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Original Article

Acute Phase Hyperglycemia among Patients Hospitalized with Acute Coronary Syndrome: Prevalence and Prognostic Significance

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Abstract

Objectives: Regardless of diabetes status, hyperglycemia on arrival for patients presenting with acute coronary syndrome, has been associated with adverse outcomes including death. The aim of this study is to look at the frequency and prognostic significance of acute phase hyperglycemia among patients attending the coronary care unit with acute coronary syndrome over the in-hospital admission days.
Methods: The study included 287 consecutive patients in the Al-Faiha Hospital in Basrah (Southern Iraq) during a one year period from December 2007 to November 2008. Patients were divided into two groups with respect to admission plasma glucose level regardless of their diabetes status (those with admission plasma glucose of <140 mg/dl (7.8 mmol/L) and those equal to or more than that). Acute phase hyperglycemia was defined as a non-fasting glucose level equal to or above 140 mg/dl (7.8 mmol/L) regardless of past history of diabetes.
Results: Sixty one point seven percent (177) of patients were admitted with plasma glucose of ≥140 mg/dl (7.8 mmol/L). There were no differences were found between both groups regarding the mean age, qualification, and smoking status, but males were predominant in both groups. A family history of diabetes, and hypertension, were more frequent in patients with plasma glucose of ≥140 mg/dl (7.8 mmol/L). There were no differences between the two groups regarding past history of ischemic heart disease, stroke, lipid profile, troponin-I levels or type of acute coronary syndrome. Again heart failure was more common in the admission acute phase hyperglycemia group, but there was no difference regarding arrhythmia, stroke, or death. Using logistic regression with heart failure as the dependent variable we found that only the admission acute phase hyperglycemia (OR=2.1344, 95% CI=1.0282-4.4307; p=0.0419) was independently associated with heart failure. While male gender, family history of diabetes mellitus, hypertension and diabetes were not independently associated with heart failure.
Conclusion: Admission acute phase hyperglycemia of ≥140 mg/dl (7.8 mmol/L) was associated with heart failure in this study.

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Introduction

Regardless of diabetes status, hyperglycemia on arrival for patients presenting with acute coronary syndrome (ACS) has been associated with adverse outcomes, including death.[1-5] Both acute phase hyperglycemia (Stress hyperglycemia) and diabetes are associated with adverse outcomes in acute myocardial infarction (MI), with higher reported incidences of congestive heart failure, cardiogenic shock, and death.[6-13]

Elevation of glucose could be due to pre-existing, but not yet detected type 2 diabetes, impaired glucose tolerance, or it can be a marker of existing insulin resistance and/or beta-cell failure that through different mechanisms other than diabetes contributed to worse outcome after myocardial infarction.[14] Acute hyperglycemia is independently associated with impaired left ventricular function; it abolishes ischemic pre-conditioning, generating oxidative stress, it worsens endothelial function, increases platelet activation, and amplifies inflammatory immune reactions after acute coronary syndrome and subsequent mortality.[14] Furthermore, it exerts a profound negative impact on the development of the coronary collateral circulation in vivo.[15]

Patients with higher baseline blood glucose levels in the absence of diabetes and after adjustment for co-variants are at a significantly greater risk of developing coronary artery disease and heart failure.[14,16,17] Some found hyperglycemia-associated risk is greater in patients with acute myocardial infarction who do not have antecedent diabetes than in those with diabetes.[3,12] Others showed that this risk is similar across patient groups.[18,19]

The aim of this study is to look at the frequency and prognostic significance of acute phase hyperglycemia among patients attending the coronary care unit with ACS over the in-hospital admission days.

Methods

This was a cross-sectional hospital based study of all patients who presented to the hospital with ACS. The study included 287

consecutive patients with ACS admitted to the CCU in the Al-Faiha Hospital in Basrah (Southern Iraq) during a one year period from December 2007 to November 2008. The patients were followed for major events and complications, only in hospital until discharge.

Patients with final discharge diagnosis of ACS, including unstable angina (UA) and MI, ST segment elevation myocardial infarction (STEMI) or non-ST segment ST elevation myocardial infarction (NSTEMI) or new LBBB were included in this study. The European Society of Cardiology/American College of Cardiology definition of myocardial infarction was adopted, which includes any of the following criteria that satisfy diagnosis of an acute, evolving or recent myocardial infarction: typical rise and gradual fall (troponin) or more rapid rise and fall (creatine kinase-MB) of biochemical markers of myocardial necrosis, with at least one of the following:

a) Ischemic symptoms
b) Development of pathological Q-waves on electrocardiogram
c) Electrocardiogram changes indicative of myocardial ischemia (ST-segment elevation or depression).[20]

Criteria for STEMI were any two of the following; a) cardiac chest pain lasting at least 30 minutes, b) > 0.1 mV ST elevation in at least one standard lead, c) > 0.2 mV ST elevation in two or more contiguous chest leads, or d) new LBBB and biochemical markers of myocardial injury.[21] Unstable angina was defined by at least one of the following: worsening of previous stable pattern of angina, chest pain at rest or minimal effort with transient ST-segment elevation or depression on ECG, or elevation of biochemical markers of myocardial injury not reaching the criteria for MI (Cardiac troponin I (cTnI) [0.1 - 1.49 ng/ml]).[22,23]

Baseline clinical characteristics including demographic, clinical, and biochemical data were collected on admission. A 'smoker' was defined as a patient smoking any cigarette in the past 3 months. Family history of diabetes was considered positive if the first degree relatives were diabetics. Previous history of ischemic heart disease (IHD) was considered positive if there was any history of admission to CCU with records by doctor suggestive of IHD. Standing height and weight measurements were completed with subjects wearing light weight clothing and no shoes. Height was measured to the nearest centimeter and weight was measured to the nearest 0.5 kg. Body mass index (BMI) was calculated as body weight in kilograms divided by the squared value of body height in meters (kg/m^2).

Blood pressure was measured with a mercury sphygmomanometer on the right arm. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or current medication with antihypertensive drugs. The admission plasma glucose concentrations from blood samples drawn on arrival in the emergency room were recorded.

Acute phase hyperglycemia was defined as a non-fasting glucose level equal or above 140 mg/dl (7.8 mmol/L) regardless of past history of diabetes.[24,25] Newly detected diabetes was defined as hyperglycemia (fasting ≥126 mg/dl [7 mmol/l]), or postprandial ≥200mg/dl (11.1 mmol/l), which required therapy on discharge. Diabetes was recorded in patients on insulin, oral hypoglycemic drugs, or dietary restriction before admission.

Within 1 hour of admission, a blood sample was taken from the patients for biochemical analysis. Plasma glucose was assessed by the enzymatic method (glucose oxidase). Lipid concentrations were determined by using enzymatic methods. Low density lipoprotein (LDL) cholesterol was calculated according to the Friedewald formula.[26] Cardiac troponin I was measured using VIDAS Troponin I by enzyme linked fluorescent assay on admission. Serum cTnI values were sorted and identified as normal ([<0.1 ng/ml] or <0.01 µg/l), intermediate (0.1 to 1.49 ng/ml), or elevated (≥1.5 ng/ml).[27] Patients were classified into 3 groups based on their history of diabetes and their plasma glucose levels on admission:

Group 1 (n=104 [36.2%]): Non-diabetic patients without acute phase hyperglycemia.
Group 2 (n=78 [27.2%]): Non-diabetic patients with acute phase hyperglycemia.
Group 3 (n=105 [36.6%]): Diabetic patients.

Complications reported in the CCU were arrhythmia, heart failure, stroke and death. The diagnosis of heart failure required there to be symptoms of breathlessness, accompanied by physical findings of basal crepitations or a third heart sound and requiring treatment with diuretics and echocardiographic finding of systolic heart failure. Arrhythmia was considered for any rhythm disturbance that required therapy.

Data are expressed as mean ± standard deviation values for continuous variables and as percentages for categorical variables. Comparisons were made by one-way analysis of variance (ANOVA) and Student t test for continuous variables. The Chi-square analysis or Fisher's exact test was used to compare categorical variables.

To determine the Independent effects of admission acute phase hyperglycemia on complications, variables were entered into the logistic regression model. A p value of <0.05 was considered statistically significant. All statistical analysis were performed using the SPSS 15.0 software package.

Results

Patient characteristics are presented in Table 1. There was no difference between all three study groups regarding the mean age, qualifications, marital, or smoking state. Males predominated in the three study groups. A family history of diabetes was more significantly higher among the diabetic group.

There were no differences between study groups regarding past history of IHD or stroke, but hypertension was more common among the diabetic group and was observed in approximately half of the cases. The weight, BMI, and admission hyperglycemia were higher in both diabetic and acute phase hyperglycemia groups in comparison with the normoglycemia group. No differences were found between groups regarding lipoprotein profile, serum cTnI levels or final diagnosis of ACS type. Heart failure was the only most common finding in the diabetic group while other complications such as arrhythmia, stroke, and death were not different among the groups.

Table 1: Study Characteristics in Patients with Normoglycemia, Acute Phase Hyperglycemia, and Diabetes (n=287).

Characteristics		Normoglycemia n=104 (36.2)	Admission acute phase hyperglycemia n=78 (27.2)	Diabetes n=105 (36.6)	*p* value
Age	Mean ±SD	63.8 ± 14.6	61.0 ± 12.0	60.5 ± 10.9	0.13
	≤60	41 (39.4)	33 (42.3)	52 (49.5)	0.321
	>60	63 (60.6)	45 (57.7)	53 (50.5)	
Gender	Male	80 (76.9)	49 (62.8)	65 (61.9)	0.03
	Female	24 (23.0)	29 (37.1)	40 (38.0)	
Qualification		3.0 ± 4.5	2.6 ± 4.1	3.6 ± 5.0	0.3
Married		90 (86.5)	61 (78.2)	84 (80)	0.2
Smoker		36 (34.6)	25 (32.0)	34 (32.3)	0.58
Family history of diabetes		25 (24.0)	26 (33.3)	67 (63.8)	0.0001
Previous IHD		27 (25.9)	23 (29.4)	38 (36.1)	0.2
Previous stroke		4 (3.8)	3 (3.8)	7 (6.6)	0.5
Hypertension		33 (31.7)	33 (42.3)	53 (50.4)	0.02
Weight (kg)		71.5 ± 13.2	75.7 ± 14.4	78.7 ± 13.3	0.002
BMI (kg/m^2)		25.6 ± 4.3	27.4 ± 5.7	27.4 ± 4.0	0.01
Admission plasma glucose (mg/dl)		111.6 ± 16.1	191.3 ± 66.7	258.2 ± 91.9	0.0001
Cholesterol(mg/dl)		212.2 ± 45.1	208.9 ± 39.8	203.0 ± 38.8	0.6
TG(mg/dl)		156.6 ± 77.0	163.5 ± 65.36	165.3 ± 55.3	0.83
HDL-C(mg/dl)		45.6 ± 9.2	50.5 ± 24.3	44.5 ± 10.7	0.2
LDL-C(mg/dl)		136.3 ± 45.4	132.5 ± 38.5	127.1 ± 34.2	0.5
Cardiac troponin I (cTnI) (ng/ml)		3.5 ± 6.5	5.8 ± 7.6	4.9 ± 6.3	0.2
Final diagnosis	STEMI	52 (50.0)	46 (59.0)	59 (56.2)	0.454
	NSEMI	18 (17.3)	8 (10.3)	19 (18.1)	
	UA	34 (32.7)	24 (30.8)	27 (25.7)	
Complications					
Arrhythmia		9 (8.6)	10 (12.8)	14 (13.3)	0.5
Heart failure		12 (11.5)	14 (17.9)	35 (33.3)	0.0001
Stroke		1 (0.9)	1 (1.2)	5 (4.7)	0.1
Death		4 (3.8)	2 (2.5)	8 (7.6)	0.2

p value for x^2 test for dichotomous variables and one way analysis of variance (ANOVA) was used for continuous variables. (Figures in parentheses are percentages).

In Table 2, patients are divided into two groups with respect to admission plasma glucose level regardless of the diabetes state. Sixty one point seven percent (177) of patients were admitted with plasma glucose of ≥140 mg/dl (7.8 mmol/L). No differences were found between both groups regarding mean age, qualifications, smoking status, but males predominated in both groups. Family history of diabetes, and hypertension, were more in those with plasma glucose of ≥140 mg/dl (7.8 mmol/L).

Table 2: Subgroup Characteristics with Respect to Baseline Glucose Determinations.

Characteristics		Plasma glucose *<140 mg/dl (N=110)	Plasma glucose ≥140 mg/dl (N=177)	*p* value
Age	Mean ±SD	61.1 ± 11.3	63 ± 14.6	0.23
	≤60	47 (42.7)	79 (44.6)	0.807
	>60	63 (57.3)	98 (55.4)	
Gender	Male	85 (77.3)	109 (61.6)	0.006
	Female	25 (22.7)	68 (38.4)	
Qualification		3.09 ± 4.6	3.2 ± 4.6	0.49
Smoker		56 (31.6)	39 (35.4)	0.29
Family history of diabetes		88 (49.7)	30 (27.2)	0.0002
Previous IHD		55 (31.0)	33 (30)	0.89
Previous stroke		7 (3.9)	7 (6.3)	0.4
Hypertension		82 (46.3)	37 (33.6)	0.03
Weight		77.2 ± 14.1	72.1 ± 13.0	0.003
BMI		27.4 ± 4.9	25.8 ± 4.3	0.007
Cholesterol		206.3 ± 39.1	210.9 ± 45.2	0.57
TG		165.7 ± 59.2	154.3 ± 77.2	0.38
HDL-C		47.5 ± 18.5	45.3 ± 9.3	0.49
LDL-C		129.9 ± 36.3	135.8 ± 45.0	0.45
Cardiac troponin I (cTnI) (ng/ml)		3.4 ± 6.5	5.4 ± 7.0	0.114
Final diagnosis	STEMI	51 (46.4)	106 (59.9)	0.071
	NSEMI	19 (7.3)	26 (14.7)	
	UA	40 (36.4)	45 (25.4)	
Complications				
Arrhythmia		9 (8.1)	24 (13.5)	0.16
Heart failure		13 (11.8)	48 (27.1)	0.002
Stroke		1 (0.9)	6 (3.4)	0.18
Death		4 (3.6)	10 (5.6)	0.4

** Some of them were diabetics with no admission acute phase hyperglycemia.*
p value for x^2 test for dichotomous variables, and the Student t test was used for the continuous variables

There were no differences regarding past history of IHD, stroke, lipid profile, troponin-I levels or type of ACS found between both groups. Again, heart failure was more common in the admission acute phase hyperglycemia group, but there were no differences in arrhythmia, stroke, and death.

In Table 3, using logistic regression with heart failure as the dependent variable, it was noted that only the admission acute phase hyperglycemia (OR =2.1344 , 95 % CI = 1.0282-4.4307; *p*=0.0419) was independently associated with heart failure. While male gender, family history of diabetes mellitus, hypertension and diabetes were not independently associated with heart failure.

Table 3: Multivariable Logistic Regression Analysis to see the Independent Association of Heart Failure with Certain Variables.

Variable	Odds Ratio	95% Confidence Interval	*p* value
Gender	1.4199	0.7665-2.6304	0.2651
Family history of diabetes	1.1185	0.5990-2.0886	0.7253
Hypertension	1.1930	0.6495-2.1916	0.5694
Diabetes	0.5298	0.2733-1.0270	0.0600
Admission acute phase hyperglycemia	2.1344	1.0282-4.4307	0.0419

Discussion

The admission plasma glucose of 140 mg/dl (7.8 mmol/L) and above was chosen to select the group of acute phase hyperglycemia. In some of the largest observational studies to date, as well as in epidemiological analyses of randomized clinical trials, the initial mean 24-hour and mean hospitalization glucose levels above ~120–140 mg/dL (6.7–8.0 mmol/L) appear to be associated with the greatest increase in short-term mortality risk, when the entire cohort of patients (including those with and without established diabetes) is considered.[28] It would appear reasonable to consider random glucose levels >140 mg/dL (7.8 mmol/L) as the definition of hyperglycemia in the acute MI setting.[29]

In this study, heart failure was the only complication significantly associated with diabetes. Arrhythmia, stroke, and death were no more seen among the diabetic or high admission acute phase hyperglycemia group. It remains unclear, however, whether glucose is behaving as an indicator of the underlying diabetic state or as a predisposition or even as a marker of the severity of the ventricular injury and its hemodynamic consequence, as opposed to a true mediator of unfavorable clinical outcomes.[30]

Why was there no increase in hospital mortality in our study? Well, both short and long-term mortality increased in a linear fashion with higher admission glucose in patients, without known diabetes.[28] However, among those with established diabetes, only patients with severe hyperglycemia (admission glucose >240 mg/dL [13.2 mmol/L]) experienced a statistically significant increase in mortality.

Properly relying on fasting glycemia may give a better prognostic indicator. Suleiman et al. demonstrated that while both admission and fasting glucose levels predicted 30-day mortality in non-diabetic patients with acute MI, fasting glucose was the better discriminator.[31]

Elevated blood glucose levels in STEMI affect the prognosis of patients without diabetes mellitus; however, it is not an independent death risk factor of patients with diabetes mellitus, treated with percutanous coronary intervention.[32] Admission serum glucose concentration was not independently associated with cardiac death in a prospective cohort study of 2,127 patients presenting with ACS from London hospitals.[2]

Similar findings were seen by Bellodi et al. among 330 non-diabetic patients with acute AMI, where cardiogenic shock, infarct site and age, were reported to be the major determinants of mortality, while admission plasma glucose failed to reach full statistical significance.[9]

Our results suggest that high admission acute phase hyperglycemia independently and regardless of gender, family history of diabetes, and diabetes state or hypertension, was associated with heart failure. While Foo et al. found that prognostic correlates of admission glycemia were unaffected by diabetes status and did not differ significantly between patients with acute MI and those with unstable angina.[2] The mechanisms of the adverse effects of acute phase hyperglycemia on ventricular function was not an aim of the current study. However, it can be due to adrenergic stress, which is itself related to the severity of myocardial injury.[33]

Conclusion

This was a single center study with a small sample size. Fasting plasma glucose and glycated hemoglobin were not measured. There was also a short-term follow-up period, and the effects of hyperglycemia in diabetics were not studied separately. However, the fair conclusion based on the findings from this study confirm that admission acute phase hyperglycemia of ≥140 mg/dl (7.8 mmol/L) was associated with heart failure in this study.

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