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Preoperative disturbances of glucose metabolism and mortality after coronary artery bypass grafting

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ABSTRACT

Background Disturbances of glucose metabolism are important risk factors for coronary artery disease and are associated with an increased mortality risk. The aim was to investigate the association between preoperative disturbances of glucose metabolism and long-term all-cause mortality after coronary artery bypass grafting (CABG).

Methods Patients undergoing a first isolated CABG in 2005–2013 were included. All patients without previously known diabetes underwent an oral glucose tolerance test (OGTT) before surgery. They were categorised as having normal glucose tolerance (NGT), pre-diabetes (impaired glucose tolerance and/or impaired fasting glucose) or newly discovered diabetes. Data were collected from nationwide healthcare registers. Cox regression was used to calculate adjusted HR with 95% CI for death in patients with pre-diabetes and diabetes, using NGT as reference.

Results In total, 497 patients aged 40–86 years were included. According to OGTT, 170 (34%) patients had NGT, 219 (44%) patients with pre-diabetes and 108 (22%) patients had newly discovered diabetes. Baseline characteristics were similar between the groups except for slightly higher age among patients with newly discovered diabetes. There were 133 (27%) deaths during a mean follow-up time of 10 years. The cumulative 10-year survival was 77% (69%–83%), 83% (77%–87%) and 71% (61%–79%) in patients with NGT, pre-diabetes and newly discovered diabetes, respectively. There was no significant difference in all-cause mortality between the groups after multivariable adjustment.

Conclusion In this study, patients with pre-diabetes or newly discovered diabetes prior to CABG had similar long-term survival compared with patients with NGT.

Key questions

What is already known about this subject?

► Disturbances of glucose metabolism are risk factors for coronary artery disease and are associated with an increased mortality risk.
► In patients with diabetes and multivessel coronary artery disease, the recommended revascularisation treatment is coronary artery bypass grafting (CABG).
► The prognostic outcome in patients with known type 2 diabetes (T2D) after CABG is poorer than in patients without T2D.
► There are also reports of similar long-term mortality after CABG in patients with known T2D and patients without diabetes.
► Less is known about the prognostic importance of pre-diabetes or newly discovered diabetes after CABG in patients with no history of diabetes.

What does this study add?

► This study adds knowledge about the prognosis after CABG in patients with pre-diabetes or newly discovered diabetes with no history of diabetes.
► In this study, there was no difference in long-term mortality between patients with pre-diabetes or newly discovered diabetes prior to CABG, compared with patients with normal glucose tolerance.

How might this impact on clinical practice?

► Disturbances of glucose metabolism are risk factors for coronary artery disease and screening is important.
► Patients with no history of diabetes undergoing CABG may not need screening with an oral glucose tolerance test to find disturbances of glucose metabolism, and haemoglobin A1c as an indicator would be sufficient.

INTRODUCTION

Type 2 diabetes (T2D) is a known risk factor for cardiovascular disease and mortality.[1] The prevalence of diabetes is estimated to increase worldwide by almost 50% in the next 25 years, from 415 million people in 2015 to 642 million people in 2040.[2] Many individuals are unaware of their metabolic state, and more than a third of patients admitted for acute coronary syndrome have previously unknown disturbances of glucose metabolism.[3]

T2D is preceded by early abnormalities of glucose metabolism, which is referred to as pre-diabetes. Disturbances of glucose metabolism can be detected by an oral glucose tolerance test (OGTT), which is a more sensitive method to find disturbances in glucose metabolism than fasting blood glucose or

haemoglobin A1c (HbA1c), respectively, and provides significant prognostic information regarding cardiovascular events in patients with coronary artery disease (CAD).[4 5] Several studies show that patients with an acute myocardial infarction (AMI) and disturbances of glucose metabolism under the threshold of diabetes have poorer prognosis compared with patients with normal glucose tolerance (NGT).[6–8]

In patients with diabetes and multivessel coronary artery disease, the recommended revascularisation treatment is coronary artery bypass grafting (CABG).[9–12] The prognostic outcome in patients with known T2D after CABG is poorer than in patients without T2D.[13–15] However, there are also reports of similar long-term mortality after CABG in patients with known T2D and patients without diabetes.[4] Less is known about the prognostic importance of pre-diabetes or newly discovered diabetes after CABG in patients with no history of diabetes. A small study published in 2013 indicated a strong association between the severity of disturbed glucose metabolism and cardiovascular events after CABG.[5] However, another study based on few patients showed that the risk of early mortality after CABG in patients with known diabetes was similar to that in patients with disturbed glucose metabolism and unknown diabetes.[6] The relationship between pre-diabetes and newly discovered diabetes and prognosis after CABG is still unclear.

The aim of the present study was to investigate the association between preoperative disturbances of glucose metabolism and long-term all-cause mortality after CABG.

METHODS
Study design
This was an observational, population-based cohort study. Study reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational studies using routinely collected data.[7]

Study population
The study population was recruited from Karolinska University Hospital and Danderyd University Hospital in Stockholm, Sweden. A total of 497 patients without previously known diabetes, aged 40–86 years, undergoing a first isolated CABG at Karolinska University Hospital in Stockholm, Sweden, were included. Out of these 497 patients, 199 were treated for an AMI at Danderyd University Hospital between 2006 and 2013 and were referred for CABG at the time of their AMI. In total, 298 patients had an elective, non-emergent CABG performed in 2005–2008. All patients underwent a standardised 75 g OGTT according to WHO criteria[8] within 3 months prior to CABG. Patients who had an AMI underwent an OGTT according to routine 5 days after the AMI. Baseline characteristics were collected from the SWEDEHEART (Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies) register[9] by

individual-level data-linking using the unique personal identity number assigned to all persons living in Sweden.[10]

Exposure
All patients underwent an OGTT prior to CABG. Based on the result of the OGTT, the patients were categorised as having either NGT, pre-diabetes (impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG)) or T2D discovered by OGTT, according to the WHO definition from 2006[8]:

► NGT: a fasting venous plasma glucose level <6.1 mmol/L and a 2-hour plasma glucose level at OGTT <7.8 mmol/L.
► Pre-diabetes (IFG and/or IGT).
  – IFG: a fasting venous plasma glucose level of ≥6.1 to <7.0 mmol/L and a 2-hour plasma glucose level at OGTT <7.8 mmol/L.
  – IGT: a fasting venous plasma glucose level <6.1 mmol/L and a 2-hour plasma glucose level at OGTT of ≥7.8 to <11.1 mmol/L.
► T2D: a fasting venous plasma glucose level ≥7.0 mmol/L and/or a 2-hour plasma glucose value at OGTT ≥11.1 mmol/L.

Outcomes
The primary outcome was all-cause mortality. Information regarding vital status was obtained by linkage to the Population Register, maintained by the national Swedish Tax Agency, using the personal identity number.[11]

Statistical methods
Patient characteristics were described using frequencies and percentages for categorical variables, and mean and SD for continuous variables. We used χ^2 test for categorical variables and analysis of variance for continuous variables to compare the three groups. The person-time in days contributed by each patient was calculated from the date of surgery to the date of death or end of follow-up (1 January 2018), whichever occurred first.

We calculated the crude incidence rates and 95% CI. We used Cox regression to estimate the risk of all-cause mortality according to the following OGTT categories: NGT, pre-diabetes and diabetes. We used NGT as the reference category. We calculated crude, age-adjusted and sex-adjusted, and multivariable adjusted HRs and 95% CIs. We included the following variables listed in table 1 as covariates in the final multivariable model: renal function (estimated glomerular filtration rate), left ventricular ejection fraction, body mass index, hypertension, pulmonary disease, peripheral vascular disease, smoking, prior myocardial infarction, prior percutaneous coronary intervention and prior stroke. Data management and statistical analyses were performed using Stata V.15.1.

RESULTS
Baseline characteristics of patients
Baseline characteristics are shown in table 1. In total, 497 patients, aged 40–86 years, were included, of whom 77

Table 1 Baseline characteristics and glucose tolerance in 497 patients prior to CABG

	% missing	NGT	Pre-diabetes	Diabetes	P value
Number of patients		170	219	108	
Age, years, mean (SD)		64.7 (8.6)	65.9 (9.4)	67.6 (8.0)	0.027
Female		32 (18.8)	33 (15.1)	12 (11.1)	0.217
Body mass index, kg/m^2, mean (SD)	0.2	26.8 (3.9)	27.4 (4.1)	27.0 (3.3)	0.398
Smoking	9.3				0.887
Never smoker		56 (35.9)	82 (40.6)	36 (38.7)	
Prior smoker		52 (33.3)	67 (33.2)	31 (33.3)	
Current smoker		48 (30.8)	53 (26.2)	26 (28.0)	
Fasting glucose, mmol/L, mean (SD)		4.49 (1.97)	5.78 (0.60)	6.82 (1.22)	<0.001
OGTT 2 hours, mmol/L, mean (SD)		5.44 (2.47)	8.91 (1.20)	12.43 (3.22)	<0.001
Systolic blood pressure, mean (SD)	11	146 (24)	147 (22)	153 (24)	0.086
Diastolic blood pressure, mean (SD)	13	84 (12)	82 (11)	84 (9)	0.125
Hypertension	1.6	104 (62.3)	151 (69.9)	74 (69.8)	0.236
Chronic pulmonary disease		9 (5.3)	7 (3.2)	7 (6.5)	0.363
Peripheral vascular disease		14 (8.2)	20 (9.1)	12 (11.1)	0.720
Prior AMI	1.4	38 (22.8)	62 (28.7)	34 (31.8)	0.220
Prior PCI	0.2	20 (11.8)	29 (13.2)	12 (11.1)	0.837
Prior stroke	2.8	9 (5.4)	5 (2.4)	9 (8.7)	0.042
Estimated glomerular filtration rate, mL/min/1.73 m^2, mean (SD)		77 (17)	79 (16)	76 (19)	0.386
Left ventricular ejection fraction					0.860
>50%		117 (68.8)	153 (69.9)	76 (70.4)	
30%–50%		45 (26.5)	60 (27.4)	29 (26.9)	
<30%		8 (4.7)	6 (2.7)	3 (2.8)	
HDL, mmol/L, mean (SD)	12	1.18 (0.46)	1.14 (0.30)	1.07 (0.29)	0.059
LDL, mmol/L, mean (SD)	16	3.06 (0.98)	2.84 (0.98)	2.71 (1.10)	0.027
Triglycerides, mmol/L, mean (SD)	12	1.49 (0.91)	1.61 (1.05)	1.78 (1.23)	0.110

Data are numbers and (%) unless otherwise stated.

AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; HDL, High density lipoprotein; LDL, Low density lipoprotein; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; PCI, Percutaneous coronary intervention.

(15%) were women. A total of 170 (34%) patients had NGT, 219 (44%) with pre-diabetes and 108 (22%) had newly discovered diabetes. Patients with diabetes were older than patients with NGT and pre-diabetes. The prevalence of prior stroke and HbA1c levels were higher in patients with diabetes and NGT compared with the pre-diabetes group. Patients with NGT had higher low density lipoprotein (LDL) levels compared with the other groups.

There were no significant differences in body mass index, smoking, blood pressure, hypertension, chronic pulmonary disease, peripheral vascular disease, prior AMI, prior percutaneous coronary intervention (PCI), prior CABG, estimated glomerular filtration rate, left ventricular ejection fraction or triglycerides between the three patient groups.

Event rates and long-term mortality

During a mean follow-up time of 10.0 (SD 3.2) years (4968 person-years), a total of 133 (27%) patients died.

Of these, 44 (26%) had NGT, 51 (23%) with pre-diabetes and 38 (35%) patients with newly discovered diabetes died. We found no difference in the incidence of all-cause mortality between the three patient groups (table 2). Figure 1 shows that there was no significant difference in crude long-term cumulative survival between the groups. The Kaplan-Meier estimated 10-year survival was 77% (69%–83%), 83% (77%–87%) and 71% (61%–79%) in patients with NGT, pre-diabetes and newly discovered diabetes, respectively.

After adjustment for confounders, there were no differences in relative risks of mortality between the three patient groups (table 2). Patients with pre-diabetes had lower relative risk of death, but the association was non-significant (HR 0.71, 95% CI 0.46 to 1.08).

DISCUSSION

In this observational, population-based cohort study including patients without previously known diabetes

Table 2 Event rates and relative risks for all-cause mortality in 497 patients prior to CABG

	Total study population	NGT	Pre-diabetes	Diabetes
	(N=497)	(n=170)	(n=219)	(n=108)
Number of deaths, n (%)	133 (27)	44 (26)	51 (23)	38 (35)
Deaths/100 patient-years (95% CI)	2.7 (2.3 to 3.2)	2.7 (2.0 to 3.6)	2.3 (1.7 to 3.0)	3.6 (2.6 to 5.0)
		HR (95% CI)		
Unadjusted model		1 (ref)	0.82 (0.55 to 1.23)	1.34 (0.87 to 2.07)
Age-adjusted and sex-adjusted model		1 (ref)	0.67 (0.44 to 1.00)	0.98 (0.63 to 1.53)
Multivariable model 1*		1 (ref)	0.68 (0.45 to 1.03)	1.07 (0.68 to 1.68)
Multivariable model 2†		1 (ref)	0.71 (0.46 to 1.08)	1.03 (0.65 to 1.64)

*Model 1 was adjusted for age, sex, renal function (estimated glomerular filtration rate) and left ventricular ejection fraction.
†Model 2 was adjusted for all variables in model 1, and also body mass index, hypertension, pulmonary disease, peripheral vascular disease, smoking, prior myocardial infarction, prior percutaneous coronary intervention and prior stroke.
CABG, coronary artery bypass grafting; n, number of patients; ref, reference category.

who underwent a first isolated CABG in 2005–2013 in Sweden, we found that patients with pre-diabetes or newly discovered diabetes prior to CABG had similar long-term survival during a mean 10 years of follow-up compared with patients with NGT.

A limited number of studies have examined the role of unknown disturbances of glucose metabolism prior to CABG and prognosis. One of the first was a single-centre study of patients undergoing primary isolated CABG in 2001–2003.[6] The study investigated whether preoperative fasting blood glucose was associated with increased mortality after CABG. Compared with our study they found higher prevalence of undiagnosed diabetes and pre-diabetes prior to CABG. They found elevated risk of death after CABG in patients with abnormal glucose tolerance and unknown diabetes and that it was similar to patients with known diabetes.[6] Compared with our study, they included patients with known diabetes and found no elevated risk in patients with NGT, and the follow-up time was 6 months to 3 years.[6]

Another study published in 2013 by Petursson et al,[5] with a follow-up time of 5.3 years and with a relatively small

Figure 1 Kaplan-Meier estimated survival in 497 patients who underwent primary isolated coronary artery bypass grafting according to glucose tolerance group. NGT, normal glucose tolerance.

number of patients (n=172) undergoing OGTT prior CABG, indicated a strong correlation between the severity of disturbances of glucose metabolism and long-term risk of death and cardiovascular events. This prospective study also found a high percentage of patients with undiagnosed abnormal glucose regulation and showed that the long-term risk of death was lowest among patients with NGT, intermediate in patients with pre-diabetes and highest in patients with diabetes.[5] However, in this study a large number of patients were excluded and the diabetes group was mixed with patients with previously known and newly discovered diabetes. In our study we excluded patients with known diabetes, which partly can explain the difference in results since patients with newly discovered diabetes are not as affected by their diabetes as patients with known diabetes.

A recent report from 2018 by Sumin et al[12] studied 700 consecutive patients who underwent an OGTT prior to CABG and the association between newly diagnosed T2D and prognosis after CABG. They found a relationship between previously diagnosed T2D and a higher number of complications and prolonged in-hospital stay when comparing with patients without diabetes. The significance of these relationships increased with the addition of newly diagnosed T2D to the regression, and they stress the importance of active preoperative T2D screening.

In 2015 we published a study where we investigated a cohort of 39 235 patients who underwent a first isolated CABG during an 11 years' time period in Sweden. The two main findings in our study were that type 1 diabetes was associated with a twofold increase in mortality and that patients with T2D had only a minimally increased risk of death compared with patients without diabetes.[4] The relative risk for all-cause mortality was adjusted for a number of clinical characteristics and previously known risk factors. The results from the current study are in line with these results and show no differences in long-term survival in patients with T2D compared with patients with NGT.
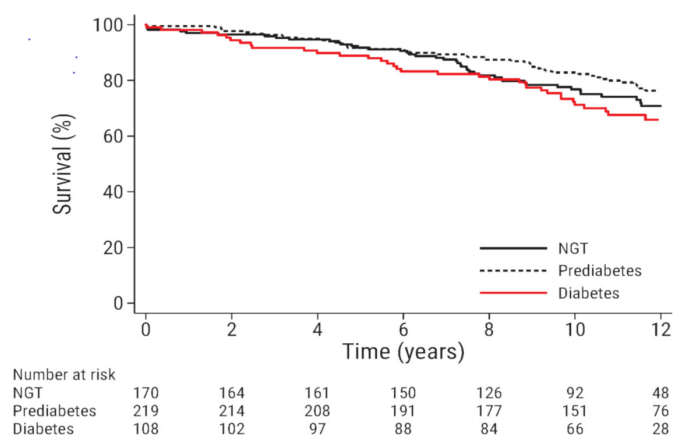
Some studies have shown that patients with AMI and disturbances of glucose metabolism under the threshold of diabetes have poorer prognosis compared with patients with NGT,[13][14] but some studies do not. In 2006, the Euro Heart Survey[1] on diabetes and the heart demonstrated that patients with CAD and known diabetes were at high risk for mortality and cardiovascular events, and demonstrated that patients with newly diagnosed diabetes were at intermediate risk for adverse outcomes. Pre-diabetes, however, could not be identified as an independent predictor of adverse outcomes during 1 year of follow-up. Perhaps the discrepancy in outcome can be explained by that cardiac surgery is a major life event with a longer rehabilitation period in comparison with coronary angiography. Therefore patients will become more aware of the seriousness of the situation and more motivated to lifestyle changes and adherence to medication. One could also speculate on whether the pre-diabetes and diabetes diagnoses 10 years earlier had an impact on the behaviour. This could partly explain our unexpected result that patients with pre-diabetes seem to do even better than those with NGT. In the present study, all patients were discharged with recommended lifestyle changes and guideline directed medical therapy.

Our analysis showed that among patients who underwent CABG and without known disturbances of glucose metabolism, 66% had pre-diabetes or newly detected diabetes. Previously published studies have reported similar prevalence numbers. Anderson et al[15] reported that among 267 patients referred for CABG with unknown diabetes, 73% had pre-diabetes or newly detected diabetes. Similarly, Greberski et al[16] found that 70% of patients with unknown diabetes planned for CABG had disturbances of glucose metabolism. These prevalence figures are in line with the results of large studies that have shown that approximately 75% of patients with CAD have disturbances of glucose metabolism.[17][18] Our results thus confirm that majority of patients with CAD have abnormal glucose regulation.

Strengths and limitations

Using the SWEDEHEART register and patients' medical records, we were able to identify all patients at the Karolinska University Hospital and Danderyd University Hospital without previously known diabetes who underwent an OGTT and isolated CABG during a 9-year period. In the SWEDEHEART register, all cardiac surgeries performed in Sweden have been registered since 1992 with almost complete coverage and high validity.[19][20] We were able to classify all patients without known diabetes using an OGTT done according to WHO criteria and investigate the importance of the different glucose tolerance groups for prognosis. In addition, our follow-up time is long compared with other studies. One limitation of this study is the relatively small number of patients undergoing OGTT, even though the number is higher compared with other similar studies. We found a trend towards an excess risk in people with newly detected diabetes, but it is not coming out significant probably because of the small numbers.

CONCLUSION

In conclusion, we found that among patients without previously known diabetes who underwent isolated CABG, two-thirds had disturbances of glucose metabolism prior to surgery. However, in this study, there was no difference in long-term mortality between patients with pre-diabetes or newly discovered diabetes prior to CABG, compared with patients with NGT.

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