ORIGINAL PAPER

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

Stress hyperglycaemia in patients with first myocardial infarction

A. Bronisz,[1] M. Kozinski,[2] P. Magielski,[2] T. Fabiszak,[2] M. Bronisz,[3] I. Swiatkiewicz,[2] A. Sukiennik,[2] B. Beszczynska,[4] R. Junik,[1] J. Kubica[2]

[1]Department of Endocrinology and Diabetology, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland
[2]Department of Cardiology and Internal Medicine, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland
[3]Department of Cardiology, Public Regional Hospital in Inowroclaw, Poland
[4]Department of Animal Physiology, Institute of General and Molecular Biology, Nicolaus Copernicus University in Torun, Poland

Correspondence to:
Agata Bronisz
Department of Endocrinology and Diabetology, 9 Skłodowskiej-Curie Street, 85-094 Bydgoszcz, Poland
Tel.: +4852 585 4020
Fax: +4852 585 4041
Email: agabrr@poczta.onet.pl

Disclosures
The authors do not report any conflict of interest regarding this research.

SUMMARY

Objective: To investigate the incidence of stress hyperglycaemia at first acute myocardial infarction (MI) with ST-segment elevation, occurrence of stress hyperglycaemia as a manifestation of previously undiagnosed abnormal glucose tolerance (AGT), and its relation to stress hormone levels. **Materials and methods:** The population of this prospective cohort study consisted of 243 patients. On admission glucose, adrenaline, noradrenaline and cortisol levels were measured. Patients without previously diagnosed diabetes ($n = 204$) underwent an oral glucose tolerance test on day 3 of hospitalisation and 3 months after discharge. **Results:** Abnormal glucose tolerance at day 3 was observed in 92 (45.1%) patients without a previous diagnosis of diabetes mellitus and resolved after 3 months in 46 (50.0%) patients ($p < 0.0001$). Stress hyperglycaemia, defined as admission glycaemia ≥ 11.1 mmol/l, affected 34 (14.0%) study participants: 28 (54.9%) patients with diabetes vs. 3 (8.8%) subjects with newly detected impaired glucose intolerance ($p < 0.00001$) and 1 (2.2%) person with AGT at day 3 ($p < 0.000001$). Multivariable analysis identified elevated glycated haemoglobin (HbA_{1c}; $p < 0.0000001$), anterior MI ($p < 0.05$) and high admission cortisol concentration ($p < 0.001$), but not catecholamines, as independent predictors of stress hyperglycaemia. The receiver operating characteristic curve analysis revealed the optimal cut-off values of 8.2% for HbA_{1c} and 47.7 μg/dl for admission cortisol with very good and sufficient diagnostic accuracies respectively. **Conclusions:** Newly detected AGT in patients with a first MI is transient in 50% of cases. Stress hyperglycaemia is a common finding in patients with a first MI with ST-segment elevation and diabetes mellitus, but is rarely observed in individuals with impaired glucose tolerance or transient AGT diagnosed during the acute phase of MI. The risk factors of stress hyperglycaemia occurrence include elevated HbA_{1c}, anterior MI and high admission cortisol concentration.

What's known

Stress hyperglycaemia is defined as a transient elevation of blood glucose occurring in the acute phase of a disease. Abnormal glucose tolerance (AGT) observed in above 60% of patients with acute myocardial infarction (MI) is a persistent disturbance there. There is a lack of researches assessing the prevalence of AGT in patients with a first MI with ST-segment elevation and studies comparing the occurrence of stress hyperglycaemia in patients with and without AGT.

What's new

Abnormal glucose tolerance in patients with a first MI with ST-segment elevation is transient in 50% of cases. Stress hyperglycaemia in this setting is a common finding in patients with diabetes, but is rarely observed in patients with newly detected impaired glucose tolerance or transient AGT diagnosed for the first time during MI. The risk factors of stress hyperglycaemia occurrence include elevated HbA_{1c}, anterior MI and high admission cortisol concentration.

Introduction

Stress hyperglycaemia, which has been increasingly studied and discussed in recent years (1–7), occurs as a consequence of stress associated with the acute phase of a disease (2–8). Stress activates the hypothalamus-pituitary-adrenal axis and the autonomic nervous system and initiates a cascade of metabolic processes leading hyperglycaemia (9,10). Currently no strict and widely accepted criteria for stress hyperglycaemia exist; however, it is commonly defined as a transient elevation of blood glucose to a level exceeding values regarded as normal. In many, but not all, previous studies the diagnosis of stress hyperglycaemia referred exclusively to patients without prior diabetes who presented with hyperglycaemia on hospital admission for life-threatening conditions (3–7,11–13). These patients are of particular interest to clinicians because they are reported to have a worse prognosis than those with diabetes despite higher blood glucose levels on admission in the latter population (6,11,12,14,15). There is a lack of studies comparing the occurrence of stress hyperglycaemia in patients with and without diabetes. Previous studies have not directly assessed whether high admission glycaemia was merely a temporary finding or a sign of pre-existing, but undiagnosed abnormalities. Moreover, despite proving very high prevalence of abnormal glucose tolerance (AGT)

Int J Clin Pract, June 2012, **66**, 6, 592–601. doi: 10.1111/j.1742-1241.2012.02917.x

in patients with acute myocardial infarction (MI) (16,17), there is a shortage of research assessing the occurrence of newly diagnosed AGT and stress hyperglycaemia in the group of patients with first MI.

The aim of this study was to compare the incidence of stress hyperglycaemia between patients with and without diabetes in the selected group with a first MI with ST-segment elevation, to investigate if it is a manifestation of previously undiagnosed carbohydrate metabolism abnormalities and to assess whether there is any relationship between admission glycaemia and circulating levels of stress hormones (adrenaline, noradrenaline and cortisol).

Material and methods

Study design and patient characteristics

The population of our prospective cohort study consisted of 365 consecutive patients admitted to the Department of Cardiology and Internal Medicine, Collegium Medicum in Bydgoszcz, Poland, because of a first episode of acute MI with ST-segment elevation. The diagnosis of MI was established accordingly to the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction recommendations published in 2007 (18). Exclusion criteria were as follows: age > 80 years; therapy with vasopressors, inotropes, steroids or immunosuppressants; severe heart failure (class III or IV according to the New York Heart Association Functional classification), creatinine level > 176.8 μmol/l, neoplasm and symptomatic infection. The study protocol was approved by the Local Bioethics Committee at Collegium Medicum of the Nicolaus Copernicus University in Torun. All patients gave voluntary informed consent for participation in the study.

Study conduction

Patients with initially established diagnosis of acute coronary syndrome with ST-segment elevation were transferred directly to the Invasive Cardiology Catheterization Laboratory in the Department of Cardiology and Internal Medicine. Blood samples were taken on admission prior to coronary angiography to measure: glucose, adrenaline, noradrenaline, total cortisol, creatine kinase, creatine kinase MB isoenzyme, troponin I, glycated haemoglobin (HbA_{1c}), creatinine, total cholesterol, low-density-lipoprotein cholesterol, high-density-lipoprotein cholesterol and triglycerides. According to the Polish Diabetes Association recommendations (19) patients without diabetes with admission glycaemia > 10.0 mmol/l and those with diabetes and admission glycaemia > 7.8 mmol/l in the first 24 h of hospitalisation were treated with insulin intravenously. Subsequently, in patients with glycaemia above > 7.8 mmol/l subcutaneous insulin therapy in the form of multiple insulin injections was applied from day 2 up to day 5.

In individuals without a previous diagnosis of diabetes, an oral glucose tolerance test (OGTT) with 75 g of glucose was performed on day 3 and again 3 months postdischarge. Glucose concentrations in venous blood plasma 2 h after glucose intake were classified as follows: normal glucose tolerance < 7.77 mmol/l; impaired glucose tolerance from 7.77 up to 11.09 mmol/l; diabetes ≥ 11.1 mmol/l. Based on the OGTT results at day 3 and month 3 the study group was divided into four subgroups (Table 1): (i) with AGT (defined as impaired glucose tolerance and diabetes) recognised at day 3 and month 3, (ii) with AGT present at day 3 and resolved at month 3, (iii) with normal glucose tolerance (NGT) at day 3 and month 3 and (iv) with NGT at day 3 and AGT at month 3. Stress hyperglycaemia was recognised as

Table 1 Results of the oral glucose tolerance test (OGTT) performed on day 3 and 3 months postdischarge in 204 patients with the first ST-segment-elevation myocardial infarction and no previous diagnosis of type 2 diabetes

	D3+/M3+ *n* = 46 (22.5%)	D3+/M3− *n* = 46 (22.5%)	D3−/M3− *n* = 94 (46.1%)	D3−/M3+ *n* = 18 (8.8%)
OGTT day 3: normal glucose tolerance	–	–	94	18
Impaired glucose tolerance	23	40	–	–
Diabetes mellitus	23	6	–	–
OGTT month 3: normal glucose tolerance	–	46	94	–
Impaired glucose tolerance	32	–	–	16
Diabetes mellitus	14	–	–	2

D3+/M3+, abnormal glucose tolerance diagnosed at day 3 and 3 months; D3+/M3−, abnormal glucose tolerance diagnosed at day 3 and ruled out at 3 months; D3−/M3−, abnormal glucose tolerance ruled out at day 3 and 3 months; D3−/M3+, abnormal glucose tolerance ruled out at day 3 and diagnosed at 3 months; OGTT, oral glucose tolerance test. Two patients from group D3+/M3+ with diabetes diagnosed in month 3 in OGTT performed on day 3 had impaired glucose tolerance.

admission glycaemia ≥ 11.1 mmol/l based on the definition of 'hospital-related hyperglycaemia' introduced by The American Diabetes Association (20).

Laboratory analyses

Biochemical measurements were performed using the following methods: blood glucose – hexokinase enzymatic glucose assay (Abbott, Wiesbaden, Germany); HbA_{1c} – immunoturbimetric Multigent™ HbA_{1c} assay (Abbott, Indianapolis, USA); catecholamines – fluorometry using a Shimadzu 1501 spectrophotometer (Shimadzu, Kioto, Japan); cortisol – AxSYM Cortisol assay (Abbott, Malvern, AR, USA); creatine kinase – enzymatic method Creatine kinase assay (Abbott, Chicago, IL, USA); creatine kinase MB isoenzyme – CK-MB liquid immunological test assay (Sentinel Diagnostics, Milan, Italy); troponin I – chemiluminescence immunoassay STAT Troponin-I Architect System (Abbott, Middletown, OH, USA); creatinine – spectrophotometric creatinine assay (Abbott, Wiesbaden, Germany); total cholesterol, high-density-lipoprotein cholesterol and triglycerides – enzymatic cholesterol, ultrahigh-density-lipoprotein and triglyceride assays (Abbott, Wiesbaden, Germany) respectively. Low-density-lipoprotein cholesterol concentration was calculated according to the Friedewald formula.

Statistical analysis

Results are presented as mean values and standard deviations for quantitative parameters and as percentages of the population for categorical data. Use of the Shapiro-Wilk test demonstrated that the investigated quantitative variables were not normally distributed. The significance of differences between groups was evaluated using the ANOVA Kruskal–Wallis test and Mann–Whitney U-test. The Wilcoxon rank test was used to evaluate dependent samples. The McNemar's test and the χ^2 test (with Yates correction when required) were used for paired and unpaired qualitative variables respectively. The Spearman's correlation rank test was used to evaluate the significance of correlation. Univariate logistic regression was performed separately for: adrenaline, noradrenaline and cortisol as well as age, gender, body mass index, time to primary percutaneous coronary intervention, HbA_{1c}, creatine kinase, creatine kinase MB isoenzyme, troponin I, creatinine, total cholesterol, low-density-lipoprotein cholesterol, high-density-lipoprotein cholesterol, triglycerides, hypertension, smoking, family history of coronary artery disease and MI localisation. Multivariate logistic-regression models were employed to identify independent predictors of stress hyperglycaemia. Variables in the final model were selected with a step-down procedure; the decision to remove terms was based on a likelihood-ratio test and p-value. Odds ratios (OR) and their 95% confidence intervals (CI) were calculated. Receiver operating characteristic (ROC) curves were constructed, and the area under the ROC curve (AUC) was determined. Statistical significance was indicated by a p-value < 0.05.

Based on the previous data from large registries we assumed the occurrence of diabetes in patients with MI to be 20% (21,22). Similarly, we expected that 20% of our study participants would develop stress hyperglycaemia (23). With these assumptions it was calculated that enrolment of 240 patients would be mandatory to demonstrate a fourfold higher prevalence of stress hyperglycaemia in patients with diabetes than in subjects without diabetes, allowing for a 99.9% power with a 2-sided α-value of 0.05.

The statistical analysis and sample size calculation were carried out using the computer package STATISTICA 10.0 (Statsoft, Tulsa, USA). In addition, MedCalc 12.0 (MedCalc Software, Mariakerke, Belgium) statistical software was applied for the ROC curve analysis.

Results

Patients

Of the total number of 365 patients 24 refused further participation in the study: 18 before discharge from hospital and further six during the first 3 months after the index episode of MI. Seven patients were excluded from the study during hospitalisation because of a false diagnosis of MI (three patients), dopamine therapy, acute pharyngitis, chronic obstructive pulmonary disease and suspicion of a lung tumour (one patient each). Forty-two patients were excluded from further analysis because of incomplete data, whereas further 49 did not attend the 3-month follow-up appointment including one person who died. The final study group consisted of 243 patients: 58 women (23.9%) and 185 men (76.1%), aged 57.0 ± 9.3 years.

The adverse events observed during 3 months of follow-up included re-MI (five patients), unstable angina (17 patients) and development of symptomatic chronic heart failure (six patients). In addition, within 3 months after study enrolment 14 patients underwent percutaneous coronary intervention including five subjects with re-MI or unstable angina and nine patients scheduled for an elective procedure during the index hospitalisation. Furthermore, at 3-month follow-up three patients were treated with elective coronary artery bypass grafting scheduled during the index hospitalisation.

Diabetes status

Among the study participants there were 39 (16.0%) patients with pre-existing diabetes and 204 (84.0%) with no prior diagnosis of carbohydrate metabolism abnormalities. In the latter, AGT was diagnosed for the first time in the acute phase of MI in 92 (45.1%) cases. Three months after the index MI, carbohydrate abnormalities regression was observed in 46 (50%) patients ($p < 0.0001$), including resolution of impaired glucose tolerance occurred in 40 (63.5%) and diabetes in 6 (20.7%) patients originally presenting with AGT at day 3. Both changes were statistically highly significant with p-values below 0.0001. Of 23 patients diagnosed with diabetes on day 3, the diagnosis was maintained at month 3 in 12 (52.2%) cases, whereas reversion into impaired glucose tolerance occurred in 11 (47.8%) patients (Table 1). Twelve subjects who had diabetes mellitus diagnosed on the basis of both OGTT results from day 3 and month 3 (4.9% of all patients) were subsequently incorporated into the pre-existing diabetes group for further analysis. Altogether the patients with diabetes constituted 21.0% of the study population. The baseline characteristics of the studied groups are presented in Table 2.

There were 34 patients with newly detected impaired glucose tolerance (14.0% of all patients). Transient AGT at day 3 was present in 46 and 3 months after discharge in 18 individuals, corresponding to 18.9% and 7.4% of all patients respectively. Patients with impaired glucose tolerance or diabetes were significantly older comparing with the normal glucose tolerance group. They were also more likely to receive inhibitors of renin-angiotensin-aldosterone system, beta-blockers and lipid-lowering drugs. Furthermore, when compared with the normal glucose tolerance group, patients with diabetes, but not with impaired glucose tolerance, showed signifi-

Table 2 Baseline characteristics and prevalence of stress hyperglycaemia in the groups of patients by presence of AGT

Assessed parameter (mean ± SD)	DM *n* = 51	IGT *n* = 34	AGT at D3 *n* = 46	AGT at M3 *n* = 18	NGT *n* = 94	p-value DM vs. NGT
Age (years)	59.9 ± 8.8	60.8 ± 8.9	56.3 ± 9.7	56.6 ± 6.8	54.5 ± 9.2	0.0052
BMI (kg/m^2)	29.0 ± 3.6	26.4 ± 4.0	27.4 ± 4.6	27.3 ± 5.5	26.0 ± 3.6	0.000067
Time to PTCA (min)	258.0 ± 166.5	248.2 ± 152.3	251.6 ± 173.9	222.2 ± 77.3	259.7 ± 162.0	NS
MI risk factors *n* (%)						
Men	35 (68.6%)	26 (76.5%)	34 (73.9%)	13 (72.2%)	77 (81.9%)	NS
Hypertension	32 (62.8%)	14 (41.2%)	18 (39.1%)	10 (55.6%)	29 (30.9%)	0.002
Hyperlipidaemia	15 (29.4%)	9 (26.5%)	10 (21.7%)	4 (22.2%)	21 (22.3%)	NS
Smoking	30 (58.8%)	20 (58.8%)	33 (71.7%)	14 (77.7%)	61 (64.9%)	NS
Positive family history of coronary artery disease	7 (13.7%)	8 (23.5%)	11 (23.9%)	4 (22.2%)	20 (21.3%)	NS
Medication before admission *n* (%)						
ACE or ARB	13 (25.5%)	7 (20.6%)	9 (19.6%)	3 (16.7%)	7 (7.4%)	0.0025
Aspirin	7 (13.7%)	3 (8.8%)	3 (6.5%)	1 (5.6%)	6 (6.4%)	NS
Beta-blocker	7 (13.7%)	8 (23.5%)	2 (4.3%)	1 (5.6%)	3 (3.2%)	0.017
Calcium channel antagonist	8 (15.7%)	3 (8.8%)	4 (8.7%)	2 (11.1%)	5 (5.3%)	NS
Diuretic	5 (9.8%)	2 (5.9%)	2 (4.3%)	3 (16.7%)	1 (1.1%)	0.012
Lipid-lowering drugs	9 (17.6%)	7 (20.6%)	1 (2.2%)	-	8 (8.5%)	NS
Anterior MI localisation *n* (%)	29 (56.9%)	13 (38.2%)	24 (52.2%)	8 (44.4%)	36 (38.3%)	0.032
Stress hyperglycaemia *n* (%)	28 (54.9%)	3 (8.8%)	1 (2.2%)	-	2 (2.1%)	< 0.000001

ACE, angiotensin-converting enzyme inhibitor; AGT at D3, abnormal glucose tolerance diagnosed at day 3; AGT at M3, abnormal glucose tolerance diagnosed at month 3; ARB, angiotensin receptor blocker; BMI, body mass index; DM, diabetes mellitus; IGT, impaired glucosae tolerance; MI, myocardial infarction; NGT, normal glucose tolerance; NS, not significant; PTCA, percutaneous transluminal coronary angioplasty; SD, standard deviation. Significant p-values were also present between: DM vs. IGT for BMI ($p = 0.02$) and prevalence of stress hyperglycaemia ($p = 0.000001$). DM vs. AGT at D3 for history of hypertension ($p = 0.019$), therapy with lipid-lowering drugs ($p = 0.013$) and prevalence of stress hyperglycaemia ($p < 0.000001$). IGT vs. AGT at D3 for therapy with beta-blocker ($p = 0.01$). IGT vs. AGT at M3 for therapy with beta-blocker ($p = 0.022$). IGT vs. NGT for age ($p = 0.0045$), therapy with ACE or ARB ($p = 0.034$) and therapy with beta-blocker ($p = 0.0003$).

cantly higher incidence of arterial hypertension, more frequent anterior location of MI as well as greater values of body mass index. Admission glycaemia and HbA_{1c} levels in these patients were also significantly higher than in all remaining groups. No differences in other parameters between the study groups were observed (Table 3).

In attempt to identify predictors of previously undiagnosed diabetes we found that among all variables from Tables 2 and 3, high admission glycaemia (OR for a 1 mmol/l increase 1.35, 95% CI 1.09–1.67; $p < 0.007$), elevated HbA_{1c} level (OR for a 1% increase 2.97, 95% CI 1.57–5.59; $p < 0.001$), high fasting blood glucose concentration in OGTT at day 3 (OR for a 1 mmol/l increase 2.34, 95% CI 1.22–4.51; $p < 0.02$), high blood glucose concentration after 2 h in OGTT at day 3 (OR for a 1 mmol/l increase 1.63, 95% CI 1.33–2.00; $p < 0.000006$) and increased body mass index (OR for a 1 kg/m^2 increase 1.13, 95% CI 1.01–1.26; $p < 0.03$) were associated with the presence of diabetes in OGTT at 3 months in the univariate analysis. Surprisingly, multivariate analysis demonstrated high blood glucose concentration after 2 h in OGTT at day 3 (OR for a 1 mmol/l increase 1.61, 95% CI 1.26–2.06; $p < 0.00004$) as the only predictor of previously undiagnosed diabetes.

The ROC curve analysis assessing the diagnostic accuracy for the detection of previously undiagnosed diabetes revealed the optimal cut-off values of 12.0 mmol/l for blood glucose concentration after 2 h in OGTT at day 3 (sensitivity 75.0%, specificity 93.6%, positive predictive value 49.9%, negative predictive value 97.8%), with AUC of 0.88 (95% CI 0.83–0.92).

Rates of major adverse cardiac events including MI, unstable angina and urgent revascularisation in patients who completed 3-month follow-up were comparable between groups with and without diabetes (13.7 vs. 7.8%; $p = 0.19$). Similarly, the occurrence of postinfarct heart failure did not significantly differ between both groups (2.0 vs. 2.6%; $p = 0.81$).

Stress hyperglycaemia

Stress hyperglycaemia was present in 34 (14.0%) patients. A significantly higher incidence of stress hyperglycaemia was found in patients with diabetes when compared with all individuals without diabetes [28/51 (54.9%) vs. 6/192 (3.1%); $p < 0.00001$]. The prevalence of stress hyperglycaemia in the other studied groups was lower than in patients with diabetes, but no significant between-group differences were observed (Table 2). Also, in patients with newly diagnosed impaired glucose tolerance [3/34 (8.8%); $p < 0.00001$] and in patients with AGT at day 3 [1/46 (2.2%); $p < 0.000001$] the occurrence rate of stress hyperglycaemia was significantly lower than in patients with diabetes.

As shown in Figure 1, in patients with stress hyperglycaemia the adrenaline and cortisol concen-

Table 3 Admission assessed parameters in the groups of patients by presence of AGT (mean ± standard deviation)

Assessed parameter (unit)	DM *n* = 51	IGT *n* = 34	AGT at D3 *n* = 46	AGT at M3 *n* = 18	NGT *n* = 94	p-value DM vs. NGT
Admission glycaemia (mmol/l)	12.3 ± 4.5	7.7 ± 1.7	7.4 ± 1.5	7.7 ± 1.6	7.4 ± 1.7	< 0.0000001
HbA_{1c} (%)	8.0 ± 1.5	6.2 ± 0.7	6.2 ± 0.9	5.8 ± 0.5	5.9 ± 0.5	< 0.0000001
Adrenaline (μg/l)	0.14 ± 0.17	0.09 ± 0.12	0.08 ± 0.14	0.09 ± 0.16	0.08 ± 0.16	NS
Noradrenaline (μg/l)	0.15 ± 0.16	0.12 ± 0.19	0.15 ± 0.23	0.22 ± 0.32	0.16 ± 0.19	NS
Cortisol (μg/dl)	32.6 ± 18.3	28.2 ± 15.6	29.9 ± 16.1	29.8 ± 17.8	26.1 ± 17.0	NS
CPK (U/l)	288.3 ± 342.1	382.2 ± 473.4	285.7 ± 327.7	306.5 ± 315.7	349.0 ± 492.4	NS
CK-MB (U/l)	41.4 ± 61.1	45.1 ± 44.2	46.1 ± 51.7	38.7 ± 32.4	53.0 ± 73.0	NS
Troponin I (ng/ml)	1.4 ± 2.9	2.4 ± 7.0	1.9 ± 4.3	2.2 ± 4.9	2.5 ± 6.2	NS
Creatinine (μmol/l)	85.5 ± 17.4	84.7 ± 18.2	86.1 ± 17.4	79.7 ± 14.5	84.8 ± 14.1	NS
Total cholesterol (mmol/l)	5.5 ± 1.1	6.0 ± 1.4	6.0 ± 1.0	5.9 ± 1.0	5.8 ± 1.2	NS
LDL cholesterol (mmol/l)	3.5 ± 1.0	3.8 ± 1.1	4.0 ± 0.9	4.0 ± 0.9	3.9 ± 1.1	NS
HDL cholesterol (mmol/l)	1.3 ± 0.5	1.4 ± 0.4	1.3 ± 0.3	1.3 ± 0.3	1.4 ± 0.3	NS
Triglycerides (mmol/l)	1.5 ± 1.1	1.7 ± 1.4	1.5 ± 1.1	1.4 ± 1.5	1.1 ± 0.7	NS

AGT at D3, abnormal glucose tolerance diagnosed at day 3; AGT at M3, abnormal glucose tolerance diagnosed at month 3; CPK, creatine kinase; CK-MB, creatine kinase MB isoenzyme; DM, diabetes mellitus; HbA_{1c}, glycated haemoglobin; HDL, high-density lipoprotein; IGT, impaired glucosae tolerance; LDL, low-density lipoprotein; NGT, normal glucose tolerance; NS, not significant. Significant p-values were also present: for AG between DM vs. IGT ($p = 0.000001$); DM vs. AGT at D3 ($p < 0.0000001$) and DM vs. AGT at M3 ($p = 0.00038$) for HbA_{1c} between DM vs. IGT and AGT groups ($p < 0.0000001$).

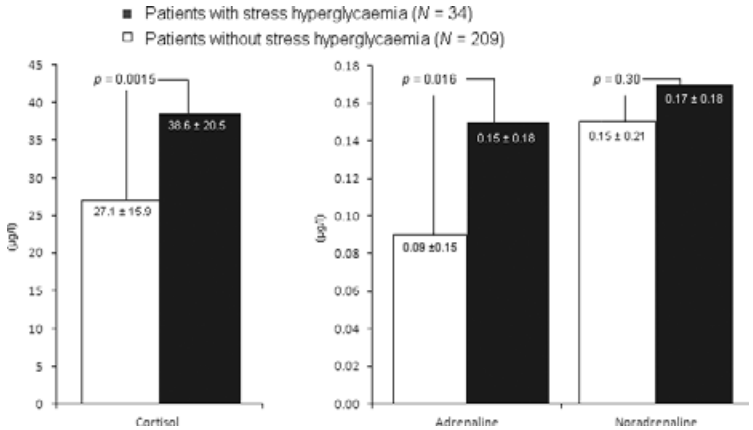

Figure 1 Comparison of cortisol, adrenaline and noradrenaline concentrations in patients with and without stress hyperglycaemia

trations on admission were significantly higher comparing with patients without stress hyperglycaemia. Drugs taken prior to the hospital admission did not influence stress hormone levels (data not presented).

Univariate analysis demonstrated significant associations between stress hyperglycaemia and high adrenaline and cortisol admission concentrations, increased body mass index, elevated HbA_{1c} level and anterior location of MI (Table 4). However, when tested in the multivariable logistic-regression model only high admission cortisol concentration, elevated HbA_{1c} level and anterior wall MI, but not catecholamines and body mass index, remained independent predictors of stress hyperglycaemia (Table 5). Levels of stress hormones and HbA1c concentration were unrelated (data not presented).

The ROC curve analysis assessing the diagnostic accuracy for the detection of stress hyperglycaemia

Table 4 Stress hormone concentrations and baseline characteristics as predictors of stress hyperglycaemia in the univariate analysis

Parameters	Odds ratio	95% confidence interval	p-value
Adrenaline [for a 1 μg/l increase]	7.20	1.06–48.89	0.042
Noradrenaline [for a 1 μg/l increase]	1.37	0.25–7.47	0.71
Cortisol [for a 1 μg/dl increase]	1.04	1.02–1.06	0.00051
Age [for a 1 year increase]	1.03	0.99–1.07	0.12
Body mass index [for a 1 kg/m^2 increase]	1.11	1.02–1.20	0.017
HbA_{1c} [for a 1% increase]	3.79	2.51–5.73	0.0000000002
CK-MB [for a 1 U/l increase]	0.99	0.99–1.00	0.48
Troponin I [for a 1 ng/ml increase]	1.00	0.94–1.08	0.92
Creatinine [for a 1 μmol/l increase]	0.99	0.97–1.02	0.56
Total cholesterol [for a 1 mmol/l increase]	0.82	0.59–1.15	0.24
LDL cholesterol [for a 1 mmol/l increase]	0.69	0.46–1.02	0.06
HDL cholesterol [for a 1 mmol/l increase]	1.09	0.37–3.21	0.87
Triglycerides [for a 1 mmol/l increase]	1.16	0.88–1.54	0.28
MI risk factors			
Men	1.93	0.89–4.22	0.096
Hypertension	1.25	0.60–2.59	0.55
Smoking	1.15	0.64–2.05	0.65
Positive family history of coronary artery disease	1.48	0.64–3.41	0.36
Anterior vs. non-anterior location of MI	2.18	1.03–4.06	0.040

CK-MB, creatine kinase MB isoenzyme; HbA_{1c}, glycated haemoglobin; HDL cholesterol, high-density-lipoprotein cholesterol, triglycerides; LDL cholesterol , low-density-lipoprotein cholesterol; MI, myocardial infarction.

Table 5 Independent predictors of stress hyperglycaemia

Parameters	Odds ratio	95% confidence interval	p-value
HbA_{1c} [for a 1% increase]	4.15	2.62–6.57	< 0.0000001
Total cortisol [for a 1 μg/dl increase]	1.06	1.03–1.09	< 0.001
Anterior vs. non-anterior wall MI	3.05	1.03–9.03	0.042

HbA_{1c}, glycated haemoglobin; MI, myocardial infarction.

revealed the optimal cut-off values of 8.2% for HbA_{1c} concentration (sensitivity 50.0%, specificity 98.5%, positive predictive value 84.2%, negative predictive value 92.6%) and 47.7 μg/dl for admission cortisol concentration (sensitivity 41.2%, specificity 91.4%, positive predictive value 43.8%, negative predictive value 90.5%). AUCs for HbA_{1c} concentration and admission cortisol concentration were 0.86 (95% CI 0.77–0.94) and 0.67 (95% CI 0.57–0.77) respectively. Comparison of the ROC curves for both parameters in terms of their diagnostic accuracy demonstrated the superiority of HbA_{1c} concentration over admission cortisol concentration ($p < 0.02$).

Major adverse cardiac events including MI, unstable angina and urgent revascularisation occurred in 5 (14.7%) and 17 (8.1%) patients who presented on admission, respectively, with and without stress hyperglycaemia ($p = 0.21$). Similarly, symptoms of postinfarct heart failure were present in comparable proportions of subjects from both groups (2.9 vs. 2.4; $p = 0.68$).

Discussion

The main findings of our study conducted on a homogenous population of patients with a first MI with ST-segment elevation are: transient nature of newly detected AGT in 50% of cases, a huge discrepancy in the prevalence of stress hyperglycaemia between patients with and without diabetes, and identification of elevated HbA_{1c}, anterior MI and high admission cortisol concentration as independent predictors of stress hyperglycaemia.

Carbohydrate metabolism abnormalities are almost twice as common in patients with acute MI than in individuals without ischemic heart disease (24,25). The Euro Heart Survey reported a 36% incidence of new onset impaired glucose tolerance and 22% of newly diagnosed diabetes in acute MI patients, whereas 31% of the study population had confirmed diabetes prior to acute MI (16). In our study, the prevalence of carbohydrate metabolism abnormalities was lower, regardless of whether diabetes preceded acute MI (16% of patients) or AGT was diagnosed for the first time during the index hospitalisation (45% compared with 58% in the Euro Heart Survey). A study by Wallander et al. indicates a progressive age-related deterioration in the function of the pancreatic beta-cells as a major cause of carbohydrate metabolism abnormalities in elderly people and the mechanism underlying AGT during acute MI (26). The progressive deterioration of the beta-cell function that occurs as an individual ages can result in an inability to respond appropriately to a stress-induced (i.e. during acute MI) increase in insulin resistance. In our opinion the reduction in the size of the studied groups with carbohydrate metabolism abnormalities observed in our study with respect to the Euro Heart Survey (16), is likely because of younger age of our patients (mean age 57 vs. 66 years in the Euro Heart Survey) and a more homogeneous cohort, as only patients with a first episode of MI were recruited into our study. The lower age of our cohort would suggest that the pancreatic beta-cell impairment was probably less frequent in our study population. This assumption might also explain why in a half of those patients who presented with AGT at day 3, the presence of carbohydrate metabolism abnormalities was not confirmed by a subsequent OGTT 3 months post-MI (Table 1). Our results are concordant with findings by Knudsen et al. obtained in a relatively young (median age of 58 years) cohort of 224 patients with predominantly first MI (92.9% of subjects) (27). However, they substantially differ from those delivered by the analysis of an older population of patients (mean age 63.5 years) unselected with respect to the number of previous MIs too (28). The latter found the incidence of AGT at 4 days and at 3 months post-MI to be similar, suggesting that in this population AGT diagnosed for the first time after MI was not because of stress hyperglycaemia, but rather because of pre-existing abnormalities. In our opinion, evaluation of the prevalence of AGT in patients with a first MI requires further research on a larger population.

Stress hyperglycaemia in our study was present in 55% of patients with diabetes compared with just 3% of those without diabetes, despite the high incidence of AGT (45%) as indicated by OGTT measurements at day 3 (Table 1). The prevalence of stress hyperglycaemia in the setting of acute MI in our cohort was similar to that previously reported for patients

with diabetes, but significantly lower (3 vs. 13–20%) than that described by other researchers for individuals without diabetes (29,30). However, it should be emphasised that diabetes might have been underdiagnosed in many studies evaluating stress hyperglycaemia including majority of these reporting on poor prognosis in patients with admission hyperglycaemia without underlying diabetes (3–6,13, 14,29–32). In these, mostly retrospective design studies, diabetes mellitus was considered present if, before the study enrolment, a patient had been informed of this diagnosis and was on prescribed treatment for diabetes. Therefore, the unfavourable prognosis demonstrated in these data in patients with seemingly pure stress hyperglycaemia (i.e. without underlying diabetes) may in fact be at least partially driven by subjects with unrecognised diabetes. Another possible explanation for the difference in the prevalence of stress hyperglycaemia in patients without diabetes is, again, younger age (57 vs. 70 years) and a better beta cells function of our study population compared with those in the quoted reports (29,30).

Wong et al. on the basis of the analysis of a subpopulation of patients from 'The Hyperglycemia: Intensive Insulin Infusion In Infarction (HI-5) Study' postulate the pre-existence of AGT and a stronger stress reaction in patients with a more serious disease course to be the basic mechanisms of stress hyperglycaemia occurrence in patients with MI (33). They base their conclusions on significantly higher cortisol values on admission in the group without AGT. In our research although, the absence of AGT had no influence on the levels of stress hormones (Table 3). However, stress hyperglycaemia was related with significantly higher blood plasma adrenaline and cortisol, but noradrenaline, levels on admission (Table 4). The acute response to stress includes immediate (up to 15 min) secretion of both catecholamines (34). Our results are compatible with the observations by McGuinness et al. who demonstrated in an animal model a pronounced stimulatory impact of adrenaline on glucose production, principally by enhancing hepatic glycogenolysis, whereas noradrenaline exerts only a minimal effect (35). The lack of admission adrenaline concentration among independent risk factors of stress hyperglycaemia is probably because of the delay between the onset of stress (often > 4 h from the onset of myocardial pain) and subsequent measurement (Table 5). Cortisol may be a better marker of MI-related metabolic stress, because of a later secretion onset and prolonged systemic persistence. Unfortunately, the study by Wong et al. did not take account of the time from pain onset to admission (33). Therefore, it is possible that the delay in the group without AGT was significantly shorter and for that reason higher cortisol concentrations were observed there. The MI clinical symptoms in patients with AGT are considerably less intensified, and a weaker pain reaction is often a cause of delayed admission to the cardiology department. The stress accompanying an acute disease seems to influence the increase of glycaemia similarly in patients with and without diabetes, however, in the former, because of initially higher plasma glucose concentrations, it will subsequently result in significantly higher glycaemia levels. The comparison of stress hyperglycaemia prevalence with other forms of AGT requires further research with special concern of the time passing from pain onset to hospital admission.

The independent predictors of stress hyperglycaemia (besides previously discussed admission cortisol) comprised elevated HbA_{1c} and anterior MI. HbA_{1c}, as the best-known diabetes control parameter, has been recommended by The American Diabetes Association since 2011 to diagnose diabetes, with a threshold of $\geq 6.5\%$ (20). The fact that high HbA_{1c} levels make the occurrence of admission glycaemia ≥ 11.1 mmol/l significantly more likely, clearly indicates a substantially higher probability of stress hyperglycaemia occurrence in the group with a first MI with ST-segment elevation and diabetes, in contrast to patients with a negative history of carbohydrate metabolism abnormalities. On the other hand, elevated HbA1c concentration, in contrast to high blood glucose level after 2 h in OGTT at day 3, failed to be an independent marker of previously undiagnosed diabetes in our study.

Anterior MI in comparison with other localisations usually results in a larger area of myocardial necrosis and a stronger stimulation of adrenergic and hormonal system in response to stress, possibly constituting one of the mechanisms influencing glycaemia in MI patients (36–38).

Our study has several limitations. First, it lacks adequate power to assess clinical end points. The low rate of clinical events observed in our patients is driven by the high efficacy of modern MI management, medium-term follow-up and application of strict inclusion and exclusion criteria. However, these criteria were established to eliminate many of potential confounders. Second, the reproducibility of OGTT in the diagnosis of AGT in patients after percutaneous coronary intervention has been reported to be poor (39). In this context, the source of doubt is the group consisting of patients with carbohydrates metabolism abnormalities recognised no sooner than in OGTT conducted 3 months after discharge (Table 1). Third, no account of time from the onset of infarction pain to revascularisation that might

have influenced the results of biochemical measurements (especially concentrations of catecholamines) has been taken. However, the time delay is not a parameter frequently mentioned in other studies and its assessment is often unreliable, particularly in patients with diabetes who present with less typical MI symptoms.

Conclusions

Newly detected AGT in patients with a first MI with ST-segment elevation is transient in 50% of cases. Stress hyperglycaemia is a common finding in patients with first MI and concomitant diabetes mellitus, but is rarely seen in patients with impaired glucose tolerance or transient AGT diagnosed for the first time during the acute phase of MI. The risk factors of its occurrence include elevated HbA_{1c}, anterior MI and high admission cortisol concentration.

Authors' contributions

Study concept and design: A. Bronisz, J. Kubica and M. Bronisz. Data collection: A. Bronisz, I. Świątkiewicz and B. Beszczyńska. Statistical analysis: P. Magielski. Analysis and interpretation of data: A. Bronisz, M. Koziński and A. Sukiennik. Preparing the manuscript: A. Bronisz, P. Magielski, M. Koziński and T. Fabiszak. Critical revision of the manuscript: J. Kubica, M. Bronisz, M. Koziński and R. Junik.

Acknowledgements

This study was supported by financial resources of The Polish Ministry of Science and Higher Education for science in years 2008–2011 (research project number N402179534) and by SERVIER Research Grant 2007 awarded in cooperation with the Polish Cardiac Society.

References

1 Webster KA. Stress hyperglycemia and enhanced sensitivity to myocardial infarction. *Curr Hypertens Rep* 2008; **10**: 78–84.
2 Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. *Lancet* 2009; **373**: 1798–807.
3 Norhammar A, Ryden L, Malmberg K. Admission plasma glucose. Independent risk factor for long-term prognosis after myocardial infarction even in nondiabetic patients. *Diabetes Care* 1999; **22**: 1827–31.
4 Sala J, Masia R, Gonzalez de Molina FJ et al. Short-term mortality of myocardial infarction patients with diabetes or hyperglycaemia during admission. *J Epidemiol Community Health* 2002; **56**: 707–12.
5 Ainla T, Baburin A, Teesalu R, Rahu M. The association between hyperglycaemia on admission and 180-day mortality in acute myocardial infarction patients with and without diabetes. *Diabet Med* 2005; **22**: 352–5.
6 Kosiborod M, Rathore SS, Inzucchi SE et al. Admission glucose and mortality in elderly patients hospitalized with acute myocardial infarction: implications for patients with and without recognized diabetes. *Circulation* 2005; **111**: 3078–86.
7 Kosuge M, Kimura K, Kojima S et al. Effects of glucose abnormalities on in-hospital outcome after coronary intervention for acute myocardial infarction. *Circ J* 2005; **69**: 375–9.
8 Mizock BA. Alterations in carbohydrate metabolism during stress: a review of the literature. *Am J Med* 1995; **98**: 75–84.
9 Mechanick JI. Metabolic mechanisms of stress hyperglycemia. *J Parenter Enteral Nutr* 2006; **30**: 157–63.
10 Charmandari E, Tsigos C, Chrousos G. Endocrinology of the stress response. *Annu Rev Physiol* 2005; **67**: 259–84.
11 Ishihara M, Kojima S, Sakamoto T et al. Acute hyperglycemia is associated with adverse outcome after acute myocardial infarction in the coronary intervention era. *Am Heart J* 2005; **150**: 814–20.
12 Gąsior M, Pres D, Stasik-Pres G et al. Effect of blood glucose levels on prognosis in acute myocardial infarction in patients with and without diabetes, undergoing percutaneous coronary intervention. *Cardiol J* 2008; **15**: 422–30.
13 Worthley MI, Shrive FM, Anderson TJ, Traboulsi M. Prognostic implication of hiperglycemia in myocardial infarction and primary angioplasty. *Am J Med* 2007; **120**: 643e1–7.
14 Ishihara M, Kojima S, Sakamoto T. et al. Comparison of blood glucose values on admission for acute myocardial infarction in patients with versus without diabetes mellitus. *Am J Cardiol* 2009; **104**: 769–74.
15 Capes SE, Hunt D, Malmberg K, Gerstein H. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet* 2000; **355**: 773–8.
16 Bartnik M, Ryden L, Ferrari R et al. The prevalence of abnormal glucose regulation in patients with coronary artery disease cross Europe. *Eur Heart J* 2004; **25**: 1880–90.
17 Hu DY, Pan CY, Yu JM. The relationship between coronary artery disease and abnormal glucose regulation in China: the China Heart Survey. *Eur Heart J* 2006; **27**: 2573–9.
18 Thygesen K, Alpert JS, White HD. Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *Eur Heart J* 2007; **28**: 2525–38.
19 Czech A, Cypryk K, Czupryniak L et al. Zalecenia kliniczne dotyczące postępowania u chorych na cukrzycę 2011. Stanowisko Polskiego Towarzystwa Diabetologicznego. *Diabetol Prakt* 2011; **12**(Suppl. A): A1–46.
20 American Diabetes Association. Standards of medical care in diabetes—2011. *Diabetes Care* 2011; **34**(Suppl. 1): S11–61.
21 Hasdai D, Behar S, Wallentin L et al. A prospective survey on the characteristic, treatments and outcomes of patients with acute coronary syndromes in Europe and Mediterranean basin. The Euro Heart Survey of Acute Coronary Syndromes. *Eur Heart J* 2002; **23**: 1190–201.
22 Franklin K, Goldberg RJ, Spencer F et al. Implications of diabetes in patients with acute coronary syndromes. The Global Registry of Acute Coronary Events. *Arch Intern Med* 2004; **164**: 1457–63.
23 Oswald GA, Yudkin JS. Hyperglycaemia following acute myocardial infarction: the contribution of undiagnosed diabetes. *Diabet Med* 1987; **4**: 68–70.
24 Bartnik M, Malmberg K, Hamsten A et al. Abnormal glucose tolerance – a common risk factor in patients with acute myocardial infarction in comparison with population-based controls. *J Intern Med* 2004; **256**: 288–97.
25 Mozaffarian D, Marfisi RM, Levantesi G et al. Incidence of new-onset diabetes and impaired fasting glucose in patients with recent myocardial infarction and the effect of clinical and lifestyle risk factors. *Lancet* 2007; **370**: 667–75.
26 Wallander M, Bartnik M, Efendic S et al. Beta cell dysfunction in patients with acute myocardial infarction but without previously known type 2 diabetes: a report from the GAMI study. *Diabetologia* 2005; **48**: 2229–35.
27 Knudsen EC, Seljeflot I, Abdelnoor M et al. Abnormal glucose regulation in patients with acute ST-elevation myocardial infarction-a cohort study on 224 patients. *Cardiovasc Diabetol* 2009; **8**: 6.
28 Norhammar A, Tenerz Å, Nilsson G et al. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *Lancet* 2002; **359**: 2140–4.
29 Ishihara M, Kagawa E, Inoue I et al. Impact of admission hyperglycemia and diabetes mellitus on short- and long-term mortality after acute myocardial infarction in the coronary intervention era. *Am J Cardiol* 2007; **99**: 1674–9.
30 Petursson P, Herlitz J, Caidahl K et al. Admission glycaemia and outcome after acute coronary syndrome. *Int J Cardiol* 2007; **116**: 315–20.
31 Dziewierz A, Giszterowicz D, Siudak Z et al. Impact of admission glucose level and presence of diabetes mellitus on mortality in patients with

non-ST-segment elevation acute coronary syndrome treated conservatively. *Am J Cardiol* 2009; **103**: 954–8.

32 Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab* 2002; **87**: 978–82.

33 Carmen Wong KY, Wong V, Ho JT et al. High cortisol levels in hyperglycaemic myocardial infarct patients signify stress hyperglycaemia and predict subsequent normalization of glucose tolerance. *Clin Endocrinol* 2010; **72**: 189–95.

34 Schömig A, Haass M, Richardt G. Catecholamine release and arrhythmias in acute myocardial ischaemia. *Eur Heart J* 1991; **12**(Suppl. F): 38–47.

35 McGuinness OP, Shau V, Benson EM et al. Role of epinephrine and norepinephrine in the metabolic response to stress hormone infusion in the conscious dog. *Am J Physiol* 1997; **273**: E674–81.

36 Ceriello A. Acute hyperglycaemia: a 'new' risk factor during myocardial infarction. *Eur Heart J* 2005; **26**: 328–31.

37 Van den Berghe G. How does blood glucose control with insulin save lives in intensive care? *J Clin Invest* 2004; **114**: 1187–95.

38 Cruz-Gonzalez I, Chia S, Owen RC et al. Hyperglycemia on admission predicts larger infarct size in patients undergoing percutaneous coronary intervention for acute ST-segment elevation myocardial infarction. *Diab Res Clin Prac* 2010; **88**: 97–102.

39 Jiménez-Navarro MF, Garcia-Pinilla JM, Garrido-Sanchez L et al. Poor reproducibility of the oral glucose tolerance test in the diagnosis of diabetes during percutaneous coronary intervention. *Int J Cardiol* 2009; **23**: 245–9.

Paper received November 2011, accepted January 2012