

**RESEARCH
ARTICLE**

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The Impact of Plasma Glucose Levels on In-Hospital and Long-Term Mortality in Non-Diabetic Patients with ST-Segment Elevation Myocardial Infarction Patients

ABSTRACT

Objective: Increased admission plasma glucose can be seen in the acute phase of acute coronary syndromes (ACS). Hence, we performed a retrospective study to evaluate the admission plasma glucose concentration in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (pPCI) and who had no previous diagnosis of Diabetes Mellitus (DM).

Methods: This retrospective study included 2504 consecutive confirmed STEMI patients treated with pPCI. The patients were divided into quantiles according to the admission glucose levels. Quantile I: 94 ± 7 mg/dL (n= 626), quantile II: 112 ± 5 mg/dL (n = 626), quantile III: 131 ± 6 mg/dL (n= 626), quantile IV: 184 ± 46 mg/dL (n= 626).

Results: Patients with higher plasma glucose (Q4) had 6.6 times higher in-hospital all-cause mortality rates (95% CI: 3.95–9.30) and 3.12 times higher (95% CI: 2.2–4.4) long-term all-cause mortality rates than patients with lower plasma glucose (Q1–Q3), who had lower rates and were used as the reference. This significant relationship remained even after adjustment for all confounders.

Conclusions: Even though glucose-lowering therapy is recommended in ACS patients with glucose levels >180 mg/dL, our results showed that high plasma glucose, even lower than 180 mg/dL, could predict in-hospital and long-term mortality.

Keywords: Hyperglycemia, Long-Term Mortality, ST-Segment Elevation Myocardial Infarction

Non-Diabetik ST-Segment Yükselmeli Myokardiyal İnfarktüs Hastalarında Plazma Glukoz Seviyelerinin Hastane İçi Ve Uzun Dönem Mortalite Üzerine Olan Etkisi

ÖZET

Amaç: Artmış başvuru plazma glukozu Akut Koroner Sendromlarda (AKS) görülebilmektedir. Bu nedenle, Diabetes Mellitus (DM) tanısı olmayan primer perkütan koroner girişi (pPKG) yapılan ST-segment elevasyonlu miyokard infarktüsülü (STEMI) hastalarda başvuru plazma glukozunu değerlendirmek amacıyla retrospektif bir çalışma yaptık.

Gereç ve Yöntem: Bu retrospektif çalışma pPKG ile tedavi edilmiş doğrulanmış 2504 ardışık STEMI hastasını içermektedir. Hastalar başvuru glukozlarına göre kuantillere bölünmüştür. Kuantil I: glukoz seviyesi 94 ± 7 mg/dL (n= 626), kuantil II: glukoz seviyesi 112 ± 5 mg/dL (n = 626), kuantil III: glukoz seviyesi 131 ± 6 mg/dL (n= 626), kuantil IV: glukoz seviyesi 184 ± 46 mg/dL (n= 626).

Bulgular: Yüksek plazma glukoz seviyesine sahip hastalar (Q4), düşük plazma glukoz seviyeli hastalara (Q1-Q3) göre 6.6 kat daha fazla tüm nedenli hastane içi mortaliteye (95% CI: 3.95–9.30) ve 3.12 kat daha fazla tüm nedenli uzun dönem mortaliteye (95% CI: 2.2–4.4) sahiptir. Bu anlamlı ilişki, tüm karıştırıcı faktörlerle düzeltme yapıldıktan sonra dahi devam etmiştir.

Sonuç: Her ne kadar glukoz seviyesi >180 mg/dL olan AKS hastalarında, glukoz düşürücü tedavi önerilse de sonuçlarımız yüksek plazma glukoz seviyesinin, 180 mg/dL'den düşük olsa dahi, hastane içi ve uzun dönem mortaliteyi ön görebildiğini göstermiştir.

Anahtar Kelimeler: Hiperglisemi, Uzun Dönem Mortalite, ST-Segment Elevasyonlu Myokard İnfarktüsü

INTRODUCTION

Increased admission plasma glucose can be seen in the acute phase of acute coronary syndromes (ACS) [1]. Even though there are several studies which showed that the patients with increased admission glucose had increased risk of death [2], stent thrombosis [3], re-infarction [4]; some studies showed inconsistent results on the long-term mortality [5-7]. Unfortunately, most of these studies were conducted in the trials of fibrinolytic therapy. Thusfar, limited evidence is available to assess the impact of admission glucose level on mortality in ST-segment elevation myocardial infarction (STEMI). Hence, we conducted a retrospective study to assess the admission plasma glucose levels in non-diabetic patients with STEMI undergoing percutaneous coronary intervention (pPCI).

MATERIAL AND METHODS

Patient Population: A total of 2660 consecutive STEMI patients undergoing pPCI (June 2011-January 2013) were enrolled in this retrospective study. The diagnostic criteria of European Society of Cardiology for STEMI were applied to all patients [8]. All patients presenting within 12 h after the onset of chest pain underwent pPCI within 60 min of admission. Either coronary angioplasty or coronary stenting was performed for the infarct-related artery. All patients were administered standard ACS therapy regarding to European Society of Cardiology Guidelines [8]. Our exclusion criteria were as follows: a) taking antidiabetic therapy, b) being diagnosed with Diabetes Mellitus (DM), c) having the level of HbA1C more than 6.5%. N=128 patients meeting the exclusion criteria were excluded from the study. N=28 patients were excluded from analysis due to the loss to follow-up. The study population were divided into quantiles regarding to the admission plasma glucose levels. Quantile I: glucose level of 94 ± 7 mg/dL (n= 626), quantile II: glucose level of 112 ± 5 mg/dL (n = 626), quantile III: glucose level of 131 ± 6 mg/dL (n= 626), quantile IV: glucose level of 184 ± 46 mg/dL (n= 626) (Table 1).

Baseline demographic data and laboratory tests of the study population are shown in Table 1. All patients were admitted to the coronary care unit and biplane Simpson method was used to assess the left ventricular ejection fraction (LVEF) at first 48 hours [9]. Hospital's medical records were used to obtain follow-up data. The study was terminated after 36 months of follow-up. The incidence of in-hospital and long-term all-cause mortality were determined as the primary endpoint. The study was approved by the ethics committee of authors' hospital.

Statistical Analysis: Continuous variables were checked for the normal distribution using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean \pm SD. Continuous variables with normal and skewed distributions were compared using

one-way analysis of variance and Kruskal-Wallis test, respectively. Categorical variables were expressed as n (%) and Pearson's χ^2 or Fisher's exact tests were used to evaluate the differences. A p-value less than 0.05 was considered statistically significant. All statistical analyses were carried out using the SPSS 21 for Mac (Chicago, Illinois, USA).

RESULTS

N= 2504 patients were analyzed. The significant difference with regard to age (P<0.001), chronic kidney disease (P<0.001), admission Killip Class (P<0.001), LVEF (P<0.001) were determined among the subgroups of plasma glucose levels (Table 1). The baseline characteristics of the study population was shown in Table 1. The patients showed significant differences with regard to in-hospital and long-term events including all-cause mortality (Table 1). The receiver operating characteristic curve analysis showed that the best cutoff value of the plasma glucose level to predict the in-hospital mortality was 140 mg/dL mg/dL with a 67 % sensitivity and 74 % specificity (AUC: 0.74; 95% CI: 0.68-0.80; P<0.001) (Figure 1). Kaplan-Meier curve for the overall survival stratified by serum glucose level was shown in Figure 2. Table 2 shows in-hospital event rates and logistic regression models for mortality and Cox proportional analysis and 3-year mortality by serum glucose levels. Patients with higher plasma glucose (Q4) had 6.6 times higher in-hospital mortality rate (95% CI: 3.95-9.30) than patients with lower plasma glucose (Q1-Q3). This significant relationship remained even after adjustment for all confounders. Patients with higher plasma glucose (Q4) had 3.12 times higher (95% CI: 2.2-4.4) long-term all-cause mortality rates than patients with lower plasma glucose (Q1-Q3). This significant relationship also remained even after adjustment for all confounders.

DISCUSSION

The possible mechanisms underlying the high glucose levels in STEMI patients could be the activation of stress hormones such as noradrenaline, cortisol, glucagon, and growth hormone [10-12]. The possible effects of high glucose levels in the STEMI patients are direct glycation of coagulation factors [13], inflammatory changes with adhesion molecule production [14], and contributing platelet-dependent thrombus formation [15]. There are some studies found that increased metabolism of glucose during ischemia was related with preservation of myocardial contraction [16]. High free fatty acid concentrations, which are released by stress mediators, were associated with reduced myocardial function and increased myocardial oxygen demand [17, 18]. It is a well established fact that hyperglycemic state may cause osmotic diuresis, which may result in volume depletion. All of these mechanisms contribute to ventricular dysfunction.

Table 1. Baseline characteristics and outcomes of patients classified by admission glucose levels

	Admission Plasma Glucose Level, mg/dL (n= 2504)				P Value
	Q1 (n= 626)	Q2 (n= 626)	Q3(n= 626)	Q4 (n= 626)	
Age	54.9 ± 11.3	56.1 ± 11.4	57.6 ± 11.4	58.5 ± 11.7	<0.001
Male gender	549 (87.8)	536 (85.5)	522 (83.4)	514 (82.1)	0.028
Body mass index	27.1 ± 3.6	26.9 ± 3.3	27.5 ± 3.7	27.2 ± 3.7	0.185
History					
Hypertension	168 (27.2)	174 (28.0)	193 (31.1)	196 (31.4)	0.247
Hyperlipidemia	109 (17.4)	116 (18.5)	91 (14.5)	122 (19.5)	0.114
Current smoking status	240 (38.4)	244 (38.9)	232 (37.1)	218 (34.8)	0.444
Previous MI	120 (19.2)	111 (17.7)	104 (16.6)	107 (17.1)	0.652
Previous PCI	114 (18.2)	106 (16.9)	93 (14.9)	95 (15.2)	0.330
Previous CABG	19 (3.0)	17 (2.7)	13 (2.1)	26 (4.2)	0.180
Chronic kidney disease	14 (2.2)	24 (3.8)	29 (4.6)	47 (7.5)	<0.001
At admission					
Systolic blood pressure (mm Hg)	135 ± 22	133 ± 22	134 ± 24	133 ± 25	0.620
Diastolic blood pressure (mm Hg)	72 ± 12	71 ± 12	72 ± 13	71 ± 14	0.482
Heart rate (beats per minute)	77 ± 13	78 ± 13	78 ± 12	79 ± 16	0.415
Killip class I	615 (98.7)	617 (98.7)	610 (97.9)	588 (94.4)	<0.001
Killip class III-IV	8 (1.3)	8 (1.3)	13 (2.1)	35 (5.6)	<0.001
Left ventricular ejection fraction (%)	51 ± 9	49 ± 9	48 ± 10	46 ± 11	<0.001
Anterior myocardial infarction	290 (47.9)	274 (44.3)	296 (47.7)	294 (47.6)	0.524
Chest pain period (hours)	3.2 ± 1.8	3.4 ± 1.9	3.2 ± 1.6	3.5 ± 1.8	0.420
Pain-to-balloon time (hours)	3.5 ± 1.8	3.7 ± 1.8	3.5 ± 1.7	3.8 ± 1.7	0.552
Door-to-balloon time (minutes)	29 ± 10	26 ± 11	28 ± 11	30 ± 12	0.114
Admission laboratory variables					
Admission CK-MB (ng/mL)	73 ± 100	85 ± 95	109 ± 131	108 ± 127	<0.001
Peak creatine kinase-MB (ng/mL)	103 ± 115	126 ± 112	161 ± 153	177 ± 167	<0.001
Creatinine (mg/dL)	0.87 ± 0.23	0.90 ± 0.50	0.90 ± 0.39	0.97 ± 0.42	<0.001
eGFR (ml/min/1.73 m ²)	116 ± 35	113 ± 38	112 ± 41	102 ± 38	<0.001
White blood cell count, cells/μL	10.5 ± 3.4	11.2 ± 3.4	12.1 ± 4.7	12.8 ± 4.8	<0.001
Hematocrit, %	40.9 ± 4.0	40.7 ± 5.1	40.6 ± 4.8	40.2 ± 5.5	0.082
Glucose (mg/dL)	94 ± 7	112 ± 5	131 ± 6	184 ± 46	<0.001
Vessel disease (stenosis > 50%)					
1 vessel	376 (60.2)	376 (60.0)	389 (62.1)	360 (57.5)	0.421
2 vessels	153 (24.5)	150 (23.9)	136 (21.7)	144 (23.0)	0.677
3 vessels	95 (15.2)	101 (16.1)	101 (16.1)	122 (19.5)	0.187
PCI type					
Only PTCA	87 (13.9)	78 (12.4)	71 (11.3)	98 (15.7)	0.128
Only Stent	88 (14.1)	95 (15.2)	96 (15.3)	72 (11.5)	0.182
PTCA and Stent	343 (54.9)	369 (58.9)	384 (61.3)	381 (60.9)	0.082
Out-hospital medication	543 (86.9)	555 (88.5)	543 (86.7)	552 (88.2)	0.706
B-blocker					
Statin	547 (87.5)	561 (89.5)	548 (87.5)	553 (88.3)	0.675
Diuretics	39 (6.2)	43 (6.9)	43 (6.9)	78 (12.5)	<0.001
ACEIs or ARBs	584 (93.4)	592 (94.4)	594 (94.9)	588 (93.9)	0.722
In-hospital course					
Cardiogenic shock	13 (2.1)	13 (2.1)	17 (2.7)	55 (8.8)	<0.001
Acute respiratory failure	17 (2.7)	18 (2.9)	19 (3.0)	44 (7.0)	<0.001
Acute kidney injury	40 (6.4)	50 (8.0)	57 (9.1)	79 (12.6)	0.001
Ventricular arrhythmia	22 (3.5)	31 (4.9)	27 (4.3)	62 (9.9)	<0.001
Stent thrombosis	12 (1.9)	15 (2.4)	11 (1.8)	34 (5.4)	<0.001
Recurrent MI	13 (2.1)	15 (2.4)	15 (2.4)	34 (5.4)	0.001
Revascularization	30 (4.8)	35 (5.6)	28 (4.5)	56 (8.9)	0.003
Major adverse cardiac events	37 (5.9)	37 (5.9)	39 (6.2)	88 (14.1)	<0.001
Mortality	11 (1.8)	9 (1.4)	14 (2.2)	63 (10.1)	<0.001
Out-hospital course					
Stent thrombosis	19 (3.1)	25 (4.0)	29 (4.7)	38 (6.7)	0.023
Recurrent MI	29 (4.7)	36 (5.8)	37 (6.0)	54 (9.6)	0.005
Revascularization	37 (6.0)	46 (7.4)	45 (7.4)	67 (11.9)	0.002
Major adverse cardiac events	44 (7.2)	50 (8.1)	58 (9.5)	78 (13.9)	0.001
All-cause mortality	18 (2.9)	19 (3.1)	27 (4.4)	49 (8.7)	<0.001

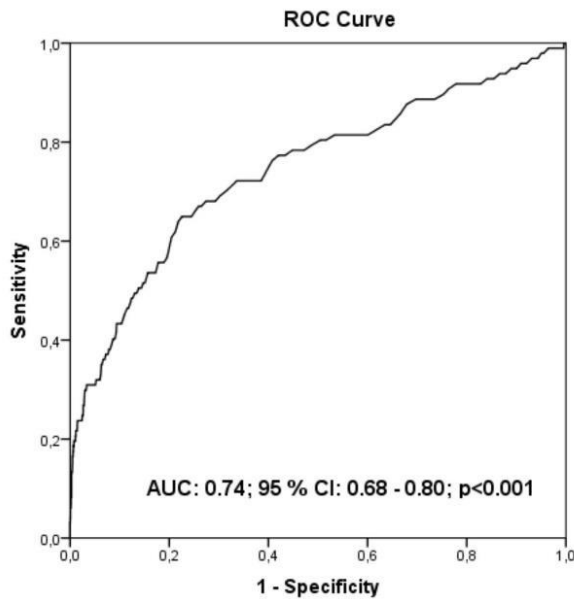


Figure 1. The receiver operating characteristic curve analysis showed that the best cutoff value of the plasma glucose level to predict the in hospital mortality was 140 mg/dL with a 67% sensitivity and 74% specificity (AUC: 0.74; 95% CI: 0.68-0.80; P<0.001).

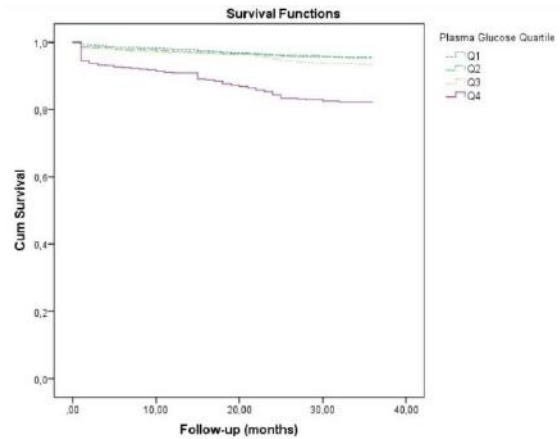


Figure 2. Kaplan-Meier curve for the overall survival stratified by serum glucose level.

Admission hyperglycemia was found to be associated with microvascular obstruction in some studies in patients with STEMI [19, 20]. Hsu CW et al. [21] performed a retrospective study to assess the association of the high plasma glucose and mortality in patients with ACS. They showed that high plasma glucose could be associated with in-hospital and long-term mortality. Since, their patient population

Table 2. In-hospital event rates and logistic regression models for mortality and Cox proportional analysis and 3-year mortality by serum glucose level.

	Serum Glucose Level, mg/dL (n=2504)	
	Q1-3 (n=1878)	Q4 (n=626)
In-hospital mortality		
Number of deaths	34	63
Mortality, %	1.8	10.1
Mortality, OR (%95 CI)		
Model 1: unadjusted	1[Reference]	6.06 (3.95 – 9.30)
Model 2: adjusted for age, sex, Killip class, and left ventricular ejection fraction	1[Reference]	4.38 (2.88 – 7.50)
Model 3: adjusted for comorbidities and GFR	1[Reference]	4.72 (3.06 – 8.12)
Model 4: adjusted for all covariates ^a	1[Reference]	3.23 (1.95 – 5.35)
In-hospital cardiogenic shock		
Number of events	43	55
Event rate, %	2.3	8.8
Event, OR (%95 CI)		
Model 1: unadjusted	1[Reference]	4.11 (2.72 – 6.19)
Model 2: adjusted for age, sex, Killip class, and left ventricular ejection fraction	1[Reference]	2.53 (1.43 – 3.45)
Model 3: adjusted for comorbidities and GFR	1[Reference]	2.61 (1.64 – 3.70)
Model 4: adjusted for all covariates ^a	1[Reference]	2.23 (1.38 – 3.58)
3-year mortality		
Number of deaths	63	63
Mortality, %	3.4	10.1
Mortality, HR (%95 CI)		
Model 1: unadjusted	1[Reference]	3.12 (2.20 – 4.44)
Model 2: adjusted for age, sex, Killip class, and left ventricular ejection fraction	1[Reference]	2.42 (1.63 – 3.02)
Model 3: adjusted for comorbidities and GFR	1[Reference]	2.48 (1.68 – 3.18)
Model 4: adjusted for all covariates ^a	1[Reference]	1.91 (1.44 – 2.76)

Abbreviations: GFR, glomerular filtration rate; OR, odds ratio; HR, hazard ratio.

^aIncludes demographics (age, sex); first measurement during hospitalization of the following laboratory values (admission glomerular filtration rate calculated by CKD-EPI, white blood cell count, hematocrit); admission and peak creatine kinase-MB level level; Killip class and left ventricular ejection fraction; chest pain and door-to-balloon period; comorbidities (chronic kidney disease, hypertension, hyperlipidemia); medications during hospitalization.

consisted of non-ST segment elevation myocardial infarction and STEMI, we cannot compare their results with our findings. In one study, admission hyperglycemia was found to be associated with short-term mortality in men with ACS but not among women with ACS [22]. Straumann E et al. [23] conducted a study whose study population were homogenous consisting of patients undergoing pPCI. It was a prospective study and they studied 978 STEMI patients. They showed the relationship between the admission glucose levels and short-term and long-term survival, which supports our findings. After 7 years, Hoebbers LP et al. [24] conducted another study in the same patient group with a large sample size (n= 1646). They found that glucose level at admission was an independent predictor of early but not late mortality. A meta-analysis published in 2015, which included 13 articles, found the relationship between the admission glucose levels and long-term mortality but they did not find any relationship with short-term mortality [25]. On account of inconsistent results of the impact of admission glucose levels on mortality, we conducted a retrospective study with a

larger sample size (n= 2504). The admission glucose levels were found to be a predictor of in-hospital and long-term mortality (Table 2), which does not support the results of the meta-analysis. Our study population were homogenous, which consisted of STEMI patients treated with pPCI. Furthermore, we checked HbA1C levels in all patients to exclude possible undiagnosed DM and we did not have any exclusion criteria other than having DM, which were not able to be done in most studies.

Limitations

There are some limitations to our study. N= 28 patients were not be able to analyze for the mortality on account of the loss to follow-up. The study was conducted in a single tertiary referral hospital. The fact that high-risk patients are referred for pPCI to our tertiary referral hospital may have affected our results.

Conclusions

Even though glucose-lowering therapy is recommended in ACS patients with glucose levels >180 mg/dL [8], our results showed that high plasma glucose, even lower than 180 mg/dL, could predict in-hospital and long-term mortality.

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