

Original Article

Effect of glycated hemoglobin on heart function of the patients with revascularization of coronary artery

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Abstract: Background: Patients with diabetes after coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI) treatment for coronary artery disease (CAD) had higher mortality rates than those without diabetes. There were limited data comparing the cardiac and metabolic differences between diabetes and non-diabetes for CABG and PCI and about impact of pre-procedure GHb level on systolic heart function in patients with diabetes. Aims: To explore the cardio-metabolic differences and to evaluate their potential as significant risk factors. Subjects and method: 124 patients with diabetes and 170 patients without diabetes were enrolled. Coronary lesions ($\geq 70\%$ stenosis in at least one major coronary artery) were documented by angiography. Patients with diabetes were divided into different groups by GHb, Coronary lesions ($\geq 70\%$ stenosis in at least one major coronary artery) were documented by angiography. CABG and PCI were performed for all the patients. Cardio-metabolic risk factors before revascularization were compared between them. Results: Diabetics with GHb $\geq 8\%$ had lower cardiac ejection fraction (EF) values than those with GHb $< 8\%$ ($P < 0.05$) or patients without diabetes ($P < 0.05$). And count of vascular lesions between the groups was not statistically significant. Observed EF as a dependent variable negatively correlated to GHb levels ($P < 0.05$). The levels of glycosylated hemoglobin A1c (GHbA1c) rose with increased fasted blood glucose (FBG) values ($P < 0.001$). Even with treatment for hyperglycemia and dyslipidemia, overall levels of fasting blood sugar (FBG, $P < 0.001$), GHbA1c ($P < 0.001$), and triglycerides (TG, $P < 0.05$) in patients with diabetes were still higher than those without diabetes respectively. Conclusion: Poorer glucose control with GHb $\geq 8\%$ and decreased systolic heart function are significant risk factors that potentially contribute to worse prognosis for CABG or PCI treatment. Elevated levels of FBG, GHbA1c, and TG are evident for patients with diabetes compared to patients without diabetes prior to revascularization.

Keywords: GHbA1c, EF, revascularization

Introduction

Patients with diabetes after coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI) treatment had higher mortality rates than patients without diabetes undergoing the same treatments for coronary artery disease (CAD). The objective of type 2 diabetes mellitus prevention and management is to reduce cardiovascular and cerebrovascular events and improve resultant mortality rates [1-5]. Randomized trials for type 2 diabetes mellitus with CAD reported no significant differences in the rates of death and major cardiovascular events between prompt revascularization and medical therapies [1, 2]. Some prospective clinical trials have shown optimal con-

trol of the levels of blood glucose, lipids, and blood pressure was critical for diabetes intervention [6-14].

Basically, the diabetes mellitus has been proved to be a strong risk factor for revascularization of patients with CAD. Blood glycosylated hemoglobin (GHb) is reflective of mean ambient fasting and postprandial serum glucose levels over the preceding 2 to 3 months. But there were limited data comparing the cardiac and metabolic differences between diabetes and non-diabetes for CABG and PCI, and about impact of pre-procedure GHb level on systolic heart function in patients with diabetes. In this retrospective study, we decided to explore the cardio-metabolic differences and to evaluate their potential as significant risk factors.

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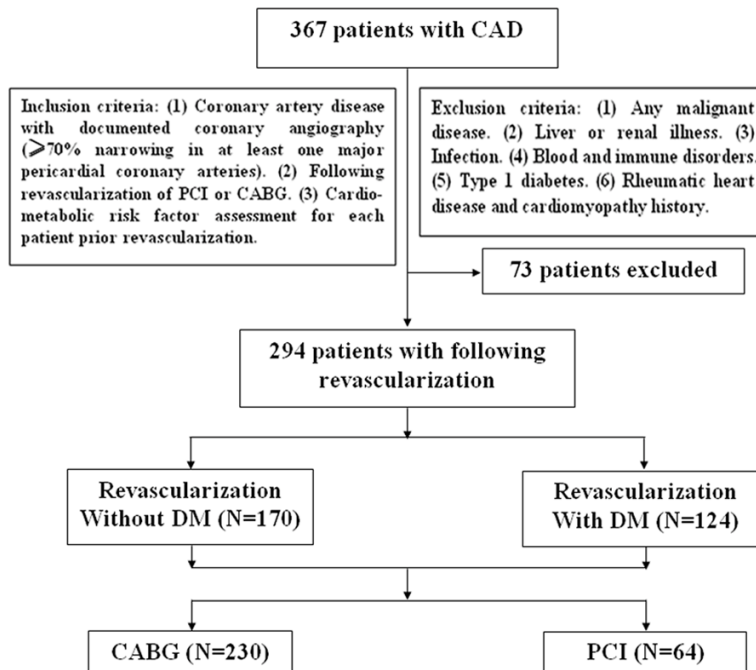


Figure 1. Study design.

Subjects and methods

Patients

In this retrospective study, 294 of 367 patients hospitalized with CAD aged 61.0 ± 9.5 years old in hospitalization from Beijing Anzhen Hospital were enrolled between January and December 2010. Subjects included 211 men and 83 women, who were separated into two groups: 124 patients with type 2 diabetes mellitus and 170 without it, patients with diabetes were divided into different groups by HbA1c. Inclusion criteria for patients were: (1) CAD was determined by documented coronary angiography ($\geq 70\%$ stenosis in at least one major pericardial coronary artery); (2) operation of revascularization procedures of PCI or CABG was based upon angina symptoms or objective evidence of myocardial ischemia; (3) cardio-metabolic risk factors were accessed for each patient prior to revascularization procedures. Exclusion criteria were: (1) any malignant disease; (2) liver or renal illness; (3) infection. (4) hematologic and immune disorders; (5) type 1 diabetes; (6) history with rheumatic heart disease and cardiomyopathy.

Methods

Hospital-based ethics committee approved the study. The study was designed as described in

Figure 1. Body weight, height, blood pressure were measured and recorded for all patients. Age, smoking, duration of the previous diseases (CAD, type 2 diabetes mellitus, hypertension, dyslipidemia), cardio-vascular events (non-fatal myocardial infarction, non-fatal stroke) and medication were recorded for assessment. Fasting blood and serum samples were collected prior to revascularization and tested for: HbA1c, serum glucose, lipid levels [total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG)], hypersensitive C-reactive protein (hsCRP), uric acid (UA) and creatinine (Cr) levels. Target values of the metabolic assessment were from American Diabetes Association

(ADA) guidelines: GHb $< 7\%$, LDL < 2.6 mmol/L, TG < 1.7 mmol/L, blood pressure $\leq 130/80$ mmHg. The target GHb value of $< 8\%$ for diabetes with CAD was also suggested by ADA, therefore, in this study, we used GHb $> 7\%$ or $> 8\%$ respectively as cut points during our analysis. Cardiac ejection fraction (EF) of left ventricle (LV) was measured by echocardiography. Diabetes was defined according to ADA: fasted glucose ≥ 7.0 mmol/L, postprandial glucose ≥ 11.1 mmol/L, or HbA1c ≥ 48 mmol/L (6.5%). Coronary lesions ($\geq 70\%$ stenosis in at least one major coronary artery) were documented by angiography. The patients are divided into more than three lesions and less than three lesions according to the count of vascular disease.

Statistical analysis

Statistics were presented as "mean \pm SD" for continuous variables, and conducted by student's *t*-test and analysis of variance (ANOVA). Frequency with percentage for categorical variables was performed with a chi-square test. *P* values were two-sided. Bivariate correlations with Pearson coefficients were studied in cardiovascular and metabolic risk factors including: age, BMI, SBP, DBP, UA, FBG, GHb, TG, TC, HDL, LDL and left ventricular ejection fraction (LVEF). Regression analysis was used in this

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Table 1. Clinical, demographic, and biochemical data for all subjects

Items	Revascularization	Revascularization	P values
	without DM N=170	with DM N=124	
Clinical & demographic			
Age, yrs	60.9±10.2	61.1±8.8	0.836
Sex ratio (Men to Women)	3.15:1 (129 vs 41)	1.95:1 (82 vs 42)	0.057
BMI, kg/m ²	26.4±4.2	26.0±3.3	0.440
Blood pressure, mmHg			
SBP	132.1±18.8	131.9±19.5	0.587
DBP	78.7±10.5	77.7±11.7	0.442
EF, %	60.3±9.3	59.6±10.9	0.574
Coronary arteries	2.36	2.41	0.214
Smoking, %	45.5	50.7	0.376
Previous disease, %			
Coronary heart disease	16.6	61.2	<0.001
Hypertension	69.0	74.3	0.304
Dyslipidemia	15.2	10.5	0.231
Duration of disease, yrs			
Type 2 diabetes mellitus	N/A	6, 0-40	
Coronary heart disease	1.2±3.4	3.8±5.0	<0.001
Hypertension	8.2±10.8	8.5±9.0	0.817
Dyslipidemia	0.65±0.17	0.67±0.14	0.753
Heart and cerebral vascular events, %			
NMI	17.2	17.1	0.975
NS	8.3	10.5	0.507
Fasting biochemical data			
FBG, mmol/L	5.7±1.2	7.9±3.1	<0.001
HbA1c (%)	6.0±0.5	7.5±1.3	<0.001
TC, mmol/L	4.6±1.1	4.7±1.4	0.332
LDL, mmol/L	2.9±0.9	2.9±1.0	0.756
HDL, mmol/L	1.1±0.2	1.1±0.3	0.529
TG, mmol/L	1.9±0.9	2.4±1.9	0.012
HsCRP, mmol/L	3.6±3.8	3.8±4.3	0.704
Cre, μmol/L	85.6±22.5	81.1±26.0	0.052
UA, μmol/L	370.4±94.0	351.1±97.4	0.105
Medications, %			
Statin	96.6	96.7	0.948
Any antihypertensive agent	69.7	73.0	0.521
Any antihyperglycemic agent	N/A	58.5	
Metformin	N/A	26.4	
Sulfonylurea	N/A	16.4	
Thiazolidinedione	N/A	0.7	
Insulin	N/A	24.8	
Patients meeting target values, %			
GHbA1c <53 mmol/mol (7%)	N/A	38.2	
LDL-c <2.6 mmol/L	43.8	41.2	0.661
TG <1.7 mmol/L	50.0	43.2	0.247
Blood pressure ≤130/80 mm Hg	46.9	54.0	0.221

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; EF, cardiac ejection fraction; NMI, nonfatal myocardial infarction; NS, nonfatal stroke; FBG, Fasting blood glucose; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride; hsCRP, hypersensitive CRP; Cre, creatinine; UA, uric acid.

study with $P \leq 0.05$ for entered variables and $P \geq 0.10$ for excluded variables. Multiple linear regression equations were obtained from regression analysis. Linear regression by the stepwise method was performed for all included variables. Any P values less than 0.05 were considered to be statistically significant.

Results

Comparison of cardiovascular risk factors between patients with diabetes and patients without diabetes prior to revascularization

Patients with history of previous CAD accounted for 61.2% in diabetes group, which was 3.8 times higher than the percentage in the group without diabetes ($P < 0.001$). The average duration of past CAD were 3.8 years for patients with diabetes compared only 1.2 years for patients without diabetes ($P < 0.001$). As shown in **Table 1**, patients with diabetes had higher FBG, GHb and TG levels than those in the group without diabetes group (7.9±3.1 vs. 5.7±1.2 mmol/L, $P < 0.001$; 7.5±1.3% vs. 6.0±

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Table 2. Cardio-metabolic risk factors between diabetes and non-diabetes in CABG and PCI sub-groups

Items	CABG		P values	PCI		P values
	Diabetes	Non-diabetes		Diabetes	Non-diabetes	
	N=92	N=138		N=32	N=32	
BMI, kg/m ²	26.0±3.4	26.5±4.5	0.409	26.0±3.3	26.6±5.7	0.593
SBP, mmHg	132.6±19.2	132.8±19.1	0.952	130.4±19.7	134.2±20.0	0.364
DBP, mmHg	78.4±11.7	78.7±10.5	0.857	76.42±12.0	78.0±10.4	0.489
FBG, mmol/L	7.9±3.3	5.6±1.2	<0.001	8.1±3.1	5.7±1.0	<0.001
HbA1c (%)	7.5±1.3	6.1±0.5	<0.001	7.4±1.3	5.9±0.5	<0.001
TC, mmol/L	4.9±1.4	4.6±1.1	0.117	4.4±1.0	4.4±1.1	0.967
LDL, mmol/L	3.0±1.0	2.9±0.9	0.390	2.7±0.84	2.7±0.7	0.922
HDL-c, mmol/L	1.1±0.3	1.1±0.2	0.779	1.1±0.3	1.1±0.2	0.779
TG, mmol/L	2.5±2.0	1.8±0.9	0.005	2.1±1.1	2.0±0.9	0.608
hsCRP, mmol/L	4.0±4.4	3.8±4.0	0.652	3.6±4.3	3.0±2.7	0.426
UA, µmol/L	348.7±97.4	367.1±96.9	0.155	359.1±102.3	376.0±96.8	0.414
EF, %	59.9±10.7	59.5±9.6	0.785	57.7±11.4	60.9±9.7	0.172

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; EF, cardiac ejection fraction; NMI, nonfatal myocardial infarction; NS, nonfatal stroke; FBG, Fasting blood glucose; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride; hsCRP, hypersensitive CRP.

0.5%, $P<0.001$; 2.4 ± 1.9 vs. 1.9 ± 0.9 mmol/L, $P<0.001$). But there were no significant differences in BMI, SBP, DBP, FBG, LDL, and HDL, hsCRP, UA, EF and smoking rates between patients with diabetes and patients without diabetes ($P>0.05$).

Compared data within CABG subgroup and within PCI subgroup

Within CABG or PCI subgroup, only FBG and GHb levels as stringent cardio-metabolic risk factors for patients with diabetes were more elevated than those for patients without diabetes ($P<0.001$ for all). No significant differences ($P>0.05$) were observed in other risk factors such as: BMI, SBP, DBP, FBG, HbA1c, LDL, and HDL, TG, hsCRP, UA and EF as shown in **Table 2**.

Relationship between cardiac LVEF and blood GHb values in patients with diabetes underwent revascularization

All patients with diabetes were analyzed with either GHb $<7\%$ or GHb $<8\%$ as a cut point, and cardio-metabolic parameters were compared between these groups. LVEF values in patients with GHb $\geq 8\%$ were reduced notably compared to non-diabetes group ($P<0.05$) or GHb $<8\%$ patients ($P<0.05$) as shown in **Table 3** and **Figure 2**.

Discussion

Hyperglycemia and hypertriglyceridemia were typical metabolic abnormalities associated with diabetes. In the PCI or CABG subgroup in this study, there were significant differences in FBG ($P<0.001$) and GHb levels ($P<0.001$) between patients with diabetes and patients without diabetes. Patients with diabetes with GHb $\geq 8\%$ had lower cardiac ejection fraction (EF) values than those with GHb $<8\%$ or patients without diabetes. Melle et al. [15] reported a correlation between GHb $\geq 6.5\%$ in patients with diabetes with stable coronary artery disease who developed heart failure compared with patients who remained free of heart failure. In addition, GHb $\geq 6.5\%$ trended towards occurrence of new onset heart failure. In some echocardiographic comparison studies, patients with diabetes presented a diminished ejection fraction, an elevated end-systolic diameter and volume compared to normal subjects. Congestive heart failure occurred more easily in patients with diabetes when compared to patients without diabetes. The possible mechanism is macrovascular disease and diabetic cardiomyopathy [16]. In our study, the left ventricular ejection function as a dependent variable negatively correlated with blood GHb levels. GHb is not only a useful biomarker of long-term glycaemic control but also a good

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Table 3. Comparison of cardio-metabolic risk factors in different GHb levels

	Non-DM N=170	DM Different cut point GHbA1c target, N=124			
		<7%		≥7%	
		N=46	N=78	N=90	N=34
BMI, kg/m ²	26.4±4.3	26.3±3.5	26.4±3.2	26.1±3.6	25.8±2.5
SBP, mm Hg	133.4±18.9	128.4±20.4	133.0±18.7	131.1±19.7	132.2±18.6
DBP, mm Hg	79.0±10.4	75.7±12.3	79.2±11.0	76.9±11.8	79.7±11.0
FBG, mmol/L	5.6±0.8	6.1±1.4	8.8±3.3	6.7±1.6	10.7±3.9
HbA1c (%)	6.0±0.5	6.2±0.4	8.1±1.0	6.8±0.7	9.1±0.8
TC, mmol/L	4.6±1.1	4.7±1.4	4.7±1.4	4.7±1.3	4.9±1.6
LDL, mmol/L	2.9±1.0	2.9±1.1	2.9±1.0	2.9±0.9	2.9±0.9
HDL-c, mmol/L	1.1±0.2	1.1±0.26	1.0±0.27	1.1±0.2	1.1±2.7
TG, mmol/L	1.9±0.9	2.2±1.5	2.4±1.1	2.2±1.3	2.9±2.9
hsCRP, mmol/L	3.6±3.7	4.1±4.7	3.7±4.0	4.2±4.6	3.0±3.6
UA, μmol/L	369.8±93.7	343.8±11.5	355.2±88.3	349.1±98.8	356.1±98.0
Coronary arteries	2.36±0.3	2.34±0.35	2.36±0.33	2.35±0.2	2.37±0.14
EF, %	60.5±9.4	60.5±10.5	59.1±11.3	60.1±9.7	56.6±13.5

All diabetic patients were divided by cut point GHbA1c 7% into two subgroups, or by GHbA1c 8% into the other two groups. Patients without diabetes were used as control for different GHbA1c cut point respectively. Among three groups as Non-DM, GHb <7% and GHb ≥7%: (1) FBG in GHb ≥7% subgroup compared with Non-DM or GHb <7% subgroup, P<0.001 respectively; (2) GHb levels in GHb ≥7% subgroup compared with <7% or Non-DM subgroup, P<0.001 respectively; (3) TG levels in GHb ≥7% subgroup compared with Non-DM subgroup, P=0.014. Among three groups as Non-DM, GHb <8% and GHb ≥8%: (1) FBG between groups, P<0.001; (2) GHb between groups, P<0.001; (3) TG levels in GHb ≥8% subgroup compared with Non-DM, P<0.001; TG levels in GHb ≥8% subgroup compared with GHb <8%, P=0.007; (4) EF values in GHb ≥8% subgroup compared with Non-DM subgroup, P=0.035; EF values in GHb ≥8% subgroup compared with GHb <8% subgroup, P=0.033.

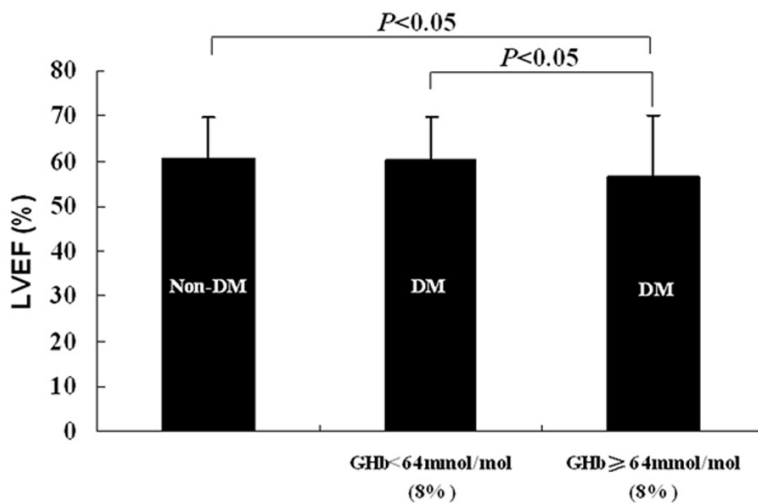


Figure 2. Comparison of left ventricular ejection fraction (LVEF) in different cut point GHb levels.

predictor of lipid profile. In diabetic patients with PCI or CABG, GHb ≥8% indicated that patients had lower LVEF and were more likely to experience future heart failure. Cardiac ejection fraction, GHb and FBG factors are possibly interlinked before revascularization therapy for

patients with CAD [17]. Although it is generally evident that targeting FBG and GHb control could lead to lower mortality and better clinical outcomes [12, 18-20], the methodology and drug-linked hypoglycemic episodes had mixed cardiovascular outcomes [10, 12, 21-24]. For revascularization, more and severe hypoglycemic events could counterbalance long-term benefit of tightly managing blood glucose levels [25].

The cluster of high fasting glucose, HbA1c, blood pressure, and LDL-c levels caused severe CAD in patients with diabetes [26-28]. In this study, with patients before revascularization, only FBG, GHb and TG levels in patients with diabetes were significantly elevated more than those in patients without diabetes, but no significant differences were found in BMI, SBP,

DBP, LDL, HDL-c and UA values. The possible reason is that more than 96% of the patients were on statin-related medication and over 69.7% of the patients were on antihypertensive agent, for the prevention and treatment of CAD. These medications against abnormal serum lipid levels and high blood pressure could result in similar rates of patients meeting target values for LDL and blood pressure between patients with diabetes and patients without diabetes. The freedom trial reported that, for patients with diabetes with PCI or CABG, GHb >7% and TG >1.7 mmol/L were the principal cardio-metabolic risk factors [1]. The steno-2 study [8], a trial of multi-factorial intervention in type 2 diabetes showed reduction in death from cardiovascular causes and cardiovascular events by significantly lowering fasting glucose (7.2 mmol/L) and TG levels (1.30 mmol/L).

In conclusion, elevated FBG, GHb and TG levels were the primary metabolic abnormalities of patients with diabetes prior to revascularization. Heart ejection fraction for patients with GHb $\geq 8\%$ was lower more than those with GHb <8% and patients without diabetes. Patients with diabetes with GHb $\geq 8\%$, and decreased left ventricular injection fraction as risk factors potentially contributed to poorer prognosis for heart revascularization when compared to those with GHb <8% and patients without diabetes. Monitoring GHb and heart ejection fraction can play a major role in predicting and improving the outcomes post cardiac revascularization for patients with diabetes. In our study, high GHbA1c and decreased EF could be a new insight and helpful for future other investigators.

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Disclosure of conflict of interest

None.

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