CARDIOVASCULAR MEDICINE

A single serum glucose measurement predicts adverse outcomes across the whole range of acute coronary syndromes

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Objectives: To analyse the relation between serum glucose concentration and hospital outcome across the whole spectrum of acute coronary syndromes.
Methods: This was a prospective cohort study of 2127 patients presenting with acute coronary syndromes. The patients were stratified into quartile groups (Q1 to Q4) defined by serum glucose concentrations of 5.8, 7.2, and 10.0 mmol/l. The relation between quartile group and major in-hospital complications was analysed.
Results: The proportion of patients with acute myocardial infarction increased incrementally across the quartile groups, from 21.4% in Q1 to 47.9% in Q4 (p < 0.0001). The trend for frequency of in-hospital major complications was similar, particularly left ventricular failure (LVF) (Q1 6.4%, Q4 25.2%, p < 0.0001) and cardiac death (Q1 0.7%, Q4 6.1%, p < 0.0001). The relations were linear, each glucose quartile increment being associated with an odds ratio of 1.46 (95% confidence interval (CI) 1.27 to 1.70) for LVF and 1.52 (95% CI 1.17 to 1.97) for cardiac death. Although complication rates were higher for a discharge diagnosis of acute myocardial infarction than for unstable angina, there was no evidence that the effects of serum glucose concentration were different for the two groups, there being no significant interaction with discharge diagnosis in the associations between glucose quartile and LVF (p = 0.69) or cardiac death (p = 0.17). Similarly there was no significant interaction with diabetic status in the associations between glucose quartile and LVF (p = 0.08) or cardiac death (p = 0.09).
Conclusion: Admission glycaemia stratified patients with acute coronary syndromes according to their risk of in-hospital LVF and cardiac mortality. There was no detectable glycaemic threshold for these adverse effects. The prognostic correlates of admission glycaemia were unaffected by diabetic status and did not differ significantly between patients with acute myocardial infarction and those with unstable angina.

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Acute phase hyperglycaemia[1–8] and diabetes[9–12] are both associated with adverse outcomes in acute myocardial infarction, with higher reported incidences of congestive heart failure, cardiogenic shock, and death. However, the association between hyperglycaemia and adverse outcomes is not confined to patients with diabetes. A recent meta-analysis reported a more significant association in non-diabetic subjects.[13] The mechanism is not clear, but it is commonly regarded as a response to stress resulting from catecholamine induced glycogenolysis.[14 15] Hyperglycaemia, therefore, is seen as an epiphenomenon that is associated with poor outcomes only because adrenergic stress is closely related to the extent of myocardial injury.[16]

The stress hypothesis of acute phase hyperglycaemia has been challenged by the finding that insulin and glucose administration in hyperglycaemic patients with acute myocardial infarction improves outcomes.[17] More recently similar benefits have been confirmed for insulin administration in other critically ill patients.[18] These observations suggest that relative insulin deficiency may be an important mechanism of acute phase hyperglycaemia and of metabolic consequences, including lipolysis, free fatty acid release, and decreased availability of gycolytic substrate for the myocardium, accounting for its associations with adverse outcomes.[19 20]

Although acute phase hyperglycaemia is associated with a poor prognosis in acute myocardial infarction, there are no data for less severe coronary syndromes. Moreover, it is not known whether this is a threshold effect in the non-diabetic population or there is a linear association between admission serum glucose concentration and adverse outcomes. These questions are potentially important if they help define for inclusion in future clinical trials those categories of patients who may benefit from insulin administration.

METHODS

Study group

Of 2542 consecutive patients with acute coronary syndromes admitted to three east London hospitals during a two year period from January 2000, admission serum glucose concentrations were available for 2127 (83.7%), who constituted the study group. Patients with a first admission during that period were included if they fulfilled criteria for acute myocardial infarction or Braunwald class 3B unstable angina. Criteria for myocardial infarction were any two of the following: cardiac chest pain lasting at least 30 minutes; ⩾ 0.1 mV ST elevation in at least one standard lead or ⩾ 0.2 mV ST elevation in two or more contiguous chest leads; or creatine kinase ⩾ 400 IU/l (upper limit of reference range 200 IU/l). Criteria for Braunwald class 3B unstable angina were cardiac chest pain at rest within the preceding 48 hours not attributable to myocardial infarction or to non-cardiac causes.[21] Among the 2127 patients, discharge diagnosis was unstable angina in 1255 and myocardial infarction in 872, of whom 221 had non-ST elevation infarction.

Data collection

Baseline clinical characteristics including demographic, clinical, and biochemical data were collected prospectively by a

Table 1 Baseline variables and major complications by quartiles of admission blood glucose concentrations

	Glucose quartiles (mmol/l)				p Value (group)	p Value (trend)
	Q1: ≤5.8 (n=551)	Q2: ≤7.2 (n=525)	Q3: ≤10.0 (n=523)	Q4: >10.0 (n=528)		
Baseline characteristics						
Age (years)	61.5 (12.9)	63.9 (12.9)	63.7 (12.9)	63.9 (11.6)	0.004	0.004
Male sex	378 (68.6%)	364 (69.3%)	374 (71.5%)	366 (69.3%)	NS	NS
Racial group						
White	369 (68.6%)	352 (68.2%)	326 (63.6%)	240 (46.1%)		
Afro-Caribbean	9 (1.7%)	10 (1.9%)	11 (2.1%)	23 (4.4%)		
Asian	154 (28.6%)	146 (28.3%)	171 (33.3%)	253 (48.6%)		
Other	6 (1.1%)	8 (1.6%)	5 (1.0%)	5 (1.0%)	<0.0001	
Hypertension	259 (47.0%)	241 (45.9%)	269 (51.4%)	290 (54.9%)	0.01	0.003
Diabetes	51 (9.3%)	60 (11.4%)	131 (25.1%)	367 (69.5%)	<0.001	<0.0001
Smoking	182 (33.5%)	173 (33.2%)	184 (35.5%)	153 (29.3%)	NS	NS
Family history of CAD	198 (36.3%)	163 (31.2%)	162 (31.1%)	130 (25.1%)	0.0001	<0.0001
Cardiac history						
Previous ACS	308 (56.1%)	239 (45.7%)	224 (42.8%)	249 (47.3%)	<0.0001	0.002
Previous revascularisation	131 (23.9%)	100 (19.1%)	84 (16.1%)	104 (19.7%)	0.02	0.04
Admission drugs						
Aspirin	335 (61.0%)	281 (53.6%)	255 (49.1%)	300 (57.0%)	0.001	0.08
ACE inhibitor	118 (21.5%)	102 (19.5%)	115 (22.1%)	152 (28.9%)	0.002	0.003
Diuretic	121 (22.3%)	114 (21.8%)	126 (24.3%)	123 (23.5%)	NS	NS
β Blocker	167 (30.5%)	133 (25.4%)	113 (21.7%)	121 (23.1%)	0.005	0.002
Statin	166 (30.3%)	131 (25.1%)	132 (25.4%)	136 (26.0%)	NS	NS
Admission haemodynamics						
Heart rate (beats/min)	74 (17)	75 (19)	75 (20)	82 (23)	<0.0001	<0.0001
Systolic BP (mm Hg)	145 (29)	144 (26)	144 (29)	146 (32)	NS	NS
Enzyme release and discharge diagnosis						
Peak creatine kinase (mmol/l)	123 (74–287)	178 (82–701)	296 (104–1189)	243 (95–881)	<0.0001	
Acute myocardial infarction	118 (21.4%)	215 (41.0%)	286 (54.7%)	253 (47.9%)		
UA	433 (78.6%)	310 (59.1%)	237 (45.3%)	275 (52.1%)	<0.0001	<0.0001
ECG changes						
ST change	196 (38.0%)	242 (49.5%)	324 (66.3%)	285 (59.5%)	<0.0001	<0.0001
T change	289 (55.3%)	305 (61.9%)	321 (65.4%)	278 (57.4%)	0.005	NS
Q waves	54 (9.9%)	104 (20.0%)	147 (28.4%)	140 (26.7%)	0.0001	0.02
Complications						
LVF	35 (6.4%)	56 (10.7%)	87 (16.8%)	133 (25.2%)	<0.0001	<0.0001
Ventricular fibrillation	3 (0.6%)	8 (1.5%)	15 (2.8%)	13 (2.5%)	0.01	0.007
Cardiac death	4 (0.7%)	12 (2.3%)	20 (3.9%)	32 (6.1%)	<0.0001	<0.0001
All cause death	4 (0.7%)	13 (2.5%)	21 (4.0%)	33 (6.3%)	<0.0001	<0.0001
Cerebrovascular accident	0 (0%)	0 (0%)	1 (0.2%)	9 (1.7%)	<0.0001	

Data are n (%) for categorical variables and mean (SD) for continuous variables except for peak creatine kinase (median and interquartile range).
ACE, angiotensin converting enzyme; ACS, acute coronary syndrome; BP, blood pressure; CAD, coronary artery disease; LVF, left ventricular failure; UA, unstable angina.

dedicated cardiologist or research nurse and stored on a purpose built electronic database. The admission serum glucose concentrations from blood samples drawn on arrival in the emergency room were recorded. Diabetes was recorded in patients on insulin, oral hypoglycaemic drugs, or dietary restriction. Hypertension was recorded in patients taking antihypertensive drugs. The diagnosis of left ventricular failure (LVF) required there to be symptoms of breathlessness accompanied by physical findings of basal crepitations or a third heart sound and requiring treatment with diuretics. All admission drugs, including β blockers, were recorded.

Within this large cohort, serum glucose concentrations were normally distributed, permitting stratification of the patients into quartile groups defined by values of 5.8, 7.2, and 10.0 mmol/l.

Statistical analysis

Major end points were in-hospital LVF and cardiac death. Heart rate was log transformed before analysis. Differences in continuous variables were tested by analysis of variance for normally or log normally distributed variables and Kruskal-Wallis test for other variables. Differences in categorical variables by quartile of glucose were tested by χ^2 test or Fisher's exact test. To examine whether the associations with glucose were linear, linear contrasts were fitted in the analysis of variance for continuous variables and in logistic regression models for the categorical variables.

The univariate association of glucose with cardiac death was examined using logistic regression models. An interaction term was fitted to assess whether the glucose effect differed by diagnosis. Variables univariately associated with both outcome and glucose were considered for entry in stepwise logistic regression models for cardiac death and LVF. Significance at the 10% level was used as the criterion for entry. In this way we obtained odds ratios relative to the lowest quartile of glucose and independent of possible confounders. Linear trend was tested by fitting quartile of glucose as a continuous variable in the model and by fitting glucose concentration as a continuous variable. A quadratic term was also fitted to look for evidence of curvature.

RESULTS
Admission characteristics

Analysis of baseline characteristics by glucose quartile showed an incremental increase in the frequency of south Asian ethnicity, diabetes, and hypertension across the quartile groups (table 1. Proportions of patients pretreated with angiotensin converting enzyme inhibitors had a similar trend but for β blockers the pattern was reversed.

Severity of myocardial injury and complications

The proportion of patients with acute myocardial infarction increased across the glucose quartile groups, from 21.4% in Q1 to 47.9% in Q4 (p < 0.0001). This was reflected in similar

Table 2 Interaction of diagnosis with association between glycaemia and major complications (LVF, death): univariate logistic regression model

	Glucose quartiles (mmol/l)				
	Q1: ≤5.8	Q2: ≤7.2	Q3: ≤10.0	Q4: >10.0	p Value
LVF					
All patients*	1.00	1.39 (0.89 to 2.18)	2.06 (1.34 to 3.15)	3.79 (2.53 to 5.67)	<0.0001
UA	1.00	1.44 (0.74 to 2.82)	2.88 (1.54 to 5.36)	4.32 (2.43 to 7.66)	<0.0001
AMI	1.00	1.31 (0.70 to 2.46)	1.72 (0.95 to 3.11)	3.62 (2.02 to 6.49)	<0.0001
Test for interaction between diagnosis, glucose quartile, and LVF					0.60
Cardiac death					
All patients*	1.00	1.99 (0.63 to 6.29)	2.67 (0.89 to 8.01)	4.97 (1.72 to 14.37)	0.003
UA	1.00			0.59 (0.07 to 4.92)	NS
AMI	1.00	1.54 (0.48 to 4.96)	1.59 (0.52 to 4.89)	4.02 (1.38 to 11.66)	0.002
Test for interaction between diagnosis, glucose quartile, and cardiac death					0.17

*Adjusted for diagnosis.
Numbers in parentheses are 95% confidence intervals.
AMI, acute myocardial infarction.

Table 3 Interaction of diabetes with association between glycaemia and major complications (LVF, death): univariate logistic regression model

	Glucose quartiles (mmol/l)				
	Q1: ≤5.8	Q2: ≤7.2	Q3: ≤10.0	Q4: >10.0	p Value
LVF					
All patients	1.00	1.83 (1.18 to 2.84)	3.15 (2.09 to 4.77)	5.30 (3.57 to 7.88)	<0.0001
Non-diabetic	1.00	2.21 (1.37 to 3.57)	3.65 (2.29 to 5.82)	7.46 (4.46 to 12.47)	<0.0001
Diabetic	1.00	0.46 (0.12 to 1.66)	1.30 (0.52 to 3.27)	2.05 (0.89 to 4.72)	0.002
Test for interaction between diabetes, glucose quartile, and LVF					0.08
Cardiac death					
All patients	1.00	3.20 (1.02 to 9.95)	5.44 (1.85 to 16.02)	8.81 (3.09 to 25.09)	<0.0001
Non-diabetic	1.00	4.37 (1.23 to 15.59)	7.97 (2.33 to 27.25)	12.08 (3.33 to 43.85)	<0.0001
Diabetic	1.00	0	0.78 (0.07 to 8.81)	3.05 (0.40 to 23.19)	0.06
Test for interaction between diabetes, glucose quartile, and cardiac death					0.09

Numbers in parentheses are 95% confidence intervals.

Table 4 Multivariate predictors of LVF (stepwise logistic regression)

Variable	Comparison	OR (95% CI)	p Value
Age	5 year increase	1.30 (1.22 to 1.39)	<0.0001
Heart rate	1SD increase	1.89 (1.63 to 2.20)	<0.0001
Admission diuretic	Yes: no	2.80 (1.98 to 3.95)	<0.0001
ST change	Yes: no	2.09 (1.41 to 3.11)	<0.0001
Systolic BP	1SD increase	0.83 (0.72 to 0.95)	0.008
Diagnosis	AMI: UA	2.81 (1.94 to 4.09)	<0.0001
Glucose	Q1	1.00	
	Q2	1.10 (0.66 to 1.86)	
	Q3	1.73 (1.06 to 2.83)	
	Q4	2.80 (1.74 to 4.50)	<0.0001

CI, confidence interval; OR, odds ratio.

trends for new ST change, Q wave development, and creatine kinase concentrations. Heart rate also increased with quartile group and was significantly correlated with glucose concentration ($r = 0.16$, $p < 0.0001$) (table 1).

The frequency of major complications increased across the quartile groups, particularly LVF (Q1 6.4%, Q4 25.2%, $p < 0.0001$) and cardiac death (Q1 0.7%, Q4 6.1%, $p < 0.0001$). The relations were linear, each glucose quartile increment being associated with an odds ratio of 1.46 (95% confidence interval (CI) 1.27 to 1.70) for LVF and 1.52 (95 CI% 1.17 to 1.97) for cardiac death. No curvature occurred when a quadratic term was fitted to the data ($p = 0.45$ for LVF, $p = 0.82$ for cardiac death), ruling out a threshold effect.

Although complication rates were higher for a discharge diagnosis of acute myocardial infarction than for unstable angina, there was no evidence that the effects of serum glucose concentration were different for the two groups (table 2), there being no significant interaction with discharge diagnosis in the associations between glucose quartile and LVF ($p = 0.60$) or cardiac death ($p = 0.17$). Similarly, there was no significant interaction with diabetic status in the associations between glucose quartile and LVF ($p = 0.08$) or cardiac death ($p = 0.09$) (table 3).

Independent effects of admission blood glucose on major complications

Variables entered into a stepwise logistic regression model for LVF were age, heart rate, admission diuretic treatment, ST change, systolic blood pressure, and discharge diagnosis. Admission serum glucose concentration retained an independent association with LVF despite adjustment for these factors, the odds of LVF increasing incrementally across the

Table 5 Multivariate predictors of cerebrovascular accident (stepwise logistic regression)

Variable	Comparison	OR (95% CI)	p Value
Heart rate	1 SD increase	2.44 (1.22 to 4.91)	0.01
Diagnosis	AMI: UA	6.75 (1.40 to 32.58)	0.02
Glucose	Q4: Q1–Q3	24.0 (2.98 to 193.4)	0.003

quartile groups. Thus, for patients in Q4 with admission serum glucose concentrations > 10.0 mmol/l, the odds of LVF were 2.80 (95% CI% 1.74 to 4.50) relative to patients in Q1 (table 4). Admission serum glucose concentration was also an independent determinant of cerebrovascular accident (table 5), with odds of 24.0 (95% CI 2.98 to 193.4) for patients in Q4 relative to patients in Q1 to Q3. However, it was not independently associated with cardiac death (table 6).

DISCUSSION

This is the largest contemporary study of the prognostic correlates of stress hyperglycaemia in acute coronary syndromes and the first to include patients with unstable angina. The data show that the relation between admission blood glucose and risk of adverse outcomes is graded across quartile groups without any detectable threshold. Importantly, there was no significant interaction with discharge diagnosis in the associations between glycaemia and adverse outcomes, which were similar for patients with unstable angina and acute myocardial infarction.

The large number of patients enrolled in this study allowed us to explore the relation between admission glycaemia and outcomes across a broad range of glucose concentrations. We found clear evidence of a linear trend between admission glycaemia and major complications, particularly LVF and cardiac death, without a threshold effect. Even in the lower quartile groups, risk was closely related to blood glucose concentrations near to or within the normal range, and certainly below concentrations for which insulin is usually recommended.[22] Nevertheless, risk was greatest for patients with admission glucose concentrations > 10.0 mmol/l, although within this upper quartile group the relation with adverse outcomes remained linear with no evidence of a critical concentration above which risk increased abruptly.

An important finding in the present study was that the prognostic correlates of admission glycaemia did not differ significantly between patients with acute myocardial infarction and those with unstable angina. This bears comparison with the findings of Savonitto and colleagues,[23] who reported that the prognostic significance of increases in creatine kinase extended across the whole spectrum of acute coronary syndromes and included patients with unstable angina, with event rates beginning to rise for creatine kinase concentrations that were within the normal range. Thus, our own study showed the increasing risk of LVF with glucose quartile applied equally to patients with unstable angina and those

with myocardial infarction. Indeed, in multivariate analysis, glycaemia was incrementally associated with LVF across quartile groups independently of admission diagnosis. For cardiac death, the picture was less clear partly because event rates were low, particularly in the group with unstable angina, only seven of whom died. Thus, while the risk of death increased progressively with glucose quartile for patients with acute myocardial infarction, there was no pattern for patients with unstable angina. Nevertheless, our interaction analysis provided no evidence that the effects of admission glycaemia on cardiac death were different for the two groups.

The prognostic correlates of admission glycaemia also applied equally to diabetic and non-diabetic subgroups. In both subgroups, the risk of LVF and cardiac death increased across the glucose quartile groups. This contrasts with the findings of a recent meta-analysis,[13] which found significant associations between admission glycaemia and LVF in non-diabetic but not in diabetic patients. In the same study, associations between admission glycaemia and hospital death were severely attenuated in diabetic patients. The authors suggested that this may reflect difficulty in defining threshold concentrations for hyperglycaemia in diabetic subjects, a difficulty avoided in our own study by analysing relations between glycaemia and outcome across the full distribution of admission glucose concentrations. Of course the distinction between diabetic and non-diabetic patients in studies of this type is not always straightforward and particularly in the upper quartile group diabetes may be have been undiagnosed in an unknown proportion of patients. Nevertheless, our data strongly suggest that relations between admission glycaemia and adverse outcomes were not confined to non-diabetic patients, there being no evidence of significant interaction with diabetic status.

Multivariate analysis of the independent association of admission glycaemia with adverse outcomes showed that the association with LVF was graded and highly significant. However, despite close univariate associations of admission glycaemia with both age and LVF—the major determinants of prognosis in acute coronary syndromes[24–28]—an independent association with cardiac mortality was not confirmed. This is at variance with some reports[1] but agrees with the findings of those investigators who, as we did, included LVF in the regression model.[4] It is clear, therefore, that the major association of admission glycaemia is with the development of LVF, which, together with age, is the most potent determinant of death in acute coronary syndromes.

Mechanisms of the adverse effects of hyperglycaemia cannot be deduced from our data, although there was a clear association with the extent of myocardial injury. Thus, peak creatine kinase increased incrementally across glucose quartile groups, as did the frequency of acute myocardial infarction and Q wave development, all of which are well recognised markers of injury. Adrenergic stress is itself related to the severity of myocardial injury,[16] and our finding of increasing tachycardia across glucose quartile groups presumably reflects this. Certainly, therefore, our data are consistent with the view that acute phase hyperglycaemia in acute coronary syndromes is a response to adrenergic stress as determined by the extent of myocardial injury, which accounts for its relation with

Table 6 Multivariate predictors of death (stepwise logistic regression)

Variable	Comparison	OR (95% CI)	p Value
LVF	Yes: no	3.47 (2.04 to 5.92)	<0.0001
Ventricular fibrillation	Yes: no	13.62 (6.28 to −29.52)	<0.0001
Age	5 year increase	1.42 (1.27 to 1.60)	<0.0001
Diagnosis	AMI: UA	8.62 (3.98 to 18.66)	<0.0001
Systolic BP	1SD increase	0.54 (0.41 to 0.70)	<0.0001
Heart rate	1SD increase	1.47 (1.16 to 1.86)	0.004

adverse outcomes. As others have argued, however, this does not discount a role for relative insulin deficiency,[13] which would exaggerate glycaemic responses to adrenergic stress and account for the benefits of insulin administration in patients with acute myocardial infarction and other critically ill patients.[18 22]

In conclusion, we found that admission glycaemia stratified patients with acute coronary syndromes according to their risk of in-hospital LVF and cardiac mortality. There was no detectable glycaemic threshold for these adverse effects. The prognostic correlates of admission glycaemia were unaffected by diabetic status and did not differ significantly between patients with acute myocardial infarction and those with unstable angina. If relative hyperinsulinaemia contributes to acute phase hyperglycaemia, our data suggest that current recommendations for insulin administration in acute coronary syndromes may be too restrictive.

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