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 ≥6.5%, Glc ≥7.8 mmol/l: n = 20; 21,7%) and subgroup D (HbA1c ≥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 (Ckap=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).
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 hyperinsulinenia, 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 ≥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 >1,5x 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:

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 ≥7.8 mmol/l).
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 ≥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 ≥7,8 mmol/l: n = 27; 29,3%), subgroup C (HbA1c ≥6,5%, Glc ≥7,8 mmol/l: n = 20; 21,7%) and subgroup D (HbA1c ≥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 sings 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](image_url)

**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).
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Original Article

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 was peculiar to the acute coronary syndrome. There were no significant differences between CK and CK-MB values 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 ≥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, than other 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±8,02%), subgroup B (4,04±7,72%) and subgroup C (0,84±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.

References

[1] Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. JAMA. 1979 May 11;241(19):2035-38. [PMID: 430798]
[2] Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care. 1993 Feb;16(2):434-44. [PMID: 8432214]
[3] Goldbourt U, Yaari S, Medalie JH. Factors predictive of long-term coronary heart disease mortality among 10,059 male Israeli civil servants and municipal employees. A 23-year mortality follow-up in the Israeli Ischemic Heart Disease Study. Cardiology. 1993;82(2-3):100-21. [PMID: 8324774]
[4] Authors/Task Force Members, Steg PG, James SK, Atar D, Badano LP, Lundqvist CB, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). European heart journal. 2012 Oct 1;33(20):2569-19.
[5] Stern MP. Diabetes and cardiovascular disease. The "common soil" hypothesis. Diabetes. 1995 Apr;44(4):369-74. [PMID: 7698502]
[6] Wagenknecht LE, Bowden DW, Carr JJ, Langefeld CD, Freedman BI, Rich SS. Familial aggregation of coronary artery calcium in families with type 2 diabetes. Diabetes. 2001 Apr;50(4):861-66. [PMID: 11289053]
[7] Kannel WB, McGee DL. Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham study. Diabetes Care. 1979 Mar-Apr;2(2):120-26. [PMID: 520114]
[8] Löwel H, Koenig W, Engel S, Hörmann A, Keil U. The impact of diabetes mellitus on survival after myocardial infarction: can it be modified by drug treatment? Results of a population-based myocardial infarction register follow-up study. Diabetologia. 2000 Feb;43(2):218-26. [PMID: 10753044]
[9] Torffvit O, Agardh C. The prognosis for type 2 diabetic patients with heart disease. A 10-year observation study of 385 patients. J Diabetes Complications. 2000 Nov-Dec;14(6):301-306. [PMID: 11204553]
[10] David LA, Grosu AA. [Abnormal glucose tolerance and long-term prognosis in patients with acute myocardial infarction]. Kardiologiia. 2013;53(9):15-20. Russian. [PMID: 24090381]
[11] Mazurek M, Kowalczyk J, Lenarczyk R, Ziełnińska T, Sedkowska A, Pruszewska-Skrzep P, Światkowski A, Sredniawa B, Kowalski O, Polonski L, Strojek K, Kalarus Z. The prognostic value of different glucose abnormalities in patients with acute myocardial infarction treated invasively. Cardiovasc Diabetol. 2012 Jun 28;11:78. [PMID: 22741568]
[12] de Lemos JA, Braunwald E. ST segment resolution as a tool for assessing the efficacy of reperfusion therapy. J Am Coll Cardiol. 2001 Nov 1;38(5):1283-94. [PMID: 11694966]
[13] Schröder R, Dissmann R, Brüggemann T, Wegscheider K, Linderer T, Tobe B, Neuhaus KL.Extent of early ST segment elevation resolution: a simple but strong predictor of outcome in patients
with acute myocardial infarction. J Am Coll Cardiol. 1994 Aug;24(2):384-91. [PMID: 8034872]

[14] Liu Y, Yang YM, Zhu J, Tan HQ, Liang Y, Li JD. Haemoglobin A1c, acute hyperglycaemia and short-term prognosis in patients without diabetes following acute ST-segment elevation myocardial infarction. Diabet Med. 2012 Dec;29(12):1493-500. [PMID: 2243832]

[15] Andres M, Konduracka E, Legutko J, Rajs T, Andres J, Žmudka K. Impact of Reactive Hyperglycaemia on Length of Hospitalisation and Prognosis in Patients with Acute ST Segment Elevation Myocardial Infarction. International Journal of Medical Research Professionals. 2020;6(5).

[16] Timmer JR, Ottervanger JP, Bilo HJ, Dambrink JH, Miedema K, Hoornjte JC, Zijlstra F. Prognostic value of admission glucose and glycosylated haemoglobin levels in acute coronary syndromes. QJM. 2006 Apr;99(4):237-43. [PMID: 16504985]

[17] Andres M, Legutko J, Konduracka E, Malecki M, Andres J, et al. The significance of dynamics of ST segment changes when assessing the effectiveness of mechanical reperfusion of the myocardium in hyperglycaemic patients with acute myocardial infarction with persistent ST-segment elevation. Journal of Integrative Cardiology. 2020 Feb 17;6:1-5.

[18] Santoro GM, Valenti R, Buonamici P, Bolognese L, Cerisano G, Moschi G, Trapani M, Antonucci D, Fazzini PF. Relation between ST-segment changes and myocardial perfusion evaluated by myocardial contrast echocardiography in patients with acute myocardial infarction treated with direct angioplasty. Am J Cardiol. 1998 Oct 15;82(8):932-6. [PMID: 9794347]

[19] Gyberg V, De Bacquer D, Kotseva K, De Backer G, Schnell O, Sundvall J, Tuomilehto J, Wood D, Rydén L; EUROASPIRE IV Investigators. Screening for dysglycaemia in patients with coronary artery disease as reflected by fasting glucose, oral glucose tolerance test, and HbA1c: a report from EUROASPIRE IV—a survey from the European Society of Cardiology. Eur Heart J. 2015 May 14;36(19):1171-77. [PMID: 25670820]

[20] Gavin III JR, Alberti KG, Davidson MB, DeFronzo RA. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes care. 1997 Jul 1;20(7):1183.

[21] Engelgau MM, Thompson TJ, Herman WH, Boyle JP, Aubert RE, Kenny SJ, Badran A, Sous ES, Ali MA. Comparison of fasting and 2-hour glucose and HbA1c levels for diagnosing diabetes. Diagnostic criteria and performance revisited. Diabetes Care. 1997 May;20(5):785-91. [PMID: 9135943]

[22] McCance DR, Hanson RL, Charles MA, Jacobsson LT, Pettitt DJ, Bennett PH, Knowler WC. Comparison of tests for glycated haemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes. BMJ. 1994 May 21;308(6940):1323-28. Erratum in: BMJ 1994 Oct;309(6958):841. [PMID: 809217]

[23] Colagiuri S. DETECT-2: early detection of type 2 diabetes and IGT. Diabetes Voice. 2003;48:11-13.

[24] Authors/Task Force Members, Rydén L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, Deaton C, Escaned J, Hammes HP, Huikuri H. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). European heart journal. 2013 Oct 14;34(39):3035-87.

[25] McCance DR, Hanson RL, Charles MA, Jacobsson LT, Pettitt DJ, Bennett PH, Knowler WC. Comparison of tests for glycated haemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes. BMJ. 1994 May 21;308(6940):1323-28. Erratum in: BMJ 1994 Oct;309(6958):841. [PMID: 809217]

[26] Solomon SD, Sutton MS, Lamas GA, Plappert T, Rouleau JL, Skali H, Moyé L, Braunwald E, Pfeffer MA. Ventricular remodeling does not accompany the development of heart failure in diabetic patients after myocardial infarction. Circulation. 2002 Sep 3;106(10):1251-55.

[27] Rao Kondapally Seshasai S, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, Sarwar N, Whincup PH, Mukamal KJ, Gillum RF, Holme I, Njolstad I, Fletcher A, Nilsson P, Lewington S, Collins R, Gudnason V, Thompson SG, Sattar N, Selvin E, Hu FB, Danesh J; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med. 2011 Mar 3;364(9):829-841. Erratum in: N Engl J Med. 2011 Mar 31;364(13):1281. [PMID: 21366474]
Original Article

[28] Grzelak P, Czupryniak L, Olszycki M, Majos A, Stefańczyk L. Age effect on vascular reactivity in Type 1 diabetes. Diabet Med. 2011 Jul;28(7):833-37. [PMID: 21388443]

[29] Joshi N, Caputo GM, Weitekamp MR, Karchmer AW. Infections in patients with diabetes mellitus. N Engl J Med. 1999 Dec 16;341(25):1906-12. [PMID: 10601511]

[30] Jawa A, Kcoma J, Fonseca VA. Diabetic nephropathy and retinopathy. Med Clin North Am. 2004 Jul;88(4):1001-36, xi. [PMID: 15308388]

[31] Angulo P. Nonalcoholic fatty liver disease. N Engl J Med. 2002 Apr 18;346(16):1221-31. [PMID: 11961152]

[32] Modan B, Schor S, Shani M. Acute myocardial infarction. Prognostic value of white blood cell count and blood glucose level. JAMA. 1975 Jul 21;233(3):266-67. [PMID: 1173836]

[33] BARI 2D Study Group, Frye RL, August P, Brooks MM, Hardison RM, Kelsey SF, MacGregor JM, Orchard TJ, Chahtman BR, Genuth SM, Goldberg SH, Hlatky MA, Jones TL, Molitch ME, Nesto RW, Sako EY, Sobel BE. A randomized trial of therapies for type 2 diabetes and coronary artery disease. N Engl J Med. 2009 Jun 11;360(24):2503-15. [PMID: 19502645]

[34] Tartan Z, Ozer N, Uyarel H, Akglu O, Gul M, Cetin M, Kaskicgiolu H, Cam N. Metabolic syndrome is a predictor for an ECG sign of no-reflow after primary PCI in patients with acute ST-elevation myocardial infarction. Nutr Metab Cardiovasc Dis. 2008 Jul;18(6):441-47. [PMID: 17981019]

[35] Zakrzewski D, Janas J, Heretyk H, Stepińska J. Inflammatory response and postoperative kidney failure in patients with diabetes type 2 or impaired glucose tolerance undergoing heart valve surgery. Kardiol Pol. 2010 May;68(5):530-36. [PMID: 20491014]

[36] Hammoud T, Tanguay JF, Bourassa MG. Management of coronary artery disease: therapeutic options in patients with diabetes. J Am Coll Cardiol. 2000 Aug;36(2):355-65. [PMID: 10933343]

[37] Przewłocki T, Pieniaksz P, Ryniewicz W, Kostkiewicz M, Olszowska M, Podolec P, Sezwy E, Tracz W. Long-term outcome of coronary balloon angioplasty in diabetic patients. Int J Cardiol. 2000 Oct;76(1):7-16. [PMID: 11121591]

[38] Abizaid A, Kornowski R, Mintz GS, Hong MK, Abizaid AS, Mehran R, Pichard AD, Kent KM, Satller LF, Wu H, Popma JJ, Leon MB. The influence of diabetes mellitus on acute and late clinical outcomes following coronary stent implantation. J Am Coll Cardiol. 1998 Sep;32(3):584-89. [PMID: 974197]

[39] Schofer J, Schluter M, Rau T, Hammer F, Haag N, Mathey DG. Influence of treatment modality on angiographic outcome after coronary stenting in diabetic patients: a controlled study. J Am Coll Cardiol. 2000 May;35(6):1554-59. [PMID: 10807460]

[40] Jaffe R, Charron T, Puley G, Dick A, Strauss BH. Microvascular obstruction and the no-reflow phenomenon after percutaneous coronary intervention. Circulation. 2008 Jun 17;117(24):3152-56. [PMID: 18559715]

[41] Romano M, Buffoli F, Tomasi L, Aroldi M, Lettieri C, Ferrari MR, Zanini R. The no-reflow phenomenon in acute myocardial infarction after primary angioplasty: incidence, predictive factors, and long-term outcomes. J Cardiovasc Med (Hagerstown). 2008 Jan;9(1):59-63. [PMID: 18268421]

[42] Kusama I, Ibi K, Kusoge M, Nozawa N, Ozaki H, Yano H, Sumita S, Tsukahara K, Okuda J, Ebina T, Umemura S, Kimura K. Impact of plaque rupture on infarct size in ST-segment elevation anterior acute myocardial infarction. J Am Coll Cardiol. 2007 Sep 25;50(13):1230-37. [PMID: 17888839]

[43] Michaels AD, Gibson CM, Barron HV. Microvascular dysfunction in acute myocardial infarction: focus on the roles of platelet and inflammatory mediators in the no-reflow phenomenon. Am J Cardiol. 2000 Mar 9;85(5A):50B-60B. [PMID: 11076131]

[44] Lee CH, Teo SG, Hong E, Wong HB, Low A, Sutandar A, Tan HC, Lim YT. Impact of glycemic control on occurrence of no-reflow and 30-day outcomes in diabetic patients undergoing primary angioplasty for myocardial infarction. J Invasive Cardiol. 2005 Aug;17(8):422-26. [PMID: 16079448]

[45] Nakamura T, Ako J, Kadowaki T, Funayama H, Sugawara Y, Kubo N, Momomura S. Impact of acute hyperglycemia during primary stent implantation in patients with ST-elevation myocardial infarction. J Cardiol. 2009 Apr;53(2):272-77. [PMID: 19304133]

[46] Kelly RV, Cohen MG, Stouffer GA. Incidence and management of "no-reflow" following percutaneous coronary interventions. Am J Med Sci. 2005 Feb;330(2):78-85. [PMID: 1571424]
Reaktív hyperglykémia kapcsolata a gyökértelmezett hemoglobinnal és a kardiovaskuláris világosodás előrehaladásai kapcsán. J Health Care and Research. 2021 Jun 01;2(2):85-96.

[47] Rezkalla SH, Kloner RA. No-reflow phenomenon. Circulation. 2002 Feb 5;105(5):656-62. [PMID: 11827935]

[48] Feskens EJ, Kromhout D. Glucose tolerance and the risk of cardiovascular disease: the Zutphen Study. J Clin Epidemiol. 1992 Nov;45(11):1327-34. [PMID: 1432012]

[49] Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med. 1998 Jul 23;339(4):229-34. [PMID: 9673301]

[50] Barrett-Connor EL, Cohn BA, Wingard DL, Edelstein SL. Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? The Rancho Bernardo Study. JAMA. 1991 Feb 6;265(5):627-31. Erratum in: JAMA 1991 Jun 26;265(24):3249. [PMID: 1987413]

[51] Ito H, Maruyama A, Iwakura K, Takiuchi S, Masuyama T, Hori M, Higashino Y, Fujii K, Minamino T. Clinical implications of the 'no reflow' phenomenon. A predictor of complications and left ventricular remodeling in reperfused anterior wall myocardial infarction. Circulation. 1996 Jan 15;93(2):223-28. [PMID: 8548892]

[52] Feldman LJ, Himbert D, Juliard JM, Karrillon GJ, Benamer H, Aubry P, Boudvillain O, Seknadji P, Faraggi M, Steg G. Reperfusion syndrome: relationship of coronary blood flow reserve to left ventricular function and infarct size. J Am Coll Cardiol. 2000 Apr;35(5):1162-69. [PMID: 10758956]