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Major adverse cardiovascular events in patients after acute myocardial infarction treated invasively and different patterns of glucometabolic disturbances evaluated at mid-term follow-up

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ABSTRACT

Aim. To assess the impact of glucometabolic status (GS) evaluated at hospital discharge and at mid-term follow-up visit (FU-visit) on major adverse cardiovascular events (MACE) in patients (pts) with acute myocardial infarction (AMI) treated invasively.

Material and Methods. Study encompassed 368 AMI-pts treated invasively, in whom GS was assessed by 2-hour post load glycemia at hospital discharge and at FU-visit after 6 months. Patients were divided into two groups with respect to GS at hospital discharge: abnormal glucose tolerance (AGT, n = 149), normal glucose tolerance (NGT, n = 219). Each of those groups was divided into two subgroups with respect to GS at FU-visit: persistent AGT (pAGT, n = 101), transient AGT (tAGT, n = 48), newly detected AGT (newAGT, n = 114), persistent NGT (pNGT, n = 105). Median follow-up duration after FU-visit was 24.5 months.

Results. There was a trend towards more subjects with MACE in AGT than NGT group (24.2% vs. 16%; p = 0.051). More AGT-pts were hospitalized due to decompensated heart failure (6% vs. 0.5%; p = 0.002). However, there were no significant differences in MACE between subjects with pAGT and tAGT, including heart failure hospitalizations. Among NGT-pts there were no significant differences in particular MACE between newAGT-pts and pNGT-pts.

Conclusions. In AMI-pts treated invasively, who had abnormal glucose tolerance at hospital discharge, the improvement in glucometabolic status after 6 months was not related to lower risk of hospitalization due to decompensated heart failure.

Keywords: abnormal glucose tolerance, coronary artery disease, mortality, oral glucose tolerance test, heart failure hospitalization.

Introduction

Two-hour post load glycemia (2h-PG) is a well established parameter used to evaluate glucometabolic status and predict long-term prognosis in patients with coronary artery disease or acute myocardial infarction (AMI) [1–7]. Abnormal glucose tolerance (AGT) was associated with major cardiovascular events (MACE) in patients with stable angina or AMI [1–7]. Nevertheless, those studies did not show that any of the particular adverse events, except all-cause mortality, was related to long-term higher event rate in patients with AGT. Recently, it has been shown, that the initial risk stratification based on 2h-PG obtained at hospital discharge improved after reevaluation of glucometabolic status by oral glucose tolerance test repeated 6 months after AMI [7]. The study showed, that the risk of any-cause death was higher in patients with persis-

tent AGT, but the differences in MACE were non-significant with respect to changes in glucometabolic status [7]. Therefore, the aim of the presented study was to analyze particular MACE in patients with different glucose abnormalities evaluated at mid-term follow-up visit (FU-visit) with respect to glucometabolic status at hospital discharge.

Materials and Methods

Study population

The presented analysis was a part of a single centre, observational study prospectively enrolling AMI patients treated with percutaneous coronary intervention (PCI) between January 2012 and December 2013 who survived in-hospital period and were discharged to ambulatory care. Patients, in whom diabetes mellitus was diagnosed before admission or discovered by elevated fasting glycaemia ≥7 mmol/l on at least two occasions during hospitalization were excluded from the study. Repeated OGTT and other laboratory tests, electrocardiogram, echocardiography were planned as a part of follow-up visit on an outpatient basis approximately 6 months after AMI. Study population encompassed 368 consecutive AMI survivors in whom oral glucose tolerance test (OGTT) was performed at hospital discharge, and who completed FU-visit. Patients were followed and data considering remote MACE defined as the occurrence of death or any of the following events: either recurrent myocardial infarction, repeated percutaneous coronary intervention, coronary artery by-pass grafting, hospitalization for heart failure or stroke were collected. Median follow-up duration after FU-visit was 24.5 months. The enrollment of patients into the study was presented in detail elsewhere [7].

Definitions of glucometabolic status

Abnormal glucose tolerance (AGT) at discharge was defined as 2h-PG ≥ 7.8 mmol/l. Patients with 2h-PG < 7.8 mmol/l were classified as having normal glucose tolerance (NGT) at discharge. Persistent AGT (pAGT) at FU-visit was defined as 2h-PG ≥ 7.8 mmol/l detected at discharge and 2h-PG ≥ 7.8 mmol/l or antidiabetic pharmacotherapy at FU-visit. Transient AGT (tAGT) at FU-visit was defined as 2h-PG ≥ 7.8 mmol/l detected at discharge and no antidiabetic pharmacotherapy at FU–visit with 2h-PG < 7.8 mmol/l. Newly detected AGT (newAGT) at FU-visit was defined as 2h-PG < 7.8 mmol/l at discharge but 2h-PG ≥ 7.8 mmol/l or antidiabetic pharmacotherapy at FU-visit. Persistent NGT (pNGT) at FU-visit was defined as 2h-PG < 7.8 mmol/l at discharge and without antidiabetic pharmacotherapy at FU-visit with 2h-PG < 7.8 mmol/l.

Patients were divided into two groups with respect to glucometabolic status at hospital discharge: AGT (n = 149) and NGT (n = 219). Each of those groups was divided into two subgroups with respect to glucometabolic status at FU-visit: pAGT (n = 101), tAGT (n = 48), newAGT (n = 114), pNGT (n = 105).

Definition of AMI

Clinical AMI criteria evaluated on admission were: chest pain persisting > 20 minutes, ST segment elevation of at least 0.1 mV in two or more contiguous electrocardiographic leads or non-diagnostic electrocardiogram (without persistent ST segment elevation, left bundle branch block or acute ischemic changes) with enzymatic confirmation of AMI.

Ethics

All clinical data were obtained as the result of the diagnostic procedures and therapy, which were in accordance with the appropriate guidelines. All patients provided informed written consent for hospitalisation, invasive treatment, and use of their data for research purposes. Follow-up visit was performed on an outpatient basis as a routine follow-up. Remote follow-up was performed by telephone contact with patients or their families as well as during routine ambulatory visits. The study protocol was in line with ethical standards and was approved by the Institutional Review Board.

Statistical analysis

Continuous parameters were expressed as means with standard deviations unless otherwise specified, categorical variables were presented as numbers and percentages. Comparative analyses between groups were performed using Student's t-test for continuous variables and Chi-square or Fisher's exact test, as appropriate, for dichotomous parameters. Log-rank tests were used to compare cumulative survival. All tests were double-sided. P value < 0.05 was considered statistically significant. All analyses were performed using the software package Statistica (version 6.1, StatSoft Inc., Tulsa, OK, USA).

Results

Comparative analysis of demographic, clinical and laboratory data between patients with AGT and NGT at discharge who completed FU-visit.

Patients who had AGT at discharge, compared to patients with NGT, were older, more often had arterial hypertension and atrial fibrillation/flutter, had worse renal function. The proportion of patients with prior myocardial infarction, presence of NYHA class ≥ 2 as well as mean left ventricle ejection fraction was similar between two groups, however patients with AGT had more often severe left ventricle dysfunction or moderate/severe mitral regurgitation. Differences in pharmacotherapy were related to comorbidities, especially arterial hypertension and reduced left ventricle ejection fraction. Therefore, patients with AGT were more often treated with angiotensin converting enzyme inhibitors or angiotensin receptor blockers, calcium channel blockers, diuretics and aldosterone receptor antagonists. Detailed data were presented in **Table 1**.

Comparative analyses of any-cause mortality and major adverse cardiovascular events

There was a trend towards more MACE after the FU-visit in patients with AGT compared to NGT patients (24.2% vs. 16%; p = 0.051). More patients were hospitalized due to heart failure in AGT group compared to NGT (6% vs. 0.5%; p = 0.002). However, there were no significant differences in MACE between subjects with pAGT and tAGT, including heart failure hospitalizations. Among patients with NGT there were no significant differences between newAGT and pNGT with respect to particular MACE. Detailed data were presented in **Tables 2** and **3**.

Table 1. Comparative analysis of demographic, clinical, laboratory and pharmacotherapy data obtained at follow-up visit

Patients' characteristics at FU-visit	AGT at discharge, n = 149	NGT at discharge, n = 219	p value
Age [yrs] ≥ 65 years – n (%)	64 ± 9.4 63 (42.3)	61 ± 10 71 (32.4)	0.004 0.054
Female sex – n (%)	40 (26.8)	52 (23.7)	0.501
CCS class ≥ 2 – n (%)	10 (6.7)	21 (9.6)	0.331
NYHA class ≥ 2 – n (%)	54 (36.2)	66 (30.1)	0.221
Prior MI (before index hospitalization) – n (%)	31 (20.8)	43 (19.6)	0.778
Pre-hospital history of arterial hypertension – n (%)	108 (72.5)	127 (58)	0.004
Atrial fibrillation/flutter – n (%)	23 (15.4)	11 (5)	0.001
eGFR [ml/min/1.73 m^2] < 60 ml/min/1.73 m^2 – n (%)	83 ± 24.5 21 (14.1)	89.9 ± 20.5 14 (6.4)	0.004 0.013
Left ventricle ejection fraction [%] ≤ 35% – n (%)	46.4 ± 8.9 22 (14.8)	47.8 ± 7.4 12 (5.5)	0.109 0.002
Moderate/severe mitral regurgitation – n (%)	15 (10.1)	7 (3.2)	0.006
Anemia – n (%)	13 (8.9)	9 (4.2)	0.340
Fasting glycemia [mmol/l]	5.93 ± 0.8	5.7 ± 0.7	0.003
2h-PG* [mmol/l]	8.34 ± 2.5	7.28 ± 2.5	<0.001
Glycosylated hemoglobin [%]	6 ± 0.5	5.86 ± 0.5	0.004
HDL cholesterol [mmol/l]	1.3 ± 0.4	1.32 ± 0.4	0.576
LDL cholesterol [mmol/l]	2.45 ± 0.9	2.65 ± 1.1	0.065
Triglycerides [mmol/l]	1.4 ± 0.9	1.34 ± 0.8	0.519
Acetylsalicylic acid – n (%)	138 (92.6)	206 (94.1)	0.567
$P2Y_{12}$ receptor inhibitor – n (%)	146 (98)	209 (95.4)	0.187
Beta-adrenergic blocker – n (%)	145 (97.3)	208 (95)	0.274
ACE-I/ARB – n (%)	143 (96)	195 (89)	0.017
Statin – n (%)	141 (94.6)	208 (95)	0.865
Dihydropyridine calcium channel blocker – n (%)	40 (26.8)	40 (18.3)	0.053
Diuretic – n (%)	56 (37.6)	43 (19.6)	<0.001
Aldosterone receptor antagonist – n (%)	46 (30.9)	45 (20.5)	0.024
Antidiabetic pharmacotherapy – n (%)	15 (14.9)	0 (0)	-
Oral hypoglycemic agent – n (%)	13 (12.9)	-	-
Insulin – n (%)	2 (2)	-	-

Values presented as means ± SD or number and percentage of subjects. 2h-PG = two-hour post load glycemia; ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor antagonist; CCS = Canadian Cardiovascular Society grading of angina pectoris; eGFR = estimated glomerular filtration rate; FU-visit = follow-up ambulatory visit; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction; NYHA = New York Heart Association Functional Classification; * in patients not treated with antidiabetic medication.

Table 2. Major adverse cardiovascular events after the FU-visit with respect to abnormal and normal glucose tolerance at hospital discharge

Adverse cardiovascular events	AGT at discharge, n = 149	NGT at discharge, n = 219	p value
Myocardial infarction – n (%)	10 (6.9)	8 (3.6)	0.183
PCI – n (%)	15 (10.1)	18 (8.2)	0.544
CABG – n (%)	2 (1.3)	7 (3.2)	0.260
Stroke – n (%)	2 (1.3)	4 (1.8)	0.720
Hospitalization due to heart failure – n (%)	9 (6)	1 (0.5)	0.001
All-cause mortality – n (%)	13 (8.7)	10 (4.6)	0.106
Total adverse events – n (%) *each event was counted only once*	36 (24.2)	35 (16)	0.051

Values presented as number and percentage of subjects. AGT = abnormal glucose tolerance, NGT = normal glucose tolerance, PCI = percutaneous coronary intervention, CABG = coronary artery by-pass graft.

Table 3. Major adverse cardiovascular events after the FU-visit with respect to abnormal and normal glucose tolerance at hospital discharge and at FU-visit

Among patients with abnormal glucose tolerance at discharge			
Adverse cardiovascular events	persistent AGT, n = 101	transient AGT, n = 48	p value
Myocardial infarction – n (%)	6 (5.9)	4 (8.3)	0.588
PCI – n (%)	9 (8.9)	6 (12.5)	0.499
CABG – n (%)	1 (1)	1 (2.1)	0.591
Stroke – n (%)	2 (2)	0 (0)	0.330
Hospitalization due to heart failure – n (%)	5 (5)	4 (8.3)	0.424
All-cause mortality – n (%)	12 (11.9)	1 (2.1)	0.034
Total adverse events – n (%) *each event was counted only once*	25 (24.8)	11 (22.9)	0.808
Among patients with normal glucose tolerance at discharge			
Adverse cardiovascular events	newly detected AGT, n = 114	persistent NGT, n = 105	p value
Myocardial infarction – n (%)	2 (1.8)	6 (5.7)	0.120
PCI – n (%)	10 (8.8)	8 (7.6)	0.758
CABG – n (%)	4 (3.5)	3 (2.9)	0.785
Stroke – n (%)	3 (2.6)	1 (1)	0.356
Hospitalization due to heart failure – n (%)	0 (0)	1 (1)	0.298
All-cause mortality – n (%)	7 (6.1)	3 (2.9)	0.242
Total adverse events – n (%) *each event was counted only once*	19 (16.7)	16 (15.2)	0.774

Values presented as number and percentage of subjects. AGT = abnormal glucose tolerance, NGT = normal glucose tolerance, PCI = percutaneous coronary intervention, CABG = coronary artery by-pass graft.

Discussion

In patients with AMI the relation of glucose abnormalities with adverse treatment outcome is undisputed [1, 2, 4–6, 8]. However, some studies showed that in patients during stable condition disturbances in glucose metabolism, which had been detected at hospital discharge, were predominantly transient [9–12]. Nevertheless, the prognosis in patients after AMI with respect to changes in glucometabolic status has not been widely studied. Recently it has been shown, that in patients who completed mid-term follow-up visit after AMI, reassessment of glucometabolic status by oral glucose tolerance test improved long-term risk stratification. Patients with abnormal glucose tolerance at discharge in whom glucometabolic profile improved had similar mortality to subjects with persistent normal glucose tolerance [7]. The presented study was undertaken to widen the scope of previously published data. It showed, that patients with AMI and abnormal glucose tolerance at hospital discharge had higher risk of hospitalization due to decompensated heart failure compared to patients with normal glucose tolerance. The risk was irrespective of changes in glucometabolic status after 6 months. Therefore, in the light of the results of previously cited study, one can conclude, that although the risk of death is lower when glucometabolic profile improves, the risk of hospitalization due to heart failure remains unchanged and high. There are several, although only hypothetical explanations of those observations. One of them, is that larger infarct size and acute hemodynamic derangement in the course of AMI is associated with insulin resistance, which resolves in stable condition. Patients with tran-

sient pattern of abnormal glucose tolerance may have increased risk of heart failure because of initial myocardial injury. Knudsen et al. showed, that patients with abnormal glucose regulation detected in-hospital had higher troponin peak value during AMI than patients with dysglycemia classified with respect to glucose metabolism after 3 months [10]. Hyperglycemia was associated with higher troponin levels, probably as a consequence of more extensive myocardial damage, and patients with hyperglycemia presented with larger infarct size compared with normoglycemic subjects [13]. Underlying microangiopathy of myocardial tissue may contribute to subsequent adverse remodeling of the heart in patients with hyperglycemia [14–16]. One should know, that the cut-off point for diabetes mellitus on 2h-PG value was primarily determined based on the prevalence of microvascular disease, especially diabetic retinopathy. Abnormal glucose tolerance in the presented study population of patients after AMI was not related to macrovascular complications, however the increased risk of heart failure hospitalization may be considered as a result of myocardial microangiopathy [17]. One cannot exclude that patients who recovered to normal glucose regulation were adherent to lifestyle modification, which may have caused decrease in insulin resistance. It has been shown, that very low-calorie diet, in some patients with diabetes mellitus, was associated with significant glucometabolic improvement, and some authors concluded that type 2 diabetes mellitus was a potentially reversible condition [18].

On the biological level, 2h-PG is associated with insulin resistance and decreased beta cell function of the pancreas, which contribute to hyperglycemia, oxidative stress and eventually endothelial dysfunction [1, 10, 19–20]. Prolonged and recurrent post-prandial hyperglycemia may play an important role in the development and progression of atherosclerosis [20]. Disturbed glucose metabolism in myocardial cells may also play role [14–16]. Therefore 2h-PG may be a direct therapeutic target in the treatment of cardiovascular disease [21–24].

Clinical implications

The major clinical implication of the presented study was, that patients, who had had overt manifestation of abnormal glucose tolerance during in-hospital period, and in whom a transient pattern of AGT was observed after 6 months did not have reduced risk of heart failure hospitalizations. Abnormal glucose tolerance detected during hospitalization due to AMI, even if transient following the acute period, has significant prognostic value. Therefore, the study emphasized the important role of oral glucose tolerance test performed during in-hospital and post-hospital period.

Study limitations

The study was nonrandomized and observational and encompassed relatively low number of patients.

Conclusions

In patients with AMI and abnormal glucose tolerance at discharge, who were treated invasively, the improvement in glucometabolic status after 6 months was not related to lower risk of hospitalization due to decompensated heart failure.

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Conflict of interest statement
The authors declare no conflict of interest.

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