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PRACA POGLĄDOWA
REVIEW

Glucose abnormalities detected by oral glucose tolerance test in patients with acute myocardial infarction: clinical significance, epidemiology, natural course and therapeutic concerns

Zaburzenia metabolizmu glukozy wykryte w doustnym teście obciążenia glukozą u chorych z zawałem serca: znaczenie kliniczne, epidemiologia, przebieg naturalny i problemy terapeutyczne

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ABSTRACT

Two-hour post load glycemia (2h-PG) obtained during the oral glucose tolerance test (OGTT) is related to adverse cardiovascular outcomes more significantly than fasting glycemia, and the association of 2h-PG with cardiovascular morbidity is graded and independent. An abnormal value of 2h-PG is defined as glycemia ≥ 7.8 mmol/l (140 mg/dl) in most studies. Patients with acute myocardial infarction with abnormal 2h-PG compared to patients with normal 2h-PG have a significantly higher long-term mortality and more concomitant diseases, however, it has not been shown that those subjects have a higher risk of myocardial infarction, coronary revascularization or stroke. Studies have shown that in some patients the glucometabolic status changes after the acute phase of the disease, and that those changes have a prognostic importance. In this review article the authors presented the significance, epidemiology, natural course of glucometabolic disturbances and the therapeutic concerns of hypoglycemic treatment.

KEY WORDS
acute myocardial infarction, oral glucose tolerance test, glucometabolic disturbances

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STRESZCZENIE

W porównaniu z glikemią na czczo, wartość glikemii po dwóch godzinach (2h-PG) uzyskana w doustnym teście obciążenia glukozą (OGTT) jest parametrem lepiej korelującym z przyszłymi niekorzystnymi zdarzeniami sercowo-naczyniowymi, a jej związek z zapadalnością na chorobę wieńcową oraz ze śmiertelnością jest stopniowy i niezależny. Nieprawidłowy wynik 2h-PG w większości publikowanych prac definiuje się jako ≥ 7,8 mmol/l (140 mg/dl). U chorych z zawałem serca, u których stwierdza się nieprawidłowy wynik 2h-PG, w porównaniu z chorymi z prawidłowym 2h-PG, rokowanie jest gorsze. Charakteryzują się również częstszym występowaniem chorób towarzyszących. Są to pacjenci, których śmiertelność odległa jest znamiennie wyższa, jednak dotychczas nie wykazano jednoznacznie, aby byli to chorzy, u których częściej występuje ponowny zawał serca, rewaskularyzacja wieńcowa czy udar mózgu. Wskazuje się również na fakt, iż u części chorych stan glukometaboliczny zmienia się po ostrej fazie choroby, co ma wpływ na śmiertelność. W prezentowanej pracy przedstawiono znaczenie zaburzeń metabolizmu glukozy, ich epidemiologię, przebieg naturalny oraz poruszono problem leczenia hipoglikemizującego.

SŁOWA KLUCZOWE

zawał serca, doustny test obciążenia glukozą, zaburzenia metabolizmu glukozy

INTRODUCTION

Hyperglycemia is one of the main concerns of public health. The risk of this abnormal glucometabolic state, related complications, and its clinical importance have been widely discussed and investigated for several decades. Patients with hyperglycemia are at high risk of cardiovascular disease and mortality – a worldwide problem that has not only not been resolved, but continues to worsen. There are various parameters used to detect disturbances in glucose metabolism, however, the two-hour post load glycemia (2h-PG) obtained during the oral glucose tolerance test (OGTT) is valuable for the evaluation of glucometabolic status and risk stratification in the general population and in patients with coronary artery disease [1,2,3,4]. 2h-PG is superior to fasting glucose in assessing the risk of future cardiovascular events, and the relation of 2h-PG to coronary heart disease incidence and cardiovascular morality is graded and independent [5]. Increased mortality was observed in people with abnormal glucose tolerance detected by 2h-PG, but not in subjects with impaired fasting glycemia, and a high 2h-PG predicted all-cause and cardiovascular mortality after adjustment for other risk factors, while a high fasting glucose was not predictive once 2h-PG was taken into account [6,7]. It should be noted that in patients with abnormal 2h-PG and normal fasting glucose, the risk of death is underestimated [8]. Elevated 2h-PG was also found to be a risk factor of mortality, independent of the levels of glycosylated hemoglobin (HbA1c), although HBA1c was a prognostic factor in patients with acute myocardial infarction (AMI) and newly detected glucose abnormalities [9,10]. The most recent guidelines dedicated to the topic of diabetes, pre-diabetes and cardiovascular disease published by the European Society of Cardiology (ESC) recommend fasting glycemia and HbA1c as primary screening methods, but also advocated OGTT as the preferred one to detect glucose abnormalities in patients with acute coronary syndrome [11]. The aim of this review article is to expound the important role of the oral glucose tolerance test in a very high risk population of patients with acute myocardial infarction.

Value of oral glucose tolerance test in acute phase of acute myocardial infarction – prevalence and significance of glucose abnormalities

In the studies which are cited below, the prevalence of abnormal glucose tolerance in the acute phase of AMI was 25–66%, of DM it was 16–40%, of IGT 22–41%. Impaired fasting glycemia (isolated or coexisting with impaired glucose tolerance) was observed in 10–15%, but it was reported infrequently.

In patients with coronary artery disease, 2h-PG has a similar diagnostic and prognostic usefulness as in other populations [12,13,14,15,16,17,18]. Tamita et al. classified AMI patients with respect to fasting glucose as subjects with normal or impaired fasting glycemia and showed that there were no significant differences in the major adverse cardiovascular events (MACE) between those groups. However, when patients were divided with respect to 2h-PG into subjects with abnormal glucose tolerance (AGT; 2h-PG ≥ 7.8 mmol/l) and normal glucose tolerance (NGT; 2h-PG < 7.8 mmol/l) the MACE rate was significantly higher in the AGT group [15]. The authors stated that the post-challenge glucometabolic status is a better risk factor for future cardiovascular events than the fasting glucose level and may critically distinguish high-risk individuals [15]. Kitada et al. presented receiver-operator charac-

teristic curves which indicated that a cut-off value of 2h-PG ≥ 160 mg/dL best predicted MACE in patients without previously known diabetes. This measure of post-load glycemia showed a sensitivity and specificity of 59% and 58%, respectively. However, impaired glucose tolerance (IGT, defined as 2h-PG < 11.1 and ≥ 7.8 mmol/l) was associated with a similar prognosis to NGT [16]. Those studies included a relatively small number of patients, therefore, comparative analyses of particular MACE between the study groups were not performed. In a recent study by Mazurek et al. encompassing 2527 patients with AMI treated with percutaneous coronary intervention, with no specific exclusion criteria, patients with IGT or newly detected DM had a higher mortality than patients with isolated impaired fasting glycemia (IFG) or NGT and a similar prognosis to patients with previously known diabetes. The authors emphasized that the main finding of their study was that IGT negatively affected the treatment outcomes and that the long-term prognosis of patients with IGT was similar to those with DM. The analysis of particular MACE which occurred during long-term observation showed that there were no significant differences between patients with normal glucose tolerance and IFG, IGT, or DM with respect to recurrent AMI, percutaneous coronary intervention, coronary artery by-pass grafting or stroke [17]. The adverse role of IGT in AMI patients was also confirmed in a study by George et al. in which 42% of the study population was treated invasively [18]. Impaired glucose tolerance, as well as newly detected DM, were independent predictors MACE. Newly detected diabetes was also associated with a higher risk of nonfatal AMI. The authors compared readmission due to heart failure, however, no significant differences between the glucometabolic groups were noted [18].

To the authors' knowledge, there is only one study which showed that newly detected dysglycemia in AMI patients had no impact on the prognosis. Knudsen et al. showed that in patients treated invasively due to ST elevation AMI, the oral glucose tolerance test performed within 24 hours after hospital admission revealed that newly detected abnormal glucose regulation was prevalent in 47% of study subjects [19]. It was associated with older age, higher proportion of female gender, higher serum peak level of cardiac troponin, a larger myocardial infarct size measured as % of left ventricular mass three months later, significantly higher levels of glycosylated hemoglobin, insulin, proinsulin, C-peptide, and a higher homeostasis model assessment-estimated insulin resistance index (HOMA-IR) [19]. Although patients with abnormal glucose regulation were not started on glucose lowering medication, had a higher serum peak level of cardiac troponin, larger myocardial infarct size, and more severe glucometabolic derangement, their prognosis was similar to those with normoglycemia [19]. The authors of the cited study suggested that a low prevalence of DM (24% of abnormal glucose regulation group and 11% of total study population) could have been related to the obtained results [19]. Patients with IFG were also included in the abnormal glucose regulation group, which could have resulted in a more favorable outcome. Nevertheless, early performance of OGTT, the exclusion of high-risk patients with heart failure and renal failure, which were shown to be independent risk factors of death in patients with glucose abnormalities [17], could have had a major impact on the obtained results.

In published studies, the clinical characteristics of patients with AMI and newly detected abnormal glucose tolerance are not equivocal, however, those patients are generally more likely to be older, female, hypertensive, overweight or obese, they have a worse left ventricle ejection fraction and renal function, higher glycemia measured on hospital admission, higher fasting glucose levels, higher glycosylated hemoglobin and insulin, proinsulin, and triglycerides than patients with normoglycemia [12,13,14,15,16,17, 18,19,20,21]. In the majority of studies there were no differences in cardiovascular medical history with respect to different glucose abnormalities, except a study by Bartnik et al. which showed that patients with abnormal glucose tolerance had a trend towards more heart failure history [21].

In summary, among patients with acute myocardial infarction, abnormal glucose tolerance is more likely to be detected in patients with other indices of disturbed glucose metabolism and comorbidities. Considering the fact that insulin resistance in patients with AMI during the in-hospital period significantly decrease from day 2 to day 5 and remain unchanged at 3--month follow-up [13], OGTT should not be administered earlier than 4–5 days after AMI onset, as stated in ESC guidelines. OGTT performed early during the acute phase may have no prognostic significance due to acute hemodynamic and metabolic derangement, which may cause false positive results of the glucometabolic status. All the studies in which OGTT was performed as recommended showed that glucometabolic status, irrespective of the treatment strategy (invasive or conservative), indicate patients with different long-term risks of an adverse outcome. The basic characteristics of the cited studies are presented in Table I. Table II shows detailed data on the major adverse cardiovascular events reported in the cited studies.

Value of oral glucose tolerance test in stable patients after acute phase of myocardial infarction – natural course and prognostic significance of glucose abnormalities

There are several studies in which the oral glucose tolerance test was repeated after the acute phase of

myocardial infarction [12,13,14,19,20,22,23]. One of the first studies was conducted by Norhammar et al. who showed that at hospital discharge the prevalence of NGT, IGT or DM was: 34%, 35%, 31%, and 35%, 40%, 25% respectively after 3 months. There was a significant correlation between 2h-PG at discharge and 2h-PG after 3 months as well as for in-hospital HbA1c and 2h-PG at 3 months, and fasting blood glucose on day 4 and 2h-PG blood glucose at 3 months. The independent predictors of abnormal glucose tolerance after 3 months were glycosylated hemoglobin and fasting blood glucose at discharge, however, no predictive values of those parameters were established [12]. The authors also did not distinguish risk factors for the persistence of newly detected abnormal glucose tolerance at follow-up.

Wallander et al. reported the prevalence of NGT, IGT or DM at hospital discharge, after 3 months and at 12--month follow-up in 122 subjects with AMI [14]. Among those with abnormal glucose tolerance at discharge, 78% still had AGT after 3 months and 83% at the 12-month follow-up. Even though, compared to hospital discharge, 49% of patients were in the same glucometabolic category after 3 months and 56% after one year, the authors concluded that OGTT performed in AMI patients at hospital discharge reliably indicated the long-term glucometabolic state [14].

In a study by Tenerz et al., among 94 patients with AGT at discharge 73% had AGT after 3 months [13]. The analysis of insulin resistance showed that it was significantly higher at day two of index hospitalization due to AMI compared to day 5, however, no significant difference was observed between day 5 and 3--month follow-up. The authors concluded that OGTT performed at discharge from hospital provides a reliable estimate of diabetes classified 3 months after AMI [7]. Nevertheless, they also indicated that intraindividual tracking of oral glucose tolerance from discharge to follow-up was fairly poor, therefore, they recommended repeating OGTT to identify true-risk individuals [13]. Some authors state that a single test is sufficient for epidemiological and screening purposes, but to establish the diagnosis it should be repeated [24,25,26].

Another study, in which OGTT was repeated 3 months after the first AMI, was conducted by Bronisz et al. [14]. It showed that in patients after the first ST elevation AMI, abnormal glucose tolerance at discharge was transient in 55% of subjects at follow-up. The authors did not extract the risk factors for the persistence of glucose abnormalities, but revealed that age > 77 years, 2h-PG ≥ 12.06 mmol/l and mean blood glucose level on day 2 > 7.5 mmol/l were independent predictors of disturbances in glucose metabolism at the 3-month follow-up. Unlike in other cited studies, glycosylated hemoglobin only weakly correlated with 2h-PG at discharge, and the impact of HbA1c on the result of OGTT at 3 months was not observed.

As previously mentioned, Knudsen et al. performed the oral glucose tolerance test within 24 hours after hospital admission in patients with ST elevation AMI treated invasively and repeated it after 3 months. At 3--month follow-up abnormal glucose tolerance was transient in 68% of subjects, which was the highest value among the cited studies in which OGTT was repeated. Glycosylated hemoglobin and glycemia on admission to the hospital analysed separately, after adjustment for confounders, remained significant predictive factors for abnormal glucose regulation at follow-up [22]. This is the only study in which the authors showed the significant role of glycemia measured on admission to the hospital as a prognostic marker of the post-AMI glucometabolic status. Studies in which patients with admission hyperglycemia (≥ 11.1 mmol/l) were not excluded showed that admission glycemia was not a useful marker of disturbances in glucose metabolism at follow-up. In all of those studies OGTT was performed shortly before or at discharge. The changes in the prevalence of different glucose abnormalities in the cited studies with repeated OGTT are shown in Table III.

More recently, two studies were published in which the oral glucose tolerance test was performed in post-AMI patients during a stable condition. Henareh et al. studied 123 patients without a history of diabetes who had experienced AMI 3–12 months before the study [27]. Not all the patients had a coronary angiography, in some of them it showed no significant stenoses, and there were also patients treated with thrombolysis only. The study did not show an increased risk of MACE in patients with diabetes mellitus or impaired glucose tolerance compared to patients with normal glucose tolerance. However, an increase in 2h-PG was independently associated with long-term MACE. In a study conducted by our group, 368 patients with AMI treated invasively in whom the oral glucose tolerance test was performed at hospital discharge and who completed a follow-up ambulatory visit with repeated OGTT after 6 months, were analyzed with respect to changes in the glucometabolic status [23]. Out of 149 patients with AGT at discharge 68% still had AGT after 6 months. A high value of 2h-PG at discharge and high fasting glycemia were significant risk factors for sustained AGT. Analysis of the receiver-operator characteristic curves showed that the highest area under the curve was calculated for 2h-PG with a cut-off concentration of 10.2 mmol/l, and that glycemia measured at the time of hospital admission had no significant value in predicting the persistence of AGT. Moreover, 52% of subjects with normal glucose tolerance NGT at discharge developed AGT after 6 months. The reported changes in prevalence were

Table I. Basic characteristics of cited studies
Tabela I. Podstawowa charakterystyka cytowanych badań

First author of study, year of publication	Inclusion criteria	Exclusion criteria	No. of patients	Reperfusion strategy	Timing of OGTT	Definition of newly detected glucose abnormalities
1	2	3	4	5	6	7
Norhammar et al. 2002[12]	patients with AMI and base-line glycemia < 11.1 mmol/l	age ≥ 80 yrs, serum creatinine ≥ 200 μmol/l, known diabetes mellitus	181	thrombolysis in 38%, PCI in 5%	≥4 days after hospital admission	IGT: fasting glycemia <6.1 mmol/l and 2h-PG 7.8-11 mmol/l DM: fasting glycemia ≥ 6.1 mmol/l or 2h-PG ≥ 11.1 mmol/l IGT+DM = abnormal glucose tolerance
Tenerz et al. 2003[13]	patients with AMI and baseline glycemia < 11.1 mmol/l, completed 3-month follow-up with repeated OGTT	the same as in study by Norhammar et al.[12]	145	thrombolysis in 40%		≥ 4 days after hospital admission same criteria as in study by Norhammar et al.[12]
Bartnik et al. 2004[21]	patients with AMI and baseline glycemia < 11.1 mmol/l in whom OGTT was performed at discharge	the same as in study by Norhammar et al.[12]	168	thrombolysis or PCI in 42%		≥ 4 days after hospital admission same criteria as in study by Norhammar et al.[12]
Wallander et al. 2008[14]	patients with AMI and baseline glycemia < 11.1 mmol/l, completed 3-month and 12-month follow-up with repeated OGTT	the same as in study by Norhammar et al.[12]	122	not shown	≥ 4 days after hospital admission	the same criteria as in study by Norhammar et al.[12]
Kitada et. al. 2010[16]	patients with first AMI who survived 30 days and completed 2-year follow-up	coronary artery vasospasm or dissection, thromboembolism, catheter related complications, left main as infarct related artery, diabetes mellitus type 1, familial hyperlipidemia	422	invasive treatment in 73%, thrombolysis in 11%	median time from admission to OGTT was 9 days	abnormal glucose tolerance: fasting glycemia 6.1–7 mmol/l or 2h-PG ≥ 7.8 mmol/l
Knudsen et al. 2009[22] **and 2011**[19]	patients with STEMI treated invasively, were hemodynamically stable, without chest pain or nausea, age < 85 years and with serum creatinine < 200 μmol/l	known diabetes mellitus, persistent hyperglycemia, clinical signs of heart failure	244	invasive treatment in 100%	median time from admission to OGTT was 16.5 hours	abnormal glucose regulation: fasting glycemia ≥ 6.1 mmol/l or 2h-PG ≥ 7.8 mmol/l
Bronisz et al. 2012[20]	patients with first STEMI and no prior DM	severe heart failure, serum creatinine > 2 mg/dl, malignancy, treatment with glucosteroids or immunosuppressive agents	200	not shown	immediately before discharge, but not specified	disturbances in glucose metabolism: 2h-PG ≥ 7.8 mmol/l
Tamita et al. 2012[15]	patients with AMI	age ≥ 80 yrs, serum creatinine > 2 mg/dl, cardiogenic shock, in-hospital death, stroke, emergency coronary artery bypass surgery, LV reconstruction surgery, non-fatal LV rupture, recurrent percutaneous coronary intervention, idiopathic dilated cardiomyopathy, neoplasm, schizophrenia, hypoxic brain damage, unwillingness to participate in the study	275	invasive treatment in 85%, thrombolysis in 5%	at hospital discharge	abnormal glucose tolerance: 2h-PG ≥ 7.8 mmol/l

cd. tab. I

1	2	3	4	5	6	7
Mazurek et al. 2012[17]	in-hospital survivors with AMI treated invasively, discharged to ambulatory care	not specified	2527	invasive treatment in 100%, thrombolysis in 3%	≥ 4 days after hospital admission	IFG: fasting glycemia 6.1–7 mmol/l IGT: fasting glycemia < 7 mmol/l and 2h-PG 7.8–11 mmol/l DM: fasting glycemia ≥7 mmol/l or 2h-PG ≥ 11.1 mmol/l
George et al. 2015[18]	patients with AMI	known diabetes mellitus, urgent cardiothoracic surgery, death before in-hospital OGTT	768	invasive treatment in 42%	≥ 3 days after hospital admission	IFG: fasting glycemia 6.1–6.9 mmol/l and 2-h PG < 7.8 mmol/l; IGT: fasting glycemia < 7 mmol/l and 2-h PG 7.8–11 mmol/l; DM: fasting glycemia ≥ 7.0 or 2-h PG ≥ 11.1 mmol/l. IGT+DM = abnormal glucose tolerance
Kowalczyk et al. 2015[10]	in-hospital survivors with IGT or newly detected DM and AMI treated invasively, discharged to ambulatory care	not specified	763	invasive treatment in 100%	≥ 4 days after hospital admission	IGT: fasting glycemia < 7 mmol/l and 2h-PG 7.8–11 mmol/l DM: fasting glycemia ≥ 7 mmol/l or 2h-PG ≥ 11.1 mmol/l

Abbreviations: OGTT = oral glucose tolerance test; AMI = acute myocardial infarction; STEMI = ST elevation myocardial infarction; DM = diabetes mellitus; IGT = impaired glucose tolerance; IFG = impaired fasting glycemia NGR = normal glucose regulation; AGT = abnormal glucose tolerance; NGT = normal glucose tolerance; 2h-PG = two-hour post-load glycemia; LV = left ventricle.

Table II. Detailed data on major adverse cardiovascular events reported in cited studies
Tabela II. Niekorzystne zdarzenia sercowo-naczyniowe raportowane w cytowanych badaniach

	MACE	Death	AMI	PCI	CABG	Stroke	heart failure hospitalization
1	2	3	4	5	6	7	1
Tamita et al.[15]	Abnormal glucose tolerance, as well as previous diabetes mellitus, no statin therapy and history of CABG, was independent risk factor of long-term MACE. MACE were defined as: cardiovascular death, stroke, non-fatal myocardial infarction or ACS, non--target vessel revascularization either by coronary artery bypass grafting or coronary angioplasty and congestive heart failure that required hospitalization.	Statistical comparisons were not performed between groups.	Statistical comparisons were not performed between groups.	Statistical comparisons were not performed between groups.	Statistical comparisons were not performed between groups.	Statistical comparisons were not performed between groups.	Statistical comparisons were not performed between groups.
Kitada et al.[16]	2-year event-free rate of patients with 2h-PG ≥ 160 mg/dL was significantly higher than that of patients with 2h-PG < 160 mg/dL and was similar to that of patients with previous diabetes. 2h-PG ≥ 160 mg/dL was only independent predictor of long--term MACE (recorded after 30 days of AMI). MACE were defined as: death from cardiovascular causes, nonfatal AMI, hospitalization for heart failure and revascularization for restenosis and de novo lesions.	Statistical comparisons were not performed between groups.	Statistical comparisons were not performed between groups.	Statistical comparisons were not performed between groups.	Statistical comparisons were not performed between groups.	Statistical comparisons were not performed between groups.	Statistical comparisons were not performed between groups.
Mazurek et al.[17]	30-day MACE: higher in previous DM compared to other study groups. 1-year MACE: more frequent in patients with previous DM and IGT than in IFG and NGT. Long-term follow-up: no significant differences in MACE with respect to glucometabolic status. MACE were defined as occurrence of death, recurrent myocardial infarction, repeated PCI, CABG or stroke.	30-day mortality: no differences with respect to glucometabolic status. 1-year mortality: higher in previous DM and IGT compared to IFG and NGT. Long-term follow-up: mortality in previously known DM, new onset DM and IGT were more frequent than in IFG and NGT.	No differences between previous DM, newly detected DM, IGT, compared to IFG and NGT during all observation periods.	No differences between previous DM, newly detected DM, IGT, compared to IFG and NGT during all observation periods.	Was performed more often in groups with newly detected DM and IGT compared to IFG and NGT within 30-day follow-up.	Stroke more often occurred in patients with newly detected DM compared to NGT during 1-year follow-up.	Event was not analyzed.
George et al.[18]	Newly detected DM and IGT were independent predictors of survival free of MACE. MACE were defined as: cardiovascular death, non-fatal re-infarction, severe heart failure or non-hemorrhagic stroke.	Newly detected DM independently predicted all-cause and cardiovascular mortality.	Newly detected DM independently predicted non-fatal myocardial infarction.	Event was not analyzed.	Event was not analyzed.	No differences between glucometabolic groups.	No differences between glucometabolic groups.
Knudsen et al.[19]	Similar long-term MACE in patients with abnormal and normal glucose regulation. MACE were defined as: non-fatal myocardial re-infarction, recurrent ischemia causing hospital admission, stroke, and all-cause mortality.	Statistical comparisons were not performed between groups.	Statistical comparisons were not performed between groups.	Event was not analyzed.	Event was not analyzed.	Statistical comparisons were not performed between groups.	Event was not analyzed.

cd. tab. II

1	2	3	4	5	6	7	1
Bartnik et al.[21]	Abnormal glucose tolerance was independent predictor of MACE. MACE were defined as: non-fatal stroke, non-fatal re-infarction, severe heart failure necessitating hospitalization or cardiovascular death.	Statistical comparisons were not performed between groups.	Statistical comparisons were not performed between groups.	Event was not analyzed.	Event was not analyzed.	Event was not analyzed.	Statistical comparisons were not performed between groups.
Kowalczyk et al.[10]	MACE were not analyzed either as combined endpoint or particular event.	Increase in HbA1c in patients with newly detected glucose abnormalities (IGT and newly detected DM) was associated with significantly reduced survival. Increase in HbA1c in those patients was independent risk factor of death.	Event was not analyzed.	Event was not analyzed.	Event was not analyzed.	Event was not analyzed.	Event was not analyzed.

Abbreviations: MACE = major adverse cardiovascular events; AMI = acute myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery by-pass grafting; ACS = acute coronary syndrome; 2h-PG = two-hour post-load glycemia; IGT-impaired glucose tolerance; DM = diabetes mellitus; IFG = impaired fasting glycemia; NGT = normal glucose tolerance; HbA1c = glycosylated hemoglobin.

Table III. Prevalence of glucose abnormalities at hospital discharge, at 3-month and 12-month follow-up
Tabela III. Stan glukometaboliczny przy wypisie ze szpitala, po 3 i 12 miesiącach

	Glucometabolic status after repeated OGTT (3-month follow-up) – percentage of patients at hospital discharge						**Glucometabolic status after repeated OGTT (12-month follow-up) – percentage of patients at hospital discharge**			
Glucometabolic status at hospital discharge	*DM at follow-up*	*IGT at follow-up*	*IFG at follow-up*	*NGR at follow-up*	*AGT (DM and IGT) at follow-up*	*NGT (IFG and NGR) at follow-up*	*DM at follow-up*	*IGT at follow-up*	*AGT (DM and IGT) at follow-up*	*NGT (IFG and NGR) at follow-up*
DM at discharge	-54.8%[14] -53%[13] -28%[20] -22.7%[22]	- 33.3%[14] -32%[13] -36%[20] -27.3%[22]	-0%[22]	-50%[22]	-88.1%[14] -85%[13] -64.3%[20] -50%[22]	-11.9%[14] -15%[13] -36%[20] -50%[22]	-64.3%[14]	- 28.6%[14]	-92.9%[14]	-7.1%[14]
IGT at discharge	-21.1%[14] -17%[13] -3%[20] -6.7%[22]	- 44.7%[14] -45%[13] -34%[20] -18.3%[22]	-6.7%[22]	-68.3%[22]	-65.8%[14] -61.7%[13] -37%[20] 25%[22]	-34.2%[14] -38%[13] -63%[20] -75%[22]	-28.9%[14]	- 42.1%[14]	- 71.1%[14]	-28.9%[14]
IFG at discharge	-0%[22]	-10%[22]	-10%[22]	-80%[22]	-10%[22]	-90%[22]	–	–	–	–
NGR at discharge	-0.9%[22]	-10.1%[22]	-5.5%[22]	-83.5%[22]	-11%[22]	-89%[22]	–	–	–	–
AGT (DM and IGT) at discharge	-38.8%[14] -35.1%[13] -10.4%[20] -11%[22]	- 38.8%[14] -38.3%[13] -34.4%[20] -20.7%[22]	-4.9%[22]	-63.4%[22]	-77.5%[14] -73.4%[13] -44.8%[20] -31.7%[22]	-22.5%[14] -26.6%[13] -55.2%[20] -68.3%[22]	-47.5%[14]	-35%[14]	-82.5%[14]	-17.5%[14]
NGT (IFG and NGR) at discharge	-4.8%[14] -4%[13] -0%[20] -0.8%[22]	-47.6%[14] -48%[13] -14%[20] -10.1%[22]	-5.9%[22]	-83.2%[22]	-52.4%[14] -52.1%[13] -14%[20] -10.9%[22]	-47.6%[14] -48%[13] -86%[20] -89.1%[22]	-11.9%[14]	-28.6%[14]	-40.5%[14]	-59.5%[14]

Abbreviations: OGTT = oral glucose tolerance test; DM = diabetes mellitus; IGT = impaired glucose tolerance; IFG = impaired fasting glycemia; NGR = normal glucose regulation; AGT = abnormal glucose tolerance; NGT = normal glucose tolerance

similar to those observed in the studies by Wallander (AGT→AGT: 77.5%; NGT→AGT: 52.4%) and Tenerz (AGT→AGT: 73.4%; NGT→AGT: 52.1%), rather than by Bronisz (AGT→AGT: 44.8%; NGT→AGT: 14%) and Knudsen (AGT→AGT: 31.7%; NGT→AGT: 10.9%). In a study by Wallander et al. the concordance between OGTT at discharge and at 1 year was even better than after 3 months (AGT→AGT: 83%; NGT→NGT: 60%). One can conclude that there is more agreement between two oral glucose tolerance tests performed in-hospital and after discharge in studies which include both STEMI and NSTEMI patients, do not exclude patients with heart failure, in which OGTT is repeated at longer intervals, and most importantly, OGTT is performed not earlier than on the 4th day after admission to hospital. A higher rate of invasive treatment appears to have no impact on changes in the glucometabolic status after hospital discharge. In the study by our group patients with persistent AGT had a significantly higher mortality than subjects with transient AGT. Newly detected AGT was associated with higher mortality than persistent NGT, however, this difference was statistically non-significant during the follow-up period. More importantly, none of the glycemic parameters measured in-hospital (admission, fasting, and 2h post load glycemia) had the ability to predict a new onset of AGT. To the authors knowledge this is the only published study which shows the prognostic usefulness of repeated oral glucose tolerance test in patients with AMI treated invasively. Whether its prognostic implications are observed because of more glucometabolic derangement or a high prevalence of comorbidities is not known. Nevertheless, the importance of repeated OGTT after acute coronary syndrome is elusive and not mentioned in the most recent ESC guidelines. Moreover, one can assume that repeated OGTT in patients with newly detected diabetes mellitus, although performed in many studies, is controversial.

Hypoglycemic treatment in patients with AMI and newly detected abnormal glucose tolerance – therapeutic concerns

Data on secondary prevention after AMI with respect to antidiabetic treatment in patients with newly detected abnormal glucose tolerance are scarce, therefore, most recommendations are based on studies encompassing patients with stable coronary artery disease and diabetes with a low proportion of subjects with newly detected diabetes. It should be emphasized that in published studies the patients were frequently defined as having DM if diabetes had been known before hospital admission or if it was diagnosed by admission glycemia ≥11.1 mmol/l. Therefore, a substantial number of patients with diabetes that would have been detected by OGTT at hospital discharge were not included. Moreover, in those studies the proportion of patients after AMI, and patients treated with percutaneous coronary intervention was relatively low.

Lifestyle modification (appropriate diet, exercise, smoking cessation, weight reduction) after AMI was associated with a substantially lower risk of diabetes onset or recurrent cardiovascular events [28,29,30]. In patients with impaired glucose tolerance, lifestyle intervention was associated with a lower incidence of newly detected diabetes mellitus and reduced cardiovascular mortality [31]. Conversion to normal glucose regulation, even if transient, was associated with a lower long-term cardiovascular risk in patients with prediabetes [32]. In men with AMI and impaired glucose tolerance there was a beneficial effect of regular physical training on reducing fasting insulinemia [33]. Schramm et al. analyzed the mortality and cardiovascular risk of adults initiating a single-agent: insulin secretagogues or metformin [34]. Monotherapy with one of the most commonly used drugs: glimepiride, glibenclamide, glipizide, and tolbutamide, seemed to be related to a higher mortality and cardiovascular risk compared with metformin, however, gliclazide and repaglinide appeared to be associated with a lower risk than treatment with the remainder of this group and a comparable risk to those treated with metformin. Those results were similar in patients with previous AMI [34]. The authors of the DIGAMI II study in diabetic patients with AMI, allocated to three treatment arms, reported that neither all-cause mortality nor morbidity differed between the three groups [35]. In a *post hoc* analysis of this study the authors concluded that although there were no differences in mortality between diabetic patients treated with sulphonylureas, metformin, and insulin, the risk of non-fatal myocardial infarction or stroke was higher in patients on insulin treatment, while metformin seemed to be protective [36]. Anselmino et al. showed that there was a pronounced decrease in cardiovascular events in patients with coronary artery disease and prescribed glucose lowering drugs for newly detected diabetes mellitus compared with those not receiving such treatment [37]. In a study by Abualsuod et al., the use of metformin in patients with diabetes was associated with a lower 30-day all-cause mortality and tendency for a lower 12-month all-cause mortality following AMI [38]. Hage et al. showed that sitagliptin improved beta-cell function and glucose perturbations in patients with acute coronary syndromes and newly diagnosed abnormal glucose tolerance [39]. Acarbose reduced the risk of MACE in patients with acute coronary syndromes and newly detected impaired glucose tolerance [40]. In patients with coronary artery disease and newly detected abnormal glucose tolerance, 6-month therapy with eicosapentaenoic acid corrected postprandial hypertriglyceridemia, hyperglycemia and insulin secretion ability. This amelioration of several

metabolic abnormalities was accompanied by recovery from concomitant endothelial dysfunction [41].

Recent ESC guidelines on cardiovascular prevention advocate lifestyle changes, blood pressure and dyslipidemia management, for all patients with diabetes and metformin as first line therapy of type 2 DM, if tolerated and not contra-indicated [42]. A target of glycated hemoglobin of < 7% is recommended for the majority of adults, however, in patients with cardiovascular disease less stringent targets could be considered. Guidelines on diabetes and prediabetes advocate intensive blood pressure and dyslipidemia management, as well as glycosylated hemoglobin < 7% for patients with cardiovascular disease and diabetes or impaired glucose tolerance [43]. Nonetheless, considering the fact that in some patients with AMI newly detected abnormal glucose tolerance is transient, there is a risk of overdiagnosis and overtreatment. Studies in which a transient pattern of disturbed glucose metabolism was observed, have not evaluated whether changes in the glucometabolic status following AMI were a result of good adherence to lifestyle and behavioral advice. In the light of this hypothesis, a very interesting study conducted by Steven et al. should be cited. The authors stated that in patients who responded to a very low calorie diet, type 2 diabetes mellitus was a reversible condition [44]. Whether such a strict diet regimen would be beneficial in terms of cardiovascular outcome in patients after AMI is not known.

CONCLUSIONS

The oral glucose tolerance test should be done in all patients with acute myocardial infarction. The appropriate moment to perform OGTT is crucial for this test to accomplish its role not only as a predictor of long-term glucometabolic status, but also as a valuable prognostic tool. The use of other glucometabolic parameters like fasting glycemia or glycosylated hemoglobin may be used to assess the risk of persistent abnormal glucose tolerance, however OGTT may be repeated to prevent overdiagnosis of AGT, improve initial risk stratification and select “true” high-risk individuals. In all patients with AMI and abnormal glucose tolerance, lifestyle modification should be advised, and intensive treatment of dyslipidemia and high blood pressure initiated according to AMI guidelines. Whether, when and in which patients hypoglycemic pharmacotherapy should be initiated is elusive. Nevertheless, according to the guidelines metformin should be the first line medication.

REFERENCES:

1. Simon D., Coignet M.C., Thibult N., Senan C., Eschwège E. Comparison of glycosylated hemoglobin and fasting plasma glucose with two-hour post-load plasma glucose in the detection of diabetes mellitus. Am. J. Epidemiol. 1985; 122(4): 589–593.

2. DECODE Study Group, the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. Arch. Intern. Med. 2001; 161(3): 397–405.

3. Bartnik M., Rydén L., Malmberg K., Ohrvik J., Pyörälä K., Standl E., Ferrari R., Simoons M., Soler-Soler J. Oral glucose tolerance test is needed for appropriate classification of glucose regulation in patients with coronary artery disease: a report from the Euro Heart Survey on Diabetes and the Heart. Heart. 2007; 93(1): 72–77.

4. Kuramitsu S., Yokoi H., Domei T., Nomura A., Watanabe H., Yamaji K., Soga Y., Arita T., Kondo K., Shirai S., Ando K., Sakai K., Iwabuchi M., Nosaka H., Nobuyoshi M. Impact of post-challenge hyperglycemia on clinical outcomes in Japanese patients with stable angina undergoing percutaneous coronary intervention. Cardiovasc. Diabetol. 2013; 12: 74.

5. Qiao Q., Pyörälä K., Pyörälä M., Nissinen A., Lindström J., Tilvis R., Tuomilehto J. Two-hour glucose is a better risk predictor for incident coronary heart disease and cardiovascular mortality than fasting glucose. Eur. Heart. J. 2002; 23(16): 1267–1275.

6. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. The DECODE study group. European Diabetes Epidemiology Group. Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe. Lancet 1999; 354(9179): 617–621.

7. The DECODE Study Group. European Diabetes Epidemiology Group. Is the current definition for diabetes relevant to mortality risk from all causes and cardiovascular and noncardiovascular diseases? Diabetes Care 2003; 26(3): 688–696.

8. Ning F., Tuomilehto J., Pyörälä K., Onat A., Söderberg S., Qiao Q. Cardiovascular disease mortality in Europeans in relation to fasting and 2-h plasma glucose levels within a normoglycemic range. Diabetes Care 2010; 33(10): 2211–2216.

9. Qiao Q., Dekker J.M., de Vegt F., Nijpels G., Nissinen A., Stehouwer C.D., Bouter L.M., Heine R.J., Tuomilehto J. Two prospective studies found that elevated 2-hr glucose predicted male mortality independent of fasting glucose and HbA1c. J. Clin. Epidemiol. 2004; 57(6): 590–596.

10. Kowalczyk J., Mazurek M., Zielinska T., Lenarczyk R., Sedkowska A., Swiatkowski A., Sredniawa B., Mencel G., Francuz P., Kalarus Z.. Prognostic significance of HbA1c in patients with AMI treated invasively and newly detected glucose abnormalities. Eur. J. Prev. Cardiol. 2015; 22(6): 798–806. doi: 10.1177/2047487314527850.

11. Rydén L., Grant P.J., Anker S.D., Berne C., Cosentino F., Danchin N., Deaton C., Escaned J., Hammes H.P., Huikuri H., Marre M., Marx N., Mellbin L., Ostergren J., Patrono C., Seferovic P., Sousa Uva M., Taskinen M.R., Tendera M., Tuomilehto J., Valensi P., Zamorano J.L. ESC guidelines on diabetes, pre-diabetes and diseases of the cardiovascular system developed in cooperation with the EASD. Kardiol. Pol. 2013; 71 Suppl. 11: S319–S394.

12. Norhammar A., Tenerz A., Nilsson G., Hamsten A., Efendíc S., Rydén L., Malmberg K. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. Lancet. 2002; 359(9324): 2140–2144.

13. Tenerz A., Norhammar A., Silveira A., Hamsten A, Nilsson G, Rydén L, Malmberg K.Diabetes, insulin resistance, and the metabolic syndrome in patients with acute myocardial infarction without previously known diabetes. Diabetes Care. 2003; 26: 2770–2776.

14. Wallander M., Malmberg K., Norhammar A., Rydén L., Tenerz A. Oral glucose tolerance test: a reliable tool for early detection of glucose abnormalities in patients with acute myocardial infarction in clinical practice: a report on repeated oral glucose tolerance tests from the GAMI study. Diabetes Care. 2008; 31(1): 36–38.

15. Tamita K., Katayama M., Takagi T. Yamamuro A., Kaji S., Yoshikawa J., Furukawa Y. Newly diagnosed glucose intolerance and prognosis after acute myocardial infarction: comparison of post-challenge versus fasting glucose concentrations. Heart 2012; 98: 848–854.

16. Kitada S., Otsuka Y., Kokubu N. Kasahara Y., Kataoka Y., Noguchi T., Goto Y., Kimura G., Nonogi H. Post-load hyperglycemia as an important predictor of long-term adverse cardiac events after acute myocardial infarction: a scientific study. Cardiovasc. Diabetol. 2010; 9: 75.

17. Mazurek M., Kowalczyk J., Lenarczyk R. Zielinska T., Sedkowska A., Pruszkowska-Skrzep P., Swiatkowski 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; 11: 78.

18. George A., Bhatia R.T., Buchanan G.L., Whiteside A., Moisey R.S., Beer S.F., Chattopadhyay S., Sathyapalan T., John J. Impaired Glucose Tolerance or Newly Diagnosed Diabetes Mellitus Diagnosed during Admission Adversely Affects Prognosis after Myocardial Infarction: An Observational Study. PLoS One 2015; 10(11): e0142045. doi: 10.1371/journal.pone.0142045.
19. Knudsen E.C., Seljeflot I., Abdelnoor M., Eritsland J., Mangschau A., Müller C., Arnesen H., Andersen G.O. Impact of newly diagnosed abnormal glucose regulation on long-term prognosis in low risk patients with ST--elevation myocardial infarction: A follow-up study. BMC Endocr. Disord. 2011; 11: 14.
20. Bronisz A., Kozinski M., Magielski P., Fabiszak T., Gierach J., Swiatkiewicz I., Sukiennik A., Kubica A., Bronisz M., Grabczewska Z., Sinkiewicz A., Junik R., Kubica J. Value of oral glucose tolerance test in the acute phase of myocardial infarction. Cardiovasc. Diabetol. 2011; 10: 21.
21. Bartnik M., Malmberg K., Norhammar A., Tenerz A., Ohrvik J., Rydén L. Newly detected abnormal glucose tolerance: an important predictor of long-term outcome after myocardial infarction. Eur. Heart. J. 2004; 25(22): 1990–1997.
22. Knudsen E.C., Seljeflot I., Abdelnoor M., Eritsland J., Mangschau A., Arnesen H., Andersen G.O. Abnormal glucose regulation in patients with acute ST-elevation myocardial infarction-a cohort study on 224 patients. Cardiovasc. Diabetol. 2009; 8: 6.
23. Francuz P., Podolecki T., Przybylska-Siedlecka K., Kalarus Z., Kowalczyk J. Long-term prognosis is related to mid-term changes of glucometabolic status in patients with acute myocardial infarction treated invasively. Kardiol Pol. 2017; 75(2): 117–125. doi: 10.5603/KP.a2016.0128.
24. Eriksson K.F., Lindgärde F. Impaired glucose tolerance in a middle-aged male urban population: a new approach for identifying high-risk cases. Diabetologia 1990; 33(9): 526–531.
25. Alberti K.G., Zimmet P.Z. Definition diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet. Med. 1998; 15(7): 539–553.
26. Köbberling J., Kerlin A., Creutzfeldt W. The reproducibility of the oral glucose tolerance test over long (5 years) and short periods (1 week). Klin. Wochenschr. 1980; 58(10): 527–530.
27. Henareh L., Agewall S. 2-h postchallenge plasma glucose predicts cardiovascular events in patients with myocardial infarction without known diabetes mellitus. Cardiovasc. Diabetol. 2012; 11: 93.
28. Chow C.K., Jolly S., Rao-Melacini P., Fox K.A., Anand S.S., Yusuf S. Association of diet, exercise, and smoking modification with risk of early cardiovascular events after acute coronary syndromes. Circulation 2010; 121(6): 750–758.
29. Mozaffarian D., Marfisi R., Levantesi G., Silletta M.G., Tavazzi L., Tognoni G., Valagussa F., Marchioli R. 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(9588): 667–675.
30. Li S., Chiuve S.E., Flint A., Pai J.K., Forman J.P., Hu F.B., Willett W.C., Mukamal K.J., Rimm E.B. Better diet quality and decreased mortality among myocardial infarction survivors. JAMA Intern. Med. 2013; 173(19): 1808––1818.
31. Li G., Zhang P., Wang J., An Y., Gong Q., Gregg E.W., Yang W., Zhang B., Shuai Y., Hong J., Engelgau M.M., Li H., Roglic G., Hu Y., Bennett P.H. Cardiovascular mortality, all-cause mortality, and diabetes incidence after lifestyle intervention for people with impaired glucose tolerance in the Da Qing Diabetes Prevention Study: a 23-year follow-up study. Lancet Diabetes Endocrinol. 2014; 2(6): 474–480.
32. Perreault L., Temprosa M., Mather K.J., Horton E., Kitabchi A., Larkin M., Montez M.G., Thayer D., Orchard T.J., Hamman R.F., Goldberg R.B. Regression from prediabetes to normal glucose regulation is associated with reduction in cardiovascular risk: results from the Diabetes Prevention Program outcomes study. Diabetes Care 2014; 37: 2622–2631.
33. Stochmal A., Jasiak-Tyrkalska B., Stochmal E., Huszno B., Kawecka--Jaszcz K. The influence of physical training on metabolic indices in men with myocardial infarction and impaired glucose tolerance. Prz. Lek. 2007; 64: 410–415.
34. Schramm T.K., Gislason G.H., Vaag A., Rasmussen J.N., Folke F., Hansen M.L., Fosbøl E.L., Køber L., Norgaard M.L., Madsen M., Hansen P.R., Torp-Pedersen C. Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study. Eur. Heart. J. 2011; 32(15): 1900–1908.
35. Malmberg K., Rydén L., Wedel H., Birkeland K., Bootsma A., Dickstein K., Efendic S., Fisher M., Hamsten A., Herlitz J., Hildebrandt P., MacLeod K., Laakso M., Torp-Pedersen C., Waldenström A. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. Eur. Heart. J. 2005; 26(7): 650–661.
36. Mellbin L.G., Malmberg K., Norhammar A., Wedel H., Rydén L. The impact of glucose lowering treatment on long-term prognosis in patients with type 2 diabetes and myocardial infarction: a report from the DIGAMI 2 trial. Eur. Heart. J. 2008; 29(2): 166–176.
37. Anselmino M., Ohrvik J., Malmberg K., Standl E., Rydén L. Glucose lowering treatment in patients with coronary artery disease is prognostically important not only in established but also in newly detected diabetes mellitus: a report from the Euro Heart Survey on Diabetes and the Heart. Eur. Heart. J. 2008; 29(2): 177–1784.
38. Abualsuod A., Rutland J.J., Watts T.E., Pandat S., Delongchamp R., Mehta J.L. The Effect of Metformin Use on Left Ventricular Ejection Fraction and Mortality Post-Myocardial Infarction. Cardiovasc Drugs Ther. 2015; 29(3): 265–275.
39. Hage C., Brismar K., Efendic S., Lundman P., Rydén L., Mellbin L. Sitagliptin improves beta-cell function in patients with acute coronary syndromes and newly diagnosed glucose abnormalities-the BEGAMI study. J. Intern. Med. 2013; 273(4): 410–421.
40. Yun P., Du A.M., Chen X.J., Liu J.C., Xiao H. Effect of Acarbose on Long-Term Prognosis in Acute Coronary Syndromes Patients with Newly Diagnosed Impaired Glucose Tolerance. J. Diabetes. Res. 2016: 1602083.
41. Sawada T., Tsubata H., Hashimoto N., Takabe M., Miyata T., Aoki K., Yamashita S., Oishi S., Osue T., Yokoi K., Tsukishiro Y., Onishi T., Shimane A., Taniguchi Y., Yasaka Y., Ohara T., Kawai H., Yokoyama M. Effects of 6-month eicosapentaenoic acid treatment on postprandial hyperglycemia, hyperlipidemia, insulin secretion ability, and concomitant endothelial dysfunction among newly-diagnosed impaired glucose metabolism patients with coronary artery disease. An open label, single blinded, prospective randomized controlled trial. Cardiovasc. Diabetol. 2016; 15(1): 121.
42. Piepoli M.F., Hoes A.W., Agewall S., Albus C., Brotons C., Catapano A.L. Cooney M., Corrà U., Cosyns B., Deaton C., Graham I., Hall M.S., Hobbs F.D., Løchen M.L., Löllgen H., Marques-Vidal P., Perk J., Prescott E., Redon J., Richter D.J., Sattar N., Smulders Y., Tiberi M., van der Worp H.B., van Dis I., Verschuren W.M., Binno S. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. Kardiol. Pol. 2016; 74(9): 821–936. doi: 10.5603/KP.2016.0120.
43. Rydén L., Grant P.J., Anker S.D. et al. ESC Guidelines on diabetes, prediabetes, 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). Eur. Heart. J. 2013; 34: 3035–3087.
44. Steven S., Hollingsworth K.G., Al-Mrabeh A., Avery L., Aribisala B., Caslake M., Taylor R. Very Low-Calorie Diet and 6 Months of Weight Stability in Type 2 Diabetes: Pathophysiological Changes in Responders and Nonresponders. Diabetes. Care. 2016; 39(5): 808–815.