The value of admission glycosylated hemoglobin level in patients with acute myocardial infarction

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BACKGROUND: Glycosylated hemoglobin (HbA1c) level on admission is a prognostic factor for mortality in patients with and without diabetes after myocardial infarction. In the present study, the authors examined the relationship between admission HbA1c level and myocardial perfusion abnormalities in patients with acute myocardial infarction.
METHODS: One hundred consecutive patients with acute myocardial infarction who were treated with thrombolytic therapy were included in the present prospective study. Blood glucose and HbA1c levels of all patients were measured within 3 h of admission. Patients were divided into three groups according to HbA1c level: 4.5% to 6.4% (n=25), 6.5% to 8.5% (n=28) and higher than 8.5% (n=47). All patients then underwent exercise thallium-201 imaging and coronary angiography to determine ischemic scores and the number of diseased coronary arteries four weeks after admission.
RESULTS: Seven patients died within the four-week follow-up period. There was a significant relationship between admission HbA1c level and mortality (P=0.009). Furthermore, there was a significant relationship between HbA1c level and total ischemic scores in patients with acute myocardial infarction (r=0.482; P=0.001). Ischemic scores increased as HbA1c levels increased in patients with acute myocardial infarction.
CONCLUSIONS: The results demonstrated that admission plasma glucose and HbA1c levels are prognostic factors associated with mortality after acute myocardial infarction.

Key Words: *Acute myocardial infarction; Diabetes; HbA1c; Ischemic score; Prognosis*

La valeur du taux d'hémoglobine glycosylée à l'hospitalisation des patients atteints d'un infarctus aigu du myocarde

HISTORIQUE : Le taux d'hémoglobine glycosylée (HbAlc) au moment de l'hospitalisation est un facteur pronostique chez les patients diabétiques ou non diabétiques après un infarctus du myocarde. Dans la présente étude, les auteurs ont examiné la relation entre le taux de HbAlc à l'hospitalisation et les anomalies de perfusion myocardique chez les adultes atteints d'un infarctus aigu du myocarde.
MÉTHODOLOGIE : Cent patients consécutifs atteints d'un infarctus aigu du myocarde recevant un traitement thrombolytique faisaient partie de la présente étude prospective. La glycémie et les taux de HbAlc de tous les patients ont été mesurés dans les trois heures suivant leur hospitalisation. Les patients ont été divisés en trois groupes, selon leur taux de HbAlc : de 4,5 % à 6,4 % (n=25), de 6,5 % à 8,5 % (n=28), et plus de 8,5 % (n=47). Tous les patients ont ensuite subi une imagerie d'épreuves d'effort au thallium 201 et une coronarographie pour déterminer les indices ischémiques et le nombre d'artères coronaires atteintes quatre semaines après l'hospitalisation.
RÉSULTATS : Sept patients sont décédés pendant la période de suivi de quatre semaines. On a constaté un lien significatif entre le taux de HbAlc à l'hospitalisation et la mortalité (P=0,009). Le lien était également significatif entre le taux de HbAlc et les indices ischémiques totaux chez les patients atteints d'un infarctus aigu du myocarde (r=0,482; P=0,001). L'augmentation des indices ischémiques était proportionnelle aux taux de HbAlc chez les patients atteints d'un infarctus aigu du myocarde.
CONCLUSIONS : Les résultats démontrent que les taux de glucose plasmatique et de HbAlc à l'hospitalisation sont des facteurs pronostiques de la mortalité après un infarctus aigu du myocarde.

Hyperglycemia during acute myocardial infarction (AMI) is associated with a poor prognosis, and blood glucose level is an independent predictor of mortality in patients with or without known diabetes (1). The future glycometabolic profile of patients suffering AMI without diabetes can be predicted in the hospital phase (2). There is also a correlation between blood glucose on hospital admission for AMI and long-term mortality in patients with or without known diabetes (3,4). Moreover, hyperglycemia in patients with ST elevation MI was found to be an important predictor of impaired epicardial flow (5). In acute coronary syndromes, glucose metabolism is modified, and stress hyperglycemia commonly occurs (6) secondary to increased catecholamine levels. Due to stress hyperglycemia, a method looking only at plasma glucose levels at the time of an AMI cannot be used to predict the prognosis. Thus, glycosylated hemoglobin (HbA1c) values may reveal diabetes in cases of AMI (7).

Elevated HbA1c is an important determinant of atherosclerosis beyond the risk associated with established diabetes (8,9). Thallium-201 (Tl-201) scintigraphy has been used to assess prognosis after AMI, and the extent and severity of perfusion abnormalities were found to be closely associated with cardiovascular outcome (10). In the present study, we evaluated the relationship between admission HbA1c levels and myocardial perfusion abnormalities in patients with AMI.

METHODS

Study population

Consecutive patients admitted to the cardiology department of the Siyami Ersek Cardiac and Thoracic Surgery Center (Istanbul, Turkey) for AMI between 1998 and 2004 were selected (100 patients; 68 men; mean age 59.5±9.6 years). AMI was defined according to the European Society of Cardiology and American College of Cardiology criteria (11): increased creatine kinase predominantly in the myocardial band fraction and/or increased cardiac troponin I (creatine kinase 400 U/L or higher, and/or cardiac troponin I 2 µg/L or higher), ischemic symptoms (mainly constrictive chest pain, lasting longer than 30 min),

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TABLE 1
Demographic and clinical patient data

	Level of glycosylated hemoglobin			
	<6.5% (n=25)	6.5%–8.5% (n=28)	>8.5% (n=47)	P
Age, years (mean ± SD)	56.6±11.5	62.2±8.4	59.6±8.9	NS
Sex, n (male/female)	11/14	19/9	38/9	0.006
Smoking, %	44	46	57	NS
Hypertension, %	52	89	64	0.01
Hyperlipidemia, %	81	54	32	0.001
Obesity (BMI >30 kg/m^2), %	19	18	22	NS
Blood glucose, mmol/L	7±1.6	8.3±1.7	9.7±3.2	0.0001
Total cholesterol, mmol/L	5.8±1.1	5.7±2.1	4.9±1.1	0.004
LDL cholesterol, mmol/L	3.6±0.8	3.8±1.65	3.1±0.9	0.01
HDL cholesterol, mmol/L	1.2±0.26	1.1±0.23	0.96±0.2	0.001
Triglycerides, mmol/L	2.23±1.36	2.26±1.55	1.8±0.71	NS
Hemoglobin, mmol/L	8.7±0.75	8.3±1.1	9.1±0.86	NS
Mortality, n	0	0	7	0.009
Exercise testing, n				
Positive	8	19	37	0.0001
Scintigraphy				
Total ischemic score	8.5±2.8	10.1±9.4	12.7±6	0.0001
Angiography (number of diseased vessels), n				
Single-vessel disease	21	17	4	0.0001
Double-vessel disease	3	5	17	0.0001
Triple-vessel disease or worse	1	6	19	0.001

BMI Body mass index; HDL High-density lipoprotein; LDL Low-density lipoprotein; NS Nonsignificant

and/or abnormal electrocardiography (ST elevation 1 mm or greater on at least two derivations). MI was defined as acute if the time elapsed between the first symptom and admission was 48 h or less. Only patients who underwent thrombolytic treatment were included in the study.

Exclusion criteria

The following patients were excluded: those in whom primary angioplasty was the choice of treatment, those with subacute or chronic MI (longer than 48 h between first symptom and admission), those with renal failure and those using antidiabetic medications.

Study protocol

Blood glucose and HbA1c levels of all patients were measured within 3 h of admission, regardless of whether they had been fasting. Blood glucose and HbA1c levels were analyzed by the AEROSET system and the ARCHITECT c8000 system (Abbott Laboratories, USA), respectively.

The five major risk factors were male sex, obesity, history of hypertension, dyslipidemia and cigarette smoking, which were carefully evaluated. Smoking status was defined as a patient never having smoked or currently smoking. Dyslipidemia was defined as a fasting concentration of serum total cholesterol higher than 5.2 mmol/L. The fasting lipid profile was determined on the morning following admission and included total cholesterol, high-density liporotein cholesterol and triglycerides. Lipoprotein analysis was determined by automated enzymatic methods.

Patients were divided into three groups according to the level of HbA1c: 25 patients with HbA1c levels of 4.5% to 6.4% (group 1), 28 patients with HbA1c levels of 6.5% to 8.5% (group 2) and 47 patients with HbA1c levels higher than 8.5% (group 3).

Patients in group 1 were accepted as nondiabetic, patients in group 2 as possibly diabetic and patients in group 3 as diabetic, regardless of whether it was known previously (12).

None of the patients received glucose, insulin or potassium infusion therapy during admission. All patients underwent exercise TI-201 imaging and coronary angiography within the four-week follow-up after AMI. The study protocol was approved by the institutional ethics committee and all patients provided written, informed consent before study entry.

Single photon emission computed tomography acquisition protocol

All patients were investigated according to a one-day rest/stress protocol using TI-201 imaging. An Elscint Apex SPX gamma camera (Elscint, Israel) equipped with a low-energy, all-purpose collimator was used. Sixty projections of 20 s each were acquired in step-and-shoot mode over a 180° arc on 64 × 64 matrix with a zooming factor of 1.4. Image reconstruction was performed using a Butterworth filter with a cut-off frequency of 0.35 Nyquist and an order of five for technetium-99m sestamibi imaging.

Image analysis

Myocardial perfusion was graded on a five-point scale, with the score representing the reduction of radioisotope uptake (0 = normal; 1 = equivocal, 2 = moderate, 3 = severe and 4 = absent) using a 20 segment model (10). Total perfusion and reversibility scores were calculated by adding up all individual segment scores for stress and resting conditions. A reversibility score was then calculated by subtracting the resting scores from the corresponding stress scores.

Exercise protocol

Patients were instructed to discontinue beta-blockers and calcium antagonists 48 h before testing and nitrates 6 h before testing. A symptom-limited treadmill exercise test using the Bruce protocol was performed. Horizontal or downsloping ST segment depression greater than 1.0 mm or upsloping more than 1.5 mm 80 ms after the J point was considered to be positive.

Coronary angiography

Selective coronary angiography was performed in multiple views with the Judkins technique. Coronary angiograms were analyzed by two experienced observers who were blinded to the identities and clinical information of the patients. Vessel scores ranged from zero to three, according to the number of diseased major epicardial vessels with significant stenosis (greater than 50% stenosis of the lumen diameter).

Next, the relationships between HbA1c and the results of exercise Tl-201 imaging, coronary angiography and mortality were statistically evaluated.

Statistical analysis

Data were expressed as proportions or mean ± SD. One-way ANOVA (with post hoc test) or Kruskal-Wallis test, as appropriate, was used to compare continuous variables, and the χ^2 test was used to compare proportions among groups. Linear regression analysis with Pearson's coefficient was used to assess the strength of association between variables. Multivariate regression analysis was used to identify determinants of ischemic score. The strength of these relationships was expressed as the beta coefficient and P value. P<0.05 was considered to be statistically significant.

RESULTS

Demographic and clinical data of the subjects are summarized in Table 1. Except for seven patients who died within 28 days after AMI, all patients underwent exercise Tl-201 imaging and coronary angiography at the end of the fourth week. When examining the results of exercise test, it was found that all patients reached a mean 7.8±1.5 metabolic equivalents during exercise testing, and the mean

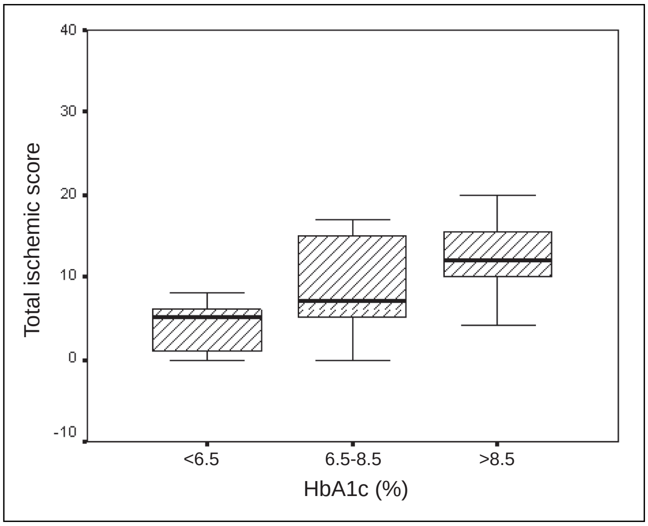

Figure 1) *Box plots of total ischemic scores according to glycosylated hemoglobin (HbA1c) levels*

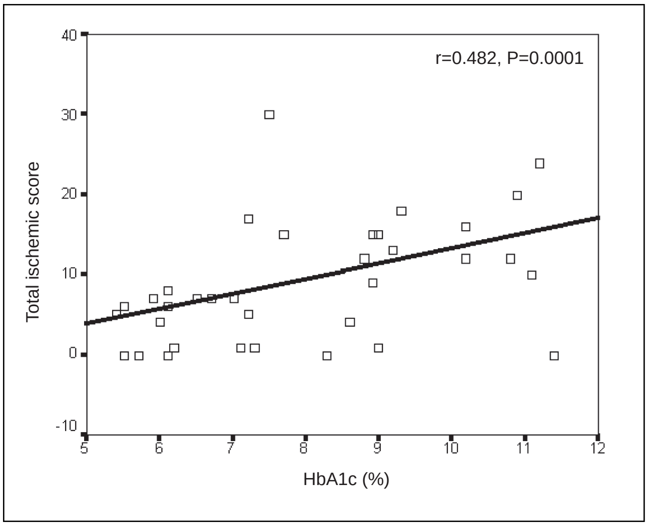

Figure 2) *The correlation between glycosylated hemoglobin (HbA1c) levels and total ischemic scores in patients with acute myocardial infarction*

total ischemic score (TIS) on Tl-201 imaging was 9.6±7.2. Because seven patients died within the four-week follow-up period, coronary angiography performed in the remaining 93 patients revealed that there was single-vessel disease in 42 patients, double-vessel disease in 25 patients and triple-vessel disease or worse in 26 patients. Two patients died of cardiogenic shock, four died of arrhythmia (ventricular fibrillation) and one died of acute mitral regurgitation because of chordal rupture in the follow-up period.

The first major risk factor was male sex. When the relationship between male sex and clinical results was examined, no significant relationship was found. However, there were significant relationships between male sex and TIS (P=0.001), and male sex and the number of diseased vessels (P=0.001).

The second major risk factor was obesity. There was no significant relationship between body mass index and mortality after AMI. Moreover, there was no significant relationship between body mass index and TIS, and body mass index and the number of diseased vessels.

The third major risk factor was smoking. When the relationship between smoking and mortality after AMI was considered, it was found that there was no significant relationship. However, there were significant relationships between smoking and TIS (P=0.002), and smoking and the number of diseased vessels (P=0.001).

When considering the other two risk factors, history of hypertension and hyperlipidemia, there was a significant relationship only between history of hyperlipidemia and TIS (P=0.0017), and between history of hypertension and positive exercise test results (P=0.001).

When the relationship between glucose metabolism at admission and clinical results was evaluated, it was found that there was a significant relationship between glucose level at admission and mortality after AMI (P<0.05). Moreover, there was a significant relationship between blood glucose level at admission and positive exercise testing (P<0.001), and TIS obtained four weeks after AMI (P<0.001).

When considering the HbA1c level as a risk factor, it was found that there was significant relationship between HbA1c level and mortality after AMI (P=0.006). The mean HbA1c level was greater than 8.5% in all seven patients who died during the four-week follow-up period. There was also significant correlation between HbA1c levels at admission and positive exercise test results after the four-week follow-up period (r=0.327; P=0.001). TIS was significantly different among the HbA1c groups (Figure 1). In addition, HbA1c levels at admission and TIS were significantly correlated (Figure 2). There was also a significant correlation between HbA1c level at admission and the number of diseased vessels (r=0.69; P=0.0001). Potential determinants of TIS were evaluated in all study subjects by performing multivariate regression analysis between the values of TIS (dependent variable) and the values of HbA1c, total cholesterol, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol (independent variables). TIS was positively correlated with HbA1c (beta=0.39; P=0.0005), but was not significantly correlated with lipid parameters.

DISCUSSION

Our study demonstrated that in patients with AMI, elevated glucose and HbA1c levels on admission are associated with higher ischemic scores and increased mortality rates compared with patients with normal levels on admission.

In a recently reported study, Timmer et al (13) reported that higher admission glucose levels in nondiabetic patients treated with reperfusion therapy for ST segment elevation MI were associated with significantly larger enzymatic infarct size and lower left ventricular ejection fraction. This is because a stress response is accompanied by high levels of catecholamines and cortisol, and these hormones increase glycogenolysis and lipolysis and reduce insulin sensitivity, resulting in elevated glucose levels (14). Therefore, patients with elevated glucose levels may represent patients with an increased stress response, for example, due to more severe hemodynamic compromise or more extensive myocardial damage (15,16). Stress hyperglycemia increases mortality, congestive heart failure and cardiogenic shock after AMI (17). Elevated cytokine, particularly tumour necrosis factor-alpha (TNF-α), also increases glucose levels. TNF-α is released in AMI and directly decreases myocardial contractility, probably by inducing myocardial apoptosis (18-22). TNF-α also causes impaired endothelial function (20). This, in turn, may be responsible for the impaired myocardial perfusion.

The subdiabetic or prediabetic state, also known as impaired glucose tolerance (IGT), is associated with a higher incidence of cardiovascular events (23,24), and because many of the studies examining AMI patients in the hyperglycemic state did not measure HbA1c, they were not able to demonstrate pre-existing diabetes. Undiagnosed diabetes was found in 4.3% of patients in one study, contributing to approximately 10% of mortality (7). Levetan et al (17) also demonstrated that one-third of hospitalized patients had at least one glucose level reading higher than 11 mmol/L. In the presence of high glucose levels, stress hyperglycemia should be differentiated from diabetes. The admission glucose level can not be used to predict the prognosis in diabetic patients. Because admission blood glucose levels had begun to lose its significance in predicting the prognosis of patients with AMI, clinicians began to focus on HbA1c level.

The Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study (3) showed that the glycometabolic state at hospital admission as defined by blood glucose and HbA1c was a long-term risk factor in AMI patients with and without diabetes. AMI patients without established diabetes had a high prevalence of insulin resistance during the hospital phase and the following three months (2). Hadjadj et al (12) recently reported that admission plasma glucose, even after adjusting for HbA1c, is a prognostic factor associated with mortality after AMI. Acute, rather than the chronic, pre-existing glycometabolic states accounted for the prognosis after AMI. The authors suggested that admission plasma glucose was an acute reaction rather than the consequence of a pre-existing metabolic disorder, because adjustment for HbA1c did not modify the association of admission plasma glucose with mortality risk. They found a positive correlation between peak creatine kinase levels and admission plasma glucose concentrations in their patients. This correlation persisted even when the analysis was restricted to those patients without previously diagnosed diabetes. However, they did not find any correlation with HbA1c values in their study.

While hyperglycemia is a marker of post AMI stress; insulin resistance is related to the intensity of the stress (12). A chronic pre-existing abnormal glycometabolic state inevitably affects the degree of metabolic response to stress; higher blood glucose levels were found during stress in patients with previously known IGT. Moreover, a chronic pre-existing abnormal glycometabolic state is inevitably related to a more diffuse coronary artery tree, and so with increased TIS. In previous studies (23,24), the relationships between clinical parameters such as mortality and morbidity were evaluated. However, in the present study, the relationship of acute and chronic glycometabolic states with the results of exercise, Tl-201 imaging and coronary angiography was evaluated, and our results support the hypothesis that both acute and chronic glycometabolic states are an indicator of mortality risk after AMI. There were significant relationships between admission glucose, HbA1c level and mortality (P=0.006 for HbA1c level and P=0.043 for glucose level). Patients with HbA1c levels higher than 6.5% have significantly higher ischemic score than the patients with HbA1c levels lower than 6.5% (P=0.0001).

CONCLUSIONS

Our study included only a limited number of patients, and specific cardiac marker levels, such as creatine phosphokinase myocardial band and cardiac troponin levels, which can clearly demonstrate the level of cellular destruction, were not evaluated and compared. Furthermore, we did not use the gold standard method to diagnose diabetes or IGT, namely, the oral glucose tolerance test, before discharge. Mortality rates are influenced by factors such as the presence or absence of recanalization, infarct sites, the time from disease onset to treatment, Killip classification at admission, ST segment elevation resolution and left ventricular function. Despite these limitations, our results clearly demonstrated that both acute and chronic glycometabolic states are an indicator of prognosis after AMI.

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