Glycated hemoglobin HbA$_{1c}$ – a new risk marker for the outcome of cardiac surgery?

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Abstract

Introduction: About 30% of patients undergoing cardiac surgery are diabetic, and glycated hemoglobin (HbA$_{1c}$) is a reliable marker for long-term glucose control. The aim of our study was to examine whether tight glucose control before a cardiac operation results in a better outcome of the surgical treatment.

Material and methods: We performed a retrospective record review of 350 diabetic patients undergoing cardiac surgery in our institution. Preoperative glycemia control was assessed by measurement of the glycated hemoglobin level. The patient population was divided into three groups: group I – patients with HbA$_{1c}$ below 7% ($n = 195$); group II – patients with HbA$_{1c}$ between 7% and 8% ($n = 88$); and group III – patients with HbA$_{1c}$ above 8% ($n = 67$).

Results: The demographic data and operating risk in all groups of patients were similar. There were 2 deaths (1.02%) in group I, 2 deaths (2.27%, $p = 0.78$) in group II and 3 deaths (4.47%, $p = 0.20$) in group III. Cardiac accidents occurred in 9 patients (4.60%) from group I, 7 patients (7.95%, $p = 0.20$) from group II, and in 6 patients (9.05%, $p = 0.40$) from group III. Cerebrovascular accidents (CVA) occurred in 7 (3.58%), 5 (5.68%, $p = 0.67$) and 5 (7.46%, $p = 0.61$) patients, respectively. Acute renal dysfunction requiring renal replacement therapy occurred in 4 patients from group I (2.05%), 3 patients from group II (3.40%, $p = 0.78$) and 4 patients from group III (5.97%, $p = 0.23$).

Conclusions: A large percentage of diabetic patients referred for cardiac operations have poorly controlled glycemia. Optimal preoperative glycemia control results in lower postoperative mortality and morbidity. In addition, the preoperative HbA$_{1c}$ level is a good indicator of the risk of postoperative complications in diabetic patients undergoing cardiac operations.

Key words: glycated hemoglobin, cardiac surgery.

Streszczenie

Wstęp: Około 30% pacjentów operowanych na oddziałach kardiochirurgicznych choruje na cukrzycę. Wyrównanie metaboliczne cukrzycy określane jest badaniem odsetka hemoglobiny glikowanej (HbA$_{1c}$). Celem pracy była ocena wyników leczenia kardiochirurgicznego u chorych na cukrzycę typu 2 w zależności od poziomu HbA$_{1c}$ przed operacją.

Materiał i metody: Przebadano 350 chorych poddanych operacjom serca. Podzielono ich na trzy grupy. Do grupy pierwszej zaliczono 195 chorych (55%), u których cukrzyca przed operacją była wyrównana optymalnie (HbA$_{1c}$ < 7%), do drugiej 88 chorych (25%), u których wyrównanie cukrzycy nie było optymalne (HbA$_{1c}$ 7–8%), natomiast w trzeciej grupie (67 chorych, 20%) cukrzyca była zdekompensowana (HbA$_{1c}$ > 8).

Wyniki: Dane demograficzne chorych, obciążenie chorobami towarzyszącymi oraz ryzyko operacyjne we wszystkich grupach były podobne. W I grupie chorych stwierdzono 2 zgony (1,02%), w grupie II odnotowano również 2 zgony (2,27%, $p = 0,78$), natomiast w grupie III – 3 zgony (4,47%, $p = 0,20$). Incydenty sercowe stwierdzono odpowiednio u 9 chorych w grupie I (4,6%), 7 chorych w grupie II (7,95%, $p = 0,20$) i 6 chorych w grupie III (9,05%, $p = 0,40$). Incydenty naczyniowo-mózgowe wystąpiły w poszczególnych grupach odpowiednio u 7 (3,58%), 5 (5,68%, $p = 0,67$) i 5 (7,46%, $p = 0,61$) chorych. Ostrą niewydolność nerek wymagającą terapii nerkozastępczej odnotowano odpowiednio u 4, 3 i 4 chorych (I – 2,05%; II – 3,40%, $p = 0,78$; III – 5,97%, $p = 0,23$).

Wnioski: Prawidłowe wyrównanie cukrzycy przed operacją wpływa na zmniejszenie liczby powikłań pooperacyjnych i zmniejszenie śmiertelności. Przedoperacyjne badanie odsetka HbA$_{1c}$ jest dobrym wskaźnikiem ryzyka wystąpienia powikłań po operacjach kardiochirurgicznych u chorych na cukrzycę.

Słowa kluczowe: hemoglobina glikowana, operacja kardiochirurgiczna.

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Introduction

Diabetes mellitus affects 6% of the adult population in Poland and its prevalence is rising [1]. In addition, there are now more cardiac surgery patients who are diabetic than in the past. As a result, about 30% of patients undergoing surgical myocardial revascularization suffer from diabetes [2, 3]. Diabetes is an independent risk factor for graft occlusion and cardiac deaths after coronary artery bypass grafting surgery. The risk of micro- and macroangiopathy is higher when glycemia is poorly controlled [4, 5]. In more precise terms, glycemia control is measured by glycated hemoglobin A$_{1c}$ (HbA$_{1c}$). HbA$_{1c}$ is formed when glucose in the blood binds irreversibly to hemoglobin to form a stable glycated hemoglobin complex.

This reflects a patient's prevailing glycemia over the previous 3 months. Some researchers suggest that a decrease in the previously elevated level of HbA$_{1c}$ can be demonstrated even within 2 weeks of a change in therapy. HbA$_{1c}$ is influenced by various factors. The HbA$_{1c}$ test result may not be affected by short-term, even very significant glycemic variability (both hyperglycemia and hypoglycemia). HbA$_{1c}$ may be underestimated because of hemolytic anemia, posthemorrhagic anemia, renal failure, and drugs (e.g. erythropoietin, iron preparations, vitamin B$_{12}$, anti-retroviral drugs). On the other hand, the level of HbA$_{1c}$ may be increased due to hypertriglyceridemia, hyperbilirubinemia, aplastic anemia, sideroblastic anemia, alcoholism, previous splenectomy, pregnancy, and medications (e.g. opiates, vitamin C, salicylates) [6]. The assessment of HbA$_{1c}$ level should be carried out using certified analytical methods recommended by the National Glycohemoglobin Standardization Program (NGSP, http://www.ngsp.org) and American (ADA), European (EASD) and Polish (PTD) Diabetes Associations. It is recommend that for microvascular disease prevention the HbA$_{1c}$ goal should be less than 7%. This level of HbA$_{1c}$ reflects an estimated average glucose level (eAG) of 154 mg/dl (8.6 mmol/l). The PTD in particular recommends that to achieve the metabolic control of type 2 diabetes in patients without a longstanding disease, the level of HbA$_{1c}$ should not exceed 6.5% and in patients older than 70 years with diabetes lasting more than 20 years it should not exceed 8.0% [7, 8]. Although the European System for Cardiac Operative Risk Evaluation (EuroSCORE) did not identify diabetes as a risk factor for cardiac surgical mortality [9], the new EuroSCORE II launched in October 2011 and the American STS SCORE do include diabetes in the risk factors. The STS SCORE also associates different risks, based on how the patient is treated [10]. No cardiac surgical risk scale mentions glycated hemoglobin.

Aim of the study

We aimed to establish whether the results of cardiac operations depend on the efficacy of glycemia control before the operation.

Material and methods

We performed a retrospective review of prospectively collected data from 350 diabetic patients (diabetes type 2) who were operated on at our institution over a period of 14 months. This represents 26% of all patients operated on within this time in our department. Procedures included isolated coronary artery bypass grafting (CABG; 267 patients, 77%), an isolated valve procedure (19 patients, 5%), and combined CABG/valve and other cardiac procedures (64 patients, 18%). In all of those patients the efficacy of preoperative glycemia control was assessed by measuring the level of HbA$_{1c}$. Patients were stratified into three groups, depending on their control of glycemia. The first group (group I) was composed of 195 patients (55%) with HbA$_{1c}$ below 7%. In the second group (group II) of 88 patients (25%), HbA$_{1c}$ was between 7 and 8%. The remaining 67 patients (20%) from the third group (group III) had HbA$_{1c}$ level above 8%. All patients were treated with the uniform perioperative intravenous insulin "Portland" protocol [11]. According to this protocol, a continuous infusion of glucose and insulin was started before the operation with a target glucose level within 100-150 mg/dl (5.5-8.3 mmol/l). This infusion was usually continued until postoperative day 2, with the blood glucose levels taken every 4 hours. Later, glycemia was managed with subcutaneous insulin administered in four doses per day (three doses of short-acting insulin before meals and one dose of long-acting insulin in the evening). The three groups of patients were compared with regard to their demographic data, operation risk, as well as their mortality and morbidity.

The following definitions of cardiac surgery complications were assumed:
- cardiac accidents: myocardial infarction was defined as creatinine kinase-MB elevation of 5 or more times the upper limit of normal and the presence of any new Q wave or the disappearance of the R wave on the postoperative electrocardiogram, while a low output syndrome was defined as the need for two catecholamines for a period of more than 30 minutes or the use of an intra-aortic balloon pump (IABP),
- a cerebrovascular accident was defined as a stroke or a transient ischemic attack (TIA),
- renal failure was defined as the need for renal replacement therapy (excluding patients requiring dialysis before the operation),
- respiratory failure was defined as the need for ventilation for a period longer than 24 hours,
- reoperation for bleeding or cardiac tamponade,
- wound infection,
- the mean blood glucose concentrations on days 1 and 2 during intravenous insulin treatment: hypoglycemia was defined as a blood glucose level below 70 mg/dl (3.9 mmol/l) and hyperglycemia as a blood glucose level above 250 mg/dl (13.9 mmol/l).

The statistical software package Statistica, version 6.0 and Microsoft® Excel 2000 were used to analyze the data. The Mann-Whitney U test was used to compare quantitative variables and the χ^2 Pearson test (with Yates' correction) was used to compare the qualitative variables.

Results

Patients from different glycemic control groups had similar demographic and clinical data: male sex of patients, mean age, body mass index, operative risk (EuroSCORE logistic), EF (left ventricular ejection fraction) and comorbidities (Table I). There were 2 deaths (1.02%) in group I (HbA$_{1c}$ < 7%), 2 deaths (2.27%, p = 0.78) in group II (HbA$_{1c}$ > 7% and < 8%) and 3 deaths (4.47%, p = 0.20) in group III (HbA$_{1c}$ > 8%). The causes of death included: in group I and II – deaths in the first days after surgery due to heart failure; in group III – 1 death during the first postoperative day due to heart failure and 2 deaths due to septic complications on day 21 and 26 after surgery (infection of the mediastinum). Cardiac accidents occurred in 9 patients (4.60%) from group I, 7 patients (7.95%, p = 0.20) from group II, and in 6 patients (9.05%, p = 0.40) from group III. Cardiac accidents included myocardial infarction, which occurred in 2 patients (1.02%) from group I, 2 patients (2.27%, p = 0.78) in group II and in 1 patient (1.49%, p = 0.72) in group III; and a low output syndrome, diagnosed in 7 patients (3.58%) in group I, 5 patients (5.68%, p = 0.62) in group II and 5 patients (7.46%, p = 0.33) in group III. Cerebrovascular accidents were diagnosed in 7 (3.58%), 5 (5.68%, p = 0.67) and 5 (7.46%, p = 0.61) patients, respectively. Among those, TIA was present in 4 patients (2.05%) in group I and was not diagnosed in the other groups. Stroke was diagnosed in 3 (1.53%), 5 (5.68%, p = 0.11) and 5 (7.46%, p = 0.04) patients, respectively. In group I, there were 3 strokes (2 of those patients had a history of previous CVA). In group II, there were 5 strokes (2 of those patients had previous CVA). In group III,

there were 5 strokes (2 of those patients had previous CVA). All patients with a prior history of CVA had carotid ultrasound performed; if the changes were significant, they were subjected to carotid artery intervention. Acute renal failure was present in 4 (2.05%), 3 (3.40%, p = 0.78) and 4 (5.97%, p = 0.23) patients. Respiratory failure was treated in 10 (5.12%), 9 (10.22%, p = 0.18) and 5 (7.46%, p = 0.68) patients. Wound infection was present in 3 (1.53%), 3 (3.40%, p = 0.57) and 4 (5.97%, p = 0.13) patients. 11 (5.64%), 7 (7.95%, p = 0.46) and 3 (4.47%, p = 0.95) patients required a reoperation for bleeding or a cardiac tamponade. Episodes of hyperglycemia with the glucose level above 250 mg/dl (13.9 mmol/l) were noted in 44, 44 and 49 patients (I – 22.56%; II – 50%, p = 0.00001; III – 73.13%, p = 0.00001). Episodes of hypoglycemia with the glucose level below 70 mg/dl (3.9 mmol/l) were observed in 28, 17 and 13 patients (I – 14.35%; II – 19.31%, p = 0.29; III – 19.40%, p = 0.33). A detailed comparison of the incidences of complications is presented in Table II.

Discussion

The percentage of patients with type 2 diabetes accepted for cardiosurgical procedures is rising. This is probably due to the rising age of such patients, which in turn may be partly due to the good results of percutaneous angioplasties which many patients undergo before they are scheduled for surgery [4]. In a large, multicenter trial from the USA, the perioperative mortality in a group of almost 150 000 diabetic patients was 3.7% [12]. It was Furnary who introduced a continuous intravenous insulin infusion

Tab. I. Demographic and clinical data: a comparison between group I (HbA$_{1c}$ < 7%), group II (HbA$_{1c}$ 7-8%) and group III (HbA$_{1c}$ > 8%)

	Group I n (%)	Group II n (%)	P value I vs. II	Group III n (%)	P value I vs. III
Patients	195 (55%)	88 (25%)	–	67 (20%)	–
Male	137 (70%)	57 (64%)	0.35	45 (67%)	0.63
Mean age (years)	66	66	0.82	64	0.14
DM treatment					
oral drugs	124 (63%)	47 (53%)	0.10	19 (28%)	0.000001
insulin	60 (30%)	39 (44%)	0.02	48 (72%)	0.000001
HTN*	166 (85%)	71 (80%)	0.34	53 (79%)	0.26
CVA*	19 (9%)	8 (9%)	0.86	10 (15%)	0.25
PAD*	32 (16%)	9 (10%)	0.15	15 (22%)	0.63
CKD*	22 (11%)	9 (10%)	0.79	6 (9%)	0.58
Type of operation					
CABG	142 (72%)	70 (79%)	0.22	55 (82%)	0.30
isolated valve	13 (6%)	3 (3%)	0.58	3 (4%)	0.80
combined CABG/valve and other cardiac surgery	40 (20%)	15 (17%)	0.31	9 (13%)	0.26
ESL* (%)	6.3	6.1	0.20	6.8	0.59
EF* (%)	49	48	0.35	48	0.51
BMI* (kg/m²)	30	30	0.87	30	0.85

HTN – hypertension, CVA – cerebrovascular accidents, PAD – peripheral arterial disease, CKD – chronic kidney disease, CABG – coronary artery bypass graft, ESL – operative risk (logistic EuroSCORE), EF – left ventricular ejection fraction, BMI – body mass index

Tab. II. Comparison of complications occurring in group I (HbA_{1c} < 7%), group II (HbA_{1c} 7-8%) and group III (HbA_{1c} > 8%)

	Group I n (%)	Group II n (%)	P value I vs. II	Group III n (%)	P value I vs. III
Patients	195 (55%)	88 (25%)	–	67 (20%)	–
Death	2 (1.02%)	2 (2.27%)	0.78	3 (4.47%)	0.20
Cardiac accidents	9 (4.60%)	7 (7.95%)	0.20	6 (9.05%)	0.40
myocardial infarction	2 (1.02%)	2 (2.27%)	0.78	1 (1.49%)	0.72
low output syndrome	7 (3.58%)	5 (5.68%)	0.62	5 (7.46%)	0.33
Cerebrovascular accidents	7 (3.58%)	5 (5.68%)	0.67	5 (7.46%)	0.61
transient ischemic attack	4 (2.05%)	0	0.41	0	0.54
stroke	3 (1.53%)	5 (5.68%)	0.11	5 (7.46%)	0.04
Respiratory failure	10 (5.12%)	9 (10.22%)	0.18	5 (7.46%)	0.68
Acute renal failure	4 (2.05%)	3 (3.40%)	0.78	4 (5.97%)	0.23
Reoperation	11 (5.64%)	7 (7.95%)	0.46	3 (4.47%)	0.95
Wound infection	3 (1.53%)	3 (3.40%)	0.57	4 (5.97%)	0.13
Hypoglycemia < 70 mg/dl (3.9 mmol/l)	28 (14.35%)	17 (19.31%)	0.29	13 (19.40%)	0.33
Hyperglycemia > 250 mg/dl (13.9 mmol/l)	44 (22.56%)	44 (50%)	0.00001	49 (73.13%)	0.000001
Creatinine levels > 2 mg/dl (177 µmol/l)	29 (14.87%)	17 (19.31%)	0.35	13 (19.40%)	0.39

protocol and showed a fall of mortality from 8 to 2% in his material [11]. In our department, the percentage of diabetic type 2 patients accepted for cardiac surgery is now close to 28%. The mortality in the analyzed groups of 350 patients was from 1% to 4%, while the mean estimated risk calculated for all three groups was 6% (ESL). ESL-operative risk (EuroSCORE logistic) is the scoring system that identifies three groups of risk factors with their weights (additive predicted mortality percentage) in brackets. Patient-related risk factors include age over 60, female, chronic pulmonary disease, extracardiac arteriopathy, neurological dysfunction, previous cardiac surgery, serum creatinine > 200 µmol/l, active endocarditis and a critical preoperative state. Cardiac risk factors include unstable angina being treated with intravenous nitrates, reduced left ventricular ejection fraction, recent (< 90 days) myocardial infarction and pulmonary systolic pressure > 60 mm Hg. Operation-related risk factors were emergency surgery, other than isolated coronary surgery, thoracic aorta surgery, and surgery for postinfarct septal rupture [9]. When analyzing the results, we found that the mortality was higher in patients with poorly controlled glycemia. Cardiac accidents (9%) and acute renal failure (6%) were high in our patients with decompensated diabetes. The results presented in published articles are usually much better, with complications only up to 5% [13-15]. Also cerebrovascular accidents in patients with decompensated diabetes were higher in our material (7.5%) than in the literature (1.5-5%) [13, 15, 16]. One reason for this may be because these studies did not divide their population into groups based on glycemia control, but gave overall results from diabetic patients instead. Interestingly, transient ischemic attacks were more common in the group of patients with HbA_{1c} < 7%, while strokes were more common in patients with decompensated diabetes. We presume that the transient ischemic attacks may be associated with episodes of hypoglycemia. Finally, sternal wound infections in our patients (from 1.5% to 6%) were as common as presented in the literature (from 1.5% to 7.9%) [12, 17]. Significantly more hyperglycemic episodes happened in patients with decompensated diabetes. Hypoglycemic episodes were less common, but there was a stronger tendency towards them also in the patients with decompensated diabetes. Glycemia control has to be individualized for every patient before each operation. This means that the treatment has to be tailored to glycemia levels and checked often enough to maintain glucose equilibrium. In addition to that, the age of the patient and comorbidities have to be taken into consideration. Engoren *et al.* and Halkos *et al.* indicate in their articles the prognostic value of HbA_{1c} testing in patients undergoing coronary artery bypass grafting [18-20]. Hudson *et al.* draw similar conclusions. They found higher mortality after elective cardiac surgery in patients with diabetes in whom preoperative HbA_{1c} was greater than 6%. They suggest that this test may be used as a screening tool for the assessment of operational risk [21]. The high percentage (20%) of patients operated on with decompensated diabetes (patients with HbA_{1c} > 8%) is alarming. These data show how serious the problem of diabetes control is in patients with coronary disease scheduled for surgical treatment. The mean time spent by elective patients on a waiting list for coronary surgery exceeds three months. This time may be used for starting and maintaining an effective program of glycemia control for every diabetic patient. Our results show that the routine preparation of each of those patients should

include an HbA$_{1c}$ level check. We would like to conclude that although intensive perioperative insulin treatment is mandatory in every diabetic patient, it is also necessary to optimize the diabetes treatment before the operation. Optimal diabetic control before the cardiac operation results in lower morbidity and mortality.

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