Admission Plasma Glucose

Independent risk factor for long-term prognosis after myocardial infarction even in nondiabetic patients

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OBJECTIVE — To investigate whether a relationship exists between admission plasma glucose level and long-term outcome in nondiabetic patients after an acute myocardial infarction.

RESEARCH DESIGN AND METHODS — This was a retrospective study with prospective follow-up of 197 consecutive nondiabetic patients with acute myocardial infarction followed for 1.5–2.5 years at the Department of Cardiology at Karolinska Hospital.

RESULTS — The mean admission plasma glucose level was 8.15 ± 3.0 mmol/l. During follow-up, 60 (30%) patients died, 20 (10%) were rehospitalized for heart failure, 12 (6%) were rehospitalized for nonfatal reinfarction, and 79 (40%) had at least one of these events. In univariate analysis, admission plasma glucose level was significantly higher in patients who had any of the predefined events than in those without these events. In a multivariate Cox proportional hazard regression model that allowed for confounding baseline predictors, admission plasma glucose level was an independent predictor of nonfatal reinfarction ($P = 0.006$), hospitalization for heart failure ($P = 0.0034$), and a major cardiovascular event ($P = 0.0042$) and was of borderline significance for death during long-term follow-up ($P = 0.09$).

CONCLUSIONS — Admission plasma glucose level in nondiabetic patients with acute myocardial infarction seems to be an independent predictor of long-term outcome. This indicates that an elevated admission plasma glucose level not only reflects acute stress, but also may be a marker of disturbed glucose metabolism that worsens the prognosis and requires intervention.

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An established relationship exists between admission plasma glucose levels and hospital mortality in patients with acute myocardial infarction. This affects patients with (1,2) and without (3,4) established diabetes. The magnitude of the rise in plasma glucose during the early phase of an acute myocardial infarction has been attributed to the degree of left ventricular failure (5), which is mainly determined by a raised concentration of catecholamines and cortisol as a response to infarct extension and myocardial dysfunction (3). The relationship between admission plasma glucose level and long-term outcome after an acute myocardial infarction is less well explored. Mak et al. (4) did not find an association between fasting blood glucose level and long-term outcome in 44 nondiabetic postinfarction patients. In contrast, Weir et al. (6) reported that admission plasma glucose level independently predicted short- and long-term outcome after stroke. Several large cohort studies have indicated that patients with impaired glucose tolerance have an increased mortality from cardiovascular disease (7,8). The term "dysglycemia" has been proposed to define a range of glucose concentrations associated with an increased risk of cardiovascular disease, including blood glucose levels even lower than those usually related to the diagnosis of impaired glucose tolerance or diabetes (9).

The aim of this study was to investigate whether a relationship exists between admission plasma glucose level and long-term prognosis in nondiabetic patients after an acute myocardial infarction. Such a relationship may indicate that an elevated plasma glucose level early in a myocardial infarction is a marker of disturbed glucose metabolism that requires secondary preventive measures.

RESEARCH DESIGN AND METHODS

Patients

All patients admitted to the coronary care unit at Karolinska Hospital in 1995 with a recorded diagnosis of acute myocardial infarction (*International Classification of Diseases* codes 410A, 410B, 410X) were eligible for this study. Baseline characteristics and admission plasma glucose levels were determined from hospital records. The final study population consisted of 197 nondiabetic patients with available admission plasma glucose levels.

Data collection

All patients were followed until 1 June 1997 (range 1.5–2.5 years). Only one patient, who was living abroad, was lost to follow-up. Data collection was conducted in two stages: *1*) a retrospective review of hospital records and 2) a prospective telephone interview with the survivors. Information on hospitalization for congestive heart failure, angina pectoris, nonfatal reinfarction, percutaneous coronary angioplasty (PTCA), and coronary artery bypass grafting (CABG) was collected. An event was only recorded once. Information on mortality and causes of death was obtained from official national death certificates. For completeness of information, death certificates were checked against available hospital records.

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Abbreviations: CABG, coronary artery bypass grafting; DIGAMI, Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction; PTCA, percutaneous coronary angioplasty.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Pertinent patient characteristics at hospital admission*

	Total	Alive at follow-up	Not alive at follow-up	*P*
n	197	137	60	
Age (years)	68 ± 12	64 ± 12	75 ± 10	<0.001
Male	141 (72)	102 (74)	39 (65)	0.23
Previous myocardial infarction	35 (18)	21 (15)	14 (23)	0.224
Previous heart failure	29 (15)	9 (6)	20 (33)	<0.001
Previous angina pectoris	68 (34)	40 (29)	28 (47)	0.023
Previous hypertension	48 (24)	33 (24)	15 (25)	1.0
Previous CABG	10 (5)	10 (7)	0	0.03
Previous PTCA	4 (2)	4 (3)	0	0.316
Smokers	62 (31)	52 (38)	10 (17)	0.002
Admission plasma glucose (mmol/l)	8.15 ± 3.0	7.8 ± 2.7	8.9 ± 3.5	0.015
Maximum serum creatinine kinase (μkat/l)	31.3 ± 24	31 ± 24	31 ± 23	0.98

Data are means ± SD or *n* (%).

Plasma glucose

Venous blood samples were routinely drawn directly after admission in the emergency department. Samples were immediately analyzed at the central laboratory of the hospital via a commercially available colorimetric glucose oxidase method (Ektachem Clinical Chemistry Slide; Johnson & Johnson, Rochester, NY).

Definitions

Acute myocardial infarction (index infarct). This diagnosis, which was taken from the records of the coronary care unit, was based on World Health Organization criteria from 1979 (10). The diagnosis was confirmed by verification of the criteria during the collection of the patient material.

Reinfarction. Reinfarction was defined as an infarct with an onset >72 h after the index infarct that caused prolonged initial or a new hospitalization.

Congestive heart failure. Congestive heart failure was defined as hospitalization for new-onset or worsening of previously known heart failure that required treatment with diuretics.

Major cardiovascular event. A major cardiovascular event was defined as the first occurrence of either congestive heart failure or a nonfatal reinfarction or death; thus, a patient could only have one recorded major cardiovascular event.

Diabetes. Patients were classified as having diabetes when diabetes had at any time been noted in the hospital records for that subject. Patients with diabetes were excluded from this study.

Statistical analysis

The main statistical comparisons were performed between patients who survived and those who died, between survivors with and without nonfatal reinfarction, between patients with and without congestive heart failure, and between patients with and without a major cardiovascular event. Several baseline variables were tested in these comparisons. Differences between groups were tested with Student's *t* test, Wilcoxon's test, or Fisher's exact test when appropriate. The main analysis used Cox's proportional hazard regression model via the PHREG procedure (SAS Version 6.12; SAS Institute, Cary, NC). The effect of admission plasma glucose level was determined after entering other univariate baseline parameters with a *P* value of <0.20 to allow for a multiple effect. The Kaplan-Meier survival analysis was performed according to the LIFETEST procedure (SAS Version 6.12), which calculates a nonparametric estimate of the survival distributions. A two-tailed *P* value of <0.05 was considered statistically significant.

Ethics

The study was approved by the ethics committee at Karolinska Hospital. All interviews were conducted after obtaining informed consent from the patients or relatives.

RESULTS — The baseline characteristics of the 197 nondiabetic patients are given in Table 1. Their mean age was 68 ± 12 years (range 37–91), and 72% were men. At hospital admission, the mean plasma glucose level was 8.1 ± 3.0 mmol/l (median 7.4 mmol/l). The patients were relatively extensively treated during the hospital stay. Of the patients, 60 (30%) received thrombolysis, and 13% underwent an acute PTCA. At discharge, 85% were taking aspirin, 79% were taking β-blockers, and 26% were taking ACE inhibitors. However, only 10% were taking lipid-lowering drugs.

A total of 60 (30%) patients died, 30 of whom died during the initial hospitalization and 30 during the remaining follow-up period. The causes of death were cardiovascular in all but two patients in whom the specific cause was unknown. During follow-up, 20 patients reached the end point of congestive heart failure, 12 had a nonfatal reinfarction, and 79 had at least one major cardiovascular event.

Univariate analysis

Patients who died were characterized by older age, more frequent previous ischemic heart disease, and congestive heart failure, and fewer of them were smokers than among the patients who survived (Table 1). Admission plasma glucose levels were significantly higher in patients with any of the end points (Table 2).

Kaplan-Meier survival curves for patients above or below the median admission plasma glucose level (7.4 mmol/l) are presented in Fig. 1. The prognosis for subjects with an admission plasma glucose level above median was significantly worse regarding both mortality and major cardiovascular events. The curves tended to sep-

Table 2—*Univariate analysis of admission plasma glucose by outcome*

Parameter	*n*	Yes (mmol/l)	No (mmol/l)	*P*
Death	60	8.9 ± 3.5	7.8 ± 2.7	0.015
Nonfatal reinfarction	12	10.7 ± 5.5	8.0 ± 2.8	0.003
Hospitalization for congestive heart failure during follow-up	20	10.1 ± 4.6	7.9 ± 2.7	0.002
Major cardiovascular event	79	9.1 ± 3.7	7.5 ± 2.4	0.0005

Data are means ± SD.

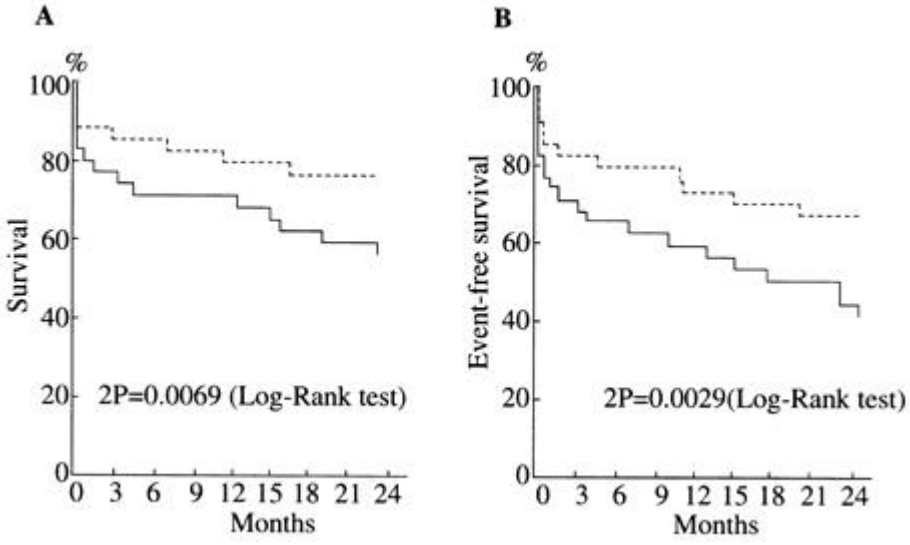

Figure 1—*Kaplan-Meier curves for patients above and below the median admission plasma glucose level (7.4 mmol/l). Dashed line indicates plasma glucose less than or equal to median.* A*: Time to fatal outcome.* B*: Time to a major cardiovascular event.*

arate further over time, which indicates a long-lasting prognostic effect of admission plasma glucose level.

Multivariate analysis

As previously stated, several baseline characteristics apart from admission plasma glucose level predicted long-term outcome. If their univariate *P* value was <0.2, these variables were entered into a multivariate Cox regression model together with admission plasma glucose level. The results of this analysis are presented in Table 3. The only remaining predictors for mortality were age and previously known congestive heart failure, whereas admission plasma glucose level was of borderline significance (relative risk 1.2, $P = 0.097$). The only independent predictor for reinfarction was admission plasma glucose level. Age together with admission plasma glucose level predicted future congestive heart failure. Admission plasma glucose level ($P = 0.0042$), age ($P = 0.036$), and previous congestive heart failure ($P = 0.0025$) remained the independent predictors of major cardiovascular events.

CONCLUSIONS — This study shows a relationship between plasma glucose level at admission for an acute myocardial infarction and long-term prognosis in nondiabetic subjects. This relationship includes both mortality and morbidity, the latter in the form of reinfarction and congestive heart failure.

The study design was that of a retrospectively collected consecutive group of patients with myocardial infarction who were prospectively followed for at least 2.5 years. A total of 57 (19%) admitted patients could not be included because of a lack of information on admission plasma glucose level. These patients were mainly referrals from other hospitals, which suggests late admission to our coronary care unit. These patients were randomly scattered and should not cause selection bias that would compromise the results. By definition, 36 patients with already established diabetes and 10 readmissions during the recruitment period were not eligible.

The retrospective design eliminated the possibility to relate admission plasma glucose level to such factors as time since last meal, diurnal variations, and the influence of the actual condition of the patient (e.g., onset and severity of pain, anxiety, and dyspnea). It also eliminated the possibility to conduct oral glucose tolerance tests. This is a limitation in that we cannot completely rule out patients with undiscovered diabetes.

Mortality was the most important outcome. Patients who died could have had a nonfatal myocardial infarction or an episode of congestive heart failure before death that resulted, if anything, in an underestimation of the true number of events, which supports our main conclusion.

The relationship between admission plasma glucose level and short-term (in-hospital) mortality in acute myocardial infarction has already been established

Table 3—*Independent relation between cardiovascular risk factors and admission plasma glucose and long-term morbidity and mortality by multivariate Cox regression analysis*

Parameter	Death (60/197)	*P*	Major cardiovascular event (79/197)	*P*	Hospitalization for congestive heart failure (20/169)	*P*	Nonfatal reinfarction (12/169)	*P*
Age (+10 years)	1.57 (1.15–2.14)	0.0045	1.32 (1.02–1.69)	0.036	1.72 (1.11–2.71)	0.018		
Sex (M)	1.2 (0.71–2.09)	0.48	1.34 (0.84–2.15)	0.22				
Previous myocardial infarction	1.06 (0.55–2.03)	0.87	1.07 (0.6–1.92)	0.81				
Previous congestive heart failure	2.16 (1.13–4.14)	0.02	2.5 (1.38–4.5)	0.003				
Smoking	0.81 (0.55–1.18)	0.28	0.93 (0.68–1.27)	0.65				
Admission plasma glucose (3 mmol/l)	1.2 (0.97–1.48)	0.097	1.29 (1.08–1.54)	0.004	1.5 (1.14–1.97)	0.003	1.95 (1.27–2.39)	<0.001

Data are relative risks (95% CI); parameters were entered if univariate analysis revealed $P < 0.20$; age (+10 years) indicates the relative risk with an increase of 10 years of age; admission plasma glucose (+3 mmol/l) indicates the relative risk of an increase in glucose level of 3 mmol/l.

(1–4). In the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study (11), there was a linear relationship between blood glucose tertiles and long-term mortality in the control group. This relationship was almost abolished in the group that received intensive insulin therapy (11). These data, which demonstrate a successively increased risk with increasing levels of admission blood glucose and its reversibility, caused us to further explore the effect of admission blood glucose levels lower than those in the DIGAMI cohort (i.e., in subjects without diabetes). Our results indicate that admission plasma glucose level may be an important risk predictor in individuals with levels below the diabetic threshold. Possibly an elevated admission plasma glucose level in a nondiabetic patient with an acute myocardial infarction identifies a subject with compromised glucose metabolism that is not solely a manifestation of acute stress. Interestingly, the prognostic effect of an increase by 3 mmol/l in the admission plasma glucose level almost corresponded to an increase in age by 10 years.

Although not yet studied in detail, there are indications that admission plasma glucose level does not relate to particularly extensive myocardial damage. In our study, as well as in the DIGAMI study (12), infarct size measured by enzyme release was not related to worse outcome. The alternative explanation to a relationship between admission plasma glucose level and prognosis would be a metabolically caused mechanism. Recent evidence has indicated that metabolic control expressed as fasting blood glucose or HbA_{1c} is important in determining the development of future heart disease among patients with type 2 diabetes (13–16). Intensive treatment with insulin caused cardiovascular events to decrease by 40% in the Diabetes Control and Complications Trial (17). Results from the U.K. Prospective Diabetes Study (18) reported that intensive blood glucose control with either sulfonylureas or insulin substantially decreased the risk of microvascular complications, and there was a reduction in risk of borderline significance for myocardial infarction ($P = 0.052$). This indicates that, regardless of whether a causal relationship exists, improved metabolic care may reverse the effect of elevated blood glucose.

Hyperglycemia may increase the risk of cardiovascular disease in diabetic patients and possibly in prediabetic subjects via several biological mechanisms. These relate to increased platelet activity (19), disturbed coagulation and fibrinolytic functions (20,21), endothelial dysfunction (22), and disturbed lipid metabolism (23). A close interrelationship exists among these mechanisms. Moreover, altered myocardial metabolism due to decreased glucose utilization and increased free fatty acid oxidation may play an important role in unfavorable prognosis (i.e., the development of heart failure) (24). Such a negative influence is not likely an "on–off" phenomenon at a defined level of plasma glucose but is rather a continuous relationship without a cutoff level. Several intervention studies have indicated that improved metabolic control by means of insulin treatment in type 2 diabetic patients results in a less atherogenic lipoprotein profile (25,26), reduces plasminogen activator inhibitor 1 activity (27), and reduces increased thromboxane A_2 production (19). Glycemic control in type 2 diabetic patients has also been related to the myocardial flow reserve (28).

Drawing any causal conclusions from this retrospectively collected material is not possible. Nonetheless, our results encourage further exploration of admission plasma glucose level as a possibly useful marker for the identification of patients with poor prognosis after myocardial infarction. If such relationship is clearly established, it may characterize a group of patients who require increased care focused on their glucometabolic state that involves pharmacological or nonpharmacological methods.

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