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ORIGINAL ARTICLE

Glucose dysregulation in nondiabetic patients with ST-elevation myocardial infarction: acute and chronic glucose dysregulation in STEMI

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ABSTRACT

Background: Admission hyperglycaemia is associated with an increased risk of mortality after myocardial infarction. Whether long-term glucose dysregulation (assessed by HbA1c) is more important than acute hyperglycaemia is unknown. We evaluated the prognostic value of admission glucose and HbA1c levels in nondiabetic patients with ST-segment elevation acute myocardial infarction (STEMI).

Methods: In 504 unselected, consecutive patients with STEMI, glucose and HbA1c levels were measured on admission. Glucose was categorised as <11.1 mmol/l (n=422) and ≥11.1 mmol/l (n=82). HbA1c levels were categorised as <6.0% (n=416) and ≥6.0% (n=88). Mean follow-up was 1.6±0.6 years.

Results: Patients with hyperglycaemia on admission were comparable with those with normoglycaemia. However, patients with HbA1c ≥6.0%, as compared with those with HbA1c <6%, were older, were more often on β-blockers and more frequently had multivessel disease. Thirty-day mortality in the subsequent glucose categories (<11.1 mmol/l and ≥11.1 mmol/l) was 4% and 19% (p<0.001) and in the subsequent HbA1c categories (<6% and ≥6%) was 5% and 12% (p=0.03). After multivariable analyses, admission glucose (OR 4.91, 95% CI 2.03 to 11.9, p< 0.001) but not HbA1c (OR 1.33, 95% CI 0.48 to 3.71, p=0.58) was significantly associated with 30-day mortality. Among 30-day survivors, neither admission glucose nor HbA1c were predictors of long-term mortality.

Conclusion: Elevated admission glucose is an important predictor of 30-day outcome after STEMI, while prior long-term glucose dysregulation is a covariate of other high-risk clinical characteristics. Among 30-day survivors, neither admission blood glucose nor HbA1c were predictors of long-term outcome.

KEYWORDS

ST-elevation acute myocardial infarction, admission glucose, HbA1c, outcome

INTRODUCTION

In patients with acute coronary syndrome (ACS), up to 40% have impaired blood glucose levels on admission.[1] This has been associated with increased mortality, irrespective of diabetic status.[2-7] Recent evidence has shown that chronic glucose dysregulation, assessed by HbA1c levels, is also of prognostic value with regard to future cardiovascular disease and congestive heart failure.[8] A previous study with a small sample size (n=146) suggested, however, that admission blood glucose but not HbA1c predicts short-term mortality after ACS.[9] It is unclear whether glucose dysregulation is associated with poor long-term prognosis among 30-day survivors.

We aimed to investigate the 30-day and long-term prognostic value of both admission glucose and HbA1c levels in patients with STEMI.

MATERIALS AND METHODS

Patients

It concerns a single-centre, prospective, follow-up study of unselected patients. During a period of 22 months, from April 2002 till February 2004, admission glucose and HbA1c were measured in 504 STEMI patients, none with previously documented diabetes mellitus. If patients revisited our hospital with one or more reinfarction during

the study period, only the first visit was recorded. Data from the patient's medical records were collected in a dedicated database.

Laboratory measurements

HbA1c was measured using a high-performance liquid affinity chromatography (HPLC) (Primus GLC 385). This method has an interassay coefficient of variation of 0.51%. Glucose was measured by a hexokinase method using a Modular PPE module device (Roche analytics).

Definitions of clinical diagnosis

STEMI was defined as the presence of chest pain, an electrocardiogram with ST-segment elevation of more than 1 mm (0.1 mV) in two or more contiguous leads and a subsequent rise of CK-MB of more than 6% of the total CK, whenever CK was >200 U/l (men) or >170 U/l (women). Previous CAD was defined as a history of myocardial infarction, coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). Diabetes was defined as the use of insulin or glucose-lowering medication on admission or a diet for diabetes documented in the medical history. Hyperglycaemia was defined as glucose ≥11.1 mmol/l based on nonfasting cut-off values for hyperglycaemia from the guidelines of the American Diabetic Association.[10] An HbA1c ≥6.0% was considered an elevated HbA1c.[11] Follow-up information with regard to mortality status was obtained in August 2005. All outpatients' reports were reviewed and general practitioners were contacted by phone. In order to distinguish the short-term and long-term effects, admission glucose and HbA1c, long-term outcome was only assessed among 30-day survivors.

Statistical analysis

Statistical analysis was performed using SPSS 12.0. Differences between group means were tested by two-tailed Student's t-test. A χ^2 statistic was calculated to test differences between proportions, with calculation of relative risks and exact 95% confidence intervals. Fisher's exact test was used when the expected value of cells was <5. Statistical significance was defined as a p value <0.05. Admission glucose was included as a categorical variable (<11.1 mmol/l and ≥11.1 mmol/l). HbA1c levels were included as a categorical variable (<6.0% and ≥6.0%). Cox proportional hazards regression models were used to estimate hazard ratios of clinical variables with regard to mortality.

RESULTS

During the study period, 587 patients with STEMI were admitted to our hospital, 504 (86%) of whom without previously diagnosed diabetes. Mean age was 63 ± 13 years and 72% were male. A total of 474 (94%) underwent immediate coronary angiography, and percutaneous intervention was performed in 428 (85%) of the patients. There were 82 patients (16%) with hyperglycaemia and 88 patients (17%) with HbA1c ≥6.0%. Of the 82 patients with hyperglycaemia, 29 (35%) also had elevated HbA1c, compared with 53 patients (14%) with normoglycaemia (p<0.001). Baseline characteristics of patient groups based on glucose and HbA1c categories are shown in *tables 1* and *2*, respectively.

Patients with hyperglycaemia were comparable with those with admission glucose <11.1 mmol/l, but less often had sinus rhythm and had higher HbA1c levels (*table 1*). Patients with HbA1c ≥6% were significantly older, had a higher prevalence of previous cerebrovascular disease, were more often on β-blockers and more often had multivessel disease.

Outcome

On discharge eight patients were treated with glucose-lowering medication. Follow-up was complete in 496 (98%) patients, with a mean duration of 1.6 ± 0.6 years.

Thirty-day mortality

At 30 days, 32 patients (7%) had died. The patients who died during follow-up were older, more often had a history of stroke, were less often smokers and less often had a positive family history. Of the patients with a glucose <11.1 mmol/l, 17 patients (4%) died compared with 15 patients (19%) with hyperglycaemia (p<0.001).

Mortality curves of the two patient groups according to admission glucose are shown in *figure 1*. Patients with an HbA1c <6.0% had a mortality of 22 (5%) compared with 10 (12%) in patients with an HbA1c of ≥6.0 (p=0.03). Mortality curves of the patient groups according to HbA1c level are shown in *figure 2*.

Figure 1. *Mortality curves according to admission glucose*

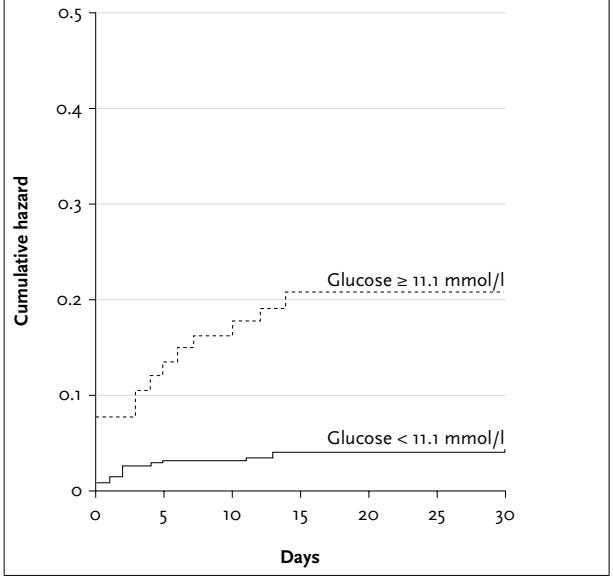


Table 1. *Baseline, angiography and outcome according to admission glucose*

Variable	N	Glucose <11.1	N	Glucose ≥11.1	P value
Age	422	63 ± 13	82	64 ± 12	0.64
Male	422	308 (73%)	82	54 (66%)	0.19
SBP	360	129 ± 24	63	126 ± 30	0.36
DBP	360	79 ± 16	63	76 ± 20	0.32
History of					
• MI	419	56 (13%)	81	8 (10%)	0.39
• PCI	418	34 (8%)	81	6 (7%)	0.83
• CABG	418	19 (5%)	81	1 (1%)	0.22
• CVA	419	11 (3%)	81	1 (1%)	0.70
Hypertension	353	99 (28%)	63	25 (40%)	0.06
Hyperlipidaemia	357	82 (23%)	64	16 (25%)	0.72
Family CAD	353	142 (40%)	63	27 (43%)	0.70
Smoke	353	187 (53%)	63	26 (41%)	0.09
Anterior infarct location	412	185 (45%)	80	39 (49%)	0.53
CAG	422	406 (96%)	82	75 (92%)	0.06
• 1-VD	396	231 (58%)	72	44 (61%)	0.81
• ≥2-VD	396	165 (42%)	72	28 (39%)	0.81
TIMI flow pre-PCI 0	380	225 (59%)	69	37 (54%)	0.15
TIMI flow post-PCI 3	371	342 (92%)	67	59 (88%)	0.26
Glucose	422	7.9 ± 1.4	82	14 ± 3.0	<0.001
HbA1c	422	5.6 ± 0.4	82	6.1 ± 1.1	<0.001
Mortality					
• 30-day	415	17(4%)	81	15(19%)	<0.001
• Long-term	398	17 (4%)	66	3 (5%)	0.92

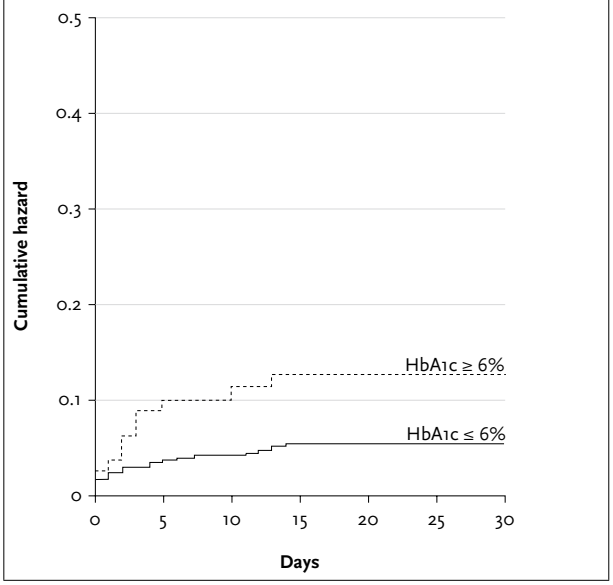
SBP = systolic blood pressure; DBP = diastolic blood pressure; MI = myocardial infarction; PCI = percutaneous coronary interventions; CABG = coronary artery bypass grafting; CVA = cerebrovascular accident; CAD = coronary artery disease; CAG = coronary angiography; VD = vessel disease; TIMI = Thrombolysis In Myocardial Infarction.

Table 2. *Baseline, angiography and outcome according to HbA1c*

Variable	N	HbA1c <6%	N	HbA1c ≥6	P value
Age	416	62 ± 14	88	68 ± 11	<0.001
Male	416	296 (71%)	88	66 (75%)	0.46
SBP	348	127 ± 24	75	133 ± 28	0.059
DBP	348	78 ± 17	75	80 ± 8	0.35
History of					
• MI	412	51 (12%)	88	13 (15%)	0.54
• PCI	411	31 (8%)	88	9 (10%)	0.40
• CABG	411	18 (4%)	88	2 (2%)	0.55
• CVA	412	7 (2%)	88	5 (6%)	0.027
Hypertension	348	99 (28%)	68	35 (37)	0.17
Hyperlipidaemia	353	80 (23%)	68	18 (27%)	0.50
Family CAD	348	142 (41%)	68	27 (40%)	0.87
Smoking	348	175 (51%)	68	37 (54%)	0.056
Anterior infarct location	408	188 (45%)	84	41 (49%)	0.58
CAG	416	400(96%)	88	81(92%)	0.09
• 1-VD	391	241 (62%)	77	34 (44%)	0.028
• ≥ 2-VD	391	150 (38%)	77	43 (56%)	0.028
TIMI flow pre-PCI 0	379	227 (60%)	69	35 (51%)	0.053
TIMI flow post-PCI 3	371	341 (92%)	67	60 (90%)	0.52
Glucose	416	8.6 ± 2.6	88	10.4 ± 3.6	<0.001
HbA1c	416	5.5 ± 0.2	88	6.6 ± 0.9	<0.001
Mortality					
• 30-day	408	22 (5%)	86	10 (12%)	0.03
• Long-term	388	15 (4%)	76	5 (7%)	0.23

SBP = systolic blood pressure; DBP = diastolic blood pressure; MI = myocardial infarction; PCI = percutaneous coronary interventions; CABG = coronary artery bypass grafting; CVA = cerebrovascular accident; CAD = coronary artery disease; CAG = coronary angiography; VD = vessel disease; TIMI = Thrombolysis In Myocardial Infarction.

Figure 2. *Mortality curves according to HbA1c*



Long-term outcome among 30-day survivors

Long-term mortality in the subsequent glucose categories (<11.1 mmol/l and ≥11.1 mmol) was 4% and 5% (p<0.92). In patients with an HbA1c of <6.0% long-term mortality was 4% compared with 7% in patients with an HbA1c ≥6.0% (p=0.23).

Multivariate analysis

To investigate whether the association between elevated glucose levels, HbA1c levels and 30-day outcome were independent of the differences in the baseline characteristics, multivariate analysis was performed. Included variables were age, gender, multivessel disease and HbA1c. Because there was a significant association between HbA1c and glucose, they were separately included in the multivariate analysis. Independent predictors of 30-day mortality were increased age (HR 1.04 per year, 95% CI 1.01 to 1.07, p=0.013) and elevated admission glucose (OR 4.91, 95% CI 2.03 to 11.9, p<0.001). An elevated HbA1c level was not significantly associated with a higher mortality (OR 1.33, 95% CI 0.48 to 3.71, p=0.58).

DISCUSSION

This study evaluated the prognostic value of admission glucose and HbA1c in patients with STEMI. Elevated glucose levels on admission were a strong and independent predictor of 30-day mortality. Elevated HbA1c was also associated with a worse prognosis but this was not an independent predictor of mortality. Neither admission glucose nor HbA1c were predictors of long-term mortality.

Prognostic value of HbA1c

HbA1c is an easy marker of long-term glucose regulation, also unmasking minor glycometabolic disease, such as impaired glucose tolerance, impaired fasting glucose or metabolic syndrome.[12-14] Previous studies have shown that an elevated HbA1c is associated with increased cardiovascular risk in patients with and without diabetes.[15,16] However, other studies reported conflicting results with regard to chronic glycometabolic states and outcome in patients with acute myocardial infarction.[5,9,17-19] Malmberg *et al*.[5] found an association between elevated HbA1c and mortality after myocardial infarction, relative risk (95% CI) 1.07 (1.01-1.21); however, Timmer *et al*. and Cao *et al*. did not confirm this, [1.63 (0.99-2.79] and 1.08 (0.31-3.23)], respectively.[18,19]

In our study, patients with an elevated HbA1c were older, more often had a history of CVA, were more often on a β-blocker on admission and more often had multivessel disease. However, HbA1c ≥6.0% was not a predictor of mortality. This is consistent with a previous small sample size study.[9]

Prognostic value of admission glucose

A number of reports have shown the association between elevated admission glucose and poor outcome in patients with myocardial infarction or unstable angina.[2,8] This adverse association may be independent of other clinical prognostic factors, also in the setting of reperfusion therapy and even after correction for HbA1c levels.[6,9,18,20,21] *Table 3* shows the individual and pooled unadjusted relative risk of hyperglycaemia for mortality in several studies. All these studies show that hyperglycaemia on admission is associated with a worse outcome after myocardial infarction.

Several studies have reported the long-term effects of hyperglycaemia.[18-20] However, most effects of hyperglycaemia may occur in the acute phase of myocardial infarction and these studies did not analyse whether the early effects dominate the entire benefit or whether subsequent follow-up also contributes to their demonstrated results. Elevated glucose is not only a symptom of glucose dysregulation, but also of stress and a more high-risk patient population. It has been shown that higher admission glucose is associated with a higher Killip class, a larger infarct size and a lower ventricular function.[18] Thrombotic properties of platelets are increased in a hyperglycaemic environment and this can result in additional cardiovascular complications.[22] Furthermore, elevated glucose levels are accompanied by increased levels of free fatty acids (FFA).[23] These FFA may increase infarct size, compromise myocardial performance during acute coronary syndromes and reduce endothelium-derived vasodilatation in myocardial tissue limiting myocardial reperfusion.[24-26] In addition, hyperglycaemic-induced endothelial dysfunction, hypercoagulability, platelet dysfunction, and vascular

Table 3. *Relative risk of in-hospital and long-term mortality after myocardial infarction in patients with admission hyperglycaemia*

Study	Publication Year	Number of patients	Follow-up	Relative risk (95% confidence interval)
Foo[2]	2003	2127	In-hospital	2.63 (1.67-4.13)
O'Sullivan[3]	1991	714	In-hospital	3.20 (1.40-6.65)
Sewdarsen[4]	1989	277	In-hospital	4.94 (2.15 -11.64)
Lynch[8]	1994	420	In-hospital	4.33 (4.25-8.54)
Bolk[20]	2001	336	≥1 year	2.92 (1.89-4.281)
Stranders[21]	2004	846	≥1 year	1.64 (1.28-2.10)
Timmer[18]	2005	356	≥1 year	1.94 (1.08-3.40)
Pooled relative risk				**1.41 (121-1.66)**

smooth muscle dysfunction may also contribute to the worse outcome in STEMI patients with hyperglycaemia on admission.[27-31]

In the current study we found no relation between admission glucose and long-term outcome among 30-day survivors. A possible explanation is that glucose levels drop after the acute phase of myocardial infarction, which is shown to be associated with an improved outcome.[32] This drop in glucose levels may at last partially be due to the drop in stress hormones after the acute phase of myocardial infarction.[33] Oswald *et al*. showed that stress hormones are the main determinants of plasma glucose in nondiabetic patients with acute myocardial infarction.[34] Others have reported the proportional release of stress hormones to the severity of myocardial infarction.[35]

In our study, there were no major differences in baseline characteristics according to admission glucose. However, elevated glucose levels on admission, but not chronic glucose dysregulation, were a strong and independent predictor of 30-day term mortality. These findings are similar to those reported in diabetes.[19]

CONCLUSION

In patients with STEMI, elevated admission blood glucose is an important independent predictor of 30-day outcome, while elevated HbA1c reflects a more high-risk patient population. Among 30-day survivors neither admission blood glucose nor HbA1c predicts worse outcome.

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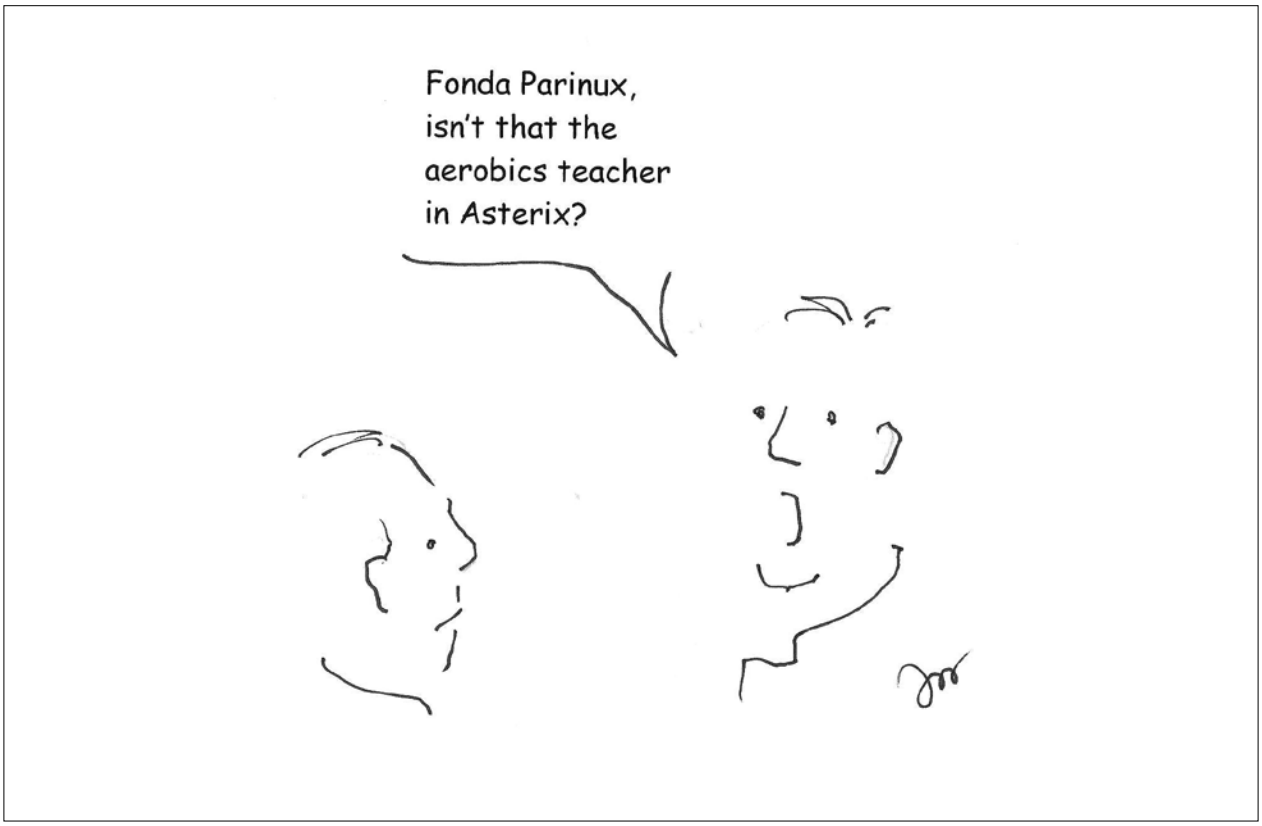

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