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RESEARCH ARTICLE

HbA1c – SHORT TERM PREDICTOR OF MORTALITY IN NON DIABETIC ST ELEVATION MYOCARDIAL INFARCTION PATIENTS

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ABSTRACT

Background: Acute glycometabolic derangement in non-diabetic patients with acute myocardial infarction (AMI) has been reported with discrepant prognostic results. The aim of the present study was to assess the prognostic impact of glycated haemoglobin (HbA1c) levels, reflecting long-term glycometabolic disturbance, in a population of patients without known diabetes mellitus.

Methods: We examined 300 consecutive prospective patients diagnosed with AMI and unknown diabetes mellitus. We analysed metabolic function as a stratified variable using three groups of patients according to HbA1c: Group 1 (< 5.5%): 111 patients (37%); Group 2 (5.5 to 6.4%): 168patients (56%); Group 3 (>6.4%): 21 patients (7%). Association between HbA1c groups and classic cardiovascular risk factor and in-hospital outcomes were assessed through univariate and multivariate analysis.

Results: In-hospital mortality was 5% (16/300 patients). Higher HbA1c was associated with poor glycometabolic control, older patients, obesity, hypertension, Killip's class>1, increased heart rate, initial bundle branch block, atrial fibrillation and higher mortality during follow-up. In a multivariate adjusted risk, in-hospital mortality was associated with age (odds ratio (OR)= 1.056; 1–1.1; p=0.006), Killip's class>1 (OR=2.4; 1–6.1; p=0.05) and HbA1c (OR=1.5; 1.15–1.9; p=0.002). Hypertension (OR=0.39; 0.18–0.87; p=0.022) and angiotensin-converting enzyme inhibitors (OR=0.28; 0.12– 0.69; p=0.005) were protective factors.

Conclusions: HbA1c is an important risk marker in the absence of a history of diabetes mellitus in patients with AMI. The optimal management strategy in these patients may contribute to decreased in-hospital mortality.

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INTRODUCTION

In recent years, much attention has been paid to the glycometabolism of patients with coronary artery disease. Measurement of admission glucose and glycated haemoglobin (HbA1c) levels in acute myocardial infarction (AMI) may identify patients with disturbed glucose metabolism and an increased risk for adverse outcome (Capes *et al*., 2000; Stranders *et al*., 2004; Selvin *et al*., 2010; Hadjadj *et al*., 2004). Although HbA1c and glucose are related, they can differentiate between mechanisms of adverse outcome. Hyperglycaemia for most patients with AMI is a manifestation of previous disturbed glucose metabolism; it is also partially caused by acute stress with raised levels of cortisol (Norhammar *et al*., 2002; Sanjuan *et al*., 2011; Giraldez *et al*., 2013).

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HbA1c level is an indicator of average blood glucose concentrations over the preceding 2–3 months, which is a convenient and well-known biomarker in clinical practice, using the HbA1c assay as the preferred method for diabetes diagnosis and treatment control (American Diabetes Association, 2013). HbA1c is minimally affected by stress hyperglycaemia during AMI and therefore reflects previous glycometabolic disturbance. Recent studies that evaluated the prognostic value of HbA1c in patients hospitalized with advanced atherosclerosis have reported discrepant results. Several studies showed that although crude mortality data was higher in patients with elevated HbA1c following adjustment for many cardiovascular risk factors, HbA1c values failed to predict in-hospital mortality (Corpus *et al*., 2003; Timmer *et al*., 2006; Cakmak *et al*., 2008). Other authors have observed that HbA1c, as a surrogate for more chronic dysglycaemia, is a more useful marker of patients with greater long-term risk of death (Timmer *et al*., 2011; Gustafsson *et al*., 2007; Chowdhury and Lasker, 1998; Rasoul *et al*., 2007; Cicek *et al*., 2011) Because the prognostic value of HbA1c levels in

patients with acute coronary syndromes had different prognostic effects based on patient's diabetes status and only smaller studies exist with different methods and results, the purpose of the present study was therefore to assess whether the HbA1c levels have a prognostic significance and could be used in short-term risk stratification in patients with AMI and unknown diabetes mellitus (DM).

MATERIALS AND METHODS

Patient population

We performed a single-centre observational prospective study including 300 patients with AMI admitted into the coronary care unit (CCU). The inclusion period was september 2012 to February 2015. The study was approved by the local ethical committee and all patients included gave informed consent to participate in the study.

Inclusion Criteria

1) Chest pain with ST segment elevation or depression of at least 1 mm in one or more peripheral leads of the ECG and/or at least 2 mm in one or more precordial leads, or
2) New onset left bundle branch block, or
3) Elevated levels of troponin according to the criteria established by current guidelines (Thygesen *et al*., 2014)

All patients received recommended standard management for AMI.

Exclusion Criteria

1) Anaemia
2) Acute inflammatory diseases
3) Hepatic failure
4) Autoimmunity
5) Cancer and
6) Patients with chronic renal failure in a haemodialysis programme
7) Known DM

DM was defined as a history of diabetes according to medical history obtained from hospital records or when the patient reported receiving pharmacological treatment with oral hypoglycaemic drugs or insulin. The present analysis is based on data from 300 AMI patients who were not previously diagnosed DM. Because milder abnormalities of glucose control (below the diagnostic threshold of DM) are associated with increased cardiovascular risk, patients were graded into three categories or groups according to baseline admission levels of HbA1c: HbA1c levels < 5.5%, 5.5–6.4%, >6.4%.

Methods

The project design included a medical examination, biochemical analyses and instrumental exams as well as echocardiography and coronary angiography results. The presence and degree of heart failure were assessed on admission at the emergency department, following the Killip classification (Killip and Kimball, 1967). Among the main cardiovascular risk factors, the presence of hypertension, type II diabetes, dyslipidaemia, smoking habits and body mass index were considered. The Global Registry of Acute Coronary Events (GRACE) risk model was obtained to predict probability of hospital death and the level of risk for individual patients. All patients received recommended standard management for AMI with regard to thrombolytic therapy, aspirin, clopidogrel, low-molecular-weight heparin, glycoprotein IIb-IIIa inhibitors, beta-blockers, statins and angiotensin-converting enzyme inhibitors (ACEis), as appropriate. All analyses were measured by conventional laboratory methods. In the CCU department the following analyses were collected: serum glucose, glycated haemoglobin, white blood cell count, platelets, haematocrit, electrolytes and cardiac biomarkers (troponin). HbA1c was analysed by ion-exchange high-performance liquid chromatography using the ADAMS HA-8180 analyser (Arkray Corp., Kyoto, Japan) (Hoelzel *et al*., 2004). In all patients coronary angiography was performed as soon as possible, and the number of coronary arteries damaged evaluated. Patients with STEMI received thrombolytic therapy at the beginning of the study. Patients with contraindications for thrombolytic therapy were taken for urgent invasive angiography with the intention of performing primary PCI. Moreover, in cases of unsuccessful fibrinolytic therapy, patients received rescue PCI. Left ventricular ejection fraction (LVEF) was assessed through two-dimensional echocardiography immediately after admission. Continuous monitoring was performed in all patients during their stay at the CCU in order to determine any type of significant arrhythmia. After discharge from the CCU, an electrocardiogram was performed daily and when patients had symptoms.

Statistical analysis

Baseline characteristics of the study population were calculated according to categories of glycated haemoglobin values. We analysed HbA1c function as a continuous and also as a stratified variable. Continuous data were summarized and given as median values with corresponding SD or SEM, and dichotomous data were given as counts and percentages. The Kruskal–Wallis test was used for categorical characteristics with more than two groups. Means between groups were compared by the use of independent-samples *t*-tests (ANOVA polynomial linear term). In multivariate analysis (Cox regression using forward stepwise variable selection methods), the association of HbA1c with the statistical significance variables and outcome (in-hospital mortality) were adjusted for age, sex, classical cardiovascular risk factors, Killip class, history of previous myocardial infarction, serum creatinine, serum glycaemia, systolic blood pressure and heart rate on admission. All statistical tests were performed with SPSS 19.0. A value of $p<0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

300 patients without prior diagnostic of DM were included in our study population (Figure 1). Three categories of patients were created according to HbA1c level: Group 1 (< 5.5%): 111 patients (37%); Group 2 (5.5 to 6.4%): 168patients (56%); Group 3 (>6.4%): 21 patients (7%).

Table 1. Baseline Subject Characteristics According To Hba1c group and global population

	Total patients	HbA1c Group 1 <5.5%	HbA1c Group 2 5.5%–6.4%	HbA1c Group 3 > 6.4%	P value
Patients	300	111 (37%)	168 (56%)	21 (7%)	
Female (%)	22	23	21	19	NS
Aged (*M* ± SD)	62 ± 13	60 ± 13	64 ± 13	64 ± 13	0.007
BMI (kg/m2)	27 ± 4	26 ± 3	28 ± 4	29 ± 3	<0.001

Table 2. Baseline Characteristics

	Total patients	HbA1c Group 1<5.5%	HbA1c Group 2 5.5%–6.4%	HbA1c Group 3 > 6.4%	P value
Patients	300	111 (37%)	168 (56%)	21 (7%)	
NYHA>2 (%)	19	16	20	24	ns
Hypertension (%)	55	48	59	71	0.001
Previous myocardial infarction (%)	19	19	19	17	ns
smoker (%)	49	54	45	57	ns
Dyslipidaemia (%)	45	46	43	57	ns
Peripheric arteriopathy (%)	5	4	5	12	0.005
Prior PCI	12	15	10	12	ns

Table 3. Baseline Characteristics

	Total patients	HbA1c Group 1 <5.5%	HbA1c Group 2 5.5%–6.4%	HbA1c Group 3 > 6.4%	P value
Patients	300	111 (37%)	168 (56%)	21 (7%)	
STEMI(%)	69	68	72	62	ns
Killip > I (%)	19	14	21	31	0.004
HR (%)	79 ± 22	79 ± 20	78 ± 21	89 ± 29	0.01
SBP (%)	135 ± 32	135 ± 30	134 ± 34	146 ± 34	ns
LVEF (%)	51 ± 11	52 ± 11	51 ± 11	50 ± 14	ns
>1 Vssel disease	34	32	34	41	ns
PCI	99	90	97	93	ns

Table 4. Average Hba1c And Egfr

	Total patients	HbA1c Group 1 <5.5%	HbA1c Group 2 5.5%–6.4%	HbA1c Group 3 > 6.4%	P value
Patients	300	111 (37%)	168 (56%)	21 (7%)	
Admission glucose (mg/dl) (*M* ± SD)	144±59	137 ± 64	142± 47	200 ± 90	0.001
eGFR (ml/min) (*M* ± SD)	68 ± 30	69 ± 28	68 ± 32	63 ± 23	ns
HbA1c (%) (*M* ± SD)	5.8 ± 0.7	5.2 ± 0.3	5.9 ± 0.2	7.6 ± 1.5	0.001

Table 5. Hospital Adverse Outcomes and In-Hospital Therapies

	Total patients	HbA1c Group 1 <5.5%	HbA1c Group 2 5.5%–6.4%	HbA1c Group 3 > 6.4%	P value
Patients	301	111 (37%)	168 (56%)	21 (7%)	
GRACE risk score (*M*±SD	159 ± 43	154 ± 41	162 ± 42	163 ± 58	
In-hospital mortality (16 pts) (%)	5	4	5	14	0.02
Atrial fibrillation (71 pts) (%)	12	6	15	19	0.001
Initial LBBB (42 pts) (%)	7	3	9	10	0.01
Primary ventricular fibrillation (36 pts) (%)	6	4	7	4	
AV block ≥2º (34 pts) (%)	6	5	6	7	
In-coronary care unit (days)	3	3	4	4	
In-hospital stay (days) (median)	7	8	8	9	

Table 6. Hospital Therapies

	Total	Group 1	Group 2	Group 3	P value
Reperfusion therapy (STEMI) (%)	69	60	75	73	0.006
Dual antiplatelet treatment (%)	98	96	99	100	0.03
Beta-blockers (%)	41	42	40	41	NS
ACE inhibitors (%)	62	62	62	62	NS
Statin (%)	95	95	95	93	NS
Diuretics (%)	22	21	21	41	NS
Inotropic agents (%)	9	6	10	12	NS
Insulin (%)	8	3	7	41	<0.001

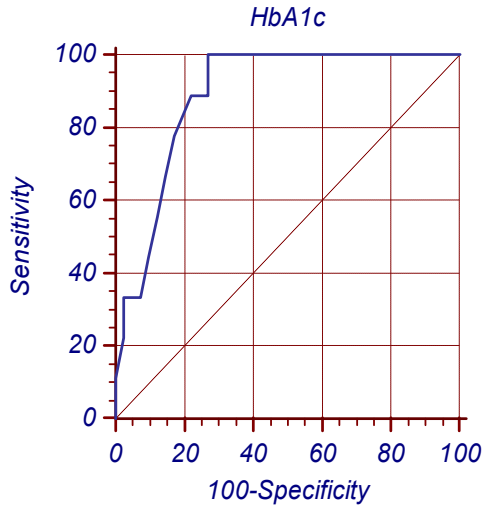
Table 7. Multivariate adjusted risk for in-hospital mortality

OR		95% CI	*p* value
Age	1.056	1–1.1	0.006
Hypertension	0.395	0.18–0.87	0.022
HbA1C	1.493	1.15–1.9	0.002
Killip > 1	2.44	1–6.1	0.05
ACE inhibitors	0.28	0.12–0.69	0.005

Table 8. ROC curve variables

S.No	Hba1c	Sensitivity	Specificity
1	≥4	100	0
2	>4	100	2.44
3	>4.5	100	14.63
4	>5.1	100	56.10
5	>5.4	100	73.17
6	>5.9	66.67	85.37
7	>6.3	44.44	90.24
8	>6.6	33.33	97.56
9	>6.9	11.11	100
10	>7.1	0	100

From the table it is clear that HbA1c >5.4 have 100% sensitivity and 73% specificity in predicting mortality.



ROC curve for mortality

Baseline characteristics of the study population are shown in Table 1. The mean age of our sample was 62 ± 13 years and 78% were males. In the subgroups analysis, patients with higher HbA1c were older; more often had a history of hypertension (48% *vs.* 59% *vs.* 71%) and arteriopathy (4% *vs.* 5% *vs.* 12%). STEMI was present in 208 patients (69%). Killip class>1, glycaemia were associated with higher HbA1c levels. The mortality in the global group was 5% (16 patients). Table 2 describes the outcomes and treatment according to HbA1c categories. Multivariate analysis is shown in Table 3. The baseline covariates included in the final model associated with mortality were Killip >1, age and HbA1c levels. A history of hypertension and pharmacological therapy with ACEis had a protective effect and was inversely associated.

DISCUSSION

We found a substantial proportion of patients suffering from AMI with underlying prediabetes and unknown overt DM after hospital admission. These patients with disturbed glucose metabolism had worse early outcomes, characterized by progressive increased rates of in-hospital mortality according to HbA1c. In hospital mortality was 14% in patients with HbA1c >6.4%. The relationship between admission hyperglycaemia (stress hyperglycaemia) and short-term mortality in subjects without known DM after AMI has been well documented. Increased glucose levels on admission conferred an almost four-fold risk of death in patients without known DM after an AMI1 and two-fold risk in patients with STEMI additive to classical risk factor parameters (Sanjuan *et al*., 2011). HbA1c level is a stable indicator of unstressed long-term glucose control and is more useful to predict abnormal glucose tolerance in AMI patients compared with admission glucose (Norhammar *et al*., 2002). HbA1c is less influenced than plasma glucose by acute stress and illness (Oswald and Yudkin, 1987; Petursson *et al*., 2006) For many patients, the AMI hospitalization represents a period in which previously unrecognized DM could be initially diagnosed. Indeed, in our

study 7% of patients met the HbA1c criteria for newly diagnosed DM (American Diabetes Association, 2013) and this group represents a particularly high-risk population that has not been recognized or treated. The frequency of 7% non-diabetic patients with elevated HbA1c found in the current study is compatible with the findings of undiagnosed diabetes in other studies (Norhammar *et al*., 2002; Oswald and Yudkin, 1987; Petursson *et al*., 2006) Recent studies that evaluated the prognostic value of HbA1c in patients hospitalized with acute coronary syndrome have reported discrepant results. Several studies showed that although crude mortality data were higher in patients with elevated HbA1c following adjustment for many cardiovascular risk factors, HbA1c values failed to be an independent factor for mortality (Corpus *et al*., 2003; Timmer *et al*., 2006; Cakmak *et al*., 2008).

HbA1c, as a surrogate for more chronic dysglycaemia, is a more useful marker of patients with greater long-term risk of death (Timmer *et al*., 2011; Gustafsson *et al*., 2007). However, other authors suggested that HbA1c level was also a potent predictor of both in-hospital and long-term mortality (Chowdhury and Lasker, 1998; Rasoul *et al*., 2007; Cicek *et al*., 2011). Mortality rate and the risk of cardiogenic shock increased with levels of HbA1c in 150 patients with AMI without history of diabetes in an earlier study, which did not present a multivariate analysis (Oswald and Yudkin, 1987). After systematic review in patients with coronary artery disease with and without recognized diabetes, Liu *et al*. (2011) found that HbA1c levels had different prognostic effects based on patients' diabetes status. A U-shaped relationship, with lower mortality among patients within the prediabetes range, has been observed. Glycometabolic disturbance per se has a pathophysiological role in determining cardiovascular outcome, which is still disputed. The current data and their analyses do not elucidate whether the glucose disturbance has a causal role or is just a marker of more severe disease. For coronary heart disease, measures of risk discrimination showed significant improvement when glycated haemoglobin was added to models including fasting glucose (Selvin *et al*., 2010). Yet, undiagnosed diabetes or impaired glucose tolerance might be associated with other cardiovascular risk factors that are also undiagnosed and therefore untreated. Several mechanisms would have been involved in the greater early mortality among patients with AMI and previously undiagnosed diabetes. The fact that HbA1c was an independent prognostic indicator in our patients, additive to initial heart failure and classical cardiovascular risk factors, suggests the possibility that it was an important outcome factor, rather than a simple consequence of a larger or smaller infarct size.

Elevated HbA1c levels are likely the result of long term insulin resistance (HOMA). Metabolic disturbances associated with insulin resistance, including metabolic syndrome, abolish the effect of ischaemic preconditioning and induce oxidative stress affecting platelet function, coagulation and fibrinolysis (Kersten *et al*., 1998; Shechter and Merz, 2000). It is known that hyperglycaemia and/or hyperinsulinaemia in the acute stage of myocardial infarction are predictors of impaired coronary flow, both before and after reperfusion therapy with the occurrence of a non-reflow phenomenon after angioplasty (Timmer *et al*., 2005; Iwakura *et al*., 2003; Lazzeri *et al*., 2013). An interesting observation in previous works (Sanjuan *et al*., 2011; Sanjuan *et al*., 2011) is the association between hyperglycaemia and the high risk of ventricular tachyarrhythmia and initial or complicated bundle branch block in patients with AMI regardless of diabetes status. The use of free fatty acids instead of glucose by the ischemic myocardium could precipitate regional oxygen or energy crisis, and may lead to damaged cardiac-cell membranes, calcium overload and arrhythmias preceding mortality in many patients (30–32). In this study we have only observed an association between atrial fibrillation and bundle branch block with HbA1c levels but these factors were not independent risk adjusted for in-hospital mortality. Hypertension is a well-established risk factor for cardiovascular disease. The prognosis for hypertensive patients after AMI is uncertain because of the sparse and somewhat contradictory data. Patients with prior hypertension are older and are more likely to have diabetes and renal dysfunction. These clinical characteristics are all predictors of poor outcome (D'Ascenso *et al*., 2012; El-Menyar *et al*., 2011). The more risk factors present, the greater the likelihood of developing death and morbidity. Nevertheless, recent studies have shown a better in-hospital outcome in hypertensive than in normotensive patients with AMI. Abrignani *et al*. (2005). observed in 4994 consecutive patients admitted to an intensive care unit that hypertensive subjects with first AMI have a better in-hospital outcome than age- and gender-matched normotensive subjects, perhaps due to a less severe extension of the infarction area or to a different pathophysiological mechanism. Using data from the GRACE risk score in patients with non-ST-segment elevation acute coronary syndrome, Lee *et al*. (2013) observed that prior hypertension and the number of antihypertensive medications used pre-admission were not associated with increased in-hospital mortality. Patients with prior hypertension presented with higher systolic blood pressure on admission than those without; therefore one might expect these patients to have lower in-hospital mortality than those without prior history of hypertension. Our findings confirm the powerful and robust protective prognostic significance of hypertension in patients with AMI and unknown diabetes (odds ratio = 0.39; confidence interval: 0.18–0.87). Because milder abnormalities of glucose control are associated with increased cardiovascular risk, patients with diagnosis of diabetes were not considered for this study. Only 7% of our patients with HbA1c >6.4% could be considered as 'true diabetic patients'.

Conclusion

We found that HbA1c level, as a surrogate for more chronic dysglycaemia, is a useful marker of short-term risk of death in AMI patients without a history of diabetes. Introducing measurement of HbA1c in the CCU seems to be a simple method to obtain important information on mortality risk.

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