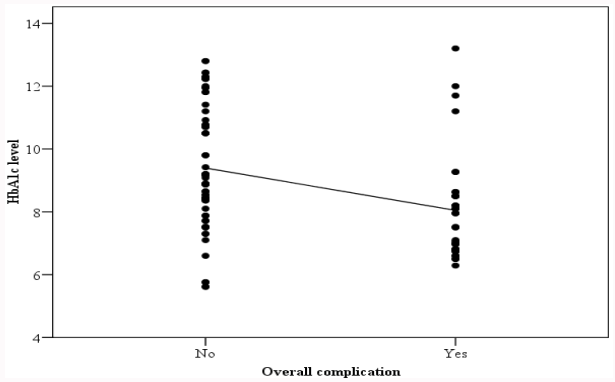

Figure 2: Correlation between MACE occurrence and HbA1c level (n=100).

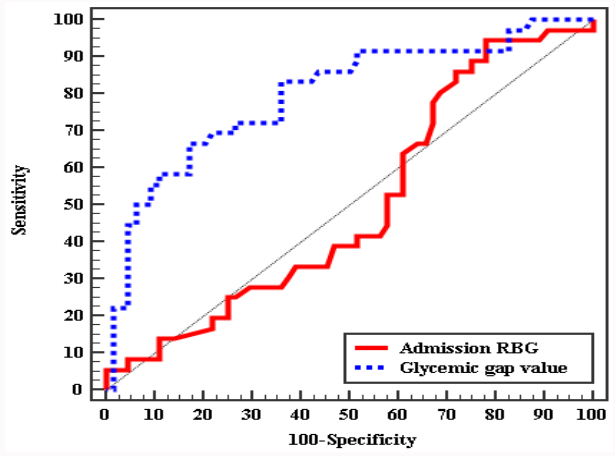

Figure 3: ROC curve for admission RBG and glycemic gap value to predict patient have complication (n=36).

significance between admission blood glucose and MACE occurrence neither collectively (p value = 0.875) nor separately in relation to each complication alone; p value for cardiac arrest = (0.299), for pulmonary edema = (0.322) and for life threatening dysrhythmia = (0.090) (Table 4).

Table 3: Relation between MACE and different glycemic parameters (n=100).

Variable	Overall complication				Test of Sig.	p
	No (n=64)		Yes (n=36)			
	No.	%	No.	%		
Admission RBG						
Min-Max	198.0-404.0		195.0-465.0		t=0.153	0.879
Mean ± SD.	284.92 ± 56.41		286.75 ± 59.17			
Median	296		266			
HbA1c level						
Min-Max	5.61-12.80		6.29-13.20		t=3.490*	0.001*
Mean ± SD.	9.39 ± 1.94		8.05 ± 1.67			
Median	8.99		7.74			
Glycemic gap value						
Min-Max	7.17-234.0		29.26-206.60		t =5.156*	<0.001*
Mean ± SD.	58.49 ± 36.27		100.28 ± 43.25			
Median	54.87		99.23			

t: Student t-test; p: p value for association between different categories; *: Statistically significant at p ≤ 0.05

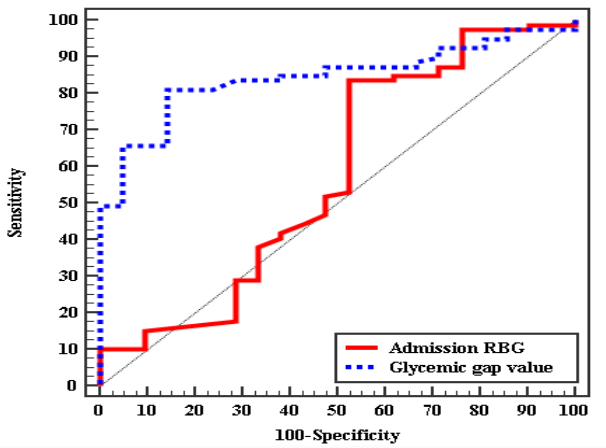

Figure 4: ROC curve for admission RBG and glycemic gap value to predict long hospital stay length (>3 days) (n=79).

Table 4: Relation between different glycemic parameters and total hospital stays (n=100).

	Total hospital stay (in days)	
	r	p
Admission RBG	0.186	0.064
HbA1c level	-0.21	0.036*
Glycemic gap value	0.514	<0.001*

The Cox proportional hazard model revealed that the hazard ratio of the glycemic gap (mg/dL) for MACEs was 1.028 (95% CI: 1.000-1.005, p<0.001). So, we find that glycemic gap is an independent predictor of MACE occurrence. Also the age was found to be an independent predictor of MACE occurrence as shown in Table 5.

In the analysis of the ROC curve for glycemic gap value to predict patient have complications, the optimal cutoff value of the glycemic gap was 55 mg/dL, with maximum AUROC of 0.796 (95% CI=0.702-0.891) (sensitivity 86.11% and specificity 56.25%) in the MACE occurrence as shown in Figure 3 and Table 6. Meanwhile, the analysis of the ROC curve for glycemic gap value to predict patient with long hospital stay revealed optimal cutoff value 48.04 mg/dL 0.767 (95% CI=0.766-0.922) (sensitivity 81.01% and specificity 85.71%) with PPV of 95.5% and NPV of 54.5 as shown in Figure 4. Moreover, glycemic gap produced higher AUROC values than did admission blood glucose for predicting all MACE and long hospital stay.

Discussion

Cardiac arrest, pulmonary edema and life threatening dysrhythmia are fatal complications that may occur following ACS. Early identification of patients who are at high risk of developing those complications may help in reducing morbidity and mortality [15]. Numerous studies have shown that hyperglycemia is a commonly encountered issue in critically-ill patients in ER and in the critical care settings even in patients without diabetes mellitus [16-20]. A recent analysis of medical records showed that hyperglycemia was present in 38% of adult patients admitted to hospital, of whom 26% had a known history of diabetes, and 12% had no history of diabetes before the admission [20].

In this context, the adverse prognostic impact of hyperglycemia which accompanies ACS has paid considerable attention of the medical societies. It is now well established that acute hyperglycemia that accompanies ACS at presentation is one of the predictors of the poor outcomes upon hospital admission and an important prognostic marker for all-cause death in patients with ACS, whether or not they had previously known diabetes mellitus [5,21,22].

Although many studies were conducted in the context of the effect of admission hyperglycemia on the short and long term outcome of the Acute Coronary Syndrome (ACS) unfortunately, there is too scarce available literature about the impact of the glycemic gap on ACS outcome [2,11,23-25].

Table 5: Univariate and multivariate analysis for the parameters affecting complications (n=100).

	Univariate		#Multivariate	
	p	OR (95%CI)	p	OR (95% CI)
Female	0.761	1.154 (0.458-2.904)	0.528	0.691 (0.219-2.180)
Age (years)	0.315	0.979 (0.939-1.021)	0.003*	1.094 (1.032-1.161)
Hypertension	0.27	1.595 (0.695-3.658)		
CCS	0.549	1.320 (0.533-3.270)		
PVD	0.491	1.559 (0.440-5.521)		
Dyslipidemia	0.351	1.606 (0.594-4.346)		
Smoking	0.523	0.765 (0.336-1.741)		
STE-ACS	0.258	1.667 (0.688-4.040)		
PCI Management	0.145	1.879 (0.804-4.391)		
Glycemic gap value	<0.001*	1.029 (1.014-1.043)	<0.001*	1.028 (1.013-1.043)

OR: Odd's Ratio; CI: Confidence Interval; LL: Lower Limit; UL: Upper Limit; #: All variables with p<0.05 was included in the multivariate; *: Statistically significant at p ≤ 0.05

Table 6: Agreement (sensitivity, specificity) for admission RBG and glycemic gap value to predict patient have complication (n=36).

	AUC	p	95% CI		Cut off#	Sensitivity	Specificity	PPV	NPV
			LL	UL					
Admission RBG	0.5	0.994	0.384	0.617	>228	94.44	21.87	40.5	87.5
Glycemic gap value	0.796*	<0.001*	0.702	0.891	>55.876	86.11	56.25	52.5	87.8

AUC: Area Under a Curve; p value: Probability Value; CI: Confidence Intervals; NPV: Negative Predictive Value; PPV: Positive Predictive Value; *: Statistically Significant at p ≤ 0.05; #: Cut off was choose according to Youden index

The main finding in our study is that the glycemic gap is strongly and significantly related to the occurrence of MACE (p value <0.001) and long hospital stay duration (p value <0.001) in diabetic patients presented to the ER with ACS. Results that mimic a retrospective observational study which was conducted by Liao et al. [11], who have found a relation between elevated glycemic gap and adverse outcomes in diabetic patients presented with acute myocardial infarction. They enrolled 331 patients to their study. Of those patients, 43 (13.0%) died during hospitalization and 61 (18.4%) experienced MACEs. Compared with survivors, non-survivors had a statistically significant higher glycemic gap and longer hospital stay results that are similar to what we have found in our study.

In our study we found that age of patients has a statistical significance on the outcome (p<0.001) and the hospital stay period (p<0.001). Similar results were obtained by Liao et al. [11], who found the age statistically significant in their study.

Reviewing previous literature have revealed a lot of studies their authors were concerned about finding an association between hyperglycemia and ACS outcome. Capes et al. [5], found that acute hyperglycemia with myocardial infarction is associated with an increased risk of in-hospital mortality in patients with and without diabetes with increased risk of congestive heart failure or cardiogenic shock in patients without diabetes.

Foo et al. [26], in 2003 have studied the relation between a single admission blood glucose value and ACS outcome. They found a marked correlation between hyperglycemia and ACS outcomes. They also found that prognostic correlates of admission glycemia were applied equally to diabetic and non-diabetic subgroups as in both subgroups, the more the hyperglycemia the more the risk of heart failure and cardiac arrest. Sousa et al. [27], in 2013 have observed that admission hyperglycemia is an independent predictive factor for in-hospital complications after ACS in diabetic and nondiabetic patients.

Angeli et al. [28] found that acute hyperglycemia documented during ACS brings an excess risk of mortality not only in the hospital setting, but also in the short-term (30 days) and long-term (up to 108 months). Lønborg et al. [29] have studied the impact of acute hyperglycemia on myocardial infarct size in patients with STEMI. They concluded that hyperglycemia could serve as a marker for the severity of myocardium at risk and injury. All those studies have given a well-established proof about the association between acute hyperglycemia and adverse outcome after ACS.

Another point of interest is that many of these studies found no difference regarding the outcome between diabetics and non-diabetics. Some of them even found poorer prognosis in non-diabetic patients. This “diabetes paradox” had been continuously observed in other studies with no explanation for that finding except for that there is a hidden factor that is only applied on diabetic patients and not on non-diabetics [3,30].

Recently, many studies have been concerned about using the glycemic gap in diabetic patients as a predictor for poor outcome in many aspects e.g. (ICU outcomes, community-acquired pneumonia, necrotizing fasciitis, acute heart failure and acute coronary syndrome). They all could relate the glycemic gap to adverse outcome and so more hospital stay length [31-35].

Generally, the stress response is known as an adaptive process for survival which benefits in drastically disturbed physiological situations, such as acute illness. Stress triggers systemic inflammatory response that accompanies secondary complications, such as acute hyperglycemia and insulin resistance. Stress-induced hyperglycemia has a direct correlation with the morbidity and mortality rates in critical illness.

Stress hyperglycemia is the result of sympathetic nervous system activation and the hypothalamic pituitary axis with subsequent increased production of catecholamine and cortisol levels that stimulate glyconeogenesis, glycogenolysis, and lipolysis. Surprisingly, morbidity and mortality associated with hyperglycemia are especially severe in patients who are not previously diagnosed as diabetics. In diabetic patient with ACS, stress-induced hyperglycemia represents the fraction of hyperglycemia that represents the damage limit on the level of myocardium. Stress-induced hyperglycemia has been reported to be associated with acute adrenergic signal of stress and endothelial cell dysfunction in acute myocardial infarction, which is partially attributed to endothelial cell apoptosis, Reactive Oxygen Species (ROS) over production and inflammation [36-38].

Most of studies which were concerned about the relation between HbA1c and ACS outcomes that were conducted in the past, whether found no relation between them or found a relation but on the long term [39-41]. Very few studies found a relation between glycosylated hemoglobin and ACS short term outcomes [42,43].

In our study, we found that HbA1c measured values was inversely related with MACE occurrence and long hospital stay with and had a statistically significant relation. Results which are discordant with most of the previously conducted studies except one study conducted by Li et al. [44], who reported that higher levels of HbA1c were associated with less risk of myocardial injury following PCI in diabetic patients because of better energy supply. As a large number of ACS patients included in our study received PCI therapy (n=57), this might account for the confounding factor in short-term prognosis.

Limitations

It is plausible that a number of limitations could have influenced this study. The sample size was relatively small, the study is hospital-based and all participants were of the same ethnicity, therefore the findings may be not generally applicable to other population. Also glycemic control during hospitalization was not implied for and correlated to the results.

We were concerned about the complications that occurred during the hospital stay only, which provided us with a short term follow up for our patients as far as a maximum of two weeks. This creates a limitation of our study to give information about the long term outcomes. Our study did not determine the day of occurrence of the complications following ACS during hospital stay. Our results regarding the protective effect of high HbA1c values on the short-term outcomes of the ACS should be further studied in the future.

Conclusion

Glycemic gap could be used as a biomarker for predicting MACE and duration of hospital length in diabetic patients with ACS. Also it could be a better marker than admission blood glucose alone in diabetic patient presented with ACS.

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