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ČETIRI TIPA ŠEĆERNE BOLESTI U AKUTNOM INFARKTU MIOKARDA

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FOUR VARIETIES OF DIABETES MELLITUS IN ACUTE MYOCARDIAL INFARCTION

Četiri tipa šećerne bolesti u akutnom infarktu miokarda

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Abstract

Patients with diabetes mellitus (DM) have a two- to four-fold increased risk of developing cardiovascular disease, three-fold for acute coronary syndrome and they experience cardiovascular events 15 years earlier than the general population. In a recent paper, among acute myocardial infarction (AMI) patients only 30% were clinically diagnosed (as having DM) in the hospital and were treated instantly. Therefore, majority of DM patients in AMI were either not diagnosed or not treated. It is important to measure glycosylated hemoglobin A1c (HbA1C) on admission to detect unrecognized patients with glucometabolic abnormalities. OGTT before discharge or within the 3 next months is recommended in the majority of guidelines, but not in all. It is reasonable not to omit OGTT at least if HbA1c is not conclusive. DM and pre-DM are important prognostically, they can be prevented or treated only if detected. There is no excuse to avoid at least one of such routine tests, as it has been occurred frequently in practice, with probable serious clinical consequence.

Key Words: diabetes mellitus, acute myocardial infarction, OGTT, glycosylated hemoglobin A1c , early detection

Apstrakt

Pacijenti koji boluju od šećerne bolesti (ŠB) imaju dvostruko do četvorostruko veći rizik za nastanak kardiovaskularnih bolesti, trostruko veći rizik za nastanak akutnog koronarnog sindroma i oni dožive kardiovaskularne događaje 15 godina ranije nego opšta populacija. Prema poslednjem istraživanju, samo 30% pacijenata sa akutnim infarktom miokarda (AIM) je klinički dijagnostikovano (da boluje od ŠB) u bolničkim uslovima i odmah tretirano. Zbog toga većina pacijenata sa ŠB u AIM ili nije bila dijagnostikovana ili nije bila lečena. Važno je da se na prijemu izmeri glikozilisani hemoglobin A1C (HbA1C) kako bi se otkrili pacijenti sa do tada neprepoznatim glikometaboličkim poremećajima. OGTT neposredno pre otpusta ili unutar 3 meseca po otpuštanju se preporučuje u većini vodiča, ali ne u svim. Razumno je uraditi OGTT ako je nalaz HbA1C suspektan. DM i pre-DM su prognostički važni i mogu se prevenirati i lečiti samo ako se otkriju. Ne postoji opravdanje da se ne uradi bar jedan od navedenih rutinskih testova, kao što se to čedto dešava u praksi sa verovatno ozbilnim kliničkim komplikacijama.

Ključne reči: šećerna bolest, akutni infarkt miokarda, OGTT, glikozilisani hemoglobin A1C, rana detekcija

Diabetes mellitus (DM) as a risk factor for acute myocardial infarction (AMI)

It is believed that 387 million patients (>8% of the global population) have DM, and almost half of them are unaware of their diagnosis (1). DM has been very important risk factor for AMI (2). Patients with DM have a two- to four-fold increased risk of developing cardiovascular (CV) disease (3), three-fold for ACS (4) and they experience CV events 15 years earlier than the general population (4,5). Patients with DM were believed to have as high risk for the new AMI as patients with previous MI (the “CAD equivalent”) (6-8). This is an overestimation, as shown by meta-analysis (9). The Euro Heart Survey and other registries / studies founded that a majority of ACS patients have had dysglycaemia, including DM, which was not previously diagnosed (1, 8,10,11). Patients with MI have the incidence of insulin resistance twice as often as individuals with no history of MI. Therefore some authors consider *MI a pre-DM equivalent* (1, 8) or a *DM risk equivalent* (12) or a *pre-DM risk equivalent* (13). Out of 2,036 DM-naïve CAD patients who were followed up for at least one year, AMI significantly increased the risk of “new-onset” DM after adjusting covariates (HR, 1.54; 95% CI, 1.14–2.07; p<0.01) (14).

Nevertheless, a short- term (4) and a long-term mortality risk in AMI patients with DM is almost doubled in comparison with non-diabetic AMI patients (2,4,7). A systematic review and meta-regression of 1,614,174 AMI or acute coronary syndromes (ACS) patients showed that patients with DM (n=432,066) had an odds ratio (OR) [95% CI] of 1.66 [1.59-1.74] (p<0.0001) for early mortality, and of 1.86 [1.75-1.97] (p<0.0001) for 6-12 months mortality in comparison with 1,182,108 nondiabetic patients (2). The mortality risk after a 10 year follow-up in patients with CAD and DM exceeds 70% (15). Glycemia on admission of 108-126 mg/dl (6-7 mmol) in AMI patients with DM is associated to 3 times higher mortality vs. AMI patients without DM (16,17). In AMI, the risk for repeat MIs, heart failure, cardiogenic shock and stroke is also greater in patients with concomitant DM, as compared to AMI patients without DM (4,18). Increased mortality in AMI patients with vs. without DM has remained constant over time (from 1970 to 2011), despite important therapeutic advantages (2). Survival curves were persistently diverging for 20 years between AMI patients with and without DM and median survival was less by 3.3 years

($p < 0.0001$) in DM patients following the AMI (5). DM confers increased in-hospital mortality risk in both STEMI and NSTEMI patients (19).

Moreover, this dismal prognosis of patients with AMI and DM is not related to body mass index, i.e., „obesity paradox“ is not relevant to them (in contrast to AMI patients without DM) (20). Indeed, a meta-analysis of 21,759 DM patients (~29% of them were insulin-treated) revealed that both short term and long term mortality, and the incidence of new AMI, target lesion revascularization, major adverse cardiac effect (MACE) and, stent thrombosis were significantly more frequent in insulin-treated DM patients (21). Also, among 243,861 patients with AMI the in-hospital mortality risk was higher in insulin-treated DM patients ($n=20,051$) vs. DM patients who did not require insulin ($n=25,364$) (19). DM is prevalent in AMI, with usually quoted figures between 20-30% (7, 22-24) or 30-40% (25) and the incidence and the prevalence of DM are expected to grow further (2, 26). Another 300 million individuals have been at risk of developing DM (26). Even higher actual prevalence has been published, as a few recent papers reported almost doubled DM prevalence in AMI (47%) (27).

Diagnosing DM in AMI has been clearly suboptimal

In a recent paper of the 3,778 AMI patients who had no history of DM before admission 18.7% had a criterion for DM during hospitalization (a fasting glucose level of at least 126 mg/dL (7 mmol), a random plasma glucose (RPG) of at least 200 mg/dL (11.1 mmol) or a glycated hemoglobin [HbA1c] level of at least 6.5%). Out of AMI patients with criteria for new-onset DM *only 30% were clinically diagnosed (as having DM) in the hospital and were treated instantly* (27). Similarly, in a study of 1,566 patients insulin or oral agents were prescribed at discharge for 80% of patients with known DM and only 25.4% of patients with newly diagnosed DM (1). Therefore, great majority of newly diagnosed DM remained without appropriate hypoglycemic treatment, which is very important finding. Indeed, the AMI patients who *met the criteria for a DM but were not diagnosed* had a significantly higher risk for a MACE 1 year following discharge compared with patients without previous diagnosis of DM (OR, 1.5; 95% confidence interval [CI], 1.3-1.7; $p < 0.0001$). On the other hand, there was not a statistically significant difference between the patients with properly newly diagnosed DM and patients without DM (OR, 1.3; 95%

CI, 0.9-1.7; $p=0.15$) (27). The authors divided their DM patients into only *three* groups 1. with history of DM (34%); 2. without history of DM, without history of DM, diagnosed during hospitalization (4%) and with criteria for DM, but undiagnosed during intra-hospital stay (9%) (27).

How many sorts of DM can be observed in AMI?

We believe that it is important to recognize that there have been actually *four sorts* of DM in ACS:

A) **Previously diagnosed** DM (1)

B) **Newly diagnosed (previously present, but not diagnosed** until this admission) DM, with HbA1c $>6.5\%$ (1, 28)

C) **New-onset** DM with HbA1c $<6.5\%$ and with either C1. Fasting blood glucose (FBG) ≥ 126 mg/dL (7 mmol) or C2. A RPG ≥ 200 mg/dL (11.1 mmol) or C3. Positive oral glucose tolerance test (OGTT) before discharge with 2-hr PG ≥ 200 mg/dL (11.1 mmol/L) (1).

D) **Undetected DM**, i.e., some of the four 2016 American Diabetes Association (ADA) criteria [in terms of fasting blood glucose ≥ 126 mg/dL (7 mmol) or a RPG ≥ 200 mg/dL (11.1 mmol/L) or A1C $\geq 6.5\%$ (48 mmol/mol) or 2-hr PG ≥ 200 mg/dL (11.1 mmol/L) during OGTT (75-g)] not fulfilled and the other analysis not performed (29).

Some frequent mistakes in categorizing DM and stress hyperglycemia in AMI

The fourth group (D) is missing in the aforementioned work (27) and with this group, the number of DM patients in AMI would be even higher. Consequently, as these patients have been neither diagnosed nor treated – *the real number of adequately diagnosed and treated DM patients in AMI is therefore even less than 30%. This should call to action.* Regarding terminology in this topic, there is a mistake with labeling “newly diagnosed” DM as “new-onset”. In AMI, patients without known (previously diagnosed) DM can be considered as having “new-onset”, which frequently is not true, because they may have unrecognized

DM for some time. It is not difficult to distinguish “new onset DM” from undiagnosed DM, because HbA1c is normal in the first and elevated in the second case.

Common methodologic mistake for decades was to use the same cut-off in AMI patients for the subgroup with the glycometabolic disease (DM) and without it. This single cut-off was artificially low for DM patients (and high for non-DM ones) and decreased somewhat the predictive accuracy of stress hyperglycemia (SH). It is particularly true for DM patients, because they are less prevalent in AMI, so that their cut-off value for SH is more remote from the artificial single cut-off of the whole AMI group (30). A hyperglycemia is common, valid for both for risk stratification and for treatment initiation and adjustments, but often underestimated parameter in critical illnesses, including AMI (31). The importance of hyperglycemia in AMI stems from two facts: AMI is one of the most common lethal diseases and glycemia is undoubtedly one of the basic parameters in general and in AMI (17). Hyperglycemia in AMI has different cut-offs for prognostic and therapeutic purposes. The common mistake is to take therapeutic threshold e.g., 11 mmol/L (198 mg/dl) for prognostic one, because AMI patients without DM have far less prognostic cut-off ~8 mmol/L (144 mg/dl) (32). Post-prandial hyperglycaemia contributed more to CAD genesis as compared to fasting hyperglycemia (33). No less than 84% of AMI patients with abnormal glucose tolerance had normal fasting plasma glucose (FPG) (34).

Comparison of the most important tools to detect DM in AMI (in addition to FPG and RPG)

Glycosylated hemoglobin A1c (HbA1c) is a marker of an increased CV risk in patients with and without DM (35). ADA recommended the HbA1c with a threshold of 6.5%, to diagnose DM, due to its preanalytical stability, convenience (fasting not required), and less day-to-day variability (28). Moreover, HbA1c is currently used to guide management decisions (4). ACS patients with HbA1c of 6.0-6.4% should have an OGTT 6-8 weeks after discharge (4). HbA1c reflects the average glycemia, including postprandial spikes during last 3 months (36). The relation of postprandial hyperglycemia and risk of CV diseases was demonstrated in a meta-analysis of 95,783 individuals (3,37). HbA1c has a low intra-

individual variability and is not influenced by the stress caused by ACS (25,36). A single measurement of HbA1c is not sufficient to diagnose DM (38). Using HbA1c, FPG, and RPG newly diagnosed DM was found in ~1/5 of all AMI patients and pre-DM in 14% (39)

OGTT has been often recommended for AMI patients (23,25,26). But neither from ADA (28) nor from NICE (40) OGTT is a valid screening tool for both DM and a high CV risk (41). OGTT in patients with ACS has comparable accuracy to that in general population. Therefore, it is sound to perform OGTT in ACS patients to improve search for such an important disease as DM (42). Bronisz et al. reported that a substantial proportion of AMI patients with abnormal result of OGTT soon after AMI can have normal glucose tolerance 3 months after AMI (43). To the contrary a meta-analysis found that <10% ACS patients diagnosed with DM by means of an OGTT before discharge will have a different result at the follow-up OGTT (42). Moreover, HbA1c is more expensive, it is not available so widely, and does not correlate adequately with the average glucyemia in certain individuals (44).

Comparing all three glycaemic parameters: FPG, OGTT and HbA1c simultaneously for mortality and CV disease risk revealed that the association is strongest for 2-hour plasma glucose concentration (2hPG) in OGTT (26). In addition to FPG and HbA1c, OGTT reveals many more cases of DM, in both the general population and CAD (45). A portion of AMI patients with new-diagnosed AMI by means of OGTT has not been negligible (8). The OGTT showed that 27.4% of CAD patients without known DM at admission actually had DM. Moreover, 33.5% were found to have impaired glucose tolerance (IGT) and another 11.2% were found to have both IGT and impaired fasting glucose (IFG) (46). On one hand HbA1c $\geq 6.5\%$ can predict DM values on OGTT (2hPG value ≥ 11.1 mmol/L) with positive predictive value of no less than 100% and could, therefore, replace the OGTT to diagnose DM following ACS (25). To the contrary, OGTT or HbA1c may not diagnose the same patients: evidence of discrepancies between the two modalities to classify abnormal glycoregulation has been accumulating (25). An OGTT is likely needed but it is a dilemma when to perform it, during the initial hospitalization or later on (e.g., within 30 days or at three months). Variable practice reflects directly the lack of consensus: some authors used to perform OGTT:

- A) Knudsen et al. performed OGTT as early as on the *day one* of hospitalization (47)
- B) On the *day three* from the admission (34, 48, 49)
- C) On the *day four* of hospitalization (50) The ESC guidelines also recommend delaying the test for *4 to 5 days* after an ACS to minimize false positive results (51, 52) because results of OGTT could be somewhat falsified by stress hyperglycemia (52)
- D) *One–three days following the hospital discharge* (53)
- E) Seven to 28 days after ACS (25).
- or F) *3 months after discharge* (42, 46).

An OGTT at discharge performed in patients with AMI detected a high proportion of patients with previously unknown abnormal glycoregulation that was significantly and independently related to dismal long-term prognosis (41). Within seven days following AMI an OGTT can detect many patients with previously unknown either newly detected DM or IGT, indicating high risk for CV events in the next decade. OGTT was a better prognosticator as compared to fasting blood glucose (FBG) or HbA1c (41).

The combination of HbA1c and OGTT to diagnose DM in AMI patients

To obtain the diagnosis of DM as soon as possible, HbA1c and FBG should be analysed during the first days of hospitalization, but both of them will leave an undetected group of patients with glucometabolic abnormalities (41). Indeed, an OGTT should be performed when HbA1c and FPG are inconclusive (51). Moreover, a combination of tests (both HbA1c and OGTT) in addition to simple FBG can be used to better risk-stratify AMI patients. The OGTT is more sensitive than fasting plasma glucose and HbA1c. AMI patients categorized as newly diagnosed DM by OGTT although HbA1c <6.5% have a poor long-term prognosis compared to patients with HbA1c <6.5% and an IFG or normal glucose tolerance (NGT) / IGT by OGTT (37). The combination of HbA1c and OGTT seems sound. For example, in AMI patients treated invasively with IGT and newly diagnosed DM (detected by OGTT) increase of HbA1c was one of the strongest

independent risk markers of death (54). An OGTT in combination with HbA1c provides additional prognostic information on all-cause mortality, as this identifies a group of high-risk patients, who would have been remained undetected if using an OGTT or HbA1c only (38). Regretably, in practice, HbA1C levels were not available in about 3/4 of AMI patients without DM (19). Moreover, the frequency of performing HbA1c varied widely was quite different among hospitals (capturing from 7.7% to 87.6% of hospitalized patients) (55).

The real world underutilization of evidence-based therapies for DM may contribute to worse outcome of patients with DM and ACS (7). Early diagnosis and treatment of dysglycemia may slow down or even reverse the adverse effects on the CV system (11). Improved glycaemic control in DM patients following AMI results in reduced long-term mortality (55). A greater benefit could be obtained from treating ACS patients with newly diagnosed DM more intensively (4). Some of the important advantages of measuring HbA1c and performing OGTT are the following:

- 1) A timely detection of abnormal glucose regulation (during AMI hospitalization or shortly after it) could give rise to the prevention strategies, such as lifestyle and pharmacological interventions, which can help *prevent DM* (45, 46).
- 2) the detection of pre-DM can be used to *avoid drugs known to impair glucoregulation*, such as diuretics, non-vasodilatory and non-selective beta blockers, some types of statins, etc (56, 57, 58) .
- 3) When DM is diagnosed, appropriate diet, *anti-DM drugs*, exercise programs, etc. can be planned to improve quality of life and prognosis (29).
- 4) Moreover, in newly diagnosed DM *prevention of CV diseases* can be improved, such as introduction / intensification of treatment (e.g., renin-angiotensin system inhibitor, statin, aspirin etc), as risk category changes substantially with the diagnosis of DM.
- 5) Timely DM diagnosis can improve even the *mode of reperfusion*, as diabetic status influence the choice of between coronary artery by-pass graft (CABG) and stent, and further – the choice of stent, as well as antiplatelet therapy. For example, <20% of the

patients with dysglycaemia detected by OGTT received drug-eluting stents (DES), since they were treated as non-diabetic patients at the time of percutaneous coronary intervention (PCI) (1,11)

6) In multivariate analysis, ACS patients with pre-DM (OR, 1.58, 95%:1.08-2.31) and undiagnosed DM (OR, 1.51, 95%:1.01–2.26) also had more frequently reduced kidney function, in comparison with AMI patients who had normal glycoregulation (23).

Consequently, detection of pre-DM and previously undiagnosed DM could enable us to pay more attention to *kidney function and prevent* its deterioration. It may be useful to have information about pre-DM and newly detected DM prior to imaging techniques requiring contrast, in order to better prevent contrast induced nephropathy (CIN), i.e., acute kidney injury (AKI). Moreover, additional care should be taken to avoid potentially nephrotoxic drugs, such as, e.g., aminoglycosides.

Conclusion: There are four different DM varieties in ACS. The real number of adequately diagnosed and treated DM patients in AMI could be even less than 30%. It is important to measure HbA1c on admission to detect unrecognized patients with glucometabolic abnormalities. OGTT before discharge or within the 3 next months is recommended in the majority of guidelines, but not in all. It is reasonable not to omit OGTT at least if HbA1c is not conclusive. DM and pre-DM are important prognostically, they can be prevented or treated only if detected. There is no excuse to avoid at least one of such routine tests, as it has been occurred frequently in practice, with probable serious clinical consequence (Table 1).

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Table 1.**Detection of DM in AMI patients**

Method Reference	Advantage	
RPG >11.1 mmol	routine, always available	1,27
FBG >7 mmol	routine, always available	1,46
HbA1C >6.5%	widely available, within 24hours	1,28
OGTT 2-hr PG \geq 11.1mmol/L	improves DM detection additionally	26,45
All above	provides optimal result in DM detection	36,41,51

RPG (random plasma glucose); FBG (fasting blood glucose); HbA1C (glycated haemoglobin A1C); OGTT (oral glucose tolerance test)

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