Prognostic implications of admission hyperglycemia for in-hospital morbidity and mortality in acute coronary syndrome

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Summary:

Background: Diabetes mellitus is a well known risk factor for acute coronary syndrome but the hypothesis that patients with acute phase hyperglycemia, regardless the previous diagnosis of diabetes, have worse prognosis than those with normal glucose values is controversial. This paper aims to estimate the prevalence of admission hyperglycemia, its effect on in-hospital prognosis of diabetic and non-diabetic patients with acute coronary syndrome, and to compare it with 2nd day fasting plasma glucose as a prognostic marker.

Methods: One hundred patients, (59) diabetic and (41) non-diabetic, with documented acute coronary syndrome enrolled in this study over the period of June/ 2009-Jan./2010 from coronary care unit of Baghdad Teaching Hospital, who were thoroughly examined, hyperglycemia documented on admission and next day, then followed up daily during hospitalization for development of complications or death.

Results: Heart failure and recurrent cardiac ischemic events were significantly more common in diabetic than non-diabetic patients (P-value:0.04 for both),while arrhythmias, cardiogenic shock and mortality rate were not significantly different between both study groups.

Admission hyperglycemia more than 200mg/dl was associated with higher incidence of cardiogenic shock, recurrent ischemic events, heart failure, and death in non-diabetic patients (P-value 0.009, 0.022, 0.025, 0.026 respectively) but no more arrhythmias, and in diabetic patients admission hyperglycemia was only associated with more recurrent ischemic events (P-value 0.017).

Second day fasting plasma glucose more than 126mg/dl was associated with higher incidence of heart failure in non-diabetic patients and more recurrent ischemic events in both study groups.

Conclusion: Admission hyperglycemia is a poor in-hospital prognostic marker in non-diabetic & to lesser extend in diabetic patients suffering acute coronary syndrome.

Keywords: admission hyperglycemia, acute coronary syndrome, diabetes mellitus, mortality, morbidity.

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Introduction:

First data about hyperglycemia in critically ill patients were recorded in 1855 by French physiologist Claude Bernard (1), while high prevalence of glycosuria in non-diabetic patients who have acute myocardial infarction was noted as early as 1931. (2) Since that time Numerous studies had established the fact that hyperglycemia on admission is common in patients with acute coronary syndrome(ACS) and is a risk factor for death and in-hospital complications.(3-4) Despite that hyperglycemia remains underappreciated as a risk factor, and glucose measurement is not included in ACS risk indexes,(5-6-7) and the ACS guidelines do not suggest specific therapeutic targets for glucose control in non diabetic patients with acute phase hyperglycemia.(8-9-10) Increased glucose level during stress is result of sympathetic nervous system activation and raised production of the catecholamines and cortisol that stimulate processes of glyconeogenesis, glycogenolysis and lipolysis which cause insulin resistance, with the resultant hyperglycemia, and insulin resistance. (11-12). Hyperglycemia, which is a marker of severe attack of myocardial ischemia, is also important mediator of adverse outcomes as multiple physiological studies demonstrate that hyperglycemia may have a direct detrimental effect on ischemic myocardium through a variety of mechanisms. (13-14) A number of randomized trials demonstrating benefit from strict glycemic control in critically ill patients in general.(15-16) however the 2004 ACC/AHA guidelines for STEMI recommend an insulin infusion to "normalize" blood glucose and the more recent 2007 ACC/AHA guidelines on NSTEMI are more specific, recommending a slightly more conservative target of preprandial glucose of less than 110 mg/dL (6.1 mmol/L) with a maximum glucose of less than 180 mg/dL (10 mmol/L) in all patients with diabetes (17). Neither of these guidelines specifically addresses the important issue of new hyperglycemia in a patient without a prior history of diabetes. Because these individuals appear to be at even greater risk than those with diabetes, equally aggressive glucose targets seem logical. (10)

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Methods:

A prospective cohort study, included 100 diabetic and non-diabetic patients aged 75 years old or less with ACS were recruited between 1st of June, 2009 to 1st of January, 2010 from patients admitted to Baghdad Teaching Hospital/ coronary care unit within 48 hours after onset of symptoms and who survived long enough to have a glycaemia determined on admission & on the second day. ACS was defined according to AHA/ACC guidelines. (17) Dyslipidemia was defined according to adult treatment panel (ATP) III of the national cholesterol education program that identified a normal triglyceride level as less than 150 mg/dL, & LDL level less than 100 mg/dl for patient with coronary artery disease. (18) or the patient taking lipid lowering drugs and lipid profile was done within first 24 hours of admission. Blood pressure was measured on admission & daily there after; hypertension was defined as blood pressure more than 140/90 mmHg or patient taking antihypertensive drugs. The exclusion criteria were chronic renal failure (defined as creatinine clearance less than 30 ml/min, according to Cockcroft Formula), prior history of symptomatic heart failure, and recent attack of ACS within 6 months, known history of chronic inflammatory disease or malignancy, & patient receiving steroid therapy. All the patients had been thoroughly examined on admission & random capillary blood glucose done before receiving any treatment, with daily ECG, cardiac troponin, second day fasting plasma glucose (2nd day FPG), S. creatinine, echocardiography & lipid profile. All patients were followed up daily in Coronary Care Unit & then in medical word till discharge from hospital for recurrence of ischemic chest pain, dyspnea, blood pressure, heart rate, evidence of heart failure, arrhythmia, & thromboembolic complications. Prognostic end points were arrhythmias (including atrial fibrillation & tachycardia, non-sustained & sustained ventricular tachycardia, & ventricular fibrillation), post-MI angina, new STEMI in patient who were admitted for UA/NSTEMI, heart failure, cardiogenic shock, and in-hospital mortality.Heart failure was defined according to modified Framingham clinical criteria (19).

Data analysis: Data were computerized using Microsoft Excel program 2007, statistical analysis were done using the (SPSS) software for windows, the Chi-square (X^2) test was used but when one of the expected values was less than 5, Fisher exact test or Mid-P exact test was used to calculate P-value. The t-test was used to compare the means of different groups for continuous variables. Study confidence interval was 95% and significant P-value was < 0.05.

Results:

Twenty one patients (35.6%) of those without history of diabetes, and 22 patients (54.7%) of those with known history of diabetes have admission capillary blood glucose >200 mg/dl (table 1). Regarding the demographic features of the patients included in the sample, this study showed that mean age was higher in non-diabetic then in diabetic patients, and body mass index (BMI) was lower in non-diabetic then in diabetic patients with ACS (table 1), but there was no statistically significant difference in age, gender or BMI in relation to admission capillary blood glucose for both study groups (P-value >0.05) (table 1). Seventeen patients (28.8%) of non-diabetic and 18 patients (43.9%) of diabetic group had hypertension, but there was no statistically significant association between hypertension and elevated admission capillary blood glucose in both study groups, P-value <0.05 (Table 1). Dyslipidemia was reported in 14 (23.7%) of non-diabetic & 16 (39%) of diabetic patients, but there was no statistically significant association with elevated admission capillary blood glucose in both study groups (table 1). There was significant statistical association between elevated admission blood glucose level & STEMI in non diabetic (P-value< 0.05), but not in diabetic patients (table 1). There was statistically significant difference in frequency of heart failure in the two study groups which was less common among non-diabetic (15.3%) then diabetic patients (24.4%), P-value<0.05 (table 2), but the study showed significant statistical association between heart failure & elevated both admission blood glucose level & 2nd day FPG in non diabetics P- value< 0.05, but not in diabetics P- value> 0.05 (table 3, 4). Arrhythmias was not significantly more common in diabetic then in non-diabetic patients, (table 2), and was not associated with elevated admission capillary blood glucose nor with 2nd day FPG (table 3, 4). Recurrent ischemic events occur more in diabetic than non-diabetic patients (29.3%, 18.6% respectively) P-value<0.05 (table 2), and there was strong statistical association of recurrent ischemic events with elevated admission blood glucose or 2nd day FPG in both study groups (table 3, 4). Cardiogenic shock occur in six non-diabetic patients (10.2%) and seven diabetic patients (17.1%) with no significant statistical difference in prevalence between both study groups (table 2), but this study shows significant statistical association between elevated admission blood glucose & cardiogenic shock in non diabetic, but not in diabetics (table 3), however cadiogenic shock was not more common in patient with elevated 2nd day FPG in both study groups (table 4). There was no significant variation in mortality rate between both study groups (table 2), but mortality in non-diabetic patients was associated with admission hyperglycemia (table 3) & not with elevated 2nd day FPG (table 4), while mortality in diabetic patients was not related to admission capillary blood glucose nor to 2nd day FPG.

Table 1. Characteristic features of study samples and their statistical analysis.

Features		Non diabetic				Diabetic			
Admission CBG		<200	>200	total	P-value	<200	>200	total	P-value
Patients No. (%)		38 (64.4)	21(35.6)	59		19(46.3)	22(54.7)	41	
Mean age (SD)		60.3(8.2)	63.7(7.8)	62.1(9.7)	0.12	58.8 (6.4)	60.1(8.3)	59.4(11.3)	0.58
BMI (SD) Kg/m^2		22.9(2.3)	24.1(2.7)	23.6(2.9)	0.38	25.2 (3.1)	26.6(2.6)	26.2(2.8)	0.13
Gender	male	26	12	38	0.28	10	14	24	0.34
	Female	12	9	21		9	8	17	
Current smoking		16	10	26	0.44	9	7	16	0.24
Hypertension		11	6	17	0.39	8	10	18	0.46
Dyslipidemia		9	5	14	0.49	7	9	16	0.47
Diagnosis on admission	UA	14	3	17		4	4	8	
	NSTEMI	9	5	14		5	7	12	
	STEMI	13	15	28	0.02	10	11	21	0.44

Table 2. Frequency of end points in study sample with statistical correlation to diabetic state of the patients

End points		Non diabetics	Diabetics	P-value	Total
Heart failure No. (%)		9 (15.3%)	10 (24.4%)	0.04	19 (19%)
Arrhythmias	Sustained VT or VF (reverted)	3	2		5
	Non-sustained VT	6	7		13
	AF	5	3		8
	SVT	1	0		1
	Heart block	7	4		11
	Total No. (%)	22 (37.3%)	16 (39%)	0.48	38 (38%)
Recurrent events	Post MI angina	8	8		16
	New STEMI	3	4		7
	Total No. (%)	11 (18.6%)	12 (29.3%)	0.04	23 (23%)
Cardiogenic shock No. (%)		6 (10.2%)	7 (17.1%)	0.23	13 (13%)
Mortality No. (%)		5 (8.5%)	4 (9.8%)	0.41	9 (9%)

Table 3. Relation of study end points to admission capillary blood glucose

Admission CBG / End points	Non-diabetics			Diabetics		
	<200	>200	P-value	<200	>200	P-value
Heart failure	3	6	0.025	4	6	0.33
Arrhythmias	12	10	0.17	6	10	0.27
Recurrent ischemic events	4	7	0.022	2	10	0.017
Cardiogenic shock	1	5	0.009	2	5	0.17
Mortality	1	4	0.026	2	2	0.44

Table 4. Relation of study end points to 2nd day FPG

2nd day FPG / End points	Non-diabetics			Diabetics		
	<126	>126	P-value	<126	>126	P-value
Heart failure	3	6	0.007	5	5	0.22
Arrhythmias	13	9	0.09	8	8	0.20
Recurrent ischemic events	5	6	0.027	4	8	0.013
Cardiogenic shock	3	3	0.13	3	4	0.16
Mortality	2	3	0.07	1	3	0.08

Discussion:

This study shows that the prevalence of acute phase hyperglycemia among non-diabetic patients with ACS was 35.6%, which was within the range of previously reported rates of about 20-50% in many other series. (3, 20, 21, 22) this wide variety could be due to contribution of undiagnosed diabetes in hyperglycemia in non-diabetic patients, Oswald et al shows that one fifth of patient with presumed stress hyperglycemia have undiagnosed diabetes. (23) Admission hyperglycemia was not related to age, gender or BMI in both diabetic & non-diabetic patient in this study, however in many other studies individuals with higher admission glucose were older, heavier, and more often female. (24, 25) this difference with international studies could be due to smaller number of patients included in our study. This study also shows no significant statistical association between admission hyperglycemia with hypertension and dyslipidemia in both study groups, this result was consistent with a nationwide French study (25). Admission hyperglycemia was significantly more common in patients with STEMI compared to those with NSTEMI/UA in non-diabetic but not in diabetic group, this could be due to more stimulation of

sympathetic nervous system & raised production of the catecholamines in patient with more severe disease in non-diabetic patients, while in diabetics many patient with milder disease might have hyperglycemia due to already poorly controlled diabetes. This fact that this paper had concluded was compatible with most of other studies that state that severity of ACS and size of infarct is related to degree of hyperglycemia. (13,14) The outcome of diabetic patients sustaining an ACS is poor, compared with that of non-diabetic patients, mainly because chronic metabolic derangement and its microvascular disease in diabetic patients, and our study shows that diabetic patients were significantly more liable for heart failure & recurrent ischemic attack, but mortality was similar in both study groups which could be attributed to small size of the studied sample.The differential impact of hyperglycemia on outcomes in patients with and without known diabetes has been a consistent finding by several investigators, this study shows that admission hyperglycemia was strongly associated with cardiogenic shock, heart failure, recurrent ischemic attack, and higher mortality in non-diabetic patient but was only associated with more recurrent ischemic attack in diabetic patients(i.e. admission hyperglycemia predict poor outcome in non-diabetic much more than in diabetic patients). Similar finding was observed by many other studies. (3, 11, 27) several potential explanations exist for this finding, some hyperglycemic patients without known diabetes likely have diabetes that was not treated before hospitalization; these patients may, therefore, represent a higher-risk patients. Furthermore, the patients without known diabetes are much less likely to be treated with insulin than those with diabetes, and finally, it is also possible that a higher degree of stress (or severity of illness) is required to produce a similar degree of hyperglycemia in patients without known diabetes than in those with diabetes.(11) These findings highlight an important potential opportunity to improve care and outcomes for hyperglycemic ACS patients without known diabetes. Unlike most of other studies that showed hyperglycemia on admission was associated with increase incidence of arrhythmias (28,29), in our study, this association was not significant, which could be due to under detection of arrhythmias compared to other studies that use 24-hours monitoring or self-record monitors for arrhythmias. This study showed that admission hyperglycemia was better prognostic marker than 2nd day FPG, this was inconsistent with many other studies which stated that 2nd day FPG was equally of even better predictor of morbidity and mortality.(27,30) However our result can have two explanation, firstly, the admission blood glucose is better reflection of the degree of stress and thus the severity of ACS as the patient receives multiple drugs after admission including insulin that may alter the blood glucose, secondly, glucose levels generally decrease during the first 24 hours of hospitalization, which likely represents the amelioration of the acute stress response.(24)

Limitations of the study: In addition to relatively small size of the sample compared to other international studies, some of the non diabetic group of our study could be, in fact, undiagnosed cases of diabetes because we had not depend on HbA_{1c} to differentiate acute phase hyperglycemia from undiagnosed diabetes.

Conclusion:

Admission hyperglycemia is poor in-hospital prognostic marker in non-diabetic & to lesser extent in diabetic patients suffering acute coronary syndrome and it was associated with higher mortality in non diabetic but not in diabetic patients. While elevated 2nd day FPG is poor predictor of morbidity and mortality in both diabetic and non diabetic patients.

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