The Value of Admission Glucose and Glycosylated Hemoglobin in Patients with acute Coronary Syndrome

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ABSTRACT:

BACKGROUND:

In nondiabetic patients, elevated admission glucose level is a strong predictor of short-term adverse outcome in patients with acute coronary syndrome. Admission glucose may be affected by meals, the circadian cycle, and also the stress response. Glycated hemoglobin A1c is a convenient marker of long-term glucose regulation. However, the prognostic value of diabetic control assessed by HbA1c level in patients with acute coronary syndrome (ACS) is still undefined.

OBJECTIVE:

To determine the association between (admission glucose and HbA1c) and short term outcome in patients not known to be diabetics presented with ACS.

PATIENTS AND METHODS:

This observational study included 50 consecutive patients without known diabetes mellitus admitted to the coronary care unit with ACS**.** Patients were sub-divided into three groups: patients with unstable angina (UA, n = 10), those with ST segment elevation myocardial Infarction (STEMI, n = 18) and those with non ST segment elevation myocardial infarction (NSTEMI, n = 22). Patients were stratified according to their HbA1c into three groups: Group 1: <6.5 (12, 24%), group 2: 6.5- 8.5 (22, 44%) and group 3: > 8.5 (16, 32%). Both glucose and HbA1c were measured on admission**.** The diagnosis of ‘‘undiagnosed DM’’ was made if patients presented with fasting glucose >7.0 mmol/L or random glucose >11.1 mmol/L together with an admission HbA1c >6.5% according to the latest ADA recommendations. Main outcome measure was left ventricular (LV) systolic function which was assessed by ejection fraction (EF); and the set point was 50%. Data were analyzed separately using multiple regression analysis.

RESULTS:

The mean age of patients was 60.6 ± 6.33 years and 74% were males. Of total, 42% were smokers, 68% were hypertensive, 48% had hyperlipidemia and BMI ≥ 30 in 22%. Eighteen percent of patients were diagnosed as new cases of DM. Mean admission glucose was higher in patients with EF< 50% compared to those with EF> 50% with statistically significant difference (P< 0.05). There was a linear correlation between EF% and HbA1c in all types of presentation. 95.5% of patients in group 2 and 100% of patients in group 3 showed EF<50% with statistically significant difference (P< 0.05).

CONCLUSION:

HbA1c on admission is a powerful predictor of LV systolic dysfunction as a major adverse event of acute coronary syndrome in patients not known to be diabetics. Measurement of HbA1c levels may improve risk assessment in those patients when presenting with ACS.

***KEYWORDS*:** stress hyperglycemia, acute coronary syndrome, glycosylated hemoglobin

INTRODUCTION:

Diabetes is considered a highly ‘vascular disease’ with both microvascular and macrovascular complications.[1] Macrovascular complications start taking place long before the patient has overt diabetes.[2] Diabetics have a greater burden of atherogenic risk factors than nondiabetics, including hypertension, obesity, lipid abnormalities, insulin, and elevated plasma fibrinogen.[3] Impaired glucose tolerance or overt diabetes may first be diagnosed in the setting of

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acute MI. This could reflect blood testing being performed during the hospitalization in patients with previously unrecognized diabetes. In addition, stress of MI unmasks or worsens the tendency toward hyperglycemia. Hyperglycemia is an independent risk factor for cardiovascular disease.[4] Mechanisms of increased risk include endothelial dysfunction, platelet activation, coagulation abnormalities, and abnormal plaque composition**.**

Endothelial dysfunction has been documented in diabetic patients who have normal coronary arteries and no other risk factors for coronary disease.[5]

Diabetes may predispose to coronary thrombosis through increased primary and secondary platelet aggregation, and increased platelet activation.[6]

In addition to platelet activation, diabetes is associated with an increase in plasma fibrinogen, which is a cardiovascular risk factor. Elevated plasma fibrinogen is also associated with other cardiovascular risk factors including older age, increased body mass, smoking, total cholesterol, and triglycerides .[7]

Fibrinolytic activity is reduced[8] , tPA activity is decreased because of increased plasma concentrations of and enhanced binding to its inhibitor, plasminogen activator inhibitor (PAI-1) .[9]

Coronary tissue from diabetics contained a greater amount of lipid-rich atheroma, more macrophage infiltration, both of which are associated with a greater risk for plaque rupture, and a higher incidence of CHD. [10]

Hyperglycemia accelerates the process of atherosclerosis by the formation of glycated proteins and advanced glycation end products, which act by increasing the endothelial dysfunction.[11]

Recent data indicated a high prevalence of abnormal glucose metabolism in patients with no history of DM at the time of acute myocardial infarction. [12]In patients with acute coronary syndrome, up to 40% have impaired blood glucose levels on admission.[13]This has been associated with increased mortality, irrespective of diabetic status.[14] In non-diabetic patients admission plasma glucose predicts both long-term morbidity (for example, re-infarction, hospitalization with heart failure, adverse ventricular remodeling) and mortality. [15]

Recent evidence has shown that chronic glucose dysregulation, assessed by HbA1c levels, is also of prognostic value with regard to future CVD and congestive heart failure.[16] Although admission glucose has good prognostic value on outcome in ACS, it may be affected by meals, the circadian cycle, and also the stress response. Stress hyperglycemia even in non-diabetics, is associated with many abnormalities like increased activation of stress responsive kinases [17] and induction of apoptosis and myocyte necrosis, which in turn leads to systolic and diastolic dysfunction.[18]

HbA1c is an easy marker of long-term glucose regulation; it also unmasks minor glycometabolic disease, such as impaired glucose tolerance, impaired fasting glucose or metabolic syndrome. [19]

So glycated hemoglobin A1c (HbA1c) is a better marker of sugar control, as it provides a good reflection of plasma glucose concentrations over 8 to 12 weeks.

We aimed to investigate the association between (admission glucose and HbA1c) and short term outcome in patients not known to be diabetics presented with ACS.

PATIENTS AND METHODS:

This is a cross-sectional study conducted at Baghdad teaching hospital, during the period (May 2011 – Jan. 2012). Fifty patients who were admitted to the CCU with ACS were selected; with mean age of (60.6 ± 6.3) year and in the range of (45-70) year. Patients' data of age, sex, body mass index, history of diabetes mellitus, hypertension, smoking and hyperlipidemia were all obtained. Serum levels of the following parameters were tabulated: Serum admission glucose (AG), glycosylated haemoglobin (HbA1c), fasting total serum cholesterol, low density lipoprotein (LDL) cholesterol and high density lipoprotein (HDL).

HbA1c was measured by spectrophotometer. Patients were excluded if they had history of severe heart failure, history of definite myocardial infarction in the past, those known to be diabetics and those having chronic kidney disease. They were subdivided into three groups: patients with STEMI (which was diagnosed according to the ESC and ACC criteria [20,21] as constrictive chest pain lasting longer than 30 min and an increase CK (MB fraction >200 U/l)and/ or increase cardiac TI more than 2 microgram\L and/ or new ST elevation at the J point in two

contiguous leads >0.2 mv leads v2-v3 or >0.1 mv in other leads), with unstable angina diagnosed as angina pectoris with at least one of three features: It occurs at rest lasting > 10 minutes, it is severe and of new onset and or it occurs with crescendo pattern. [22] Finally patients with NSTEMI which was diagnosed if a patient with clinical features of unstable angina develops evidence of myocardial necrosis as reflected in elevated cardiac biomarker above threshold levels.[23] Furthermore, patients were stratified according to their HbA1c level into three groups; group 1: <6.5 (n = 12) and group 2: 6.5- 8.5 (n= 22) and group 3: > 8.5 (n = 16) based on values reported by the American Diabetes Association for diagnosing impaired glucose tolerance and diabetes after oral glucose tolerance tests.[24]

The diagnosis of ''undiagnosed diabetes mellitus'' was made if patients with fasting glucose >7.0 mmol/L or random glucose >11.1 mmol/L showed an admission HbA1c >6.5% according to the latest ADA recommendations.[25] Left ventricular systolic dysfunction was the main outcome and it was defined as ejection fraction less than 50%. [26]

EF was measured by Simpson's method using (2 dimentional ECHO machine). BMI was measured as weight (kg)/ height (m^2) and obesity was defined as BMI $\geq$ 30kg\m^2 [27]

Statistical analysis:

By using *SPSS (statistical package for social sciences)* software all data of different variables were entered and analyzed with appropriate statistical tests and procedures.

Chi-square(X^2) was used for categorical variables, *student's (t)* test for continuous variables and to compare means. Bivariate *Pearson's correlation coefficient* was calculated to evaluate the associations among different variables. Partial correlation regression and multivariate analysis were used to determine the association between HbA1C level and Ejection fraction with controlling of other variables.

In all statistical analysis level of significance (P.value) was set at P ≤ 0.05.

RESULTS:

Thirty six percent of patients presented with STEMI, 44% with NSTEMI and 20% with unstable angina. The data of 50 patients was evaluated in the study. Table 1shows the baseline characteristics of the study group.

Table 2 shows the Demographic and biochemical data of patients based on hemoglobin A1c Levels. Table 3 shows the distribution of study groups according to BMI, hypertension, hyperlipidemia, smoking, and EF. Table 4 shows the distribution of study groups according to AG. Figures 1, 2, and 3 show the correlation between HbA1c level and EF among patients presented with unstable angina, STEMI, and NSTEMI respectively.

Outcomes:

As shown in table 2; the mean value of age, BMI, AG, and LDL was higher in group 2 (Hb A1C, 6.5- 8.5) and group 3 (Hb A1C > 8.5) compared to that of group 1 (Hb A1C < 6.5). Mean HDL was lower in group 2 and 3 compared to group 1. As shown in table 3, there was an association between BMI, hyperlipidemia, hypertension, and smoking with elevated HbA1C but without statistically significant difference.

The mean EF% was significantly lower in group 2 and 3 compared with that of group 1 (p= 0.0001).

As shown in table 4; about 91% of patients in group 2 and 56% in group 3 had AG in the range of 7-11 mmol/L compared to 50% in group 1. So 70% of total sample had impaired glucose tolerance. About 9% in group 2 and 44% of patients in group 3 had AG more than 11 mmol/L, so 18% of total sample were considered as newly diagnosed cases of DM according to the latest ADA recommendations.[25]

A linear decrease in EF% was found with raised level of HbA1C levels in patients presented with unstable angina (P value = 0.0043), with STEMI (P value = 0.0290), and NSTEMI (P value = 0.0015) as shown in figures 1, 2, and 3 respectively.

Table1: Baseline Characteristics of patients (N=50).

Variable	No. of patients	Percents
Gender		
Male	37	74%
Female	13	26%
BMI(kg/m^2)		
< 30	39	78%
≥ 30	11	22%
Smoking		
Smoker	21	42%
Non smoker	29	58%
Hypertension		
Yes	34	68%
No	16	32%
Hyperlipidemia mmiamia		
Yes	24	48%
No	26	52%
EF (%)		
< 50 %	46	92%
≥50 %	4	8%
HbA1C level		
<6.5	12	24%
6.5-8.5	22	44%
>8.5	16	32%

Table 2: Demographic and biochemical data of the study groups based on hemoglobin A1c Levels.

Variable/ mean ± SD	HbA1C		
	<6.5 (no 12)	6.5-8.5 (no 22)	>8.5 (no 16)
Age (year)	58 ± 7.5	60.8 ± 5.4	61.8 ± 6.4
Male count (%)	7 (58.3%)	19 (86.4%)	12 (75%)
Female count (%)	5 (41.7%)	3 (13.6%)	4 (25%)
BMI (kg/m^2)	26.2 ± 7.8	26.3± 4.8	26.9 ± 4.7
Blood glucose (mmol/l)	7.4 ± 1.1	8.9 ± 1.4	11.2 ± 0.9
Total cholesterol (mmol/l)	6.1 ±0.8	5.1 ± 1.6	5.2 ± 0.63
LDL cholesterol (mmol/l)	3.2 ±0.7	3.5 ± 1.3	3.6 ± 0.37
HDL (mmol/l)	1.2 ± 0.23	1.1 ± 0.22	1.1 ± 0.25
EF%	54.3± 3	42.8 ± 6	37 ± 3.5

Table 3: Distribution of study groups according to BMI, hypertension, hyperlipidemia, smoking, EF.

Variable		HbA1C			*P.value*
		<6.5	6.5-8.5	>8.5	
BMI	≤30	83.3%	81.8%	68.8%	0.56
	>30	16.7%	18.2%	31.2%	0.53
Hyperlipidemia	No	8.3%	72.7%	56.2%	0.024
	Yes	91.7%	27.3%	43.8%	
Hypertension	No	58.3%	13.6%	43.8%	0.13
	Yes	41.7%	86.4%	56.2%	
smoking	No	33.3%	54.5%	68.8%	0.312
	Yes	66.7%	45.5%	31.2%	
EF	< 50%	41.7%	95.5%	100%	0.0001
	≥ 50%	58.3%	4.5%	0%	

Table 4: Distribution of study groups according to AG.

AG(mmol/L)		HbA1C			
		<6.5	6.5-8.5	>8.5	Total
7- 11	Count	6	20	9	35
	% within HbA1C	50%	90.9%	56.3%	70%
>11	Count	0	2	7	9
	% within HbA1C	0%	9.1%	43.7%	18%
Total	Count	6	21	16	44
	% within HbA1C	50%	95.4%	100%	88%

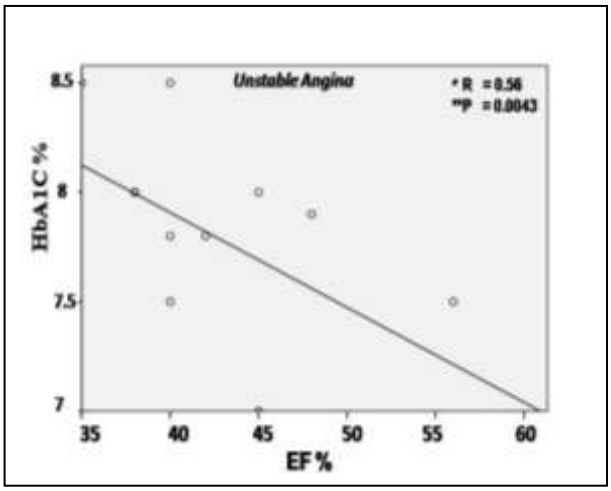

Figure 1: Correlation between HbA1c level and EF among patients presented with unstable angina. *R= correlation coefficient (< 0.4= weak, 0.4-0.7 = moderate, > 0.7 = strong) association. **P value is statistically significant at P≤ 0.05

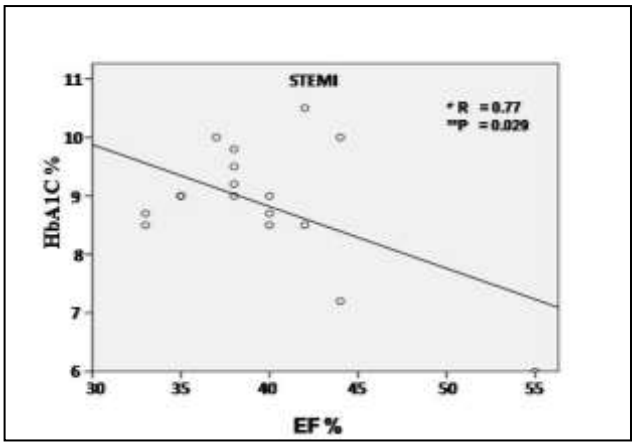

Figure 2: correlation between HbA1c level and EF among patients presented with STEMI.

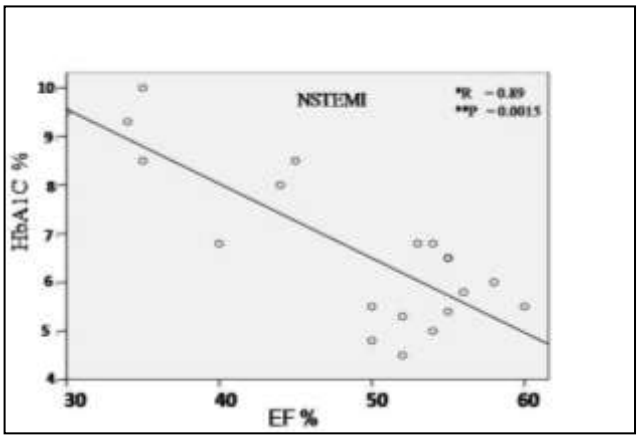

Figure 3: Correlation between HbA1c level and EF among patients presented with NSTEMI.

DISCUSSION:

In the current study we found a relation between both (AG, HbA1c) and poor outcome among acute phase of ACS survivors. Elevated HbA1c levels on admission were a strong and independent predictor of reduced EF.

Selvin E, et al. and Khaw KT, et al. showed that an elevated HbA1c is associated with increased cardiovascular risk in patients with and without diabetes[28, 29] Malmberg *et al.* found an association between elevated HbA1c and mortality after myocardial infarction, relative risk (95% CI) 1.07 (1.01-1.21)[30] ; however, Timmer *et al.* and Cao *et al.* did not confirm this, [1.63 (0.99-2.79] and 1.08 (0.31-3.23)], Respectively[31,32]. Increasing HbA1c levels were clearly associated with adverse baseline characteristics such as a higher cardiovascular risk profile, explaining part of the poor outcome of ACS.

In a systematic review of 15 studies (1966–1998) on AMI, the association of hyperglycaemia with increased in-hospital mortality was stronger in non-diabetic patients than in diabetic patients[33]. Majority of our non diabetic patients i.e. 22/ 50 (44%) had HbA1c levels ≥ 6.5% and 16/50 (32%) had HbA1c levels ≥ 8.5% (Table 1). In a study conducted in Asian Indians with normal glucose tolerance (NGT), a strong correlation of HbA1c and cardiovascular risk factors was found. NGT subjects with three or more metabolic abnormalities had the highest HbA1c levels and an HbA1c cut off point of ≥ 6.5% was found to have the highest accuracy in predicting both metabolic syndrome and coronary artery disease. [34]

Elevated glucose is not only a symptom of glucose dysregulation, but also of stress and a more high-risk patient population. Stress hyperglycemia is a common occurrence in patients admitted to the intensive care units with acute coronary syndromes.

In our study, 18% of total sample were diagnosed as new cases of DM. So elevated HbA1c levels can be predictive for cardiovascular disease and mortality in patients without diabetes mellitus, regardless of fasting glucose levels, a finding that was shown in a recent cohort study. [35]

In addition to the effect of associated insulin resistance, excess glucose may be directly detrimental during ACS, offering a target for treatment. The molecular mechanisms for this adverse effect include the promotion of oxidative stress, non-enzymatic glycation of platelet glycoproteins with abrupt changes in aggregability, amplification of inflammation, and suppression of immunity.[36].

In fact, some studies have shown even higher cardiovascular mortality and morbidity in patients with hyperglycemia in previously undiagnosed diabetes than in patients with known diabetes or normoglycemic subjects.[37]

It has been shown that higher AG is associated with a larger infarct size, a lower ventricular function and a higher Killip class.[31] Killip classification is a system used in individuals

with an acute myocardial infarction (MI) in order to risk stratify them. Individuals with class I (no signs of HF) and II (lung rales, S3 and raised JVP) are less likely to die within the first 30 days after their MI than individuals with a high Killip class (class III, with frank pulmonary edema) and class IVwho develop cardiogenic shock).[38]

In addition, part of the association between long-term abnormalities in glucose control and outcome is due to the same complex mechanisms responsible for the adverse association between overt diabetes mellitus and cardiovascular outcome.[39]

CONCLUSION:

Multivariate logistic regression analysis in this study showed that in ACS patients without known diabetes mellitus, both short and long-term abnormalities in glucose control assessed by AG and HbA1c respectively; are associated with poor outcome. HbA1c may be used to assess cardiovascular risk in a nondiabetic population with ACS.

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