RESEARCH REPORT

Short-term mortality of myocardial infarction patients with diabetes or hyperglycaemia during admission

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Accepted for publication 23 November 2001
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Aim: The hypothesis that patients with hyperglycaemia during admission, regardless of previous diagnosis of diabetes, have worse prognosis than those with normal glucose values is controversial. The objective was to assess the role of hyperglycaemia on short-term mortality after myocardial infarction (MI).

Methods and Results: A cohort study nested in a prospective registry of MI patients in the reference hospital of Gerona, Spain was performed. All consecutive MI patients under 75 were registered between 1993 and 1996. Patient and clinical characteristics, including previous diagnosis of diabetes, glycaemia on admission and in the next four days, were recorded. Patients with glycaemia on admission or four day mean glycaemia >6.67 mmol/l were considered hyperglycaemic. The main outcome measure was mortality at 28 days. Of 662 patients with MI included, 195 (29.7%) had previously known diabetes mellitus, but 457 (69.0%) had glycaemia >6.67 mmol/l on admission. Patients with hyperglycaemia on admission were older, more often female, more frequently had a previous diagnosis of diabetes, developed more complications, and had higher 28 day mortality. The effect of admission glycaemia >6.67 mmol/l on 28 day mortality was independent of major confounding factors, particularly previous diagnosis of diabetes (OR=4.20, 95% confidence intervals 1.18 to 14.96).

Conclusions: Higher 28 day mortality was observed among MI patients with glycaemia on admission >6.67 mmol/l compared with patients with lower levels, independently of major confounding variables and, particularly, previous diagnosis of diabetes. This early, simple, and inexpensive marker of bad prognosis after MI should prompt the application of more aggressive treatment of MI and risk factors and, probably, of glycaemia during admission.

Coronary heart disease is the main cause of death in diabetic patients[1] and patients with myocardial infarction (MI) previously diagnosed of diabetes have worse short-term prognosis than non-diabetic patients.[2][3] Although some authors have found a correlation between blood glucose on admission and severity of acute MI,[4][5] there is no agreement on whether patients with hyperglycaemia on and during admission, regardless of previous diagnosis of diabetes, have worse prognosis than those with normal glucose concentrations.[6]

Hospital MI registries include good assessment of severity and comorbidity. In particular, the REGICOR (Registre Gironí del Cor) study—an ongoing prospective registry of consecutive, diabetic, and non-diabetic MI patients in the only reference hospital in Girona, Spain—provides an appropriate setting for assessing the above issue.[7][8]

The aim of this study was to assess whether hyperglycaemia on or during admission was associated with worse 28 day mortality in patients with MI.

METHODS

Patients

Patients analysed were recruited between 1993 and 1996 for this cohort study. All consecutive MI patients 74 years old or younger who attended the emergency room within 48 hours after onset of symptoms and who survived long enough to have a glycaemia determined on admission were included. Residence outside the study area was considered an exclusion criterion.

MI, diabetes mellitus, and end point definition

MI was diagnosed based on an adaptation of WHO-MONICA project[9] methods, which take into account the type of symptoms, electrocardiographic (ECG) findings, cardiac enzyme values, and history of ischaemic heart disease and necropsy interpretation in fatal cases. Diagnosis of Q wave MI was based on the presence of a definite electrocardiogram (new Q or QS waves) and at least one of the following two findings: increased MI enzymes (twofold or greater increase beyond upper normal value), and typical pain (located in the anterior chest wall and lasting 20 minutes or more for which no cause other than ischaemic heart disease was found). Non-Q wave MI diagnosis was based on serial electrocardiograms with only ST segment and/or T wave changes in patients with cardiac enzyme activities at least twice the normal limit, together with typical chest pain lasting more than 20 minutes. An event in the same patient was considered a new episode when more than 28 days had elapsed after a preceding event.[9] The study hospital applies written MI management routines in accordance with international guidelines.[10] All patients (or their relatives when necessary) were asked about previous diagnosis of diabetes and any related treatment.

Sample size

Sample size was calculated to provide a statistical power of 0.80 in a two tailed test with an α risk of 0.05 if a difference greater than or equal to eight percentage units in the 28 day mortality was observed between hyperglycaemic patients and the rest (the hypothesis was 15% and 6%, respectively). With these conditions, 301 patients were required for each group. This sample size permits detection of adjusted relative

Table 1 Characteristics of myocardial infarction patients by admission glycaemia levels in the REGICOR study (Gerona, Spain, 1993–96)

	Glycaemia ≤6.67 mmol/l on admission	Glycaemia >6.67 mmol/l on admission	p Value	Four day mean glycaemia ≤6.67 mmol/l	Four day mean glycaemia >6.67 mmol/l	p Value	Without previous diagnosis of diabetes	Previous diagnosis of diabetes	p Value
Number of patients	205	457		242	362		445	195	
Age*	57.7 (11.4)	62.7 (9.4)	<0.001	58.8 (11.5)	62.7 (9.3)	<0.001	64.3 (8.4)	60.1 (10.7)	<0.001
Women (%)	9.3	22.8	<0.001	12.4	23.5	<0.001	13.0	31.8	<0.001
Hypertension	43.7	47.4	NS	43.4	46.6	NS	42.4	53.9	0.007
Smoking	52.2	41.9	0.013	51.3	40.7	0.011	30.7	51.4	<0.0001
Diabetes	8.2	40.3	<0.001†	8.5	45.1	<0.001			
History of angina	54.4	47.7	0.111	50.8	47.1	NS	47.1	56.7	0.025
History of heart failure	6.9	12.3	0.035	7.9	12.8	0.061	8.6	16.5	0.003
Previous myocardial infarction	1.9	2.9	NS	1.7	3.6	NS	1.5	3.1	NS
Arrhythmias‡	15.1	25.1	0.005	17.6	24.4	0.049	21.2	24.5	NS
Anterior myocardial infarction	32.8	35.0	NS	30.8	35.4	NS	34.7	33.9	NS
Non-Q wave myocardial infarction	18.7	18.1	NS	18.8	17.8	NS	17.4	21.1	NS
Angina post myocardial infarction	25.9	25.0	NS	22.2	28.1	0.123	24.4	27.9	NS
28 day re-infarction	2.7	2.7	NS	2.8	2.5	NS	1.5	5.6	0.006
28 day APE or cardiogenic shock	4.9	18.4	<0.001	4.6	20.2	<0.001	8.8	25.1	<0.001
28 day mortality	1.5	10.3	<0.001	1.7	9.1	<0.001	5.4	12.3	0.002
Thrombolysis	34.0	38.3	NS	40.4	37.0	NS	41.6	27.3	<0.001
Antiplatelet drugs	98.0	96.5	NS	98.8	97.0	0.154	97.5	96.4	NS
28 day coronary angiograms	19.5	17.4	NS	17.5	18.3	NS	17.0	20.8	NS

n, Number of patients; NS, non-statistically significant; APE, acute pulmonary oedema. *Mean (SD). †κ=0.24. ‡Occurrence of ventricular fibrillation or sustained ventricular tachycardia requiring immediate medical intervention during the acute phase of myocardial infarction within 72 hours of myocardial infarction onset.

Table 2 Characteristics of 28 day deceased and survivors after an acute myocardial infarction in the REGICOR Study (Gerona, Spain, 1993–96)

	Deceased n=50	Survivors n=612	p Value
Age*	63.1 (10.4)	61.0 (10.3)	NS
Women	28.0%	17.8%	0.075
Hypertension	44.9%	46.4%	NS
Diabetes	50.0%	28.9%	0.002
Smoking	29.2%	46.4%	0.021
Glycaemia >6.67 mmol/l on admission	94.0%	67.0%	<0.001
Four day mean glycaemia >6.67 mmol/l	89.2%	58.0%	<0.001
History of angina	60.0%	48.9%	0.132
Previous myocardial infarction	4.0%	2.5%	NS
History of heart failure	28.0%	9.2%	<0.0001
Post myocardial infarction angina	17.4%	26.0%	NS
Arrhythmias†	52.1%	19.6%	<0.0001
Anterior myocardial infarction	59.5%	32.5%	0.001
Non-Q wave myocardial infarction	16.7%	18.4%	NS
APE or cardiogenic shock	71.4%	9.7%	<0.001
28 day re-infarction	4.2%	2.6%	NS
Therapeutic and diagnostic procedures			
Thrombolysis	14.0%	38.9%	<0.001
Antiplatelet drugs	86.0%	97.9%	<0.001
28 day coronary angiograms	8.2%	18.8%	0.062

n, Number of patients; NS, non-statistically significant; APE, acute pulmonary oedema. *Mean (SD). †Occurrence of ventricular fibrillation or sustained ventricular tachycardia requiring immediate medical intervention during the acute phase of myocardial infarction within 72 hours of myocardial infarction onset.

risks for hyperglycaemia greater than or equal to 2.1 as statistically significant (p<0.05). Primary end point was 28 day mortality.

**Study variables measured in the acute phase of MI**

The following variables were recorded: demographics, history of hypertension, diabetes mellitus with a questionnaire that included questions on previous diagnosis by a physician and treatment for diabetes, MI location, presence of Q waves on electrocardiogram, development of acute pulmonary oedema or cardiogenic shock, presence of severe arrhythmia (defined as the occurrence of at least one episode of ventricular fibrilla-

tion or sustained ventricular tachycardia requiring immediate medical intervention) within the first 72 hours, use of thrombolysis, and coronary angiography. As this was a retrospective analysis of a prospective registry, only standard measures of hyperglycaemia management in the acute phase of AMI during hospital admission were recorded. Intensive management of hyperglycaemia was not a practice at the time of inclusion in the registry.

Glycaemia on admission before any treatment or infusion were started, and successive basal glycaemias in samples obtained after eight hour fasting were determined in the following four days. When at least two fasting glucose
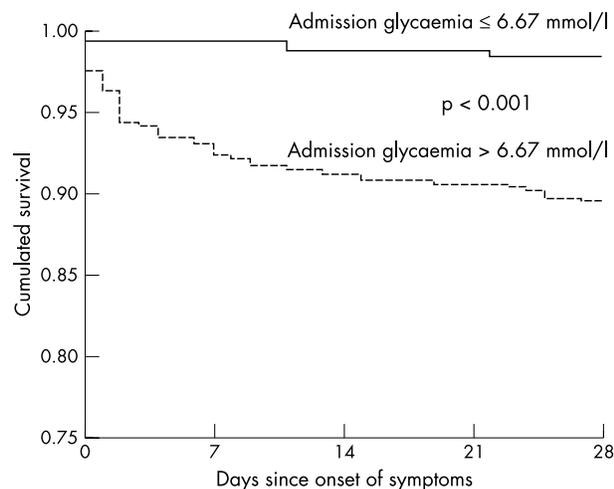
Figure 1 Unadjusted 28 day survival by glycaemia levels on admission after MI in the REGICOR Study (Gerona, Spain, 1993–96).
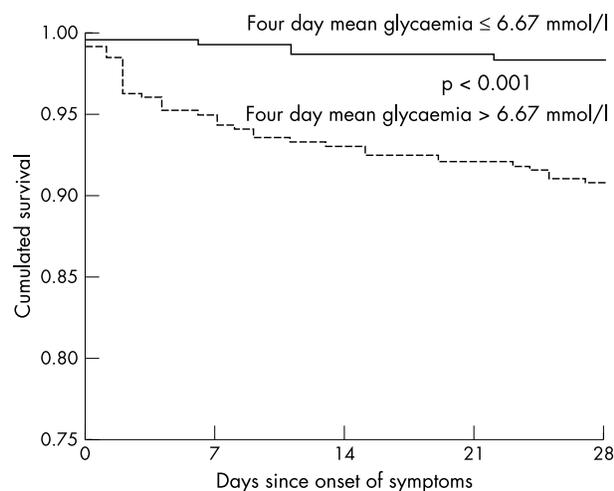
Figure 2 Unadjusted 28 day survival by glycaemia levels during the first four days of admission after MI in the REGICOR Study (Gerona, Spain, 1993–96).

determinations existed after that made on admission, a mean was calculated and used as a predictor of mortality.

Statistical analysis
Differences between hyperglycaemic patients and the rest were assessed with the χ^2 test for categorical variables and Student's t test or Mann-Whitney U test as appropriate for continuous variables.

Receiver operating characteristic curves were used to establish the optimum cut off value for admission and four day mean glycaemias to obtain a sensitivity higher than 90%, using several cut off points (that is, from 5.55 mmol/l to 11.11 mmol/l every 0.55 mmol/l).

Concordance between the diagnosis of diabetes and presence of hyperglycaemia on admission and mean four day hyperglycaemia was calculated by κ statistics.

Survival curves were estimated with the Kaplan-Meier method and compared between hyperglycaemic and non-hyperglycaemic patients by Mantel-Cox test. Adjusted relative risks for 28 day mortality were estimated using unconditional logistic regression. To control for differential characteristics between hyperglycaemic patients and the rest, all variables that met confounding factor criteria (that is, factors that statistically differed at an α risk level of 0.05 in bivariate analysis

between categories of previous diagnosis of diabetes, glycaemia >6.67 mmol/l on admission and mean admission glycaemia >6.67 mmol/l, and were further associated with mortality but could not be claimed as mechanisms of death) were included in the models together with age and sex.

RESULTS
Seven hundred and forty two patients were included in the registry between 1993 and 1996. Eighty patients (10.9%) with suspected MI who died on admission before a glycaemia determination was possible were excluded. Of the 662 patients left for analysis, 195 (29.7%) had previously known diabetes mellitus (6.9% type I and 22.9% type II), but 457 (69.0%) had glycaemia above 6.67 mmol/l on admission. Among the 604 patients who had at least two glycaemia measurements within four days after admission, 362 (59.9%) had mean glycaemia during admission above 6.67 mmol/l. No patient was lost to follow up.

Patients previously diagnosed of diabetes had higher admission and mean four day glycaemias than non-diabetic patients (14.06 mmol/l standard deviation (SD) 7.89 mmol/l and 7.83 SD 3.05, and 11.67 SD 5.00 and 7.05 SD 2.22, respectively). Glycaemia was above 6.67 mmol/l in 192 (47.3%) patients previously undiagnosed with diabetes and in 167 (69.8 %) with diabetes.

### Variables associated with hyperglycaemia on admission (>6.67 mmol/l)
Compared with the rest, patients with hyperglycaemia on admission were older, were more often female, more frequently had a previous diagnosis of diabetes, and developed acute pulmonary oedema or cardiogenic shock and severe ventricular arrhythmias. Mortality at 28 days was significantly higher in patients with hyperglycaemia on admission (table 1). Kaplan-Meier survival curves showed a large difference in survival between patients with and without hyperglycaemia on admission (fig 1), between patients with and without mean four day hyperglycaemia (fig 2), between patients with and without previous diagnosis of diabetes (table 2).

In 604 patients with more than two measurements within the four days after onset of symptoms, concordance between glycaemia on admission and mean of the subsequent glycaemias was high ($\kappa=0.65$); correlation coefficient was 0.88 (p<0.001). However, concordances of admission glycaemia >6.67 mmol/l with previous diagnosis of diabetes ($\kappa=0.25$) and with mean four day glycaemia >6.67 mmol/l ($\kappa=0.41$) were low. Thrombolysis, antiplatelet drugs, and coronary angiography were similarly used in all types of patients. The effect of hyperglycaemia in patients with and without history of diabetes was similar: patients with glycaemias >6.67 mmol/l had worse outcome in both groups (table 1).

Variables associated with mortality
Compared with deceased patients, 28 day survivors were younger, less frequently had a previous diagnosis of diabetes and heart failure and less often presented severe ventricular arrhythmias, anterior MI, acute pulmonary oedema, or cardiogenic shock. However, a greater proportion of non-Q wave MI was observed. Thrombolysis, antiplatelet drugs, and coronary angiography were more often used in survivors (table 2).

Glycaemia >6.67 mmol/l was associated with higher mortality in patients who were not previously diagnosed of diabetes (8.5% versus 1.1%, p<0.001). Although in patients with previous diagnosis of diabetes the difference in 28 day mortality was high (6.3% versus 12.8%) it did not reach statistical significance. However, only one of 16 patients previously diagnosed with diabetes with admission glycaemia ≤6.67 mmol/l died within 28 days (fig 3).
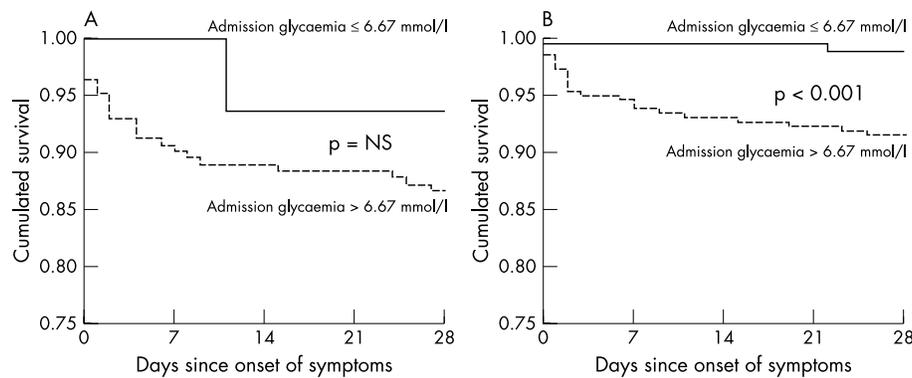
Figure 3 Unadjusted 28 day survival after MI by glycaemia levels on admission in patients with (panel A) and without previous diagnosis (panel B) of diabetes in the REGICOR Study (Gerona, Spain, 1993–96).

Table 3 Adjusted relative risks (RR) and 95% confidence intervals (CI) of 28 day mortality after myocardial infarction for patients with previous diagnosis of diabetes, admission glycaemia >6.67 mmol/l, and mean glycaemia >6.67 mmol/l, in the REGICOR Study (Gerona, Spain, 1993–96)

	Adjusted RR (95% CI)		
	Model 1	Model 2	Model 3
(A) Previous diagnosis of diabetes	1.93 (1.04 to 3.58)	0.99 (0.47 to 2.06)	–
(B) Glycaemia >6.67 mmol/l on admission	7.66 (2.32 to 25.30)	4.13 (1.18 to 14.41)	4.63 (1.29 to 16.58)
(C) Mean admission glycaemia >6.67 mmol/l	5.39 (1.86 to 15.66)	2.88 (0.90 to 9.17)	3.15 (0.95 to 10.51)

Model 1 adjusted for age, sex, smoking, and thrombolytic treatment (A, B, and C). Model 2 adjusted as model 1 and for history of heart failure, occurrence of cardiogenic shock or acute pulmonary oedema during admission (A, B, and C), and for the presence of severe arrhythmias (ventricular fibrillation or ventricular tachycardia requiring immediate medical intervention) during first 72 hours of hospital stay (B and C). Model 3 adjusted as model 2 and for previous diagnosis of diabetes (B and C).

Adjusted risk of 28 day death

As shown in table 3, previous diagnosis of diabetes was independently associated with worse 28 day mortality (Model A-1: RR=1.93, p=0.04), which was mostly explained by occurrence of cardiogenic shock or acute pulmonary oedema and severe ventricular arrhythmias (Model A-2: RR=0.99, non-statistically significant). The effect of glycaemia above 6.67 mmol/l on admission on 28 day mortality was independent of comorbidity, severity, coronary risk factors and previous diagnosis of diabetes (Model B-3: RR=4.63 p<0.001). The risk of 28 day mortality was higher in patients with mean four day hyperglycaemia than in those without (Model C-1 in table 3), but the main reason for the higher mortality was again the occurrence of cardiogenic shock or acute pulmonary oedema, or severe ventricular arrhythmias (model 2 in table 3).

DISCUSSION

Hyperglycaemia independently of diabetic status is a well known predictor of cardiovascular disease and its progression, resulting in increased mortality in the long term. It was first shown by the Whitehall Study,[11] and by the Rancho Bernardo Study.[12] It is becoming increasingly clear from recent studies that the glucose level is a lineal risk factor in diabetic and non-diabetic subjects in a fashion similar to others (blood pressure, blood cholesterol), without a definite threshold.[13–15] In a recent meta-analysis of several studies including more than 95 000 patients, hyperglycaemia, below the accepted diabetic threshold, was associated with increased risk of cardiovascular events.[6]

Hyperglycaemia is also a common finding in patients with acute MI and likewise has been found to be an independent predictor of early cardiovascular death.[17–19] The risk of early death after MI in diabetic patients found in this study (RR 1.98) is close to that described in recent revisions.[20 21] We found that plasma glucose above 6.67 mmol/l optimised sensitivity (96%) for 28 day mortality prediction. This cut off provides an

early, simple, and inexpensive marker of bad prognosis independently of whether or not stress hyperglycaemia is a marker of MI damage. This association is independent of and stronger than previous diagnosis of diabetes. Whether this merely represents a stress response or is, in fact, a harbinger of diabetes remains to be formally established. Approximately 20% of patients with admission hyperglycaemia (admission plasma glucose levels >1.11 mmol/l) have previously undiagnosed diabetes.[22] It must be emphasised that this cut off point was selected after it was found to have the strongest association with 28 day mortality and that it was not pre-established when patients were registered in the study or when the data were analysed. This may explain the differences in the glucose levels used in various studies to define hyperglycaemia, even though the differences found in mortality are similar. A recent review includes 16 studies using values ranging between 6.7 and 11 mmol/l.[21] It is very remarkable the fact, clear from the previous observations, that there is no universal agreement on the glucose values in the acute phase in relation to diabetes and hyperglycaemia and, consequently, the degree of risk associated with it.

Several mechanisms may explain the role of hyperglycaemia in this setting. Plasma noradrenalin and cortisol concentrations increase in the acute phase of MI and trigger a non-specific stress reaction leading to an impaired plasma insulin response resulting in hyperglycaemia.[23 24] Independently of the cause of hyperglycaemia, there is evidence for toxic effects of high blood glucose levels on cell function. Acute hyperglycaemia has been found to induce oxidative stress, probably via generation of free radicals.[25] This may occur by auto-oxidation of glucose, labile glycation, or intracellular activation of the polyol pathway. The free radicals may then mediate some of the effects associated with hyperglycaemia such as vasoconstriction through NO decrease, activation of coagulation, and increased expression of adhesion molecules.[26] Increased glucose levels can also increase protein

kinase C activity.[27] This is an immediate effect of hyperglycaemia, although there is evidence to suggest that the effect of hyperglycaemia may persist for some time after blood glucose levels return to normal.[28] Various cellular changes associated with this acute hyperglycaemia are probably mediated via protein kinase C activity, for example, increased endothelin secretion, increased collagen IV and fibronectine secretion and also increased expression of adhesion molecules on the vascular endothelium involved in macrophage migration.[29 30]

Other than cellular toxicity, it has been shown that hyperglycaemia has deleterious effects on endothelium dependent vasodilatation,[31] worsening myocardial ischaemia, and that treatment with insulin attenuates these effects. Furthermore, basal fibrinolytic activity is diminished in diabetics [32] and the excess of insulin present in diabetes type II patients increases plasminogen activator inhibitor 1 (PAI 1), also causing a decrease of fibrinolytic activity. Thus, an accentuation of ischaemia and an increase of thrombogenicity contribute to a greater severity of MI in hyperglycaemic patients.

Study characteristics and clinical implications

Non-fasting sampling could be claimed to have been responsible for some glycaemias over 6.67 mmol/l on admission. However, successive determinations were obtained after eight hour fasting and yielded results similar to those obtained with admission blood sample, as shown by the excellent concordance found between them. The number of subsequent determinations decreased as some patients died early after admission. This contributed to decreasing somewhat the intensity of the association between four day mean fasting glycaemia and mortality in 24 hour survivors.

All factors that may confound the relation between glycaemia levels and 28 day case fatality (that is, severity, comorbidity, age, sex and, particularly, previous diagnosis of diabetes) were adjusted for in a logistic model. Therefore, admission glucose concentration is a powerful predictor of early mortality after MI, regardless of any other consideration. Glycosylated haemoglobin was not determined, which constitutes a limitation of the study.

This study shows that many patients who met diabetes criteria according to their admission and four day glycaemia measurements during admission had not been previously diagnosed. It should be emphasised that these were consecutive patients of a general population, including diabetics and non-diabetics. Furthermore, hyperglycaemia on admission was associated with higher 28 day mortality independently of previous diagnosis of diabetes and was a stronger predictor of outcome. This suggests that management of hyperglycaemia during the acute phase of MI could be a major issue requiring further investigation and could be important for future therapeutic approaches. In fact, only the DIGAMI MI trial showed the benefit of treating diabetic patients with pump insulin infusion.[33 34] In this Scandinavian trial, one year mortality was significantly reduced by 25% in MI patients assigned to aggressive plasma insulin lowering treatment compared with those who were not. Appropriate control of glycaemia might have a large impact on mortality since more than half of MI patients display glycaemia values over 6.67 mmol/l. Moreover, a more aggressive approach to controlling glycaemia could be adopted, at least in MI patients with glycaemia >6.67 mmol/l on admission in an attempt to reduce case fatality, given the fact that mortality is not concentrated in the first days after onset of symptoms. Glucose-insulin-potassium studies offer an interesting field of research that might help to mitigate the deleterious effects of hyperglycaemia.[35 36]

Admission glycaemia is an early, simple, and inexpensive marker of bad prognosis after MI. As suggested by other authors, this marker should prompt the clinician to apply more aggressive management of MI, risk factors and, probably, admission glycaemia, in these patients.[37 38]

Key points

- A glycaemia concentration >6.67 mmol/l on admission and during hospital stay is found in most patients with MI.
- Many patients may have unrecognised diabetes mellitus at the time of presenting to the hospital with MI.
- MI patients with a glycaemia >6.67 mmol/l on admission are at high mortality risk regardless of any other characteristic.
- In consequence, such a finding should prompt the application of more aggressive treatment of MI and risk factors.

Our data support the idea that higher 28 day mortality exists among MI patients younger than 75 years with admission glycaemia >6.67 mmol/l compared with patients with lower levels, independently of major confounding variables, particularly previous diagnosis of diabetes. Whether this is only an epiphenomenon or an effect of glucose toxicity that worsens myocardial injury remains to be elucidated.

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