Glycated hemoglobin, admission blood glucose delta, and associated mortality in patients with acute ST-segment elevation myocardial infarction

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ABSTRACT

The importance of glucose metabolism in patients with acute coronary syndrome has been increasingly recognized. We conducted a retrospective study of the associations between prior glycated hemoglobin (HbA1c) levels, admission glucose values, HbA1c-derived estimated average glucose levels (eAG), admission glucose delta (admission glucose – eAG), and mortality in patients presenting with ST-segment elevation myocardial infarction. A total of 676 and 566 patients were included in the in-hospital and 12-month mortality models, respectively. Mean admission blood glucose values were higher in the in-hospital and 12-month mortality groups in patients with no prior diagnosis of diabetes ($P < 0.001$). Pre, post, and admission HbA1c levels and eAG levels were not associated with in-hospital or 12-month all-cause mortality. The admission glucose delta was higher in patients with in-hospital mortality (87.3 ± 122.7 mg/dL) than in patients who survived (35.88 ± 81.23 mg/dL; $P = 0.040$). The in-hospital death rate was significantly higher (17% vs 4%, $P = 0.017$) for patients with admission glucose delta ≥ 140 mg/dL compared to lower values. In conclusion, HbA1c-derived admission glucose delta is associated with in-hospital mortality in patients with ST-segment elevation myocardial infarction. The mechanisms for the association of acute hyperglycemia with increased acute coronary syndrome mortality are unclear.

KEYWORDS Acute coronary syndrome; diabetes mellitus; glycated hemoglobin; hyperglycemia; ST-segment elevation myocardial infarction

The importance of glucose metabolism in patients with acute coronary syndrome and acute myocardial infarction has been increasingly recognized. Glycated hemoglobin (HbA1c) levels correlate well with the average glucose levels over the preceding 8 to 12 weeks and are used in diagnosing diabetes mellitus.^{1–3} HbA1c has also been proposed as a marker for the risk and even severity of coronary artery disease, but there are conflicting results on the intensity of glucose control and cardiovascular events.^{4–6} Some but not all studies have found a positive association between admission HbA1c levels and poor clinical outcomes in patients with acute coronary syndrome.^{7–10} Some investigators found an association between higher HbA1c levels and mortality in patients with coronary artery disease without diabetes but not in patients with established diabetes.¹¹ Recent high HbA1c levels may increase the risk for non-ST-segment elevation myocardial infarction.¹² There are no published data on the prognostic utility of fluctuations in HbA1c levels with regards

to acute coronary syndrome mortality. In addition, the speed and intensity of HbA1c reduction to prevent future cardiovascular events have not been well established.⁵ This study analyzed the association between glucose levels—admission glucose levels, mean glucose levels prior to admission based on HbA1c, and changes in glucose levels based on admission levels and prior glucose levels derived from HbA1c—and outcomes in patients with acute myocardial infarction.

METHODS

We retrospectively studied the association between mortality rates in patients with ST-segment elevation myocardial infarction who had recent HbA1c measurements (on admission and up to 6 months prior to admission) to determine whether there was an HbA1c threshold for differences in in-hospital and 1-year mortality. To estimate acute changes in blood glucose levels, we defined the term “admission glucose

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Table 1. Patient characteristics

	In-hospital mortality					12-Month mortality				
	Alive		Dead		P	Alive		Dead		P
All	591	87%	85	13%		457	81%	109	19%	
Male	448	76%	52	61%	0.004	342	75%	68	62%	0.009
Female	143	24%	33	39%		115	25%	41	38%	
Age	58.7	±12.9	68.3	13.2	<0.0001	58.9	±13.1	66.6	±13.5	<0.001
Diabetes	163	28%	26	31%	NS	128	28%	31	28%	NS
No diabetes	428	72%	59	69%	NS	329	72%	78	72%	NS
On metformin	69	12%	12	14%	NS	54	12%	15	14%	NS
Other diabetic drug	48	8%	6	7%	NS	41	9%	7	6%	NS
On insulin	38	6%	9	11%	NS	29	6%	11	10%	NS
Smoker	294	50%	17	20%	<0.001	225	49%	30	28%	<0.001
Current smoker	251	42%	9	11%	<0.001	190	42%	19	17%	<0.002
ACEI use	173	29%	26	31%	NS	133	29%	37	34%	NS
Hypertension	348	59%	50	59%	NS	271	59%	68	62%	NS
Hyperlipidemia	191	32%	20	24%	NS	147	32%	27	25%	NS
Statin use	171	29%	28	33%	NS	136	30%	36	33%	NS
PAD history	15	3%	6	7%	0.025	10	2%	8	7%	0.006
Known CAD	192	32%	32	38%	NS	148	32%	42	39%	NS
Previous ACS	53	9%	2	2%	0.037	37	8%	6	6%	NS
Previous stent	78	13%	11	13%	NS	65	14%	14	13%	NS
On aspirin	155	26%	31	36%	0.048	123	27%	42	39%	0.016
Other antiplatelet drugs	59	10%	10	12%	NS	46	10%	16	15%	NS
Previous CABG	22	4%	4	5%	NS	20	4%	4	4%	NS
CHF history	29	5%	22	26%	NS	16	4%	8	7%	NS
ESKD	4	1%	3	4%	0.015	10	2%	6	6%	NS

ACEI indicates angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CHF, congestive heart failure; ESKD, end-stage kidney disease; NS, not significant; PAD, peripheral arterial disease.

delta” as the difference between admission blood glucose and the estimated average blood glucose (eAG) derived from admission HbA1c levels, when available. Our study also aimed to determine whether changes between recent, admission, and follow-up HbA1c levels and eAG values were associated with increased mortality.

A comprehensive chart review was performed for all adults with ST-segment elevation myocardial infarctions (*International Statistical Classification of Diseases and Related Health Problems* code 410) admitted to our academic medical center from January 1, 2010 to May 1, 2015. Adult patients aged 18 to 89 years at the time of admission were included. We reviewed all patients using documentation from all physicians during their index hospitalizations. We excluded patients who did not have an HbA1c measurement during the index admission for acute coronary syndrome, and we

manually reviewed charts to obtain the cases with HbA1c measurements up to 180 days prior to admission.

The following variables were collected and organized in our database: age, sex, ethnicity, admission vital signs (systolic and diastolic blood pressure and heart rate), time from symptom onset to presentation, past medical history (smoking; hypertension; peripheral arterial disease; coronary arterial disease, including previous acute myocardial infarction and/or revascularization; heart failure, including type and ejection fraction; hyperlipidemia; diabetes), medications used at time of admission (insulin, metformin, aspirin and other antiplatelet drugs, statins, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers), laboratory values on admission (high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, glucose, hemoglobin, red cell distribution width, creatinine, HbA1c), and laboratory values

Table 2. HbA1c, admission blood glucose, and in-hospital all-cause mortality in patients with ST-segment elevation myocardial infarction

	N	Mean	SD	In-hospital mortality						P
				Alive			Dead			
				N	Mean	SD	N	Mean	SD	
All patients										
Age	676	59.92	13.35	591	58.71	12.93	85	68.3	13.3	<0.001
Hemoglobin	665	14.02	3.11	585	14.29	2.87	80	12	4.02	<0.001
Glucose	668	161.6	119.7	588	153.6	109.7	80	221.2	166.1	<0.001
HbA1c on admission	230	7.30	2.29	218	7.3	2.32	12	6.60	1.30	NS
Average pre HbA1c	78	7.42	2.00	70	7.44	2.065	8	7.23	1.43	NS
Average post HbA1c	134	7.2	1.83	132	7.217	1.84	2	6	0.28	NS
Average HbA1c change preadmission	26	0.29	1.16	24	0.263	1.17	2	0.68	1.31	NS
Average HbA1c change postadmission	57	−0.73	1.70	57	−0.73	1.7	0	0	0	NA
eAG	78	162.2	65.6	218	162.00	65.8	12	164.2	65.5	NS
Acute glucose delta	230	38.56	84.31	218	35.88	81.23	12	87.3	122.7	0.040
Patients with known prior diabetes										
Hemoglobin	186	13.34	3.3	161	13.7	3.07	25	11.02	3.75	<0.001
Glucose	187	215.9	139.7	162	215	134.6	25	219.4	172	NS
HbA1c on admission	78	9.01	2.3	74	9.09	2.3	4	7.35	1.57	NS
Average pre HbA1c	51	8.25	1.97	44	8.38	2.02	7	7.41	1.44	NS
Average post HbA1c	69	8.16	1.89	68	8.19	1.88	1	5.8	0	NS
Average HbA1c change preadmission	18	0.37	1.36	16	0.331	1.4	2	0.675	1.308	NS
Average HbA1c change postadmission	30	−1.08	2.01	30	−1.08	2.01	0	0	0	NS
eAG	78	158.9	63.7	74	156.4	62.3	4	187.4	80.2	NS
Acute glucose delta	78	38.81	115.03	74	37.14	112.6	4	69.76	173.26	NS

eAG indicates estimated average blood glucose; HbA1C, hemoglobin A1C; NA, not applicable; NS, not significant; SD, standard deviation.

prior to admission. HbA1c was recorded up to 180 days prior to the event; if more than one value was available, the two most recent values were averaged. HbA1c levels >30 days from event but within 12 months were also recorded (if more than one was available, the first two values were averaged). Reperfusion strategy and results were also recorded when available. Mortality status and time from admission to death were recorded. Values for eAG were derived for each patient's HbA1c using a validated formula ($eAG = [28.7 * HbA1c] - 46.7$).³ A new diagnosis of diabetes mellitus was made if the admission HbA1c was $\geq 6.5\%$.¹³ Acute hyperglycemia was defined as ≥ 200 mg/dL, and chronic hyperglycemia was defined as an eAG ≥ 200 mg/dL. A significant acute glucose delta was, for the purpose of this study and statistical analyses, an admission glucose delta ≥ 140 mg/dL. The study protocol was approved by the institutional review board at Texas Tech University Health Sciences Center (#96 FWA #6767) in Lubbock, Texas.

Categorical variables were analyzed using chi-square or Fisher's exact test when applicable. Continuous variables were analyzed with Student's *t* tests and multivariate analysis. Descriptive statistics and adjusted logistic regression were used to determine associations. Odds ratios were calculated comparing interquartile glucose values and acute/chronic hyperglycemia subgroups.

RESULTS

The initial chart screen identified 1787 acute coronary syndrome admissions; 683 had an ST-segment elevation myocardial infarction diagnosis. Seven patients were omitted completely due to absence of necessary laboratory values for this study, and 110 patients did not have a 12-month follow-up. A total of 676 and 566 were included in the in-hospital and 12-month mortality models, respectively. General patient characteristics, in-hospital mortality rates, and 12-

Table 3. In-hospital mortality, admission glucose, and estimated average glucose subgroup analysis

		N	In-hospital mortality			P
			Alive (n)	Dead (n)	Rate	
Admission glucose subgroups						
AG ≥ 200 mg/dL	AGD ≥ 140 mg dL				0.014 ^a	
No	No	153	147	6	3.92%	
No	Yes	0	0	0	0%	
Yes	No	50	48	2	4.0%	
Yes	Yes	27	23	4	17%	
Estimated average chronic glucose and acute increase in glucose subgroups						
eAG ≥ 200 mg/dL	AGD ≥ 140 mg dL				0.027 ^a	
No	No	12	12	0	0%	
No	Yes	160	153	7	5%	
Yes	No	43	42	1	2%	
Yes	Yes	15	11	4	36%	
Acute increase in glucose subgroups						
	AGD ≥ 140 mg dL				0.017 ^b	
Yes		27	23	4	17%	
No		203	195	8	4%	

AG indicates admission glucose; AGD, admission glucose delta; eAG, estimated average glucose.

^aFisher's exact test.

^bChi-square test.

month mortality rates are summarized in [Table 1](#). Coronary angiography was performed in 637 patients (94%), percutaneous coronary interventions were performed in 621 patients (92%), and a final Thrombolysis in Myocardial Infarction grade 3 flow was obtained in 554 patients (87%). Non-Hispanic white ethnicity was significantly associated with in-hospital mortality ($P=0.018$); Hispanic ethnicity was significantly associated with 12-month mortality ($P < 0.0001$).

The mean admission blood glucose level was higher in patients with in-hospital and 12-month mortality. This difference was significant in patients with no known prior diabetes ($P < 0.001$). The odds ratios for death in patients with a glucose ≥ 219 mg/dL (quartile 4) compared to those with a glucose ≥ 60 to 124 mg/dL (quartile 1) were 13.59 (confidence interval [CI], 5.29–34.91) for in-hospital mortality and 7.08 (CI, 3.28–15.29) for 12-month mortality.

The HbA1c levels, blood glucose values, and in-hospital all-cause mortality associations are summarized in [Table 2](#). The admission glucose delta was higher in patients with in-hospital mortality (+150.84 mg/dL; SD = 146.11) than in patients alive at discharge (+68.84 mg/dL; SD = 124.74; $P < 0.006$). Multivariate analysis (including gender, age, prior myocardial infarction, known diabetes, smoking, insulin use, aspirin use, creatinine, and hemoglobin) demonstrated that admission glucose levels were significantly

associated with in-hospital and 12-month all-cause mortality ($P < 0.001$). This same model demonstrated that admission glucose delta, but not eAG, was significantly associated with in-hospital mortality ($P=0.0079$). The number of patients with HbA1c values obtained within the prior 6 months, on admission, or within 6 months of discharge was 78 (11%), 230 (34%), and 134 (24%), respectively. HbA1c levels $\geq 6.5\%$ were present in 68 and 33 patients with diagnosed and undiagnosed diabetes, respectively. No statistical difference was found in mean HbA1c or mean eAG levels when comparing in-hospital and 12-month mortality groups (for both patients with and without diabetes). The average pre-event to admission HbA1c change (+0.68%, $N=28$) was highest in the in-hospital mortality group, but this did not reach statistical significance.

The in-hospital death rates for eAG and admission glucose subgroups in relation to admission glucose delta are summarized in [Table 3](#). The groups with a significant admission glucose delta had statistically significant higher in-hospital mortality for both acute ($P=0.014$) and chronic hyperglycemia ($P=0.027$) subgroups. The nonadjusted odds ratio for in-hospital death for patients with admission glucose delta >140 mg/dL was 4.24 (CI, 1.18–15.18; $P=0.017$). In the subgroup of patients with acute hyperglycemia (admission glucose ≥ 200 mg/dL), the nonadjusted odds ratio for

in-hospital death was 4.14, but this was not statistically significant (CI, 0.71–24.47; $P=0.176$).

DISCUSSION

Acute hyperglycemia in patients with acute coronary syndrome has several clinical implications. These patients could have established diabetes, undiagnosed diabetes or impaired glucose tolerance, or stress-related hyperglycemia. Patients with diabetes or a new diagnosis of diabetes could have either established or subclinical vascular disease. The important question is whether or not hyperglycemia has independent pathophysiological effects in the clinical course of patients with acute coronary syndrome. Other studies have reported associations with hyperglycemia and mortality in acute coronary syndrome.¹⁴ One strength of our study is the simultaneous analysis of both acute hyperglycemia and HbA1c as a marker of chronic hyperglycemia. This allowed us to analyze the relation between the absolute glucose level on admission, the chronic glucose level prior to admission, and the change in glucose levels from the chronic level and mortality outcomes in this study.

Our study does not explain why acute hyperglycemia but not chronic hyperglycemia (based on the eAG) was associated with increased mortality. Aronson et al reported that fasting glucose levels measured within 24 hours of admission in patients with acute coronary syndromes were independent predictors of mortality in nondiabetic patients but not in patients with diabetes.¹⁵ Earlier studies have found an association with acute hyperglycemia, infarction size, and a prothrombotic state.^{16,17} Animal studies have shown suppression of diastolic function with acute hyperglycemia.¹⁸ In contrast, chronic hyperglycemia might limit reperfusion injury in patients with acute coronary syndrome.¹⁹ The concept of admission glucose delta (also reported in the literature as “glycemic gap”) could be a possible addition to current prognostication scores for acute coronary syndrome and possibly other acute cardiovascular conditions.^{20,21} Aronson et al reported that adding the fasting glucose level to the Global Registry of Acute Coronary Events risk score increased the C statistics for this tool.¹⁵ However, other studies did not find that the addition of glucose levels changed the prognostic value of the Global Registry of Acute Coronary Events risk score in patients with non-ST-segment elevation acute coronary syndromes or in patients with myocardial infarction.^{22,23} Acute hyperglycemia, which, as seen in this study, usually accompanies a significant admission glucose delta (Table 3), can be both a mediator of injury and a marker of acute physiological stress.^{24,25}

This study did not allow for adequate assessment of a possible correlation between hyperglycemia and markers of acute stress. Choi et al studied 30 patients with acute myocardial infarction at the end of their hospitalization using an oral glucose tolerance test.²⁶ They reported that the patients with acute myocardial infarction and impaired glucose tolerance or diabetes had higher C-reactive protein levels and higher interleukin-6 levels than patients with acute

myocardial infarction who had normal glucose tolerance or a control group of patients with type 2 diabetes. There were no differences in these levels in these patient groups 3 months after discharge. Wong et al studied the effect of insulin infusion and tight glycemic control on C-reactive protein levels in patients with acute myocardial infarction.²⁷ C-reactive protein levels were significantly higher on the second postinfarction day in patients receiving conventional therapy than in patients receiving intensive insulin therapy. There was a positive correlation between serum C-reactive protein levels on day 2 and mean glucose levels during the first 24 hours of hospitalization for the entire cohort enrolled in this study. This study demonstrates that both insulin therapy and tight glycemic control likely reduce the inflammatory response associated with myocardial infarction.

There is uncertainty about the optimal treatment of these metabolic derangements in acute coronary syndrome. Two trials have evaluated the potential benefit of glucose-insulin-potassium infusions in patients with acute myocardial infarction.^{28,29} The Clinical Trial of Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation—Estudios Cardiológicos Latinoamerica trial randomly assigned patients with acute ST-segment elevation myocardial infarction to 24-hour glucose-insulin-potassium infusions or placebo infusions.²⁸ There was no difference in 30-day mortality rates, but significantly more symptomatic hypoglycemia was reported in the treatment group (hazard ratio=3.11; CI, 1.57–6.13; $P<0.001$). The Out of Hospital Administration of Glucose, Insulin, and Potassium trial (IMMEDIATE trial) randomly assigned glucose-insulin-potassium infusions to patients with acute coronary syndrome (ST-segment elevation myocardial infarction in approximately 40%) administered out of hospital and continued for 12 hours.²⁹ There was no difference in mortality rates at 30 days between treatment and placebo groups. These two studies indicate that complex efforts to manage glucose levels in patients hospitalized with acute myocardial infarction, including the systematic administration of insulin, do not have a definite effect on outcomes.

Our study had several limitations. First, it was a retrospective chart review from a single tertiary care hospital, and this information may not be generalizable to other medical centers. Second, the number of patients with qualifying HbA1c results may have not been adequate to identify complex associations. Third, we did not evaluate glucose management strategies either in the hospital or after discharge; both the success and the adverse effects associated with any treatment for hyperglycemia could affect outcomes.

In conclusion, our results identify a significant association between acute elevations in blood glucose and mortality in ST-segment elevation myocardial infarction, particularly in nondiabetics. Neither HbA1c levels nor eAG levels were independently associated with all-cause mortality in this cohort. In addition, the rates of in-hospital death in the subgroup of patients with admission glucose delta ≥ 140 mg/dL was significantly higher (17% vs 4%; $P=0.017$) than in patients with

lower values. This admission glucose delta effect was noted in the subgroups of patients with elevated admission (acute hyperglycemia) and elevated eAG (chronic hyperglycemia), as seen in [Table 3](#). These findings imply that acute increases in glucose, in addition to the absolute admission glucose level, may be a factor in morbidity and mortality in patients with acute coronary syndrome. The precise mechanisms for the association with acute hyperglycemia with increased acute coronary syndrome mortality and the best management strategies are unclear and require further investigation.³⁰

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