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Association between admission blood glucose and prognosis in non-diabetic patients with first-ever acute myocardial infarction

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Background: Admission hyperglycemia has been associated with major adverse cardiovascular and cerebrovascular events (MACCEs) in patients with acute coronary syndrome.

Methods: In this study we sought to determine the association between admission blood sugar (ABS) and the outcomes of non-diabetic patients with first-ever acute myocardial infarction (MI). Non-diabetic patients with MI were evaluated from March 2016 to March 2019. Baseline characteristics, laboratories, electrocardiogram, and baseline left ventricular ejection fraction (LVEF) were recorded. All patients were followed up and outcomes were obtained. Follow-up data comprised of repeating electrocardiogram and echocardiography at 1 year, and MACCE, including re-MI, stroke, and mortality.

Results: A total of 312 patients with a mean age of 54.2 ± 11.9 years were evaluated. All patients were followed up for a median of 38 months. The frequencies of in-hospital mortality and MACCE at late follow-up were higher in third tertile of ABS compared with those in first and second tertiles (both $p < 0.05$). Based on the Cox regression analysis, the independent predictors of MACCE included age (hazard ratio [HR] 1.068, 95% confidence interval [CI] 1.033 – 1.105, $p < 0.001$), third tertile of ABS >172 mg/dL (HR 21.257, 95% CI 2.832 – 159.577, $p=0.003$), and baseline LVEF (HR 0.947, 95% CI 0.901 – 0.995, $p=0.031$).

Conclusion: Admission stress hyperglycemia is associated with increased rates of in-hospital mortality and MACCE at late follow-up in non-diabetic patients with MI. Moreover, elevated ABS, older ages, and a decreased value of baseline LVEF predicted MACCE during follow-up.

Key words: myocardial infarction, acute coronary syndrome, hyperglycemia, blood glucose, mortality.

INTRODUCTION

Acute coronary syndrome (ACS) includes a full spectrum of clinical manifestations from unstable angina to acute myocardial infarction (MI), and numerous biomarkers are implemented to diagnose such a life-threatening clinical entity and predict the prognosis of the patients [1]. Atherosclerotic plaques get ruptured and lead to thrombus formation and the initiation of inflammatory mechanisms, through which those result in the development of ischemic events, the so-called ACS phenomenon [2, 3]. In the emergency department, about half of patients with suspected ACS have hyperglycemia [4]. Diabetic patients with ACS have been demonstrated to have worse outcomes than those with normal blood glucose levels or impaired glucose regulation [5–7]. The abnormal levels of serum glucose at admission time have been found to predict clinical outcomes in ACS patients [8, 9].

Acute phase hyperglycemia has been associated with major adverse cardiovascular events after MI in patients with or without diabetes mellitus [10, 11]. Although the pathophysiology of this epiphenomenon is not clearly defined, it is postulated to be a response to stress resulting from catecholamine-induced glycogenolysis and accumulation of excessive free fatty acids in cardiac muscle [12, 13]. Therefore, decreased myocardial contractility can lead to pump failure and arrhythmias, and also it can influence on coronary perfusion in MI patients [13]. The association between blood glucose and prognosis has been confirmed by the improved outcomes of MI [14] and critically ill patients [15] after administration of insulin. A meta-analysis showed that the higher levels of serum glucose during MI increased the risk of death in patients with or without diabetes mellitus, and it also enhanced the development of congestive heart failure

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or cardiogenic shock following MI among non-diabetic patients [16]. Hence, in this study we sought to determine the association between admission blood sugar (ABS) concentration and the outcomes of non-diabetic patients who were diagnosed with first-ever acute MI, both ST-segment and non-ST-segment elevation MI.

MATERIALS AND METHODS

Study population

In a retrospective study, patients with an initial diagnosis of ACS admitted to the emergency department were evaluated from March 2016 to September 2018. The study protocol was approved by the local ethics committee of our institution with an identification number of IR.IUMS.FMD.REC.1397.183. The inclusion criteria included individuals >18 years, non-diabetic patients with a diagnosis of first-ever acute MI, and the availability of measurement of ABS. Patients were excluded if they had a prior history of MI, had known diabetes mellitus, were on insulin and/or oral anti-diabetic agents, had a prior history of impaired glucose concentration, were on regimen of dietary restriction for hyperglycemia status, and were diagnosed with diabetes mellitus before discharge. Moreover, individuals with sepsis, uremia, hypothyroidism, alcohol consumption, hemoglobinopathies, and a history of gestational diabetes were also excluded. Of 1078 consecutive patients with a diagnosis of acute MI, a total 312 non-diabetic patients fulfilled inclusion criteria were recruited in this study. The study protocol was approved by the local ethics committee of our institution. Due to being retrospective study, obtaining consent from patients was waived for this cohort.

Data collection and follow-up assessments

Baseline characteristics (age, sex, and conventional cardiovascular risk factors), laboratories (ABS, white blood cell count [WBC], hemoglobin, creatinine, peak creatine kinase MB isoenzyme, and peak cardiac troponin), and electrocardiogram (ECG) changes at presentation were obtained. The amount of left ventricular ejection fraction measured by two-dimensional transthoracic echocardiography at initial presentation was also recorded. The diagnosis of acute MI was based on the latest recommendations during the study period [17]. All diagnostic coronary angiographies were performed through femoral or radial arteries using the Judkins' method (Siemens, Forcheim, Germany). The identification of coronary artery disease was based on invasive coronary angiography during which the significant narrowing of the coronary artery lumen was considered as coronary artery disease.

All patients were also followed up and their clinical outcomes were obtained via visiting in outpatient clinic and telephone interview. Follow-up data comprised of repeating ECG and echocardiography at 1 year after first admission. Laboratories (i.e., WBC, hemoglobin, and creatinine) were assessed at admission to the hospital. The occurrence of major adverse cardiovascular and cerebrovascular events (MACCE) was collected during follow-up period which were included MI, stroke, and all-cause of mortality. The identification of MACCE during follow-up period was based on hospital discharge note provided by patient or its family members.

Statistical analysis

The study population was categorized into tertiles based on the ABS percentiles (<120 mg/dL, 120–172 mg/dL, and >172 mg/dL). In addition, patients were also divided into two groups using the median values of continuous variables, including age and left ventricular ejection fraction (LVEF). Continuous variables were expressed as mean ± SD or median (interquartile range), and categorical variables were mentioned as number (percentage). The chi-squared test or the Fisher's exact test was implemented to compare categorical variables between groups as appropriate. Continuous variables were compared between the defined groups using t-test, ANOVA, Mann-Whitney U test, or Kruskal-Wallis test as appropriate. The differences between paired groups were analyzed using post hoc test. Receiver operating characteristics curve (ROC) was implemented to identify the best cut-off point for ABS levels discriminating patients with MACCE from those without MACCE at follow-up period. The Kaplan-Meier curve was constructed to evaluate the freedom from MACCE at follow-up period among study groups by the ABS tertiles; the log rank test was applied to compare ABS tertiles. Moreover, a multivariable Cox regression analysis was conducted to found the main predictors of MACCE at follow-up period. To perform multivariable analysis, variables shown to be associated with prognosis of patients with acute MI were entered into the regression model (i.e., age,

sex, hypertension, dyslipidemia, smoking, laboratories, LVEF, the extension of coronary artery disease, and the type of MI). Two-sided p-values were reported. All statistical analyses were performed using STATA software (StataCorp, TX, USA).

RESULTS

A total of 312 non-diabetic patients with an acute MI were evaluated. The mean of age was 54.2 ± 11.9 years, and 252 (80.8%) of patients were male. The median of ABS level in the study population was 138 (114, 195) mg/dL, and 247 (79.2%) patients had ST-segment elevation MI. seventy-one (22.8%) had three-vessel coronary artery disease, and two-hundred forty (76.9%) patients underwent primary percutaneous coronary intervention. Based on the ABS levels, patients were divided into tertiles. Patients in third and second tertiles were older than those in first tertile, while the distribution of male was comparable between groups. Hypertension was significantly higher in third and second tertiles than that in first tertile (p = 0.002). Other baseline values are summarized in Table 1.

Table 1

Baseline characteristics of population in groups by ABS tertiles

	First tertile* **n = 103**	**Second tertile*** **n = 107**	**Third tertile*** **n = 102**	**P value**
Age, year	49.4 ± 10.8	54.2 ± 11.5 [c]	59.2 ± 11.5 [a,b]	<0.001
Male sex	85 (82.5)	86 (80.4)	81 (79.4)	0.845
BMI, kg/m^2	27.8 ± 3.7	26.8 ± 5	27.3 ± 4.6	0.290
Hypertension	31 (30.1)	53 (49.5)	53 (52)	0.002
Dyslipidemia	48 (46.6)	51 (47.7)	56 (54.9)	0.432
Smoking	47 (45.6)	49 (45.8)	44 (43.1)	0.912
Type of MI				0.093
STEMI	77 (74.8)	82 (76.6)	88 (86.3)	
NSTEMI	26 (25.2)	25 (23.4)	14 (13.7)	
CAD involvement				0.104
1VD	63 (61.2)	76 (71)	63 (61.8)	
2VD	13 (12.6)	16 (15)	10 (9.8)	
3VD	27 (26.2)	15 (14)	29 (28.4)	
Treatment type				0.584
Primary PCI	80 (77.7)	85 (79.4)	75 (73.5)	
Thrombolytic	23 (22.3)	22 (20.6)	27 (26.5)	
Baseline LVEF, %	43 ± 6.5	40.6 ± 6.9	36.7 ± 7.1	<0.001
Admission laboratories				
ABS, mg/dL	106 (100, 114)	138 (126, 155) [c]	226 (195, 314) [a,b]	<0.001
WBC, 10^9/l	9.9 (8.3, 12.3)	9.7 (7.9, 12.3)	10.8 (8.7, 12.8)	0.265
Hemoglobin, g/dL	14.6 (12.4, 15.9)	14.8 (13.3, 15.8)	14.2 (12.7, 15.8)	0.476
Creatinine, mg/dL	1 (1, 1.2)	1 (0.9, 1.1)	1.1 (1, 1.2) [b]	0.066
Peak CK-MB, U/l	89 (58, 135)	85 (53, 213)	81 (65, 161)	0.583

Data are presented as mean ± SD, number (%), or median (interquartile range)

* Some patients had similar values of ABS and that is why number of patients are not equal in tertile groups

[a] A significant difference between first and third tertile groups

[b] A significant difference between second and third tertile groups

[c] A significant difference between first and second tertile groups

ABS, admission blood sugar; CAD, coronary artery disease; CK-MB, creatine kinase MB isoenzyme; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-segment-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment-elevation myocardial infarction; VD, vessel disease; WBC, white blood cell count

The median of ABS was significantly higher in older patients than that in younger ones (191 [136, 310] vs. 131.5 [112, 180] mg/dL in age ≥65 and age <65 years, respectively, p <0.001) and in patients with hypertension than that in non-hypertensive ones (154 [121, 213] vs. 131 [112, 186] mg/dL, p = 0.006). The ABS level was comparable in subgroups by sex, smoking, type of MI, dyslipidemia, and the extent of coronary artery disease (all had p >0.05). On the other hand, patients with baseline LVEF <44% had a higher level of ABS compared with patients with LVEF ≥44% (161 [123, 217] vs. 118.5 [105, 148] mg/dL, p <0.001).

The rate of in-hospital mortality was 12 (3.8%), and all of them occurred in patients

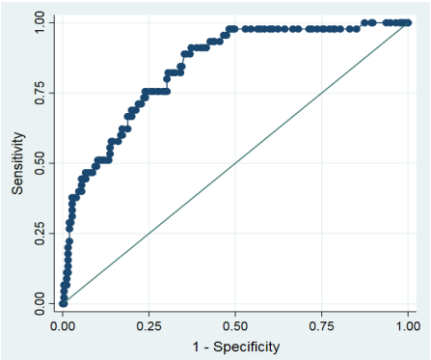
assigned as third tertile of ABS (p <0.001). After discharge, all patients were also followed up for a median of 38 months (2 to 54 months). Admission WBC was comparable between patients with or without MACCE at follow-up period (p >0.05); however, the median of ABS was significantly higher among patients with MACCE at follow-up compared with patients without it (214 [170, 316] vs. 125 [111, 168], p <0.001). When compared the study outcomes among ABS tertiles, the frequency of the patients with normal ECG at 1-year follow-up decreased with increasing ABS tertiles (p = 0.003). Moreover, the numbers of patients with all-cause mortality were significantly higher in third tertile than those in second and first tertiles (p <0.001). The rate of MACCE in groups enhanced with advancing ABS tertile, and it was significantly different between groups (1%, 11.2%, and 35.6% by order in ABS tertiles, p <0.001; Table 2). When compared groups by LEVF level at 1-year follow-up, patients with LVEF <45% had a higher level of ABS compared with patients with LVEF ≥45% (177 [144, 226] vs. 117 [105, 135], p <0.001).

Table 2
Outcomes of patients during long-term follow-up in groups by ABS tertiles

	First tertile n = 103	**Second tertile n = 107**	**Third tertile* n = 90**	**P value**
Normal ECG**	18 (17.5)	8 (7.8)	4 (4.4)	0.003
LVEF after 1 year	50.3 ± 4.5	44 ± 5.9 [c]	40 ± 6.1 [a,b]	<0.001
Re-MI	1 (1)	10 (9.3)	28 (31.1)	<0.001
Stroke	0 (0)	0 (0)	3 (3.3)	0.029
Late mortality	0 (0)	4 (3.7)	13 (14.4)	<0.001
MACCE	1 (1)	12 (11.2)	32 (35.6)	<0.001

Data are presented as mean ± SD or number (%)
** Patients with in-hospital mortality were excluded so that to be able to evaluate mid-term outcomes in survived patients
* Normal ECG taken 1 year after admission defined as the resolution of changes caused by MI
[a] A significant difference between first and third tertile groups
[b] A significant difference between second and third tertile groups
[c] A significant difference between first and second tertile groups
ECG, electrocardiogram; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction

Based on the ROC curve analysis, the optimal level of ABS for discriminating patients with MACCE from those without MACCE was 147 mg/dL (area under the curve = 0.839, 95% confidence interval [CI] 0.781 – 0.897, sensitivity 89%, specificity 65%; Figure 1). The rate of freedom from MACCE at follow-up period was significantly different among ABS tertiles (log rank test p <0.001, Figure 2). Based on the Cox regression analysis, the independent predictors of MACCE included age (hazard ratio [HR] 1.068, 95% confidence interval [CI] 1.033 – 1.105, p <0.001), third tertile of ABS >166 mg/dL (HR 21.257, 95% CI 2.832 – 159.577, p = 0.003), and baseline LVEF (HR 0.947, 95% CI 0.901 – 0.995, p = 0.031). Other findings are summarized in Table 3.



Area under the curve = 0.839, 95% confidence interval [CI] 0.781 – 0.897

Figure 1. ROC curve showing ABS levels discriminating patients with or without MACCE at follow-up.

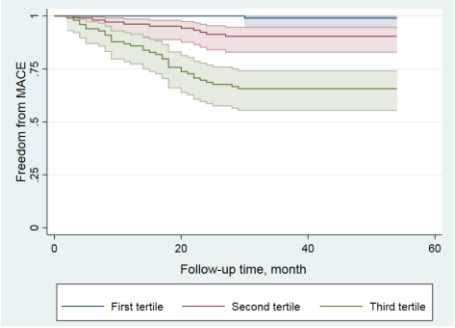


Figure 2. Kaplan-Meier curve showing freedom from MACCE at follow-up period in study groups by ABS tertiles.

Table 3

Predictors of MACCE during follow-up period in study population

	HR	95% CI	P value
Male vs. female	0.850	0.353 – 2.047	0.716
Age	1.068	1.033 – 1.105	**<0.001**
Hypertension	1.902	0.896 – 4.040	0.094
Dyslipidemia	1.126	0.576 – 2.199	0.729
Smoking	1.406	0.665 – 2.972	0.373
CAD involvement			
2VD vs. 1VD	2.031	0.776 – 5.315	0.149
3VD vs. 1VD	1.260	0.591 – 2.686	0.550
STEMI vs. NSTEMI	0.965	0.401 – 2.320	0.936
Baseline LVEF	0.947	0.901 – 0.995	**0.031**
ABS tertiles			
Second vs. first	6.663	0.842 – 52.717	0.072
Third vs. first	21.257	2.832 – 159.577	**0.003**
Admission creatinine	1.189	0.578 – 2.446	0.639
Admission WBC	0.991	0.886 – 1.108	0.872
Admission hemoglobin	1.002	0.840 – 1.196	0.980
Admission peak CK-MB	1.004	0.998 – 1.010	0.164

ABS, admission blood sugar; CAD, coronary artery disease; CI, confidence interval; CK-MB, creatine kinase MB isoenzyme; HR, hazard ration; NSTEMI, non-ST-segment-elevation myocardial infarction; STEMI, ST-segment-elevation myocardial infarction; VD, vessel disease; WBC, white blood cell count

DISCUSSION

In this observational study we found that ABS level was associated with prognosis in non-diabetic patients with first-ever acute MI. Patients with higher levels of ABS had a higher frequency of in-hospital mortality and MACCE (i.e., re-MI, stroke, and all-cause mortality) during follow-up period. Moreover, older ages and third tertile of ABS >172 mg/dL strongly predicted the development of MACCE during follow-up period. Moreover, the amount of baseline LVEF predicted MACCE at follow-up. All these findings are in lines with prior studies in which admission hyperglycemia and/or fasting blood sugar have been associated with poor prognosis of ACS [4, 8, 10, 16, 18–23].

Some studies investigated the association between ABS and outcomes of ACS patients [4, 18, 24], in which they demonstrated that ABS levels correlate with poor prognosis. Among 2127 patients with ACS, Foo *et al*. [24] found that elevated ABS levels increased risk of in-hospital mortality irrespective of ACS type, MI versus unstable angina. Bellodi *et al*. [10] evaluated non-diabetic patients with acute MI and showed that mortality increased with advancing ABS levels. In multivariable analysis, age, infarct site, and cardiogenic shock predicted mortality, but ABS did not. In a retrospective study on 2,482 patients with ST-segment-elevation MI, admission hyperglycemia was associated with long-term cardiovascular mortality [20]. Timmer *et al.* [25] showed that both elevated admission glycosylated hemoglobin and blood glucose in non-diabetic patients with ST-segment-elevation MI were associated with adverse outcomes, but after multivariate analysis, only glycosylated hemoglobin (HR 1.2 per interquartile range, p <0.01), but not ABS, predicted long-term mortality. In contrast, Naito *et al*. [26] found that a combination of increased ABS and increased glycosylated hemoglobin was associated with long-term evnets in non-diabetic ACS patients. In another study among 188 non-diabetic patients with ST-segment-elevation MI [19], ABS >170 mg/dL, inflammatory markers (WBC and C-reactive protein), and heart rate predicted cardiovascular events (i.e., death, re-MI, as heart failure) at 6-month follow-up period. In our study, we also showed that increased ABS, reduced baseline LVEF, and advancing age were independent predictors of MACCE at mid-term follow-up. However, baseline WBC did not correlate with poor prognosis in our study.

The effect of ABS on ACS outcome can be influenced by the presence of diabetes mellitus. Cid-Alvarez *et al.* [18] demonstrated that

increased ABS and fasting blood glucose levels increased risk of death during follow-up among 811 non-diabetic ACS patients, but not diabetics. On the other hand, Ergelen *et al.* [20] revealed that elevated ABS correlated with in-hospital death among both diabetic and non-diabetic ACS patients. Moreover, Dziewierz *et al.* [8] assessed 607 acute MI patients and found an association between elevated ABS and in-hospital mortality in both non-diabetic and diabetic patients [8]. A meta-analysis of 15 studies revealed that stress hyperglycemia was associated with an increased rate of in-hospital mortality in MI patients with and without diabetes [16]. In another meta-analysis Hao *et al.* [22] demonstrated that elevated ABS has a poorer prognostic effect on long-term death than early death among non-diabetic patients with MI. All these findings are similar to our findings indicating the association between elevated ABS and the development of short-term and late events. Particularly, patients in third tertile of ABS had a high rate of in-hospital mortality compared to other tertiles, indicating the higher risk of events in patients with elevated ABS that might benefit from more aggressive therapies and/or intervention. Given strong association between stress hyperglycemia and ACS outcomes, American Heart Association advised glucose control in hyperglycemic patients with MI [27]. Hence, some trials investigated the effect of insulin infusion on blood glucose control in MI patients. Although the DIGAMI study demonstrated a decrease in mortality among MI patients giving insulin-glucose infusion [14], the DIGAMI-2 and the HI-5 trials were not able to improve outcomes of patients with acute MI compared with conventional management [28, 29]. Some recent studies have also found the prognostic value of fasting glucose in patients with MI, indicating the association between fasting glucose and the risk of heart failure and left ventricular systolic dysfunction in non-diabetic patients with MI [30] as well as microvascular obstruction after primary percutaneous coronary intervention in patients with MI [31]. While the effect of stress hyperglycemia on ACS prognosis is repeatedly demonstrated, there are controversies regarding the management of glucose level, so that future large-scale trials are urgently required to reach a consensus about the proper approach to ACS patients presenting with abnormal ABS levels.

Study limitations

The main strength of our study is that we enrolled only non-diabetic patients with first episode of acute MI, and followed up them within a mid-term period. Moreover, the association between outcomes and ABS was confirmed in an adjusted multivariable model. However, this study suffers from some shortcomings needs to be addressed in further studies. First, this report was a retrospective study with a small sample size. Second, we could not measure other inflammatory markers, which could provide further insights into the pathogenesis of this hypothesis. Third, it has been demonstrated that the homeostatic model assessment (HOMA) index might be a novel tool for evaluating the acute hyperglycemic state, insulin resistance, in patients with ACS [32, 33]; however, we did not measure this parameter and further studies are required to evaluate such tool in predicting non-diabetic MI patients. Finally, further large-scale studies are required to explore the effect of ABS on outcomes of non-diabetic patients with MI, and to examine the impact of insulin infusion on outcomes of patients with acute MI.

CONCLUSIONS

Our observational study showed that admission stress hyperglycemia was significantly associated with increased rates of in-hospital mortality and of MACCE at late follow-up period in non-diabetic patients with first-ever acute MI. Moreover, elevated ABS, older ages, and a decreased value of baseline LVEF independently predicted MACCE at follow-up period.

Introducere. *Hiperglicemia la internare se asociază cu evenimente cardiovasculare adverse severe (MACCEs) la pacienții cu sindrom coronariar acut.*

Metode. *Scopul studiului a fost de a evalua asocierea dintre glicemia la internare (ABS) și efectele la pacienții non-diabetici cu infarct miocardic. Au fost incluși pacienți din martie 2016 și martie 2019. Pacienții au fost evaluați clinic și paraclinic și au fost urmăriți timp de 1 an pentru efectele – reinfarctizare, deces, dezvoltare atac vascular cerebral.*

Rezultate. *312 pacienți cu vârste între 54,2 ± 11,9 ani au fost evaluați. Toți pacienții au fost evaluați un timp mediu de 38 luni. Pacienții din a treia terțilă ABS au avut mortalitate și reinfarctizare mai mari decât cei din a doua sau prima terțilă. Predictorii independenți pentru MACCEs au fost vârsta (HR 1,068, 95% [CI] 1,033 – 1,105, p <0,001), ABS ; 172 mg/dL (HR 21,257, 95% CI 2,832 – 159,577, p=0,003) și fracția de ejecție la internare (HR 0,947, 95% CI 0,901 – 0,995, p=0,031).*

Concluzii. *Hiperglicemia de stress s-a asociat cu mortalitate mare intraspitalicească.*

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