ORIGINAL ARTICLE

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Evaluation of Myocardial Damage in Relation to HbA1c in patients with Previously Unrecognized Diabetes Presenting with STEMI

STEMI ile Başvuran Önceden Tanı Almamış Diyabetli Hastalarda HbA1c ile İlişkili Miyokard Hasarının Değerlendirilmesi

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ABSTRACT

Objective: *The mechanisms underlying worse clinical outcomes in previously unrecognized diabetic (DM) patients in ST-elevation myocardial infarction (STEMI) are unclear. It was hypothesized that poor chronic glucose control might be related to greater myocardial damage.*

Material and Method: *51 newly diagnosed DM patients with glycated hemoglobin A1c (HbA1c) > 6.5 comprised the DM group, 54 sex- and age-matched individuals with normal glucose metabolism served as the non-DM group. Each patient underwent primary angioplasty for STEMI. The levels of cardiac specific markers before angioplasty, during angioplasty, at 6, 12, and 18 h after angioplasty were recorded. SPSS 10 package program was used to analyse data.*

Results: *In both DM and non-DM groups troponin peaked at 6 h. Peak troponin levels were similar in both groups (diabetics, 22.89 ± 18.19 vs. non-diabetics, 32.67 ± 17.68 ng/ml, p=0.168).*

Conclusion: *HbA1c > 6.5 is not related to extent of infarction in previously unrecognized DM patients presenting with STEMI. Future studies assessing the effects of other factors unrelated to chronic glucose control on myocardial damage and cardiovascular event rates in these patients would be of great interest.*

Keywords:
Acute coronary syndrome
Diabetes mellitus
Coronary angioplasty
Cardiac markers
Acute ST-segment elevation myocardial infarction

ÖZET

Amaç: *Daha önce tanısı konulmamış diyabetik hastalarda ST elevasyonlu miyokard enfarktüsünde (STEMI) kötü klinik sonuçların altında yatan mekanizmalar belirsizdir. Kötü glisemik kontrolün daha büyük miyokard hasarı ile ilişkili olabileceği hipotezi oluşturulmuştur.*

Gereç ve Yöntem: *Glikolize hemoglobin A1c (HbA1c)> 6.5 olan yeni tanı konmuş 51 DM hastası DM grubunu, normal glikoz metabolizması olan 54 cinsiyet ve yaş eşleşmeli birey DM olmayan grup olarak çalışmaya dahil edildi. Her hastaya STEMI için primer anjiyoplasti yapıldı. Anjiyoplasti öncesi, anjiyoplasti sırasında, anjiyoplastiden 6, 12 ve 18 saat sonra kardiyak spesifik belirteç seviyeleri kaydedildi. Veriler SPSS 10 paket program eşliğinde analiz edildi.*

Bulgular: *Hem DM hem de DM olmayan gruplarda troponin 6. saatte zirve yaptı. Pik troponin düzeyleri her iki grupta da benzerdi (diyabetliler, 22.89 ± 18.19 ve nondiyabetikler, 32.67 ± 17.68 ng / ml, p = 0.168).*

Sonuç: *HbA1c'nin 6.5'tan büyük olması, STEMI ile başvuran ve daha önce DM tanısı olmayan hastalarda infarkt alanının genişliği bakımından fark bulunmamıştır. Bu hastalarda miyokard hasarı ve kardiyovasküler olay oranlarını etkileyecek kronik glikoz kontrolü dışında faktörleri değerlendirmek için gelecek çalışmalara ihtiyaç vardır.*

Anahtar Kelimeler:
Akut koroner sendrom
Diabetes mellitus
Koroner anjiyoplasti
Kardiyak belirteçler
Akut ST segment elevasyonlu miyokard infarktüsü

INTRODUCTION

Diabetes mellitus (DM) is associated with a twofold to fourfold increased risk for cardiovascular death compared with non-diabetic individuals (1). Cardiovascular disease remains the principal morbidity and constitutes 70 to 80% of mortality in the setting of DM (2). Diabetic individuals have worse cardiovascular outcomes after acute coronary syndrome (ACS) events.

Type 2 DM is often discovered following a cardiovascular event. The best screening approach in the setting of ACS is debated. However, glycated hemoglobin A1c (HbA1c) has been proposed as the preferred test, although pragmatic (3). HbA1c provides a good reflection of plasma glucose concentrations over 8 to 12 weeks with no effect from meals, the circadian cycle and the stress response. Thus, HbA1c levels might be of prognostic value with regard to clinical outcomes. Specific cardiac marker levels can clearly demonstrate the level of cellular destruction in myocardium. These markers are cardiac troponins, creatine phosphokinase myocardial band (CK-MB), and myoglobin in the order of specificity. The levels are closely related to infarct size (4).

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Recent studies demonstrated that increased HbA1c values in previously undiagnosed DM was associated with increased long-term mortality (5,6). The mechanisms involved in the greater early mortality among patients with previously undiagnosed DM are unclear. Only a few of the studies examining the relationship between admission HbA1c values and the myocardial damage considered the contribution of previously unrecognized DM (7-9). In addition, there is a paucity of data regarding the role of optimal DM control as reflected by HbA1c values on the level of cellular destruction evaluated by specific cardiac marker levels in patients with acute ST-elevation myocardial infarction (STEMI). Therefore, the purpose of this study was to determine the relative contribution on post-acute myocardial infarction cellular destruction of chronic gluco-metabolic state preceding acute MI. It was hypothesized that previously unrecognized DM with HbA1c > 6.5 would be associated with increased levels of cellular destruction. To address this question, we carried out a prospective study of patients with previously unrecognized DM, admitted for acute MI treated with coronary angioplasty.

MATERIAL AND METHOD

Participants

Consecutive patients admitted to our hospital for acute STEMI, treated with primary angioplasty between June 1, 2010, and June 1, 2012, were eligible in this prospective study. The diagnosis of STEMI was based on American College of Cardiology (ACC) / American Heart Association (AHA) guidelines. Analysis of HbA1c on admission was done in every patient. The measurement of HbA1c was done by Cobas 6000 system by immunoturbidimetry. All patients, who received the diagnosis of DM, were unaware of this status at admission. As the use of fasting plasma glucose or HbA1c alone leaves a majority of patients with impaired glucose tolerance or type 2 DM undetected when screening for unknown glucose perturbations, we used all screening tools (i.e, oral glucose tolerance test, fasting plasma glucose, and HbA1c), where appropriate (10). The diagnosis of DM was established if patients had fasting glucose ≥ 126 mg/dL or random glucose > 200 mg/dL together with an admission HbA1c > 6.5% according to the latest the American Diabetes Association (ADA) 2010 Revised Clinical Practice Guidelines for DM diagnosis (11). A total of 105 patients (51 newly diagnosed diabetic and 54 non-diabetic individuals) were included in the study. Individuals with a history of cardiogenic shock, acute renal failure, septic shock, acute gastrointestinal bleed, acute pulmonary emboli, subarachnoid hemorrhage, ascending aortic dissection, recent treatment with cardiotoxic agents, troponin peak levels <1 ng/ml, the start of symptoms greater than 3 h before admission, the need for more than 1 vessel angioplasty at the time of index procedure, the decision for surgical revascularization were excluded. Patients who died during angioplasty were also excluded. The Killip classification was used to classify patients as follows: I = no signs of heart failure; II = the presence of S3 or rales at the bases; III = acute pulmonary edema with rales extending 2/3 of the lung fields; IV = cardiogenic shock (12). Coronary collaterals were assessed by Rentrop classification: 0 = no filling of collateral vessels; 1 = filling of the side branches of the occluded artery without any epicardial filling of the recipient artery; 2 = partial epicardial filling by collateral vessels of the recipient artery; 3 = complete epicardial filling by collateral vessels of the recipient artery (13).

The study protocol was in accordance with the Declaration of Helsinki and approved by Medical Ethics Review Committee of Pamukkale University. All participants gave a written informed consent.

Study Design

At the time of enrollment, a detailed history and physical examination were obtained. Patient demographic and clinical characteristics included sociodemographic variables (gender, age), anthropometric measurements (body weight and height), medical history, social history, the use of medications. Body mass index (BMI) was calculated as weight divided by squared height (kg/m²). Admission electrocardiograms (ECG) were obtained for all patients in the emergency department. All patients underwent immediate coronary angiography using General Electric Innova 2100. All angioplasties were performed by experienced interventional cardiologists. The decision to proceed with primary angioplasty was based on clinical characteristics, electrocardiographic, and angiographic findings. The success criteria for angioplasty included relief of chest pain, > 50% resolution of ST-segment elevation, and restoration of TIMI (Thrombolysis in Myocardial Infarction) III flow (14). ST-segment measurements were done using admission ECGs and ECGs obtained 60 minutes after the restoration of TIMI III flow. ST-segment elevation was measured at 20 ms after the J point. The measurement of cardiac markers was done by Advia Centaur CP by electrochemiluminescence. Blood samples for cardiac markers were drawn before coronary angioplasty, at the time of coronary angioplasty, and at 6 h, 12 h, and 18 h after coronary angioplasty. Specific cardiac markers were troponin I and CK-MB. Glucose levels at admission were also measured.

Statistical Analysis

A statistical software package (SPSS 10.0, Chicago, IL) was used to perform all analyses. Continuous and categorical data are reported as mean ± standard deviation and percentages, respectively. Mann-Whitney- U Test assessed differences in continuous data. Differences in categorical data were assessed by chi-square analysis or Fischer's exact test. A p value < 0.05 was considered statistically significant for all tests.

RESULTS

Patients (n=105; Killip classification, I (80%) – II (20%); age, 61.24 ± 12.28 years; 78:27, male: female) with acute STEMI treated with primary angioplasty, were enrolled into the study. The patient groups were well-matched for baseline clinical and laboratory characteristics, and medications (Table 1). Electrocardiographic findings with respect to ST-segment elevation were similar in the 2 groups (p=0.476); as were admission plasma glucose values (p=0.586); infarct localizations as assessed by electro- and echo-cardiographically (p=0.472); renal function tests (p=0.578); peak CK-MB values (129±98 vs. 175±92 ng/ml, p=0.192); the severity of coronary artery disease (one-vessel vs. multi-vessel) (p=0.418); coronary collateral development as assessed by Rentrop classification (p=0.156); time elapsed from symptom onset to

Table 1: Clinical and laboratory characteristics of all participants

	Diabetic Patients (n=51)	Non-diabetic Patients (n=54)	p Value
Age, yrs	62.33±12.91	58.14±13.31	p>0.05
Male, n (%)	35 (69)	45 (83)	p>0.05
BMI, kg/m2	28±5	27±3	p>0.05
Hypertension, n (%)	6 (12)	18 (33)	p>0.05
Heart failure,n (%)	10 (21)	6 (11)	p>0.05
Hyperlipidemia, n (%)	16 (31)	23 (43)	p>0.05
CAD, n (%)	16 (31)	8 (15)	p>0.05
Current smoking, n (%)	18 (35)	23 (43)	p>0.05
Prior PCI, n (%)	2 (4)	0 (0)	p>0.05
Prior MI, n (%)	3 (6)	2 (11)	p>0.05
Prior CABG, n (%)	1 (2)	0 (0)	p>0.05
Angina pectoris, n (%)	42 (82)	45 (83)	p>0.05
Killip class I+II, n (%)	51 (100)	54 (100)	p>0.05
RAAS inhibitors, n (%)	18 (35)	3 (5)	p>0.05
Aspirin, n (%)	21 (41)	5 (9)	p>0.05
Beta-blockers, n (%)	14 (27)	8 (15)	p>0.05
ST-elevation, 2 vs. 3 vs. 4 leads, n (%)	3 (6), 37 (73), 12 (24)	0 (0), 39 (72), 15 (27)	p>0.05
Glucose at admission, mg/dl	121.21±19.16	131.24±21.24	p>0.05
Creatinine, mg/dl	0.92±0.28	0.96±0.36	p>0.05
Peak CK-MB, ng/ml	129±98	175±92	p>0.05
MACEs, n (%)	3 (6)	5 (9)	p>0.05
Time to treatment, 1-2 h vs. 2-3 h, n (%)	16 (31), 35 (69)	8 (15), 45 (83)	p>0.05

Values are given as percentages or means ± SD. BMI: body mass index; CABG: coronary artery bypass grafting surgery; CAD: coronary artery disease; CK-MB: creatine phosphokinase myocardial band; MACEs: major adverse cardiovascular event; MI: myocardial infarction; PCI: percutaneous coronary intervention; RAAS: renin angiotensin aldosterone system.

coronary angioplasty (p=0.564); in-hospital mortality rates (p=0.314); major cardiac event and bleeding rates (p=0.286) (Table 2). Troponin values are depicted in Figure 1. Troponin peaked at 6 h after coronary angioplasty in both groups and peak values were similar in both groups (diabetics, 22.89 ± 18.19 vs. non-diabetics, 32.67 ± 17.68 ng/ml, p=0.168). The mean values of HbA1c for the groups were 7.63±0.82 and 5.12±0.45 respectively.

DISCUSSION

In the present study, we have shown that chronic glucometabolic state was not associated with extent of infarct in previously unrecognized DM. The reports on the relationships between admission HbA1c values and the extent of infarct are very scarce. Thus, in this paper, for the first time, we unexpectedly report that HbA1c > 6.5 at admission was not associated with greater myocardial damage in previously unrecognized DM in the setting of acute MI. The role of admission HbA1c values in patients with ACS has been evaluated in some studies (6,8,9,15-18). Those studies largely included patients with suspected ACS (the whole spectrum), in contrast only STEMI patients were enrolled into the present study. In addition, those studies have several limitations, including retrospective nature, lack of standardization for elevated glucose levels at admission, and uncertainty of ACS diagnosis. Although the present study suggested that HbA1c may not be related to extent of infarct, in recent meta-analysis elevated HbA1c was associated with increased short-term mortality in ACS patients without DM history and without DM (17). In another meta-analysis elevated HbA1c level among STEMI patients was an indicator of 1.25-fold 30-day mortality risk and 1.45-fold long-term mortality risk, respectively (19).

Individuals with undiagnosed DM are at high risk of developing diabetic complications, including cardiovascular disease (20). Elevated glucose levels at admission have been associated with worse clinical outcomes, irrespective of the presence of DM (21). Pathophysiological mechanisms, including endothelial dysfunction, increased oxidative stress at the vessel wall with activation of platelets, inflammation, and thrombosis might be affected more severely in the setting of ACS in previously unrecognized DM (22). However, Hadjadj et al. (15) found no link between the chronic glycometabolic states and outcome. Likewise, we did not observe greater myocardial damage in our diabetic group with HbA1c

Table 2: Angiographic characteristics of all participants

	Diabetic Patients (n=51)	Non-diabetic Patients (n=54)	p Value
Age, yrs	16 (31)	23 (43)	p>0.05
Male, n (%)	0 (0)	2 (4)	p>0.05
BMI, kg/m²	27 (53)	15 (27)	p>0.05
Hypertension n (%)	47 (92)	49 (91)	p>0.05
Heart failure n (%)	28 (55)	17 (31)	p>0.05

Values are given as percentages or means ± SD. Cx: circumflex arter; LDA: left anterior descending artery; RCA: right coronary artery.

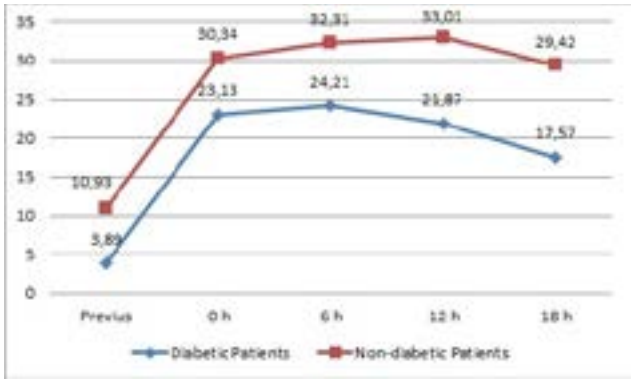

Figure 1: Time course of troponin values after coronary angioplasty in diabetic (HbA1c > 6.5) (n=51) and non-diabetic (HbA1c <6.5) (n=54) participants. Symbols represent mean. *p=0.168 for comparison between troponin peaks at 6 h in the 2 groups.

> 6.5, suggesting chronic gluco-metabolic state may not play a role in the worse clinical outcomes. One possible explanation is that all our patients, with or without DM responded so well to aggressive management of STEMI, including early reperfusion and revascularization (23). Another potential explanation is that our diabetic patients' average HbA1c values were less than 8, suggesting our group of patients had lesser severity of poor glycemic control. Another possibility is that glucose levels at admission were similar in the 2 groups and were below 180 mg/dL, resulting in no difference in myocardial damage.

HbA1c is a reliable marker of long-term glucose control. HbA1c values are not only a diagnostic parameter of DM, but also a prognostic biomarker for cardiovascular disease (24,25).Prospective studies have shown that poor long-term metabolic control, as reflected by the HbA1c value, is associated with a risk of both myocardial infarction and congestive heart failure (26). Chronic gluco-metabolic state might be relevant in the context of AMI in patients without previously diagnosed DM. Lee et al. (27) compared major adverse cardiac events (MACEs) in diabetic and non-diabetic patients with AMI stratified according to HbA1c values (> 6.5 or ≤ 6.5). In their study, the rates of MACEs during the 12 months follow-up period did not differ between the groups and HbA1c level was not the independent predictor of MACEs. Similar findings have been reported by Britton et al. (28) and Riddle et al. (29).

Recent evidence showed conflicting results regarding HbA1c levels and severity of coronary artery disease. Those studies looked at the future cardiovascular events and mortality as clinical end-points rather than acute events (5,15,30-32). The severity of coronary artery disease (one-vessel vs multi-vessel) and coronary collateral development were similar in our two groups. Fasting blood glucose, HbA1c and the presence of diabetes were associated with the severity and progression of coronary atherosclerosis (30). There was an increasing trend of hemoglobin A(1c) levels with the increasing number of vessels with CAD (33). Both admission glycemic excursion and chronic hyperglycaemia were associated with the severity of CAD in newly diagnosed DM patients (34). There was no significant relationship between the Gensini score and HbA1c, fasting and postprandial blood glucose levels, lipid profile, and hs-CRP levels in patients with nondiabetic ACSs (35). HbA1c was not an independent predictor of the severity of CAD in non-diabetic adult patients (36).

Our data on the relationship between admission HbA1c values and extent of infarct are in line with the results of a recent study by Chan et al. (8), who reported similar TnT peaks between HbA1c < 7% and > 7% groups before admission in diabetic patients. This study suggests that HbA1c levels before admission are not associated with short-term cardiovascular outcome in diabetic patients subsequently admitted with ACS. In contrast Lazzeri et al. (32), reported higher troponin peaks in their diabetic patients with HbA1c > 6.5 compared to those with HbA1c < 6.5.

Several limitations of this study are important to consider. The main limitation is the small number of patients enrolled in this study. We did not report on long-term follow-up. Additional studies are certainly needed to replicate and extend our findings in a larger population.

In conclusion, in this study, we showed that in patients with previously unrecognized DM presenting with STEMI, HbA1c > 6.5 does not predict greater myocardial damage. This result suggests that optimal control of chronic gluco-metabolic state preceding acute MI (HbA1c < 8) may not be beneficial to limit myocardial damage. Further research should focus on other factors unrelated to chronic glucometabolic state, including acute glucose perturbations which might portend worse clinical outcomes associated with this group of patients.

Conflict of interest: No conflict of interest was declared by the authors.

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