Clinical research

Does stress hyperglycemia affect mortality? Acute myocardial infarction – case control study

Hayri Cinar[1], Akkan Avci[1], Muge Gulen[1], Begum Seyda Avci[2], Ertan Comertpay[1], Salim Satar[1]

[1]Department of Emergency Medicine, Health Science University, Adana City Research and Training Hospital, Adana, Turkey
[2]Department of Internal Medicine, Health Science University, Adana City Research and Training Hospital, Adana, Turkey

Submitted: 1 July 2019
Accepted: 18 July 2019

Arch Med Sci Atheroscler Dis 2019; 4: e201–e207
DOI: https://doi.org/10.5114/amsad.2019.87303

Corresponding author:
Akkan Avci MD
Department of Emergency Medicine
Health Science University
Adana City Research and Training Hospital
01060 Adana, Turkey
E-mail: drakkanavci@gmail.com

Abstract

Introduction: We aimed to investigate the effect of stress (acute) hyperglycemia in patients with acute coronary syndrome who had not been previously diagnosed with diabetes mellitus (DM) on the prognosis of the disease in terms of mortality.
Material and methods: Patients who were admitted to the Adana Numune Training and Research Hospital Emergency Service Clinic between August 2010 and August 2013 and whose plasma blood glucose level was over 140 mg/dl at the time of admission but were not previously diagnosed with DM, who were over the age of 18 and considered to have acute myocardial infarction were included.
Results: A total of 259 patients whose data were fully attainable were included in the study. 80.3% (n = 208) of the patients were male and 19.7% (n = 41) were female. Non-ST elevation myocardial infarction was found in 71.6%, ST elevation myocardial infarction was found in 28.4% of the patients with stress hyperglycemia. It was determined that 10.1% of patients with stress-related hyperglycemia and 1.3% of patients without stress-related hyperglycemia had died.
Conclusions: The plasma blood glucose level at presentation of patients diagnosed with acute myocardial infarction at the emergency room is associated with early in-hospital mortality.

Key words: acute myocardial infarction, hyperglycemia, mortality.

Introduction

Ischemic necrosis of the myocardium is called myocardial infarction. Despite improvements in medical and interventional treatments in the last 40 years, acute myocardial infarction (AMI) is still an important cause of mortality and morbidity. It has been reported that there are approximately 230,000 new coronary events each year, 160,000 men and 120,000 women die annually and approximately 66,000 men and 61,000 women die annually from a coronary cause, in the long-term study of Cardiac Disease and Risk Factors in Turkish Adults (TEKHARF) in our country [1].

Stress hyperglycemia is a transient increase in blood glucose during acute physiological stress in the absence of diabetes (normal glucose homeostasis before stress). This phenomenon usually will be determined in critically ill patients and the concentration of glucose varies in the range of 140–300 mg/dl [2].

Hyperglycemia and impaired glucose tolerance are common during AMI. The hyperglycemia seen at the onset of AMI appears to be related to the introduction of stress mechanisms. This mechanism is a reflection of steroid hormones and insulin resistance, excess of adrenaline, glucagon and high free fatty acids [3]. In fact, this mechanism, which enters the circuit in order to adapt to the stress situation, becomes harmful due to mitochondrial damage, oxidative stress-related damage in cells, endothelial damage and cardiac potassium channel dysfunction, and affects the course of critical illness negatively [4, 5].

We aimed to investigate the effect of stress (acute) hyperglycemia in patients who applied to the Emergency Medical Clinic of our hospital, have been diagnosed with AMI and had not been previously diagnosed with diabetes mellitus (DM), on the prognosis of the disease in terms of mortality.

Material and methods

Patient selection

The study's ethics committee approval was received on September 22, 2013 with decision number 46 of the Ethics Committee of Non-Interventional Clinical Research of Adana Numune Education and Research Hospital's Ethics Committee. Patients admitted to Adana Numune Education and Research Hospital Emergency Service Clinic between August 2010 and August 2013, with a blood sugar level over 140 mg/dl, based on the guidelines of the 2009 American Association of Clinical Endocrinologists (AACE) and the American Diabetes Association (ADA) stress hyperglycemia criteria, but not previously diagnosed with DM, whose medical data were completely accessible, and accepted as AMI according to the European Society of Cardiology (ESC) 2011 Third Universal Myocardial Infarction description. Patients' consent was not taken, because this study was done retrospectively.

Inclusion criteria

Male and female patients over the age of 18, whose file information was fully accessible and who do not have coronary artery disease (CAD), hypertension (HT), acute/chronic renal disease (ARD/CRD), cerebrovascular event (CVE) and malignancy in their histories; who have not been diagnosed with DM or a glycated hemoglobin (HbA_{1c}) value measured in the last 3 months was less than 6.5; whose blood sugar at admission was > 140 mg/dl, and the HbA_{1c} level was lower than 6.5 in the last 3 months; who had at least two findings relevant to AMI in addition to chest pain, electrocardiograpohy (ECG) findings and high CK-MB/high-sensitivity troponin T values at the time of admission to the hospital were included in the study.

Exclusion criteria

Patients who were younger than 18 were excluded from the study. Patients who had acute coronary syndrome (ACS), HT, ARD/CRD, CVE, or malignancy in their history; who has been diagnosed with DM or had a HbA_{1c} level measured in the last 3 months over 6.5; who did not have at least 2 symptoms that were relevant to AMI in addition to chest pain, ECG findings and high CK-MB/high-sensitivity troponin T values at the time of admission; who refused to be admitted to the hospital or refused the angiography and patients who had missing information in their files were excluded.

At the beginning of our study, files of all patients admitted to Adana Numune Training and Research Hospital Emergency Medical Clinic between 2010 and 2013 and hospitalized with acute myocardial infarction were retrospectively reviewed through the hospital automation system. From the file information, the age, sex, preexisting DM and ACS and other comorbid diseases, the blood glucose levels at the time of admission, ECG findings, CK-MB levels at presentation, high-sensitivity troponin T, blood urea nitrogen (BUN), creatinine, sodium (Na), potassium (K), calcium (Ca), white blood cells (WBC), hematocrit (HCT), platelets (PLT), mean platelet volume (MPV), angiography results, hospital admission and outcome data of the patients were obtained.

Statistical analysis

SPSS 16.0 software was used in the statistical analysis of the data obtained from the study. Categorical measures such as gender were summarized as number and percentage, while other numerical measures were summarized as mean and standard deviation (median and min-max where necessary). The χ^2 test was used to compare categorical measurements between groups. Independent groups used the *T* test if assumptions were made in comparing numerical measures between groups, and the Mann-Whitney *U* test was used if no assumptions were made. For the general comparison of more than two groups of numerical measurements without normal distribution, the Kruskal-Wallis test was used. Pearson correlation was used when the assumptions of interaction between the numerical measurements were met, and Spearman correlation was used when the assumptions were not met. The statistical significance level was accepted as $p < 0.05$ in all tests.

Results

A total of 259 patients whose data were fully attainable were included in the study. 80.3% (n = 208) of the patients were male and 19.7% (n = 41) were female.

The median age of the patients was 60 years (32–104). The median age of the male patients was 58 years (32–104), while the median age of the female patients was 70 years (37–90 years).

When the ECG of patients at the time of admission to the hospital were reviewed, 35.5% of the patients (n = 92) were found to have normal sinus rhythm as their first ECG finding. In the ECG of ST-elevation myocardial infarction (STEMI) patients, the most frequent finding was anterior (30.9%; 80 patients) and lower wall infarction (30.1%; 78 patients) (Table I).

64.5% of the patients (n = 167) were diagnosed with non-ST-elevation myocardial infarction NSTEMI and 35.5% (n = 92) were diagnosed with STEMI.

Patients were found to have lesions most frequently (84.9%) in the left anterior descending artery (LAD) (Table II).

When the coronary angiographic findings of STEMI and NSTEMI patients were compared, there was no statistically significant difference between the groups (Table III).

Stress hyperglycemia was detected in 42.1% (109 patients) of the patients studied. It was determined that 76.1% of patients with stress hyperglycemia and 83% of patients without stress hyperglycemia were male. There was no statistically significant difference between the presence of stress hyperglycemia and patient gender ($p > 0.05$).

It was determined that 54.1% of patients with stress hyperglycemia and 36.7% of patients without stress hyperglycemia had a higher WBC value. There was a statistically significant difference between the groups in terms of high WBC values between patients with or without stress hyperglycemia (Table IV).

NSTEMI was found in 71.6%, and STEMI was found in 28.4% of the patients with stress hyperglycemia; NSTEMI was found in 59.3% and STEMI in 40.7% of the patients without stress hyperglycemia. It was observed that the rate of NSTEMI detection in patients with stress hyperglycemia was statistically significantly higher than that of STEMI detection (Table V).

It was determined that 6.4% of patients with stress hyperglycemia and 1.3% of patients without stress hyperglycemia had a stenosis at the left main coronary artery (LMCA). Comparing patients with or without stress hyperglycemia, there was a statistically significant difference between the groups in terms of stenosis in the LMCA (Table VI).

Table I. Distribution of ECG findings of patients

Parameter	Number	Percentage
Normal sinus rhythm	92	35.5
Anterior wall MI	80	30.9
Inferior wall MI	78	30.1
Posterior wall MI	2	0.8
Anterior + inferior wall MI	1	0.4
Anterior + lateral wall MI	1	0.4
Inferior + posterior wall MI	3	1.2
Left branch block	1	0.4
Asystole	1	0.4
Total (n)	259	100.0

Table II. Comparison of coronary angiography results of patients

Parameter	Present		Absent	
	Number	Percentage	Number	Percentage
LCMA lesion	9	3.5	250	96.5
LAD lesion	220	84.9	39	15.1
CXA lesion	140	54.1	119	45.9
RCA lesion	169	65.3	90	34.7

LCMA – left coronary main artery, LAD – left anterior descending artery, CXA – circumflex artery, RCA – right coronary artery.

Table III. Comparison of coronary angiography findings of STEMI and NSTEMI patients

Parameter	STEMI (%)	NSTEMI (%)	*P*-value
LCMA lesion	5.4	2.4	0.105
LAD lesion	82.6	86.2	0.24
CXA lesion	53.3	54.5	0.251
RCA lesion	58.7	68.9	0.097

LCMA – left coronary main artery, LAD – left anterior descending artery, CXA – circumflex artery, RCA – right coronary artery.

Table IV. WBC elevation rates in patients with stress hyperglycemia

Parameter	Stress hyperglycemia		*P*-value
	Yes (%/n)	No (%/n)	
WBC elevation	54.1/59	36.7/55	0.016

The mean duration of hospitalization was 4.05 ±2.737 days (range: 1–55).

There was no statistically significant difference between the groups with respect to the length of hospitalization in patients with stress hyperglycemia and those without stress hyperglycemia ($p > 0.05$).

Table V. NSTEMI/STEMI detection rate in patients with stress hyperglycemia

Stress hyperglycemia	NSTEMI (%/*n*)	STEMI (%/*n*)	*P*-value
Yes	71.6/78	28.4/31	0.49
No	59.3/89	40.7/61	

Table VI. Stenosis rates in LCMA between patients with and without stress hyperglycemia

Parameter	Stress hyperglycemia		*P*-value
	Yes (%/*n*)	No (%/*n*)	
LCMA lesion	6.4/7	1.3/2	0.033

Table VII. Comparison of outcome in patients with and without stress hyperglycemia

Variable	Stress hyperglycemia		*P*-value
	Yes (%/*n*)	No (%/*n*)	
Exitus	10.1/11	1.3/2	0.002
Discharge	89.9/98	98.7/148	
Total	100/109	100/150	

It was determined that 10.1% of patients with stress-related hyperglycemia and 1.3% of patients without stress-related hyperglycemia had died. There was a statistically significant difference between the groups in terms of rates of death when patients who had stress-related hyperglycemia and patients who did not were compared ($p < 0.05$) (Table VII).

Discussion

Cardiovascular diseases are currently the leading cause of death in industrialized countries and are expected to be the same in developing countries by 2020 [6]. Among cardiovascular diseases, death is most commonly caused by coronary artery disease and this is associated with high mortality and morbidity [7]. Coronary artery disease is the leading cause of mortality and morbidity in developed countries [8]. It is the leading cause of death in Turkey [9, 10]. There are many studies emphasizing that stress hyperglycemia has a negative effect on the mortality and duration of hospital stay of patients with acute cardiovascular disease [11–13].

The mean age in the study performed by Rafael *et al.* on 834 patients was 64 ±13 (25–94) [14]. In another study, the mean age was 63.3 ±13.8 [15]. The average age in our study was close to the literature. In a study which Aggarwal *et al.* performed on non-diabetic patients with myocardial infarction, the male to female ratio was 4 : 1 [12]. In a similar study the female to male ratio was found to be 3 : 1 [14]. As is known, female patients are at increased risk for cardiovascular disease after menopause; this has been associated with decreased levels of estrogen. It is thought that the higher rate of women in the data we obtained in our study may be related to the increased risk of female gender. In addition, the average life span of women in our country is higher than that of men [16]. The vast majority of the patients consisted of a group after their 6th decade. As the average life span of women is longer, advancing age is also another reason why more cardiac events occur in women.

It has been reported that WBC elevation in AMI causes a larger thrombus and more inflammation in small lesions and that more heart failure develops in AMI cases with high WBC and this may be a guide for aggressive treatment choice [17, 18]. In a study conducted by Açıkel, they correlated the high WBC level measured at the first admission with severe heart failure and high mortality in the hospital [19]. In our study, WBC was found to be high in AMI patients with stress hyperglycemia. In our study, increased mortality in AMI patients with stress hyperglycemia could be attributed to the increased WBC value.

When the anatomy of the coronary artery is examined, the anterior wall myocardium is fed from the LAD; and the lower wall myocardium is fed from the circumflex artery (CXA) in 85% of cases and from the right coronary artery (RCA) in 15% of them. It is known that most of the feeding of the posterior wall myocardium is from the RCA in most cases and less frequently from the CXA [20]. In the abnormal ECG findings of the patients we included in our study, anterior or posterior wall MI was found in 158 patients. The angiographic findings of our patients were found to be predominantly lesions in the LAD and CXA. According to the results of this angiography, it is expected that the patients will show anterior and inferior wall MI intensively on the arriving ECGs.

In patients undergoing coronary angiography for any reason, the incidence of left main coronary artery lesions varies from about 4% to about 10% [21, 22]. Left main coronary artery stenosis was detected in 3.5% of the patients included in the study. In addition, the angiographic results of the patients with stenosis showed stenosis in the LMCA branches and RCA. In a study performed in arteries in which coronary angiography and stenting were performed, the most common lesion was in the LAD [23]. According to the incidence of coronary artery involvement, it can be said that the arterial distribution in which the lesions are detected is similar to the rates reported in the literature. The most common coronary artery was the LAD in our study. In addition, it was found that when the male and female patients were compared, the coronary angiography findings were not statistically significant.

In one study, it was emphasized that hyperglycemia at the time of emergency service admission was a strong predictor of mortality in STEMI patients and that this could be used to determine the risk of the patients [14]. Another study emphasized that stress hyperglycemia following MI in non-diabetic patients could be an important predictor of risk stratification and affect treatment strategies [24]. Budzyński *et al.* found that low-density lipoprotein (LDL) cholesterol, non-high-density lipoprotein (HDL) cholesterol, triglycerides and fasting blood sugars were significantly higher in patients with abnormal HDL cholesterol levels than in patients with normal levels [25]. In a study conducted by Dönmez *et al.* on 86 patients which examined the mortality of patients who underwent transcatheter aortic valve implantation, they found that fasting blood glucose levels were high in both living and dying patients [26]. In our study, it was observed that the mortality rate in patients with stress hyperglycemia was significantly higher than the group without stress hyperglycemia. In normal aerobic conditions, a significant portion of myocardial energy needs is satisfied by the oxidation of free fatty acids [27]. Oxygen in the veins and attached to myoglobin may be sufficient for only 2 to 6 heart beats. In humans, there is a decrease in the function of the heart's contractile function in the 10th pulse following coronary occlusion [28]. Thus, the myocardium oxygen reserve is consumed within a few seconds from the start of ischemia, and the oxidative phosphorylation, electron transport, and mitochondrial ATP production cease when the tissue oxygen pressure drops below 5 mm Hg. Reduction of mitochondrial activity results in anaerobic glycolysis becoming the main source of energy, rather than aerobic metabolism [29]. Thirty minutes after AMI, the amount of epinephrine and free fatty acids (FFA) due to the effect of tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6) in the plasma increase due to stress factors. Increased plasma FFA/albumin ratio and lack of FFA β-oxidation of myocardial mitochondria in ischemia cause acyl-CoA and acylcarnitine to accumulate in the myocardium. Accumulation of these substances activates Ca channels while inhibiting the sarcoplasmic Ca pump, Na-Ca and Na-K pumps. This leads to an increase in the amount of cytosolic Ca. This increase in Ca is directly related to arrhythmia [30–32]. One of the common complications that determine mortality in AMI is arrhythmias. The most lethal arrhythmia is ventricular fibrillation. Stress hyperglycemia itself may be a factor that causes these arrhythmias.

Apart from necrotic dead tissue in the area of infarction, AMI has a field of apoptotic dead cells in the perimeter of the infarct area [33]. It has been shown that free oxygen radicals (FOR) formed by hyperglycemia triggered apoptosis in cardiomyocytes by triggering the pathway of cytochrome c and KASPAS-3 [34]. While insulin regulates glucose transport via PI-3 kinase, it also stimulates endothelial nitric oxide (NO) synthesis. Increased blood flow through NO-induced vasodilatation accelerates glucose uptake into tissues. An important effect of nitric oxide is the reduction of the expression of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1), E-selectin and intercellular adhesion molecule-1 (ICAM-1). NO also inhibits platelet adhesion and platelet interaction with the vascular wall and enhances the inhibitory effect of prostacyclin on platelet aggregation. In the case of insulin resistance, insulin is reduced by vasculoprotective effects via NO. The atherogenic effect through the production of vascular smooth muscle cell proliferation, migration and plasminogen activator inhibitor (PAI-1) production is accelerating [35]. Clinical trials have shown that insulin resistance may also be important in PAI-1 expression and regulation, which is one of the independent risk factors for coronary artery disease [36]. Due to the increase in PAI-1 levels, the susceptibility to impaired fibrinolytic activity and coagulation in hyperinsulinemia is expected [37].

LMCA lesions show a clinically catastrophic course in patients with unprotected coronary artery disease and the frequency of it is low. Cardiogenic shock has been shown to be a serious trend with this lesion, as well as a high mortality rate even after successful revascularization attempts [38–42]. In our study, 7 of the 9 patients with LMCA stenosis were found to have stress hyperglycemia, and this is a statistically significant difference compared to patients without stress hyperglycemia. LMCA lesions lead to global cardiac involvement leading to ischemia and necrosis in a very wide myocardial area, leading to high mortality. Increased glucose levels may also be a factor affecting mortality by adversely affecting the pathophysiological processes.

In conclusion, hyperglycemia is seen in critical disease with the combined effects of increased stress hormones and activated HPA axis, increased cytokine levels and peripheral insulin resistance. This adaptive mechanism is detrimental to uncontrollable hyperglycemia over time due to undesirable effects on the cellular and metabolic levels (mitochondrial damage, oxidative stress-related damage in cells, endothelial damage and cardiac potassium channel dysfunction) and affects the course of the critical illness in a negative way.

Conflict of interest

The authors declare no conflict of interest.

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