Reactive Hyperglycaemia Connected with Low Glycated Haemoglobin - Risk Factor for Cardiovascular Adverse Events

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Abstract

Introduction: Concomitance of glucose metabolism disturbances and ischemic heart disease is well known and connected to several times higher incidence of cardiovascular events resulted from atherosclerosis. Aim of this study was to assess impact of reactive hyperglycaemia accompanying chronic and not always optimally treated hyperglycaemia assessed with glycated haemoglobin level on cardiovascular prognosis among patient hospitalised in the course of acute myocardial infarction.

Methods: 92 patients diagnosed with ST – segment elevation myocardial infarction (STEMI) qualified to primary percutaneous coronary intervention (pPCI) was included in the study. Study population was divided into subgroups, depending glucose level on admission (reactive hyperglycaemia) and HbA1c concentration: subgroup A (HbA1c <6.5%, Glc <7.8 mmol/l: $n = 37$; 40,2%), subgroup B (HbA1c <6.5%, Glc ≥ 7.8 mmol/l: $n = 27$; 29,3%), subgroup C (HbA1c $\geq 6.5\%$, Glc ≥ 7.8 mmol/l: $n = 20$; 21,7%) and subgroup D (HbA1c $\geq 6.5\%$, Glc <7.8 mmol/l: $n = 8$; 8,7%). Level of myocardium damage was assessed on the basis of concentration of myocardial necrosis enzymes: creatine kinase (CK) and creatine kinase MB fraction (CK-MB) in the 0 and 90th minute and thereafter 8, 16, 24 and 48 hours after hospital admission and also echocardiographic examination. Prognosis in long and short term observation was assessed by major adverse cardiovascular events (MACE) such as death, myocardial infarction, stroke, heart failure requiring hospitalisation and repeated revascularisation and level of glucose metabolism disturbances in intrahospital phase, 4 months and 4 years follow up observation.

Results: Results in study population revealed significant change of average value of creatine kinase ($p < 0,001$) and its MB fraction ($p < 0,001$) during first 48 hours of hospitalisation in particular subgroups of patients. Mean values of CK and CK-MB assessed in subsequent hours of hospitalisation (1,5, 8, 16 and 48 hours) were significantly higher in subgroup B (CK $p = 0,034$ and CK-MB $p = 0,01$, respectively). It means that area under curve was significantly higher for subgroup B. In 4 months and 4 year follow up observation, statistically significant difference in frequency of MACE in particular subgroups of patients has been shown ($p = 0,016$; $p = 0,01$).

Conclusions: Patients with STEMI undergoing pPCI, who were diagnosed with disturbed carbohydrate metabolism, have inferior clinical outcomes in long term follow up observation. Noticeable difference was observed particularly in subgroup B (HbA1c <6.5%, Glc $\geq$ 7.8 mmol/l).

Keywords

Reactive Hyperglycaemia, Low Glycated Haemoglobin, Atherosclerosis, Cardiovascular Adverse Events, Segment Elevation Myocardial Infarction, Primary Percutaneous Coronary Intervention

Introduction

Concomitance of glucose metabolism disturbances and ischemic heart disease is well known. Risk of cardiovascular events associated with atherosclerosis remains always several times higher in patients diagnosed with diabetes [1-3]. Pathogenesis of both diseases enfolds not only environmental factors but also genetic background [4-6]. Cascades of pathophysiologic processes are initiated simultaneously on cellular, tissue and systemic level. Increased mortality is a consequence of rapid development of ischemic heart disease in this group of patients [5-9]. This results from initially worsened clinical condition of the patient, higher incidence of classic atherosclerosis and also diabetes related risk factors. Obesity, insulin resistance with hyperinsulinemia, coagulation and fibrinolysis disorders, microalbuminuria, hyperuricaemia and dyslipidaemia characterized by hypertriglyceridemia and lowered HDL cholesterol fraction are observed more frequently.

Symptoms of coronary artery disease are more often atypical, remain sparse with lack of classic anginal pain (silent ischemia). Moreover, signs of heart failure and neuropathy are common. Accelerated heart rate and inadequate, stiff response of stimulus conducting system may be a reason of life threatening arrhythmia, including sudden cardiac death. It has been widely accepted that every third patient treated for cardiac causes demonstrates some level of carbohydrate metabolism disturbances, which results in inferior outcomes of short and long term medical interventions in these group of patients [10,11]. Aim of this study was to investigate role of reactive hyperglycaemia accompanying chronic and not always optimally treated hyperglycaemia assessed by glycated haemoglobin level on cardiovascular prognosis in

patient hospitalised because of acute myocardial infarction.

Material and Methods

Present report is a prospective study conducted in Clinical Department of Interventional Cardiology John Paul II Hospital in Kraków, Poland in 2014 – 2016. Initially 165 patients with ST segment elevation myocardial infarction were enrolled in the study. Inclusion criteria were recent myocardial infarction with persisted ST segment elevation in electrocardiographic examination defined as new, lasting at least 30 minutes elevation of ST segment measured in point J in at least two adjacent leads with cut-off point $\geq$ 1 mm in every lead and qualification to immediate primary percutaneous coronary intervention (pPCI). Exclusion criteria were diagnosis of diabetes before hospital admission, signs of chronic heart failure (III or IV degree according to Killip-Kimball scale), necessity of glucose solution or catecholamines intake on admission, a history of coronary artery bypass graft procedure, myocardial infarction, cancer or autoimmune disease, liver failure (ALAT level $>1.5\times$ upper limit of normal), renal failure (GFR <30 ml/min/1.73 m²) assessed on the basis of laboratory tests performed on admission, prior fibrinolytic treatment or current cardiac arrest and resuscitation and lack of complete carbohydrate metabolism diagnostics during hospitalisation.

Finally study population consisted of 92 patients, aged 32-87 years who had a first acute myocardial infarction. Men dominated in the analysed population (76, which constituted 82.6% of the whole group).

The following studies were performed:
Laboratory Tests:

- A. Glucose level in venous blood serum tested on admission and on the following day in the fasted state,
- B. Oral 75g glucose tolerance test (glucose level tested in venous blood serum in the fasted state and 2 hours after glucose intake) – on the day of discharge from the hospital,
- C. Concentration of glycated haemoglobin (HbA1c) in capillary blood,
- D. Concentration of cardiac necrotic markers: creatine kinase (CK) fraction MB of creatine kinase (CK-MB) tested in 0 and 90th minute and thereafter in 8, 16, 24 and 48 hours since hospital admission,
- E. Level of leucocytes and hs-CRP,
- F. Assessment of creatine level and eGFR (glomerular filtration rate)

Table-1: Clinical characteristics of patients treated with PCI in an acute phase of myocardial infarction with chronic ST segment elevation in particular subgroups

	number (n)	subgroup	present	p value
Arterial hypertension	37	A	17 (47.8%)	0.296
	27	B	15 (58.7%)	
	20	C	12 (60.1%)	
Lipid metabolism disorders	37	A	23 (60.9%)	0.832
	27	B	16 (58.7%)	
	20	C	12 (58.1%)	
BMI ≥30,0	37	A	6 (17.4%)	0.343
	27	B	6 (23.1%)	
	20	C	4 (22.9%)	
Tobacco addiction	37	A	24 (65.2%)	0.204
	27	B	14 (52.2%)	
	20	C	11 (53.9%)	
CAD at family history	37	A	11 (30.4%)	0.482
	27	B	6 (23.9%)	
	20	C	5 (25.0%)	
Kidney diseases	37	A	1 (4.3%)	-
	27	B	2 (6.5%)	
	20	C	1 (6.0%)	
Thyroid diseases	37	A	3 (8.7%)	-
	27	B	2 (8.7%)	
	20	C	1 (7.3%)	
A history of CAD	37	A	10 (26.1%)	0.203
	27	B	5 (19.6%)	
	20	C	4 (20.0%)	
State after myocardial infarction	37	A	1 (4.3%)	0.456
	27	B	3 (10.9%)	
	20	C	2 (10.0%)	

Electrocardiographic Assessment:

Twelve-lead electrocardiogram (Edan SE-12 Express device, record speed 25 mm per second, reference pulse 10 mm/1 mV) was performed during admission to the catheterization laboratory, directly after pPCI procedure and subsequently in 60th minute and 24 hours after pPCI procedure. Consecutively, ST segment elevation resolution (sum STR) was assessed 20 ms upon point J in regard to the primary records. According to Schröder's criteria resolution of the ST segment elevation $\geq 70\%$ was considered as complete reperfusion, 30-70% reduction as partial and reduction $< 30\%$ of primary value as a sign of absence of ST – segment elevation resolution [12,13].

Echocardiographic Assessment:

Echocardiography was performed during hospitalization and at 4 month follow up visit after discharge, using the GE Vivid 3 Pro (GE Healthcare, US), equipped with a multifrequency harmonic transducer (2.5–4 MHz). Systolic function of the left ventricle was estimated with left ventricle ejection fraction by means of the Simpson method. The average values of 3 consecutive measurements were recorded.

Angiographic Assessment:

Examination was performed using Axiom Artis dFC SIEMENS apparatus. Angiographic recordings comprised of at least three cardiac cycles. Left coronary artery was recorded at four standard projections (LAO 50/CRAN 20, RAO 30/CAUD 20, LAO 40/CAUD 40, AP CRAN 30), whereas right coronary artery at two projections (LAO 40, RAO 40). Images were blinded and evaluated by two experienced operators. The evaluation included identification of the target, infarct-related artery, progress of atherosclerosis in remaining segments of coronary arteries, use of aspiration thrombectomy and assessment of collateral circulation to the occluded vessel via Rentrop scale. Flow in infarct-related artery was assessed by semi-quantitative TIMI scale at baseline and after primary coronary intervention (pPCI).

Study population was divided into subgroups depending on glucose level on admission (reactive hyperglycaemia) and HbA1c concentration: subgroup A

(HbA1c $< 6,5\%$, Glc $< 7,8$ mmol/l: $n = 37$; 40,2%), subgroup B (HbA1c $< 6,5\%$, Glc $\geq 7,8$ mmol/l: $n = 27$; 29,3%), subgroup C (HbA1c $\geq 6,5\%$, Glc $\geq 7,8$ mmol/l: $n = 20$; 21,7%) and subgroup D (HbA1c $\geq 6,5\%$, Glc $< 7,8$ mmol/l: $n = 8$; 8,7%). Subgroup D was not taken into account for statistical analysis due to small sample size (**Table-1**).

Study End Points:

1. Short and long term prognosis was considered as complex end point assessed on the basis of frequency of major adverse cardiovascular effects (MACE) such as: death, myocardial infarction, stroke, heart failure requiring hospitalisation and repeated revascularisation.
2. Degree of glucose metabolism disfunction in hospitalised patients in four years follow-up observation.

Ethical Issues:

The study protocol complied with the Declaration of Helsinki and was approved by the Ethics Committee of Jagiellonian University (no. KBET/120/B/2007 to JZ). Each study participant provided written informed consent before enrollment.

Pharmacological Treatment

Directly after diagnosis of acute coronary syndrome with persisted elevation of ST segment and qualification for urgent coronary angiography patients were administered orally with double antiplatelet therapy: acetylsalicylic acid (loading dose 300mg, consecutively chronic dose 75mg daily) and clopidogrel (loading dose 600mg, consecutively chronic dose 75mg daily) and intravenously with unfractionated heparin at dose adapted to body weight (50-100 U/kg). In the vast majority of cases (82) the percutaneous coronary angioplasty procedure was completed with the implantation of one stent, in 8 cases, it was necessary to implant a second stent to the target vessel. In two cases only, procedure ended up after balloon angioplasty. In case of angiographic conditions suggesting higher risk of no-reflow phenomenon (presence of massive intravascular thrombus, exceeding 4 mm of reference diameter, image suggesting sudden occlusion or contrast retention distal from occlusion) operator could decide about

administration of glycoprotein IIb/IIIa receptor antagonist such as abciximab (0,25 mg/kg intravenous bolus, thereafter 0,125 µg/kg/min intravenous infusion for the next 12 hours) or perform aspiration thrombectomy.

In case of multivessel disease percutaneous coronary intervention was limited to target, infarct-related artery. Further treatment depended on overall clinical condition and results of coronary reserve examination performed during staged invasive examination. During hospitalisation all patients were administered with dual antiplatelet therapy and statin at maximum tolerated dose. Beta-blockers (95,7% of study group) and ACE-inhibitors (96,7% study group) were applied according to current guidelines, especially in patients with signs of heart failure with or without left ventricle dysfunction. Remaining pharmacological treatment such as calcium blockers were applied among 10,9% patients, nitrates 15,2% patients and mineralocorticoids or loop diuretics in 33,7% patients of whole study population.

Results

Above presented measurements did not reveal any statistically significant difference between particular sum STR level among subgroups, respectively $p=0.148$ (measurement performed directly after procedure), $p=0.203$ (measurement 60 minutes after procedure)

and $p=0.187$ (24 hours after procedure).

In the vast majority of cases angiographic examination revealed total occlusion of target artery with absence of any antegrade flow beyond a coronary occlusion (TIMI 0). There were 29 such patients in subgroup A (78,4%), 21 patients in subgroup B (77,8%) and 16 in subgroup C (80,0%). 4 patients (10,8%) in subgroup A, 2 patients (7,4%) patients in subgroup B target vessel had proper contrast flow which filled distal coronary bed completely (TIMI 3) before coronary intervention. No patient with unobstructed coronary target artery was observed in subgroup C.

Optimal result coronary angioplasty with TIMI 3 flow occurred in 30 patients (81,1%) in subgroup A, 19 patients (70,4%) in subgroup B and 12 patients (60,0%) in subgroup C. There was not any single case of lack of vessel reopening (TIMI 0) in analysed subgroups, suboptimal result however (TIMI 1, TIMI 2) occurred in 25 cases (7 patients (17,9%) in subgroup A, 8 patients (29,6%) in subgroup B and 8 patients (40,0%) in subgroup C). Collateral circulation was assessed using Rentrop scale. In most patients the lowest Rentrop grades were observed, respectively in 20 patients (54,1%) in subgroup A, 13 patients (50,0%) in subgroup B and 12 patients (60,0 %) in subgroup C.

Fig-1a & 1b:

Enzymatic analysis of CK [U / l] (a) and CKMB [U / l] (b) in pPCI treated patients in acute myocardial infarction with persistent ST segment elevation divided into subgroups A, B and C. Area under the curve (AUC) for mean cardiac necrotic enzymes was significantly higher for subgroup B; respectively for CK ($p = 0.034$) and CKMB ($p = 0.01$).

Analysis of cardiac necrosis markers revealed significant change of average creatine kinase level ($p < 0,001$) and its MB fraction ($p < 0,001$) in first 48 hours of hospitalisation. Enzymatic evolution curve waspeculiar to the acute coronary syndrome. There were no significant differences between CK and CK-MBvalues between subgroups A, B and C immediately after admission to the hospital ($p = 0,999$). On the other hand, however, mean values of cardiac necrotic enzymes assessed on the following hours of hospitalisation (1,5, 8, 16 and 48 h) were significantly higher in subgroup B (characterized by glycaemia on admission $\geq 7,8$ mmol/l and glycated haemoglobin

level $< 6,5\%$); respectively for CK $p = 0,034$ and CK-MB $p = 0,01$. That also means, that area under curve (AUC) was significantly higher for subgroup B (**Fig-1a**, and **Fig-1b**).

During 4 month follow up observation there was significant difference between frequency of major cardiovascular events between particular subgroups of patients ($p = 0,016$, exact Fisher test). Percentage of noted cases of MACE was significantly higher among subgroup B, thanother two investigated subgroups (**Table-2**).

Table-2: The occurrence of adverse cardiovascular events in 4-month and 4-year follow-ups of patients treated with PCI in the acute phase of myocardial infarction with persistent ST segment elevation in particular subgroups

MACE	number (n)	subgroup	after 4 moths	p value	after 4 years	p value
Total	37	A	2 (5,4%)	0,016	8 (21,6%)	0,01
	27	B	6 (22,2%)		15 (55,6%)	
	20	C	3 (15%)		8 (40%)	
Death	37	A	0		1 (2,7%)	
	27	B	1 (3,7%)		2 (7,4%)	
	20	C	0		2 (10%)	
Cardiac death	37	A	0		1 (2,7%)	
	27	B	1 (3,7%)		0	
	20	C	0		0	
Myocardial infarction	37	A	0		2 (5,4%)	
	27	B	1 (3,7%)		5 (18,5%)	
	20	C	1 (5%)		3 (15%)	
PCI/CABG	37	A	1 (2,7%)		3 (8,1%)	
	27	B	2 (7,4%)		6(22,2%)	
	20	C	2 (10%)		3 (15%)	
Hospitalisation due CHF	37	A	1 (2,7%)		1 (2,7%)	
	27	B	2 (7,4%)		2 (7,4%)	
	20	C	0		0	
Diabetes mellitus	37	A	-		2 (5,4%)	0,001
	27	B	-		5 (18,5%)	
	20	C	-		10 (50%)	

Echocardiographic examination performed during 4 month follow up appointment did not reveal statistically significant difference between subgroup A ($5,26 \pm 8,02\%$), subgroup B ($4,04 \pm 7,72\%$) and subgroup C ($0,84 \pm 7,55$), $p = 0,286$ (Fig-2).

Significant correlation between adverse cardiovascular events in particular subgroups was observed in 4 year follow up observation ($p=0,01$, chi-

square test). Percentage of MACE in subgroup B was significantly higher than in two remaining investigated groups of patients (Table-2).

Groups of patients also differed significantly regarding frequency of de novo diagnosed cases of diabetes in 4-year observation ($p<0,001$). In subgroup C percentage of patients newly diagnosed with diabetes was the highest (Table-2).

Fig-2:

Differences in the ejection fraction of the left ventricle (EF) [%] in the assessment of echocardiography in the studied patients treated with pPCI in the acute phase of myocardial infarction with persistent ST segment elevation in particular subgroups A, B and C.

Discussion

Division of the study group regarding glycated haemoglobin level (HbA1c) as the expression of constantly increased blood glucose level and also reactive hyperglycaemia as an indicator of dynamic change of glycaemia during acute myocardial infarction, had to underline coexistence of carbohydrate metabolism disturbances and cardiovascular risk in these groups of patients. Is newly diagnosed carbohydrate disturbance or chronic hyperglycaemia more important factor affecting short and long term prognosis?

The most numerous subgroups consisted of patients characterized by low level of HbA1c and glycaemia on admission. The least numerous subgroup consisted of patients characterized by higher HbA1c and lower glycaemia on admission. Current study revealed significant difference between mean values of cardiac necrosis enzymes during subsequent measurements

between investigated subgroups. The highest CK and CK-MB concentration was noted among subgroup of patients characterized by higher level of glycaemia on admission and lower level of HbA1c. On the other hand, the lowest values were present in subgroup with low level of glycaemia on admission and HbA1c. At the same time patients with the highest level of necrotic enzymes significantly more often presented adverse cardiovascular events as well as in 4 months and 4 year follow up observation.

Similarly, patients with the least level of cardiac necrotic enzymes had also the lowest rates of adverse cardiovascular events. Comparable findings were reported in available studies. Liu et. al. investigated 493 patients with STEMI divided into groups regarding HbA1c level and glucose concentration on admission and concluded that group of patients characterized by increased glycaemia and HbA1c $<6,5\%$ had high mortality and risk of major adverse cardiovascular

events [14]. Other studies pointed out that coincidence between reactive hyperglycaemia and higher values of glycated haemoglobin adversely affecting long term prognosis [15-17]. However, we should remember, that both parameters reflect different population of patients. Probably, through different pathogenesis long term prognosis is also different. It was noted that reactive hyperglycaemia more clearly affects cardiovascular risk among patients without diabetes, than those who had it diagnosed before [18]. The exact reasons of this dependence are not known. It is very possible that this is the result of higher accumulation of interrelated risk factors of atherosclerosis in advanced diabetes. Then, role of hyperglycaemia as single factor loses its statistical power and importance.

In own study; during analysis of carbohydrate metabolism, I noticed significant difference in frequency of diabetes among investigated subgroups. After 4 years of observation diabetes was diagnosed the most commonly in subgroup, which patients were characterised by increased level of glycaemia on admission and increased glycated haemoglobin level but oral glucose tolerance test was normal during hospitalisation. At the same in subgroup characterized by lower glycaemia on admission and lower glycated haemoglobin concentration, diabetes was diagnosed the rarest in 4-year observation. Other analysis confirmed that glycated haemoglobin index reliably predicts and enables diagnosis of diabetes among patients with ischemic heart disease, but on the other hand oral glucose tolerance test remains more reliable [19]. Nonetheless examinations indicating deteriorated glucose metabolism obtained during hospital stay should be repeated and patient should remain under strict control.

Despite constant, routine testing of glucose level during hospitalisation and, if necessary, administration of insulin in case of acute hyperglycaemia, benefits from prevention of macroangiopathic complications remain unsatisfactory. Partially it results from diagnostic threshold for diabetes. This cut-off point was derived from blood glucose levels that accounted for the risk of retinopathy. It has been noted, that occurrence of non-proliferative diabetic retinopathy increases in patients with fasting glucose level at

around 7,0 mmol/l, 11,1 mmol/l measured in second hour of oral glucose tolerance test or HbA1c concentration higher than 6,5% [20-23]. Moreover, it has been observed, that risk of macroangiopathic complications increases even in case of lower levels of glycaemia [24,25].

Own work confirmed that course of acute myocardial infarction with persisted ST elevation among patients with impaired glycaemia is always linked with higher risk of death, repeated myocardial infarction, stroke and heart failure. Risk is noticeable even during hospitalisation and persists for at least 4 years since myocardial infarction [26,27]. It is believed, that diabetes, type I especially, shortens patient's life around 10-15 years, mainly due to increased frequency of myocardial infarctions, strokes and peripheral artery disease [28]. Increased glycaemia causes more frequent infections, which results from impaired cell-mediated immunity, renal and liver failure [29-31].

For the first time correlation between increased glycaemia and mortality was invoked by Modan in a study published in The Journal of the American Medical Association in 1975 [32]. Whole series of studies conducted following years indicate, that the main reason of aggravated outcome are diffuse atherosclerosis, heart failure, inflammatory process located in epicardial and intramural coronary artery wall, microcirculation damage, metabolic disturbances and also advanced age [33,34]. Concomitance of autonomic cardiovascular neuropathy and diseases worsening prognosis such as renal failure is also important [35]. Atherosclerotic changes localized in distal parts of coronary arteries impede optimal percutaneous or surgical revascularisation and through it worsen short or long term effects of treatment [36-39]. Efficacy of mechanical reperfusion in acute myocardial infarction is limited by microcirculatory vulnerability, degree of damage to the myocardium or distal microembolization [40-45]. No reflow phenomenon, complication observed in diabetic patients reflects ineffective reperfusion [46,47]. Own work did not prove significant difference between subgroups regarding angiographic scales after primary percutaneous coronary intervention and this may be a

result of small sample size.

Consequence of impaired flow in epicardial coronary artery is larger infarction area, impaired left ventricle ejection fraction and increased frequency of heart failure caused by unfavourable left ventricle remodelling. It correlates with increased risk of repeated coronary syndrome [48-50] and impaired cardiovascular prognosis among patients with diabetes [51,52]. Study revealed, that patients with persisted ST segment elevation myocardial infarction, who were diagnosed with disturbed carbohydrate metabolism during hospitalisation have impaired prognosis in 4 months and 4 years follow up. Noticeable difference was especially observed among patients with reactive hyperglycaemia and low glycated haemoglobin level. It underlines necessity of complex carbohydrate metabolism evaluation in patients hospitalised urgently on cardiology wards, even amongst those who were not diagnosed with diabetes before. Selected patients with carbohydrate metabolism disturbances should remain under accurate observation.

Competing Interests

All authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

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