

Prospective evaluation of glucose metabolism in patients undergoing coronary artery bypass grafting

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Abstract

Introduction: Disturbances of glucose metabolism are associated with increased risk of ischaemic heart disease (IHD). It is not uncommon that IHD and its complications precede diagnosis of glucose metabolism disturbances. Since publication of the American Diabetes Association's 2004 Guidelines for the assessment of glucose metabolism, no prospective evaluation of prevalence of carbohydrate metabolism disorders in patients referred for coronary artery bypass grafting (CABG) has been performed.

Aim: Evaluation of prevalence of glucose balance disturbances in consecutive patients with stable IHD who underwent elective CABG procedures.

Methods: Prospective analysis of glucose metabolism was carried out on a group of 117 consecutive IHD patients (including 31 women) aged below 80 years, selected for elective CABG surgery. In all patients, history assessment and physical examination as well as basic biochemical studies and resting echocardiography were performed. Additionally, in all individuals without previous diagnosis of diabetes mellitus, oral glucose tolerance test (OGTT) was carried out.

Results: History analysis revealed glucose balance disturbances in 35 (29.9%) patients, including diabetes mellitus in 33 (28.2%) subjects and impaired glucose tolerance in 2 (1.7%) individuals. Based on OGTT results, among the remaining 82 (70.1%) subjects without previously known glucose metabolism disturbances 4 (3.4%) patients had abnormal fasting glycaemia, 32 (27.4%) subjects had impaired glucose tolerance, and diabetes mellitus was diagnosed in 12 (10.3%) individuals. No impaired glucose balance was found in only 34 (29.1%) examined subjects.

Conclusions: Over 70% of all patients undergoing elective CABG procedure presented various forms of carbohydrate metabolism disturbances that were not diagnosed previously. Thus, it seems that the assessment of glucose regulation should be mandatory in all patients undergoing elective CABG surgery.

Key words: ischaemic heart disease, coronary artery bypass grafting, glucose metabolism disturbances

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Introduction

In recent years, increasing prevalence of type 2 diabetes mellitus (DM) and other forms of glucose balance disturbances, such as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), has been observed. [1]. Presence of glucose metabolism disorders is associated with an increased risk of atherosclerosis and its complications, including ischaemic heart disease (IHD). In some cases, IHD and its complications such as myocardial infarction

(MI) precede diagnosis of glucose metabolism disturbances [2,3]. In the past, hyperglycaemia in the acute phase of MI was thought to be a reactive and transient glucometabolic state. However, in most patients carbohydrate balance remains impaired even several months following MI [3].

Estimated prevalence of DM in the general population is around 3.6-6.3% [4, 5]. In IHD patients, prevalence of DM is much higher and accounts for approximately 18-20% [6]. Similar DM prevalence is

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Table I. Classification criteria of glucose metabolism according to the American Diabetes Association guidelines [17]

	NGM	IFG	IGT	DM
Fasting glucose concentration (mg/dL)	60-99	100-125	<126	≥126
	and	and	and	or
Glucose concentration after 120 minutes (mg/dL)	<140	<140	140–199	≥200

NGM – normal glucose metabolism, IFG – impaired fasting glucose IGT – impaired glucose tolerance, DM – diabetes mellitus

observed in patients undergoing coronary artery bypass grafting (CABG) [7-10].

However, it has been shown recently that incidence of the various forms of glucose metabolism deregulations, including DM, is markedly underestimated in the group of patients with established diagnosis of IHD. Bartnik et al. found the presence of carbohydrate metabolism disorders in more than 50% of all patients with acute coronary syndromes treated with percutaneous transluminal coronary angioplasty [3, 11, 12].

Impaired glucose metabolism has an adverse impact on the perioperative course in patients undergoing CABG with higher incidence of complications such as renal dysfunction, nervous system impairment, respiratory and heart failure and infection of postoperative wounds as well as increased in-hospital mortality [13-16]. It seems that earlier diagnosis and identification of specific type of impaired glucose metabolism could facilitate initiation of adequate treatment and improve prognosis prediction in patients referred for CABG.

The Updated American Diabetes Association (ADA) 2004 Guidelines for medical management of diabetes mellitus presented (among other issues) recent criteria of diagnosis of glucose metabolism disturbances. So far, no data on prospectively assessed prevalence of the various forms of glucose metabolism disturbances in patients undergoing elective CABG procedures and based on aforementioned criteria have been published.

The purpose of this study was to evaluate the prevalence of glucose balance disturbances in consecutive IHD patients undergoing elective CABG surgery.

Methods

Patients

This study involved a group of 117 consecutive individuals aged below 80 years, qualified for elective CABG and who were operated on between February and July 2005. In all patients history assessment and physical examination as well as basic biochemical studies and resting echocardiography were performed.

Based on history and clinical reports analysis, patients with previously diagnosed either diabetes mellitus or other forms of glucose metabolism disturbances were selected. In all patients fasting plasma glucose concentration in venous blood was measured. Additionally, in subjects

without earlier history of DM oral glucose tolerance test (OGTT) was performed utilising 75 g of glucose diluted in 200 ml of water. According to the results of fasting plasma glucose concentration in venous blood, OGTT and current ADA guidelines (Table I), patients were defined as those with normal glucose metabolism (NGM), IFG, IGT or DM [17].

Additionally, in all patients prior to CABG, concentration of glycosylated haemoglobin (HbA_{1c}) was calculated by means of ion-exchange chromatography method employing chromatographic-spectrophotometric test (BioSystems, Spain). Meanwhile, 24 hours after surgery, in all patients total activity of creatine kinase (CK) using spectrophotometric method and enzymatic test (Randox, Ireland) as well as cardiac troponin T level utilising commercially available tests (BioMérieux, France) were assessed.

Statistical analysis

Statistical analysis comprised the groups of patients:

- with normal glucose metabolism (NGM),
- with impaired glucose tolerance (IGT) or abnormal fasting glycaemia (IFG),
- with previously or *de novo* diagnosed DM.

Qualitative data were presented as numbers and as percentages of all examined subjects. Trend estimation between groups was performed by means of Pearson's χ^2 test. Continuous data were expressed as mean \pm standard deviation (SD) and statistical comparisons between examined patient groups were carried out using non-parametric ANOVA for unpaired variables (Kruskal-Wallis test). Statistical analysis was carried out and curves were plotted using the computer software Prism 4.0 for Windows (GraphPad, USA). A value of $p < 0.05$ was considered statistically significant.

Results

Clinical characteristics of examined patients

Mean age of patients was 59.8 \pm 9.2 years. In the study group, there were 31 (26.5%) women, 20 (17.1%) active smokers, 57 (48.7%) former smokers, 77 (65.8%) patients with previous MI, 9 subjects after stroke, and 92

Table II. Comparison of demographic and clinical parameters (qualitative data) between the studied groups

	NGM n=34	AGM-noDM n=38	DM n=45	p
Women	7 (20.6%)	10 (26.3%)	14 (31.1%)	NS
Active smokers	7 (20.6%)	8 (21.1%)	5 (11.1%)	NS
Smoking in history	19 (55.9%)	18 (47.4%)	20 (44.4%)	NS
Previous myocardial infarction (s)	21 (61.8%)	24 (63.2%)	32 (71.1%)	NS
Stroke	1 (2.9%)	3 (7.9%)	5 (11.1%)	NS
Arterial hypertension	24 (70.6%)	31 (81.6%)	37 (82.2%)	NS
Diuretics	4 (11.8%)	11 (28.9%)	19 (42.2%)	0.030
Biguanids	0 (0.0%)	2 (5.3%)	4 (8.9%)	0.079
Sulphonylurea-derived drugs	0 (0.0%)	0 (0.0%)	6 (13.3%)	0.005
Insulin	0 (0.0%)	0 (0.0%)	17 (37.8%)	<0.001
Alpha glucosidase inhibitor	0 (0.0%)	1 (2.2%)	1 (0.9%)	NS
Angiotensin-converting enzyme inhibitors	20 (58.8%)	25 (65.8%)	33 (73.3%)	NS
Aspirin	33 (97.1%)	37 (97.4%)	43 (95.6%)	NS
β -blockers	22 (64.7%)	27 (71.1%)	28 (62.2)	NS
Cytoprotecting drugs	2 (5.9%)	3 (7.9%)	9 (7.7%)	NS
Digoxin	0 (0.0%)	1 (2.6%)	4 (3.4%)	NS
Fibrates	2 (5.9%)	3 (7.9%)	4 (8.9%)	NS
Nitrates	17 (50%)	26 (68.4%)	30 (66.7%)	NS
Statins	24 (70.6%)	28 (73.7%)	30 (66.7 %)	NS
Thienopyridine antiplatelet agents	5 (14.7%)	5 (13.2%)	8 (17.8 %)	NS

NGM – normal glucose metabolism, AGM-noDM – impaired glucose balance without diabetes diagnosis, DM – diabetes mellitus

(78.6%) with hypertension. The following drugs were used in medical therapy: diuretics in 34 (29.1%) subjects, biguanids in 6 (5.1%), sulphonylurea-derived agents in 6 (5.1%), insulin in 17 (14.5%), alpha glucosidase inhibitor in 1 (0.9%), angiotensin-converting enzyme inhibitors in 78 (66.7%), aspirin in 13 (96.6%), thienopyridine antiplatelet drugs in 18 (15.4%), β -blockers in 77 (65.8%), cytoprotecting medications in 9 (7.7%), digoxin in 4 (3.4%), fibrates in 9 (7.7%) and statins in 82 (70.1%) patients.

Glucose metabolism assessment

Preliminary evaluation of glucometabolic balance performed based on history and medical records analysis showed presence of glucose metabolism disturbances in 35 (29.9%) patients, including DM in 33 (28.2%) and IGT in 2 (1.7%) individuals. At that time it was assumed that the remainder (82 subjects; 70.1%) had no disorders of glucose regulation.

Assessment of fasting plasma glucose concentration in venous blood and OGTT performed in 82 individuals without previously known glucose metabolism disturbances revealed IFG in 4 (3.4%) patients, IGT in 32 (27.4%) patients, and DM in an additional 12 (10.3%) examined subjects.

Finally the number of patients without any glucose metabolism disturbances decreased to 34 (29.1%), and impaired glucose control defined as IFG was noted in 4 (3.4%), as IGT in 34 (29.1%) and as DM in 45 (38.5%) patients.

Because of the small number of patients with IFG, they were pooled with the IGT group to form a group of 38 individuals (32.5%) with abnormal glucose metabolism not meeting criteria of DM (AGM-noDM). Patients' clinical characteristics in these specific groups are outlined in Table II (qualitative data) and in Table III (continuous data).

A significant trend of increased frequency of diuretics use ($p=0.030$) among patients with glucose metabolism disturbances was observed. As expected, only patients with previously diagnosed DM received insulin and sulphonylurea-derived agents. Biguanids were prescribed not only to patients with previously diagnosed DM but also to 2 individuals with earlier diagnosis of IGT (both referred for CABG from the same regional hospital). No other differences in dichotomous data distribution between analysed groups were observed.

Both body weight and BMI were higher in patients with glucose metabolism disturbances, especially with previously established diagnosis of DM. Moreover,

Table III. Comparison of demographic and clinical parameters (continuous variables) between the studied groups

	NGM	AGM-noDM	DM	P
Age (years)	58.7±10.1	58.9±8.8	61.4±8.7	NS
Weight (kg)	78.2±11.5	79.1±13.2	84.9±13.2	0.028
Height (cm)	170.7±7.4	169.7±6.4	168.2±7.1	NS
BMI (kg/m ²)	26.9±4.0	27.4±3.6	30.0±4.1	0.002
Heart rate (beats/min)	73.9±9.6	74.9±9.8	72.0±9.2	NS
Systolic arterial pressure (mmHg)	128.7±15.9	129.6±17.5	131.6±15.0	NS
Diastolic arterial pressure (mmHg)	77.8±9.9	78.2±8.7	79.9±12.7	NS
Pulse pressure (mmHg)	50.9±12.8	51.4±13.1	51.7±12.2	NS
Haematocrit (%)	41.1±4.7	42.8±3.6	40.1±5.0	0.010
Haemoglobin (mmol/L)	10.2±2.3	9.8±2.1	9.5±1.8	NS
Na ⁺ (mmol/L)	137.2±3.1	135.9±4.0	136.8±3.6	NS
K ⁺ (mmol/L)	3.7±0.3	3.7±0.5	3.8±0.3	NS
Right ventricular dimension (mm)	27.8±3.2	28.7±3.3	29.5±2.8	0.058
Left ventricular dimension (mm)	54.4±5.0	53.7±6.3	55.8±6.2	NS
Interventricular septum thickness (mm)	12.3±1.6	12.5±2.5	12.5±2.1	NS
Left ventricular posterior wall thickness (mm)	11.8±2.0	11.5±1.8	11.9±1.9	NS
Aortic root dimension (mm)	23.1±1.9	23.3±2.5	23.2±2.1	NS
Left atrial dimension (mm)	36.9±4.0	36.5±6.6	38.8±6.7	NS
Left ventricular ejection fraction (%)	46.8±7.5	47.2±8.0	45.0±7.8	NS
Left ventricular end-diastolic volume (cm ³)	157.1±44.7	156.2±51.3	178.9±58.6	0.097
Left ventricular end-systolic volume (cm ³)	91.8±44.2	93.8±66.0	102.5±45.5	NS

Abbreviations – see Table II

lower haematocrit was noted and statistically borderline higher right ventricular diastolic dimension and end-diastolic left ventricular volume were seen. No significant differences between examined groups were found with respect to other continuous variables.

Glucose metabolism

Fasting glucose concentration increased as severity of carbohydrate metabolism worsened (Figure 1A). Amongst patients without carbohydrate balance disturbances, mean glucose concentration was 86.1±10.6 mg/dl, in the group of patients with abnormal glucose metabolism without DM 100.4±14.2 mg/dl, and in patients with established diagnosis of DM – 114.6±36.0 mg/dl, respectively (p <0.0001).

Normal fasting glucose concentration (<100 mg/dl) was found not only in all patients without glucose metabolism disturbances (by definition), but also in 19 (50.0%) subject of AGM-noDM group (only patients with IGT) and in 18 patients (40.0%) with diabetes. The frequency trend of normal glucose concentration was significantly decreased (p <0.0001) in a manner dependent on severity of metabolic disorder.

Significantly lower (p <0.0001) HbA_{1c} concentration was observed in the NGM group. The value increased from 6.0±0.5% in NGM patients, through 6.5±0.9% in the AGM-noDM group, to 7.4±1.2% (Figure 1B) in subjects with diabetes (p <0.0001).

Level of myocardial injury markers at 24 hours following CABG

No significant differences between the analysed groups were noted in regards to either CK activity (593.5±470.9, 627.9±471.9 and 902.7±978.9 U/L, respectively; NS) or cardiac troponin T concentration (2.1±3.2, 1.7±2.6 and 1.7±2.6 ng/mL, respectively; NS).

Discussion

Recently published reports have indicated increasing trends of prevalence of glucose metabolism disturbances in patients with IHD. Abramow et al. observed increased rate of DM incidence from 18% in 1990 to approximately 27% in 1998 among patients undergoing CABG [18]. In our study involving 117 consecutive individuals referred for elective CABG, the percentage of patients with any form of glucose balance disorder reached 70% and was

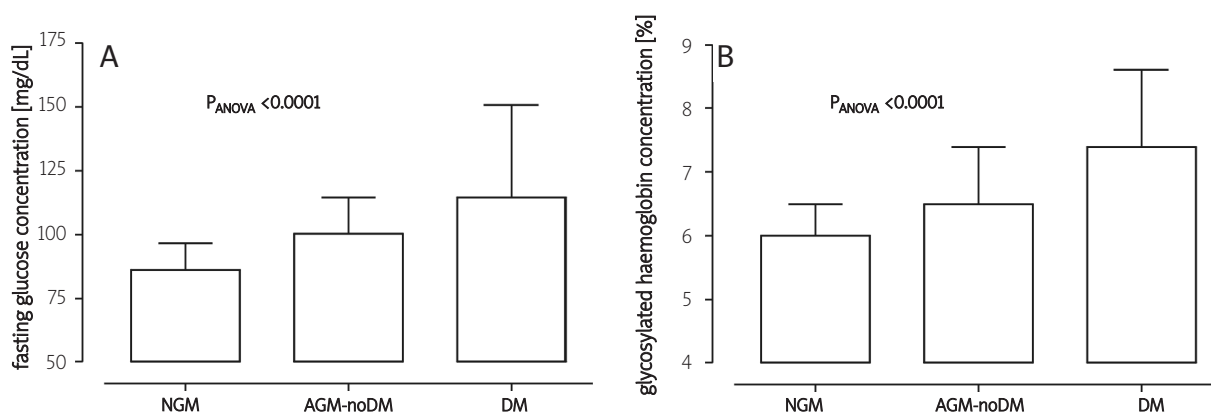


Figure 1. Panel A: Comparison of fasting glucose concentration between the examined groups. Panel B: Comparison of concentration of glycosylated haemoglobin in the examined groups
 NGM – normal glucose metabolism, AGM-noDM – impaired glucose balance without diagnosis of diabetes mellitus, DM – diabetes mellitus

markedly underestimated by physicians taking care of those patients previously. Diabetes prevalence in our study reached almost 40%, including 1/4 (10% of all population) with newly detected DM. Other authors indicate also that earlier misdiagnosed DM is present in a significant number of patients selected for CABG. Lauruschkat et al. analyzed data of 7310 patients referred for CABG, estimating prevalence of non-diagnosed DM and its influence on postoperative clinical course. Diabetes was diagnosed in 34.8% of examined subjects, and newly detected in 5.2% of patients [19]. In another study performed on a group of 1895 patients, Anderson et al. observed a significant, unfavourable impact of previously non-diagnosed diabetes and IFG on postoperative mortality. Diabetes prevalence in this group was 32%, including 8% with newly detected DM during current in-hospital stay [20].

In the studies reported by Lauruschkat et al. [19] and Anderson et al. [20] glucose metabolism disturbances were evaluated according to the latest ADA guidelines, although data analysis was retrospective and was based only on measurements of fasting glucose concentration. As we observed, fasting plasma glucose concentration <100 mg/dl could be noted in 50% of patients with IGT and in 40% with DM. Thus, it seems that diagnosis of carbohydrate balance disturbances based only on the assessment of fasting glucose concentration may lead to the wrong conclusions.

In our study we evaluated prospectively the incidence of glucose metabolism disorders not only according to the measurements of fasting glucose concentration, but also 120 minutes after oral challenge with 75 g of glucose. Owing to this fact, evaluation of glucose metabolism in patients who undergo CABG seems to be more complete and accurate. Besides diabetes, we noted the presence of other forms of abnormal carbohydrate metabolism, such

as IFG and IGT, that not uncommonly precede the development of diabetes, and they are called “prediabetes”. As observed by de Vegt et al., 60% of subjects with IGT or IFG developed DM within the following 5 years [21]. Patients referred for CABG have usually advanced form of IHD and not uncommonly history of MI. The presence of carbohydrate balance disorders could have been expected in these patients. However, most of our patients have never had simple and cheap OGTT that would add detailed information on preoperative glucose metabolism.

In patients with carbohydrate metabolism disturbances, cardiovascular complications are the most common causes of mortality and morbidity [2, 3, 6-10, 13-16, 20-23]. They present severe atherosclerotic degeneration of many arteries, including coronary vessels. Thus, 20% of deaths in patients with diabetes are caused by MI. Moreover, recurrent MI and heart failure are more common in this group of patients [24]. It is a strong argument for general practitioners to perform more efficient evaluation of glucose metabolism disturbances in subjects at higher risk rather than delay this valuable diagnostic process.

Routinely, patients referred for CABG should be properly prepared by general practitioners and clinicians of the departments where patients were hospitalised previously. In our group, each patient qualified for and then referred for CABG had previous coronary angiography, echocardiographic examination, ECG, exercise test, biochemical studies, not uncommonly SPECT, and occasionally CT and MRI. The aforementioned studies enable severity of IHD to be detected and evaluated in detail and indications for CABG to be established. It is strange that during the costly diagnostic process preceding referral for CABG, there were no funds and/or will for careful and inexpensive analysis of glucose metabolism. It seems that coronary angiography was

much easier to carry out than OGTT, but more likely that the problem of glucose balance disturbances was ignored by many physicians. It seems that the issue is related not only to diagnosis but also management of previously established glucose metabolism disturbances. It was reflected in the group of patients with DM who presented not only higher fasting glucose concentration, but also elevated HbA_{1c} level, which is an index of mean plasma glycaemia within approximately 3 months preceding an examination. In the studied group of patients with diabetes, mean HbA_{1c} rate (7.4%) exceeded the recommended level of 7% [17]. However, it must be kept in mind that guidelines of other societies are even more restrictive (recommended level of HbA_{1c} <6.5% or even <6.1%) [25, 26].

The limitation of this study was the fact that fasting glycaemia was measured only once, not twice, as recommended by WHO and the Polish Society of Diabetology. It could have an impact on the prevalence of detected glucose metabolism disturbances.

Conclusions

In the prospective analysis based on current ADA guidelines, underestimation of the number of patients with various forms of impaired glucose metabolism was noted. It reflected inadequate preparation of patients for CABG procedure. Because of the necessity to recognise all possible types of carbohydrate balance disorders it seems OGTT should be mandatory in all patients referred for elective CABG who had not manifested earlier any forms of glucose metabolism disturbances.

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Prospektywna ocena metabolizmu glukozy u pacjentów poddanych planowanemu zabiegowi pomostowania aortalno-wieńcowego

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Streszczenie

Wstęp: Zaburzenia metabolizmu glukozy są związane ze wzrostem ryzyka rozwoju choroby niedokrwiennej serca (IHD). Nierzadko IHD i jej powikłania wyprzedzają rozpoznanie zaburzeń metabolizmu glukozy. Po opublikowaniu w 2004 r. wytycznych *American Diabetes Association* dotyczących m.in. oceny metabolizmu glukozy nie określono prospektywnie częstości zaburzeń gospodarki węglowodanowej u kierowanych do pomostowania aortalno-wieńcowego (CABG).

Cel: Określenie częstości występowania zaburzeń metabolizmu glukozy u kolejnych pacjentów ze stabilną IHD poddawanych planowanemu zabiegowi CABG.

Metodyka: Prospektywną ocenę metabolizmu glukozy przeprowadzono w grupie 117 kolejnych chorych (31 kobiet) z IHD w wieku do 80. roku życia zakwalifikowanych do planowanego CABG. U wszystkich pacjentów wykonano badanie podmiotowe i przedmiotowe, podstawowe badania biochemiczne oraz spoczynkowe badanie echokardiograficzne. U osób bez rozpoznanej wcześniej cukrzycy wykonano dodatkowo test doustnego obciążenia glukozą (OGTT).

Wyniki: Na podstawie wywiadu stwierdzono obecność zaburzeń metabolizmu glukozy u 35 (29,9%) chorych, w tym cukrzycę u 33 (28,2%) i upośledzoną tolerancję glukozy u 2 (1,7%) pacjentów. Analizując wyniki OGTT u pozostałych 82 (70,1%) osób bez znanych wcześniej zaburzeń metabolizmu glukozy, rozpoznano występowanie: nieprawidłowej glikemii na czczo u 4 (3,4%), upośledzonej tolerancji glukozy u 32 (27,4%) oraz cukrzycy u kolejnych 12 (10,3%) osób. Bez zaburzeń metabolizmu glukozy pozostało jedynie 34 (29,1%) badanych.

Wnioski: U ponad 70% chorych poddawanych planowanemu zabiegowi CABG są obecne różne formy zaburzeń gospodarki węglowodanowej, których zwykle wcześniej nie rozpoznano. Wydaje się, że ocena metabolizmu glukozy powinna być obowiązkowym postępowaniem u wszystkich chorych poddawanych planowanemu CABG.

Słowa kluczowe: choroba niedokrwiennej serca, pomostowanie aortalno-wieńcowe, zaburzenia metabolizmu glukozy

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