

Elevated glycated haemoglobin in non-diabetic patients is associated with an increased mortality in myocardial infarction

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Summary

Diabetes is associated with increased mortality following acute myocardial infarction compared to the general population. Elevated glycated haemoglobin (HbA_{1c}) in diabetic patients is also associated with increased mortality following acute myocardial infarction, while mild elevations in HbA_{1c} are associated with impaired glucose tolerance. The aim of this study was to determine the influence of HbA_{1c} on outcome of acute myocardial infarction in 253 non-diabetic patients, 46 of whom died in one year. In univariate analysis, risk factors for death included smoking, glucose, cholesterol and HbA_{1c}. In logistic regression analysis HbA_{1c} was an independent risk factor for death. Over one-third of the fatality group had an HbA_{1c} in the highest quartile, compared to one-fifth of the surviving group (p=0.02). Elevated HbA_{1c} is a risk marker for short-term mortality following acute myocardial infarction in non-diabetic subjects.

Keywords: glycated haemoglobin; myocardial infarction; mortality

Patients with diabetes mellitus have a poorer outcome after acute myocardial infarction (AMI) than the general population.¹ Cardiovascular mortality is also increased in subjects with impaired glucose tolerance.² Hyperglycaemia is common during AMI, and may be a result of stress-induced catecholamine release or previously unidentified diabetes mellitus. Glycated haemoglobin (HbA_{1c}) is a measure of glycaemia over the preceding months, and may be helpful in detecting abnormalities of glucose tolerance as there is an inverse relationship between HbA_{1c} and glucose tolerance.³ Elevated HbA_{1c} levels are associated with an increased mortality following AMI in diabetic patients.⁴ The aim of this study was to determine whether HbA_{1c} levels at presentation of AMI had an influence on the short-term outcome in non-diabetic subjects.

Methods

Patients with no known history of diabetes admitted to three hospital coronary care units with their first AMI over the period January to December 1995 were studied. Patients with a

random blood glucose of >11.1 mmol/l were excluded. Those with random blood glucose on admission between 7.8–11.1 mmol/l underwent a standard 75-g oral glucose tolerance test prior to discharge, and were excluded from the analysis if 2-hour glucose was >11.1 mmol/l. AMI was defined as a history of chest pain with evolving changes on the electrocardiogram diagnostic of AMI (ST elevation or T-wave inversion) with elevation in serial creatine kinase levels. Plasma for HbA_{1c} was taken at admission, and measured in a central laboratory (normal range 3.5–6.5%). All patients were given thrombolysis unless contraindicated. Clinical evidence of heart failure (radiographic evidence of pulmonary venous congestion, basal crackles or presence of a third heart sound) was treated with the introduction of an angiotensin-converting enzyme (ACE) inhibitor. Cholesterol >6.5 mmol/l was treated with a statin. Surviving patients were re-assessed one year later in early 1997, and causes of death for the fatalities were established from hospital or general practice records and patients' relatives. Statistical differences in characteristics between survivors and fatalities over one year follow-up was assessed using the Students' *t*-test for parametric data and the Mann-Whitney U-test for non-parametric data with significance achieved at $p < 0.05$. Stepwise logistic regression analysis was undertaken using all the variables associated with relapse in the univariate analysis using the statistical software, Minitab. The R² value was adjusted according to the number of variables introduced into the model.

Results

A total of 301 patients with AMI and no previous history of diabetes were studied, of whom 21 were excluded due to a random blood glucose >11.1 mmol/l. A total of 58 patients had a random blood glucose between 7.8–11.1 mmol/l, and underwent a standard 75-g oral glucose tolerance test. Almost half (27) of these subjects had a 2-hour blood glucose of >11.1 mmol/l, and hence were diabetic, while 16 (27.6%) had evidence of impaired glucose tolerance (2-hour blood glucose 7.8–11.1 mmol/l), although they were not excluded from subsequent analysis. Thus, 48 patients were excluded due to newly diagnosed diabetes. Clinical characteristics of the 253 non-diabetic subjects are shown in table 1.

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Table 1 Clinical characteristics of fatalities and survivors of AMI

	Dead	Alive
n	46	207
Mean age (years)	63.2 (SD 6.3)	64.0 (SD 5.9)
Male sex	28 (60.6)	124 (58.4)
Smokers*	18 (39)	73 (34.2)
Median plasma glucose (mmol/l)†	6.9	5.3
Impaired glucose tolerance*	6 (13)	10 (4.8)
Median diastolic blood pressure (mmHg)	90	90
Median systolic blood pressure (mmHg)	150	150
Median cholesterol (mmol/l)†	5.7	5.3
ACE inhibitor*	12 (26)	36 (17.4)
Aspirin	42 (96)	201 (97)
Beta blocker	14 (30)	66 (31.9)
Median HbA _{1c} (%)†	5.9	4.3

Data are n (%) unless otherwise stated; *p<0.01; †p<0.001

Table 2 Fatalities and survivors of acute myocardial infarction divided into quartiles of HbA_{1c}

HbA _{1c}	<4.0	4.1–5.2	5.2–6.0	>6.1
Dead	5 (10.8)	10 (21.7)	14 (30.4)	17 (36.9)
Alive	59 (28.5)	56 (27.0)	49 (23.7)	43 (20.8)

Data are n (%), $\chi^2=9.881$, p=0.02.

In total, 46 deaths occurred within one year from AMI, 19 of these within the first month. No significant difference was seen in the age, sex and ethnic distribution of the survivors and fatalities. The two groups had similar blood pressures and proportion on aspirin and β -blockers. Significant heterogeneity between the survivors and fatalities was seen in smoking status, plasma glucose, proportion with impaired glucose tolerance, serum cholesterol, proportion on an ACE inhibitor and HbA_{1c}. Dividing HbA_{1c} into quartiles (table 2), a significantly higher proportion of patients who died within one year of AMI had an HbA_{1c} in the highest quartile ($\chi^2=9.881$, p=0.02). In stepwise logistic regression analysis, introducing all variables showing a significant association with fatality from AMI in univariate analysis, HbA_{1c} was an independent risk factor for death (odds ratio [HbA_{1c} >6.1] / [HbA_{1c} <5.2] = 2.36 (95% confidence intervals 1.65–4.23), p<0.001).

Discussion

Elevated HbA_{1c} was found to be associated with an increased mortality in non-diabetic subjects suffering an AMI. Although the fatality group had a higher proportion of subjects with other risk factors associated with poorer

Summary points

- diabetes mellitus is associated with a higher mortality following myocardial infarction
- hyperglycaemia is common during myocardial infarction and may not indicate the presence of diabetes mellitus
- poorer glycaemic control in diabetic subjects is associated with a higher mortality following myocardial infarction
- in non-diabetic subjects, higher HbA_{1c} levels and impaired glucose tolerance are independent risk factors for mortality following myocardial infarction
- HbA_{1c} may be a useful risk marker for mortality after myocardial infarction in non-diabetic subjects

prognosis after AMI (smokers, higher cholesterol), HbA_{1c} remained an independent risk factor for death. One-third of subjects dying from an AMI within one year had an HbA_{1c} in the highest quartile, compared to only one-fifth of the surviving group. The present study confirms previous observations in diabetic subjects suggesting that higher glucose levels during AMI are associated with increased mortality.⁵ The reason for this phenomenon is unclear, although elevated plasma glucose in the context of AMI may be due to stress-induced catecholamine release. Thus, larger infarcts may be associated with greater release of catecholamines, and hence higher random blood glucose levels.⁶

Whilst it is well established that diabetes mellitus confers a greater risk of death following AMI, it has not been fully established whether impaired glucose tolerance also predicts a poorer outcome. In our study, a greater proportion of patients who died within one year of AMI had impaired glucose tolerance (13% vs 4.8%). Excess risk of AMI is seen in subjects with impaired glucose tolerance,² and aggressive treatment of hyperglycaemia during AMI has been shown to reduce mortality in diabetic subjects.⁷ The mechanism by which impaired glucose tolerance may influence mortality after AMI is unclear, but its association with the metabolic syndrome (syndrome X) may explain this excess mortality.⁸ Thus, patients with mild increases in HbA_{1c} may have other metabolic or genetic factors which confer greater coronary risk.

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