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Glycemia in patients with type 2 diabetes during inpatient treatment for acute myocardial infarction: impact on prognosis

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Aim. To investigate the relationship between abnormal glycemia levels during inpatient treatment for acute myocardial infarction (AMI) in patients with type 2 diabetes (T2D) and long-term prognosis.

Material and methods. The single-center cohort study included patients with AMI and concomitant T2D who were hospitalized consecutively for 200 days. A total of 237 patients were included. The median number of blood glucose measurements during hospitalization was 15 [8; 20] times. Long-term outcome was estimated at 365 days after hospitalization.

Results. The first glycemic value on admission was 13,6±5,9, while the average glycemia during hospitalization was 10,0±3,5 mmol/L. Within 12 follow-up period, 53 deaths were recorded. It was found that exceeding the glycemic threshold of 10,0 mmol/L in more than 45% of measurements during hospitalization was associated with a 3-fold increase in the risk of an unfavorable outcome within 12 months. Predictors of poor glycemic control are insulin therapy before MI and blood glucose at admission >12,1 mmol/L.

Conclusion. Poor glycemic control (>45% of glucose measurements above the threshold of 10,0 mmol/L) during hospitalization for AMI in patients with T2D is associated with an increased risk of in-hospital death and during the next 12 months, including in patients who underwent endovascular treatment.

Keywords: myocardial infarction, diabetes, glycemic control.

Relationships and Activities: none.

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Type 2 diabetes mellitus (T2DM) is a serious medical and social problem, which is due to its high prevalence, a steady trend towards an increase in number of patients and its impact on mortality. The presence of T2DM is associated with an increased risk of acute cardiovascular diseases, in particular, the risk of acute myocardial infarction (AMI) is 1,5-3,0 times higher than in the general population [1]. According to various registers, at least a quarter of all AMI patients suffer from T2DM [2]. At the same time, the mortality rate due to AMI in patients with T2DM, despite the use of modern reperfusion technologies, remains 1,5-2,0 higher than in people without diabetes [3].

There are numerous follows-up demonstrating an association between elevated glycemic levels and an unfavorable prognosis in myocardial infarction (MI) [4]. Experimental studies [5] reveal a direct negative effect of acute hyperglycemia on various processes that can potentially lead to a worse prognosis in AMI, but the true hyperglycemia clinical significance remains unclear. One of the counter-versions is

Table 1

Clinical characteristics of the study cohort

Value		Meaning
Number of patients, n		237
Age, years		68±11
Men/women, n (%)		96 (41%)/141 (59%)
STEMI/NSTEMI, n (%)		134 (57%)/103 (43%)
Duration of hospitalization from the beginning of symptoms, n (%)	<2 hrs	27 (11%)
	2-12 hrs	112 (47%)
	12-24 hrs	39 (16%)
	>24 hrs	59 (25%)
SCG performance, n (%)		173 (73%)
PCI performance, n (%)		136 (57%)
Acute infarction responsible artery, n (%)	ADA	79 (46%)
	Cx	30 (17%)
	RCA	57 (33%)
	MINOCA	7 (5%)
EF, %		47 [40; 54]
Acute heart failure	ALVF	45 (19%)
	Cardiogenic shock	22 (9%)
Atrial fibrillation, n (%)		37 (16%)
Previous myocardial infarction in anamnesis, n (%)		68 (29%)
T2DM duration >10 years, n (%)		67 (28%)
Previous hypoglycemic therapy, n (%)	Insulin	53 (22%)
	Metformin	90 (38%)
	Sulfonylurea	86 (36%)
	DPP4i	6 (3%)
	SLGT2i	3 (1%)
Hypoglycemic therapy in hospital, n (%)	CIIT	4 (2%)
	Basal-bolus insulin therapy	149 (68%)
	Metformin	74 (31%)
	Sulfonylurea	64 (27%)
Maximum troponin I level, pg/ml		11470 [2060; 31420]
eGFR, ml/min		61 [45, 80]

Abbreviations: DPP4i — type 4 dipeptidyl peptidase inhibitors, MINOCA — myocardial infarction without obstruction of coronary artery, NSTEMI — non-ST segment elevation myocardial infarction, STEMI — ST-segment elevation myocardial infarction, SLGT2i — sodium-glucose co-transporter 2 inhibitors, CIIT — continuous intravenous insulin therapy, Cx — circumflex artery, ALVF — acute left ventricular insufficiency, RCA — right coronary artery, ADA — anterior descending artery, eGFR — estimated glomerular filtration rate, T2DM — type 2 diabetes mellitus, SCG — selective coronary angiography, EF — ejection fraction, PCI — percutaneous coronary intervention.

Table 2

Parameters of glycemic control during inpatient treatment for AMI

Value		Meaning
Number of glycemic measurements per 1 patient during inpatient treatment		15 [8; 20]
First value of glycemia at admission, mmol/l		13,6±5,9
Glycemia before leaving the hospital, mmol/l		7,9±3,0
Average glycemia during hospitalization, mmol/l		10,0±3,5
Glycemic variability during hospitalization (SD), mmol/l		2,7±1,7
Number of patients with at least 1 measurement of glycemia <3,9 mmol/l, n (%)		36 (15%)
Percentage of glycemic measurements in the cohort in different ranges	<6,1 mmol/l	13%
	6,1-10,0 mmol/l	49%
	>10,0 mmol/l	38%

Note: SD — standard deviation.

that hyperglycemia in AMI may be not so much a damaging factor as a marker of the severity of AMI and its complications [6]. There are conflicting data on the possibility of improving the prognosis in AMI by actively correcting hyperglycemia [7]. It should be noted that in the works on AMI in patients with diabetes mellitus, glycemia is most often studied during the first days; the relationship between the glycemia level during entire hospital stage and prognosis for MI, as a rule, remains beyond the researchers' interest.

To this date, a consensus on target range of glycemia and how to achieve it in acute coronary syndrome exists. According to the Russian recommendations, the target level of plasma glucose before meals during the day is 6,1-7,8 mmol/l, in the presence of medical and organizational factors that prevent the achievement of strict control of glycemia, its periodic increase to 10,0 mmol/l is acceptable, it is necessary to avoid a decrease in plasma glucose <6,0 mmol/l [8]. Formulated differently, the range of acceptable values is 6,1-10,0 mmol/l. The work presented below examines the issue of how the deviations of glycemia from the target range determine the prognosis of patients with MI.

Goal: to investigate the relationship between the deviations of glycemia from the target range during inpatient treatment for AMI in patients with T2DM and long-term prognosis.

Material and methods

The single-center cohort study included patients with AMI and coexisting T2DM who were sequentially hospitalized in the Regional Vascular Center at the City Clinical Hospital No. 13 of Avtozavodsky district of Nizhny Novgorod for 200 days from January 01, 2018 to July 19, 2018. The study protocol was approved by the Local Ethics Committee of the above-mentioned medical institution. Of the 927 patients with AMI admitted during this period, 237 cases were diagnosed with T2DM (26%), and these patients made up the study cohort. The clinical characteristics of the patients are presented in Table 1. The duration of hospitalization was 11 [9; 14] days. The median number of glycemia measurements during hospitalization was 15 [8; 20] times, at admission, glycemia was examined regardless of the last meal, from the second day, glycemia was examined under fasted conditions and before the main meals. The long-term outcome was assessed at 365 days from the moment of hospitalization.

Quantitative data are presented in the form of medians and interquartile intervals (Median [Q1; Q3]), arithmetic mean ± standard deviation (Mean±SD). Statistical processing was carried out in the program Statistica 10.0 and STATA/MP 16.1. To assess the reliability of differences in quantitative data, the Mann-Whitney test was used, shares — Pearson χ^2, to study the factors that determine the binary outcome — discriminant analysis, to find the optimal cut-off point — ROC analysis, to study survival — the construction of Kaplan-Meier curves, Gehan's-Wilcoxon test and the Cox proportional hazards model.

Results

The main parameters of glycemic control in the study cohort during inpatient treatment for AMI are presented in Table 2.

During hospitalization, 34 patients out of 237 patients with a combination of MI and T2DM died (mortality rate is 14,3%). For comparison: out of 690 patients with MI and without diabetes, death in hospital occurred in 38 cases (mortality

Table 3

Assessment of nformativeness and significance of various factors in relation to unfavorable outcome (discriminant analysis, Wilks' λ: 0,669, F (12,190) =7,875, p<0,001)

Factor	F-remove	p	Tolerance	Multiple correlation coefficient (R^2)
Age	0,021812	0,882	0,819438	0,180562
Anamnesis of MI	1,286801	0,258	0,833960	0,166040
Presence of AF	1,974040	0,162	0,846977	0,153023
Anamnesis of ACA	1,583287	0,209	0,905133	0,094867
STEMI or NSTEMI	0,212681	0,645	0,632060	0,367940
PCI performance	7,087564	0,008	0,778469	0,221531
max troponin	0,013522	0,907	0,716539	0,283461
LV EF	8,770147	0,003	0,835703	0,164297
ALVF and/or cardiogenic shock	7,769934	0,006	0,875151	0,124849
Percentage of glycemic measurements <6,5 mmol/l	0,921981	0,338	0,664080	0,335920
Percentage of glycemic measurements >10,0 mmol/l	7,912016	0,005	0,683180	0,316820
eGFR	4,093605	0,044	0,846277	0,153723

Abbreviations: MI — acute myocardial infarction, STEMI — ST-segment elevation myocardial infarction, NSTEMI — non-ST segment elevation myocardial infarction, ALVF — acute left ventricular insufficiency, ACA — acute cerebrovascular accident, eGFR — estimated glomerular filtration rate, LV EF — left ventricular ejection fraction, AF — atrial fibrillation, PCI — percutaneous coronary intervention, max — maximum value.

was 5,5%, p<0,001, χ^2 Pearson). On the 365th day from the moment of hospitalization, out of 203 discharged patients with T2DM, death occurred in 19 cases (9,4%), thus, the total number of fatal cases during 1 year, taking into account deaths during hospitalization, was 53 (22,3%).

As expected, the level of glycemia at admission, as well as the average glycemia during hospitalization, in patients with an unfavorable outcome were significantly higher compared to the surviving patients — 16,3 [10,8; 21,6] vs 11,6 [9,1; 16,3] mmol/l and 11,7 [9,4; 15,3] vs 8,9 [7,6; 10,5] mmol/l, respectively (for both comparisons, p<0,001, Mann-Whitney). Note the fact that the study cohort was in the acceptable range of glycemia (6,1-10,0 mmol/l) for less than half of hospital stay (49% of all glycemic measurements, Table 2). It goes without saying, the duration of glycemia within the acceptable range for each patient was individual. Therefore, in the future, in accordance with the study goals, the prognosis of patients will be correlated with the proportion of glycemic measurements outside the acceptable range. To assess the contribution of various factors associated with an unfavorable outcome during the follow-up period, a discriminant analysis was used, the results of which are given in Table 3.

Percutaneous coronary intervention (PCI), the presence of acute heart failure (AHF) during AMI, and the left ventricular ejection fraction (EF) had an expected and quite obvious effect on the outcome. The association between the duration of glycemia in the range below 6,1 mmol/l and the adverse outcome was insignificant and unreliable. At the same time, the retention time of glycemia in the range above acceptable values (>10,0) was a strong predictor of death within 1 year (see column F-remove). It can be seen that the factors included in the model are independent (see the columns "Tolerance" and "Multiple correlation coefficient").

To assess the quality of glycemic retention time index >10,0 mmol/l as a predictor of unfavorable outcome, a ROC analysis was conducted. The area

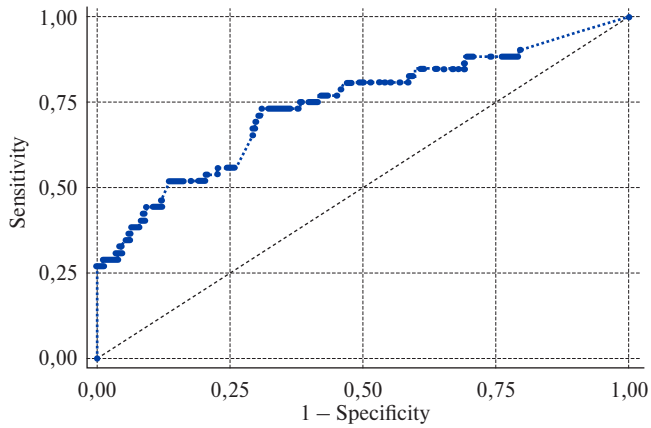

Figure 1. ROC-curve for glycemic retention time >10,0 mmol/l during inpatient treatment for AMI with respect to predicting an adverse outcome over 12 months.

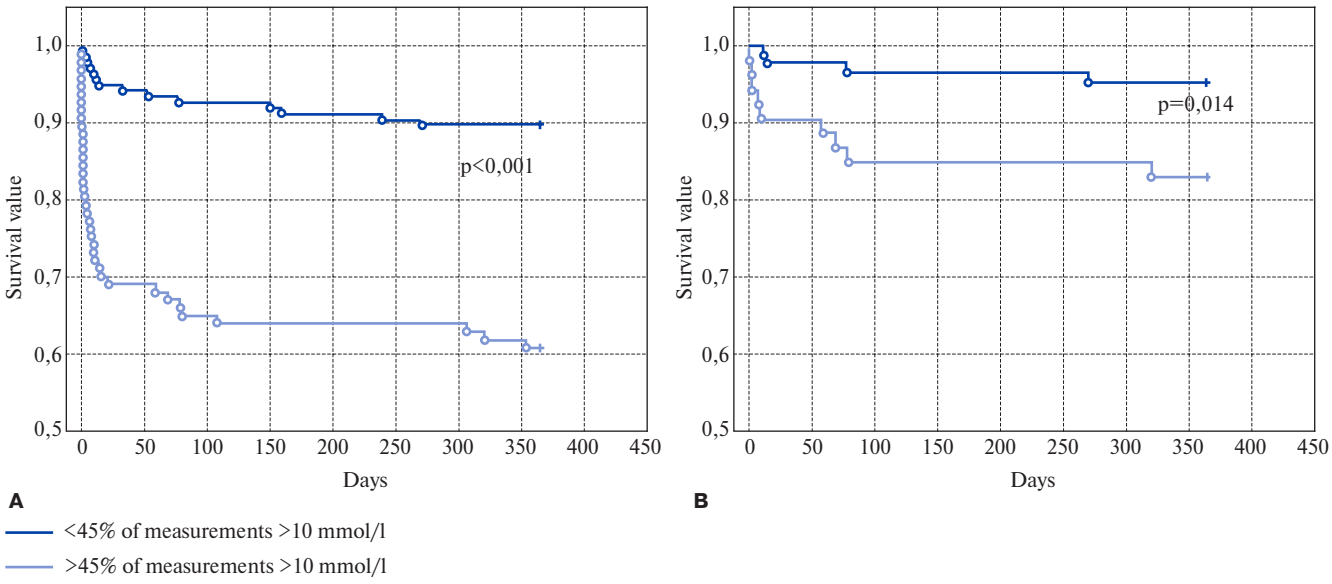

Figure 2. Survival curves (Kaplan-Meier) of patients with different glycemic status **A**) in the general cohort, **B**) in the subgroup with performed PCI (to compare the survival of the Gehans` Wilcoxon test.

Table 4

Results of multivariate regression analysis of 12-month survival (Cox proportional hazard model, p<0,001)

Value	RR	95% RR CI	p
PCI performance (yes/no)	0,32	0,17-0,63	0,001
ALVF and/or cardiogenic shock (yes/no)	4,40	2,38-8,11	<0,001
LV EF <40% (yes/no)	1,58	0,87-2,83	0,129
Percentage of glycemic measurements above 10,0 mmol/l >45% (yes/no)	3,26	1,75-6,09	<0,001
eGFR <55 ml/min (yes/no)	1,93	1,03-3,61	0,041

Abbreviations: CI — confidence interval, ALVF — acute left ventricular failure, eGFR — estimated glomerular filtration rate, LV EF — left ventricular ejection fraction, PCI — percutaneous coronary intervention, RR — relative risk.

Table 5

Results of discriminant analysis of glycemic retention predictors >10,0 mmol/l >45% of the time during hospitalization (Wilks' λ: 0,738, F (7,92) =4,669, p<0,001)

Factor	F-remove	p	Tolerance	Multiple correlation coefficient (R^2)
First value of glycemia at admission	13,61304	<0,001	0,890903	0,109097
max troponin	0,17673	0,675	0,923125	0,076875
Body weight	2,11712	0,149	0,948427	0,051573
ALVF and/or cardiogenic shock	0,02699	0,870	0,902161	0,097839
Pre-admission insulin therapy	6,84471	0,010	0,837085	0,162915
Metformin before admission	3,67191	0,058	0,935785	0,064215
Sulfonylurea before admission	3,79453	0,054	0,820996	0,179004

Abbreviations: ALVF — acute left ventricular failure, max — maximum value.

under ROC-curve was 0,74 (95% confidence interval 0,62-0,82) (Figure 1).

The optimal cut-off point for glycemic residence time above the range of acceptable values in relation to an unfavorable outcome was also determined, it turned out to be 0,45 (sensitivity 73% and specificity 69%), in other words, if a patient with T2DM has >45% of blood glucose measurements during

inpatient treatment for myocardial infarction >10,0 mmol/l, the chances of an unfavorable outcome increase. Indeed, out of 97 patients with >45% of measurements >10,0 mmol/l, death occurred within a year in 38 cases (39%), for comparison — out of 140 patients with <45% of measurements >10 mmol/l, death occurred in 15 cases (11%), p<0,001 (χ^2 Pearson). Importantly, a significant association between sustained hyperglycemia during hospitalization and 1-year prognosis was found not only in the general cohort of patients, but even in the subgroup of patients subjected to PCI, although the number of deaths in this subgroup was naturally lower (Figure 2).

ROC analysis was used to determine the optimal cut-off points for EF and the estimated glomerular filtration rate (eGFR) for an unfavorable outcome during the year. For EF, it was 40% (sensitivity 63%, specificity 79%), for eGFR — 55 ml/min (sensitivity 68%, specificity 73%). A multivariate regression analysis of survival was conducted. The model includes factors determined by discriminant analysis. The results are presented in Table 4. It can be seen that the presence of >45% of glycemic measurements >10,0 mmol/l is accompanied by a more than 3-fold increase in the risk of death within 12 months.

The search for predictors of the presence of glycemia >10,0 mmol/l >45% of the time during hospitalization for AMI was carried out. It is important to include in the model the factors that become available in the next few hours after admission. According to the discriminant analysis results, it was found that such predictors can be considered: 1) the initial (before AMI development) regular use of insulins and 2) the first value of glycemia at admission (Table 5). Note that persistent hyperglycemia during hospitalization does not depend on AMI severity — the level of troponins (indirectly reflects the mass of nonreversibly damaged myocardium) and the presence of AHF in acute stage. Using ROC analysis, the optimal cut-off point for the first glycemic value was determined, it was 12,1 mmol/l (sensitivity 77%, specificity 65%).

Discussion

The study confirmed the presence of a stable association between the glycemia level during hospitalization for AMI in patients with T2DM and the prognosis during the year. It should be emphasized that the importance is not only the first value of glycemia at admission, but also glycemia throughout the inpatient treatment stage. The first value of glycemia at admission always includes a stress hyperglycemia component, is largely determined by severity of hemodynamic disorders and is in some sense a marker of AMI severity (in particular, in patients with acute left ventricular failure and/or cardiogenic shock, the first value of glycemia at admission was 16,3 [10,6; 21,6] vs 11,6 [9,0; 15,8] mmol/l in patients with AMI without AHF, p<0,001 Mann-Whitney). It is obvious that the first value of glycemia at admission is an unmodifiable factor.

In contrast to the first glycemia value at admission, persistent hyperglycemia during the entire inpatient stage of treatment is less dependent on AMI severity. Pay attention to the discriminant analysis results (Table 5) — the presence of glycemia above the range of acceptable recommended values was not determined by either the maximum level of troponin or the presence of AHF. An association of the glycemic measurement proportion above the recommended range not only with mortality rate during hospitalization, but also with a long-term prognosis over the next 12 months indicates in favor of the pathogenetic hyperglycemia value. In other words, the discovered fact allows to consider hyperglycemia in AMI not so much as a marker of stress caused by severe cardiovascular pathology, but as an important and potentially controlled parameter that affects the further disease course. It is equally important that the glycemia state determines the prognosis not only in patients who did not receive endovascular treatment (which provided the greatest contribution to the total number of fatal cases during hospital treatment), but also in patients undergoing PCI (Figure 2 B).

The study answers the question of what predictors of target range critical excess can be detected at the time of admission of a patient with AMI to inpatient hospital. The answer to this question creates prerequisites for determining the phenotypes of patients who need a different approach to the management of glycemia during inpatient AMI treatment. Nowadays recommendations imply variability in hypoglycemic therapy in MI. It seems clear that patients with a dysfunctional phenotype, determined on the basis of identified predictors, will require a more intensive approach to the management of glycemia. Taking into account the discriminant analysis results (Table 5), predictors of unfavorable glycemic profile during inpatient treatment are insulin therapy at the pre-hospital stage and the first value of glycemia at admission >12,1 mmol/l. Such patients constitute an unfavorable phenotype and require more intensive methods of glycemic management from the moment of hospitalization due to AMI.

Study limitations. The result limitations are primarily related to the retrospective nature of the study. The number of glycemic studies varied from patient

to patient. In cases of death on the first day of stay, the number of glycemia studies was obviously insignificant, which could affect the final result. It should also be noted that the study was a single-center study, so the state of glycemic control in AMI described in the article primarily characterizes the routine clinical work of a particular institution and may differ from institutions that use a different practice.

Conclusion

1. Hyperglycemia during inpatient treatment for AMI in patients with T2DM, in contrast to the first value of glycemia at admission, it does not depend on the AMI complications and is not a marker of cardiovascular pathology severity.

2. Bad glycemic control (>45% of glucose measurements above the threshold of 10,0 mmol/l) during AMI hospitalization in patients with T2DM is associated with an increased risk of death in the hospital and during the next 12 months, including in patients who received endovascular treatment.

3. Predictors of bad glycemic control were identified (insulin therapy before AMI, glucose level at admission >12,1 mmol/l), which creates prerequisites for determining the phenotype of patients who need more intensive methods of glycemic management from the moment of admission to the hospital.

Relationships and Activities: none.

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