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Prognostic value of glucose metabolism for non-ST-segment elevation infarction patients with diabetes mellitus and single concomitant chronic total occlusion following primary percutaneous coronary intervention

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Abstract

Glucose metabolism status may play a predictive role in the severity of the complications among patients with type 2 diabetes mellitus (DM). However, few studies have focused on the prognostic value of glycosylated hemoglobin (HbA1c) and Homeostatic Model Assessment 2 for Insulin Resistance (HOMA2-IR) in patients with DM, non-ST-segment elevation infarction (NSTEMI), and single concomitant chronic total occlusion (CTO) following primary percutaneous coronary intervention (PCI). Short- and long-term prognostic value of HbA1c and HOMA2-IR in patients with DM with NSTEMI and single CTO who received primary percutaneous transluminal coronary intervention (pPCI).

Data from 202 patients with NSTEMI and single CTO in nonculprit vessels were included. The incidence of revascularization, cardiogenic shock, ischemic stroke, major bleeding (ie, cerebral hemorrhage or massive hemorrhage of gastrointestinal tract), and cardiac death were combined as composite end points (CEPs). HbA1c was measured on admission and at 12 and 24 weeks after discharge. HOMA2-IR was measured on admission and at 6 and 12 weeks after discharge. The mean value of HbA1c and HOMA2-IR was calculated to determine the impact on 2.5-year CEPs. All patients were assessed during hospitalization and followed for up to 2.5 years after discharge.

Mean age was 62.4 ± 11.8 years and 76% were male. Previous MI, lower left ventricular ejection fraction, and higher HbA1c (hazard ratio [HR] = 1.216; 95% confidence interval [CI] = 1.023–1.445; $P = .023$) were independently associated with a poor prognosis at 2.5 years. Higher HbA1c and HOMA2-IR on admission was associated with CEPs during hospitalization. Mean HOMA2-IR prior to pPCI was associated with revascularization (HR = 1.129; 95% CI = 1.008–1.265; $P = .036$) and ischemic stroke (HR = 1.276; 95% CI = 1.044–1.560; $P = .017$) during the 2.5 years follow-up period.

Glucose metabolism status reflected by HbA1c and HOMA2-IR may provide prognostic value to patients with NSTEMI, type 2 DM, and single concomitant CTO following PCI. Therefore, patients with NSTEMI, CTO, and poor glycemic control should be carefully evaluated prior to PCI.

Abbreviations: CAD = coronary artery disease, CEP = composite end point, CI = confidence interval, CTO = chronic total occlusion, eGFR = estimated glomerular filtration rate, GPI = glycoprotein IIb/IIIa inhibitor, HbA1c = glycosylated hemoglobin, HOMA2-IR = Homeostatic Model Assessment 2 for Insulin Resistance, HR = hazard ratio, IR = insulin resistance, IRA = infarct-related artery, MI = myocardial infarction, pPCI = primary percutaneous transluminal coronary intervention.

Keywords: chronic total occlusion, diabetes mellitus, glycosylated hemoglobin, Homeostatic Model Assessment 2 for Insulin Resistance, NSTEMI, primary percutaneous coronary intervention

1. Introduction

Multivessel coronary artery disease (CAD) is common among patients with non-ST-segment elevation infarction (NSTEMI)[1] and their risk for a major adverse cardiac events (MACEs)[2] is varied. The presence of noninfarct-related artery chronic total occlusion (non-IRA CTO) and diabetes mellitus (DM) in patients with NSTEMI further increases their risk of mortality at 12 months.[3] Hyperglycemia is common among patients admitted to hospital with NSTEMI and may play a role in predicting short- and long-term prognosis after primary percutaneous coronary intervention (pPCI), irrespective of DM status.[4–6]

Selvin et al[7] demonstrated high-glycosylated hemoglobin (HbA1c) levels are associated with an increased risk of cardiovascular events in patients with DM who do not have CAD. HbA1c levels have a U-shaped correlation with MACEs and target lesion revascularization in patients with CAD with stent implants, either as a continuous variable or a categorical

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variable.[8] A recent meta-analysis demonstrated HbA1c levels are associated with higher risk of nonfatal myocardial infarction (MI) and target vessel revascularization progression among patients with DM after PCI.[9]

Pathological responses of insulin resistance (IR), assessed by Homeostatic Model Assessment 2 for Insulin Resistance (HOMA2-IR), was triggered by intracellular lipid accumulation in ectopic tissue and resulted in subsequent impairment in insulin signaling.[10] HOMA2-IR plays an important role in the pathogenesis of DM and metabolic syndrome.[11]

The present study aims to characterize the relationship between HbA1c, HOMA2-IR, and prognosis of NSTEMI patients with DM and single concomitant CTO following pPCI.

2. Methods

2.1. Study population

A total of 202 patients with NSTEMI were enrolled in the study upon admission to The First Affiliated Hospital of Xinjiang Medical University between January 2008 and September 2014. Exclusion criteria included: STEMI; type 1 DM; severe cardiomyopathy and valvular disease; rescue PCI, prior coronary artery bypass grafting, and plans to undergo prior coronary artery bypass grafting; no CTO in coronary angiography; left main disease; estimated life expectancy <12 months; history of cerebrovascular attack (within 1 year); severe renal insufficiency requiring dialysis; known contraindication to antiplatelet drugs, lipid-lowering agents, heparin, and contrast or glycoprotein IIb/IIIa inhibitor (GPI); and incomplete clinical data. Written informed consent was obtained, and the Research Ethics Committee of The First Affiliated Hospital of Xinjiang Medical University approved the study.

All patients were admitted to the Department of Cardiology and received intervention in the culprit vessel within 24 hours of presentation. All patients received 300 mg oral aspirin and clopidogrel as well as standard heparin (initial 10,000 IU and boost as the operation progressed). Angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, GPI (tirofiban), statin, unfractionated heparin, low molecular weight heparin, and beta-blocker were administered by the attending physician. Oral antihyperglycemic drugs and insulin were maintained to lower glucose.

2.2. Therapy strategy and definitions

NSTEMI was diagnosed according to the criteria from European Society of Cardiology (ESC).[12] DM was defined by prior history based on the medical institution standard diagnostic criteria, diet utilization, oral glucose-lowering medication, and/or insulin or a HbA1c ≥6.5%, which is recognized by the American Diabetes Association (ADA) as sufficient for the diagnosis of DM. Medical history, laboratory results, and angiographic findings were collected and recorded. Each patient underwent an echocardiograph within the first 96 hours after admission and estimated glomerular filtration rate (eGFR) upon admission was estimated using the simplified Modification of Diet in Renal Disease formula.[13]

2.3. Laboratory measurements

Plasma glucose was measured by the enzymatic method using a glucose analyzer. Fasting insulin levels were determined using radioimmunoassay (coat-A-count diagnostic products). HOMA2-IR was calculated using an online calculator downloaded from http://www.dtu.ox.ac.uk. HbA1c was assessed on admission and again at 12 and 24 weeks after discharge. HOMA2-IR was measured on admission and again at 6 and 12 weeks after discharge. Preprocedural means of HbA1c and HOMA2-IR were used to predict composite end points (CEPs) at 2.5 years.

2.4. Angiographic strategy

A coronary artery was considered to be the culprit vessel if one of the following criteria was present: definite or suspected thrombus; ruptured or ulcerated plaque; presence of thrombolysis in myocardial infarction (TIMI) flow grade ≤2; and tight stenosis ≥70% consistent with noninvasive ischemia tests. A CTO was defined as a non-IRA with 100% luminal narrowing before PCI and without anterograde flow or with anterograde or retrograde filling through collateral vessels. Given current practice guidelines for managing NSTE-ACS published by the ESC,[14] the culprit vessel was selected for PCI to decrease the rate of procedure complication and homogenize our research subjects.

2.5. Follow-up and recorded events

The following events were regarded as CEPs in our study and recorded: revascularization; cardiogenic shock; ischemic stroke; major bleeding (including cerebral hemorrhage and massive hemorrhage of gastrointestinal tract); and cardiac death. CEPs were recorded once and the patient was then removed from the study. After discharge, all patients underwent periodic and prospective follow-up by telephone interview and clinic referrals for 2.5 years.

2.6. Statistical analysis

Baseline characteristics of patients are expressed as mean ± standard deviation or median ± interquartile range for continuous variables and absolute figure (percentage) for categorical variables. Pearson X^2 was performed for between-group comparisons for qualitative variables and Student *t* or Mann–Whitney *U* test for continuous variables. Long-term survival curves for combined levels of HbA1c and HOMA2-IR were obtained using the Kaplan–Meier method and compared with the log-rank test. Further, Cox proportional hazard regression model was performed to analyze the independent variables associated with the incidence of CEPs. Variables selected for the multivariate Cox proportional hazard analysis were those with $P < .1$ in the above analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated by backwards stepwise regression analysis (Wald). The final follow-up was completed on March 31th, 2017. All statistical tests were 2-tailed and performed using SPSS 17.0 (SPSS, Inc, Chicago, IL); a *P*-value $< .05$ was considered statistically significant.

3. Results

3.1. Epidemiological characteristics

Mean age was 62.4 ± 11.8 years, 76% were men. Fifteen suffered CEPs during hospitalization. Nine cases were lost to follow-up. Table 1 shows the initial characteristics of patients according to CEPs occurrence. White blood cells (10.07 ± 4.16 vs 8.83 ± 3.54,

Table 1

Basic clinical characteristics, laboratory examinations, electrocardiogram results, angiographic, and procedural characteristic.

	CEPs (N = 70)	Non-CEPs (N = 132)	P
Clinical characteristics			
Age, y	64.1 ± 13.2	61.7 ± 10.9	.119
Female, n, %	13 (18.6)	35 (26.5)	.207
Heart rate, beats per min	81.7 ± 19.4	77.5 ± 14.7	.066
SBP, mm Hg	138.8 ± 26.1	134.7 ± 23.4	.271
Killip classification > I, n, %	20 (28.6)	32 (24.2)	.503
Hypertension, n, %	37 (52.9)	72 (54.5)	.819
Previous MI, n, %	19 (27.1)	19 (14.4)	.027*
Previous stroke, n, %	9 (12.9)	11 (8.3)	.306
Lab examination			
WBC × 10^9/L	10.07 ± 4.16	8.83 ± 3.54	.038*
Neutrophil, %	75.6 ± 13.1	74.8 ± 14.4	.241
Hemoglobin, g/L	141.7 ± 17.8	144.4 ± 20.8	.932
Platelet × 10^9/L	247.5 ± 58.3	231.9 ± 60.8	.860
Albumin, g/L	37.9 ± 3.7	38.5 ± 3.6	.964
TC, mmol/L	5.99 ± 0.99	5.75 ± 1.43	.201
TG, mmol/L	1.14 ± 0.64	1.15 ± 0.90	.523
HDL-C, mmol/L	1.24 ± 0.27	1.21 ± 0.26	.708
LDL-C, mmol/L	2.96 ± 0.73	3.16 ± 0.79	.597
FBG, mmol/L	9.89 ± 2.78	9.14 ± 2.32	.096
FINS, pmol/L	12.76 ± 7.38	10.76 ± 7.61	.504
HOMA2-IR	5.38 ± 3.31	4.42 ± 2.36	.391
HbA1c, %	8.5 ± 1.4	7.0 ± 1.2	.088
Mean HOMA2-IR	5.06 ± 2.98	3.08 ± 2.12	.081
Mean HbA1c, %	8.4 ± 1.3	6.8 ± 1.2	.020*
BUN, mmol/L	6.83 ± 1.77	6.67 ± 2.18	.159
Creatinine, mmol/L	76.6 ± 16.7	73.7 ± 31.5	.832
Uric acid, mmol/L	329.2 ± 80.4	324.6 ± 72.5	.286
eGFR, mL/min*1.73 m^2	92.2 ± 26.4	101.8 ± 24.5	.031*
D-dimer, mg/L	0.8 (0.2–1.6)	1.0 (0.2–1.7)	.268
Peak CK-MB, U/L	81.5 (21.6–128.5)	53.0 (9.3–113.4)	.279
Peak cTnI, ng/mL	14.2 (6.1–21.4)	8.3 (2.0–19.0)	.034*
Treatment			
ACEIs/ARBs, n, %	42 (60.0)	86 (65.2)	.470
b-Blocker, n, %	39 (55.7)	81 (61.4)	.437
CCBs, n, %	17 (24.3)	39 (29.5)	.427
Statins, n, %	58 (82.9)	110 (83.3)	.931
Diuretics, n, %	11 (15.7)	21 (15.9)	.971
Antiplatelet, n, %	60 (85.7)	116 (87.9)	.662
Insulin dependent, n, %	30 (42.9)	51 (38.6)	.560
GPI, n, %	10 (14.3)	15 (11.4)	.548
Sulfonylureas, n, %	20 (28.6)	26 (19.7)	.152
α-Glucosidase inhibitor, n, %	32 (45.7)	51 (38.6)	.331
Euglycemic agent, n, %	21 (30.0)	45 (34.1)	.555
Biguanides, n, %	38 (54.3)	66 (50.0)	.562
Echocardiogram and electrocardiogram			
LAD, mm	38.4 ± 5.2	36.0 ± 5.9	.220
LVEDD, mm	52.7 ± 6.7	50.0 ± 6.0	.148
LVEF, %	43.3 ± 6.9	47.0 ± 7.4	.040*
Any ST depression, n, %	17 (24.3)	26 (26.7)	.448
Culprit vessels, n, %			
LAD	39 (55.7)	75 (56.8)	.374
LCX	12 (17.1)	14 (10.6)	
RCA	19 (27.1)	43 (32.6)	
Location of CTO, n, %			
LAD	19 (27.1)	35 (26.5)	
LCX	22 (31.4)	31 (23.5)	.402
RCA	29 (41.4)	66 (50.0)	
Stent number	1.33 ± 0.55	1.42 ± 0.55	.739
Type B2/C lesion, n, %	53 (75.7)	92 (69.7)	.366
Time interval from symptom to PCI, h	11.6 ± 3.7	14.2 ± 4.2	.043*

Data are n/N (%) or mean ± standard deviation or median (25th to 75th percentile).

* $P < .05$.

ACEI = angiotensin-converting enzyme inhibitors, ARB = angiotensin receptor blocker, BUN = blood urea nitrogen, CCB = calcium channel blocker, CEP = composite end point, CK-MB = creatinine kinase MB, cTnI = cardiac Troponin I, CTO = chronic total occlusion, eGFR = estimated glomerular filtration rate, FBG = fasting blood glucose, GPI = glycoprotein IIb/IIIa inhibitor, HbA1c = glycosylated hemoglobin, HDL-C = high-density lipoprotein, HOMA2-IR = Homeostatic Model Assessment 2 for Insulin Resistance, LAD = left anterior descending, LAD = left atrial diameter, LCX = left circumflex coronary artery, LDL-C = low-density lipoprotein, LVEDD = left ventricular end diastolic diameter, LVEF = left ventricular ejection fraction, MI = myocardial infarction, PCI = percutaneous transluminal coronary intervention, RCA = right coronary artery, SBP = systolic blood pressure, TC = total cholesterol, TG = triglyeride, WBC = white blood cells.

$P = .038$), mean HbA1c (8.4% ± 1.3% vs 6.8% ± 1.2%, $P = .02$), eGFR (92.2 ± 26.4 vs 101.8 ± 24.5, $P = .031$), peak cardiac Troponin I (cTnI) (14.2 [6.1–21.4] vs 8.3 [2.0–19.0], $P = .034$), left ventricular ejection fraction (43.3% ± 6.9% vs 47.0% ± 7.4%, $P = .040$), and time interval from symptom to PCI (11.6 ± 3.7 hours vs 14.2 ± 4.2 hours, $P = .043$) were significantly different between the 2 groups. Previous MI was more likely in the MACEs group compared with those with no MACEs ($P = .027$). Heart rate (81.7 ± 19.4 vs 77.5 ± 14.7, $P = .066$), fasting blood glucose (9.89 ± 2.78 vs 9.14 ± 2.32, $P = .096$), HbA1c (8.5 ± 1.4 vs 7.0 ± 1.2, $P = .088$), and mean HOMA2-IR (5.06 ± 2.98 vs 3.08 ± 2.12, $P = .081$) were approach significance between the 2 groups. Medical treatment including diuretics, nitrates, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists (angiotensin receptor blocker), antiplatelet drugs, glucose-lowering drugs, insulin before admission and low molecular weight heparin, and GPI administration during hospitalization were not significantly different between the 2 groups.

3.2. Independent predictors

Through the multivariate Cox regression analysis, previous MI (HR = 1.346, 95% CI = 1.065–1.702, $P = .013$), left ventricular ejection fraction (HR = 0.965, 95% CI = 0.941–0.990, $P = .006$), and HbA1c (HR = 1.216; 95% CI = 1.023–1.445; $P = .023$) were independent predictors of CEPs within 2.5 years after pPCI, while eGFR was approaching significance (HR = 0.226, 95% CI = 0.047–1.090, $P = .064$) (Table 2). Patients in both groups were followed for 2.5 years from NSTEMI onset. A total of 15 patients were followed for fewer than 24 weeks due to death (11) or loss of contact (4). The mean value of glucose metabolic index was calculated for all data prior to CEPs, regardless of whether all assessments were completed 3 times. The predictive value of HbA1c and HOMA2-IR on individual adverse events are recorded in Tables 3 and 4, respectively. HbA1c and HOMA2-IR on admission were both found to be independent predictors of poor prognosis during hospitalization. When considering the long-term ischemic stroke only, although not reaching statistical significance, a trend toward high incidence rate was discovered in high level of HbA1c (HR = 1.189, 95% CI = 0.987–1.432, $P = .068$). Similar condition was found in predicting revascularization by HOMA2-IR (HR = 1.289, 95% CI = 0.964–1.724,

Table 2

Multivariate Cox regression analysis for predictor of CEPs.

Variables	P	OR	95% CI
Heart rate	.110	1.013	0.997–1.028
Previous MI	.013*	1.346	1.065–1.702
WBC	.200	1.044	0.978–1.114
FBG	.110	0.313	0.075–1.301
HOMA2-IR	.607	1.044	0.886–1.230
eGFR	.064	0.226	0.047–1.090
cTnI	.249	1.009	0.994–1.024
LVEF	.006	0.965	0.941–0.990
HbA1c	.023	1.216	1.023–1.445
Time interval from symptom to PCI	.358	1.146	0.857- 1.532

* Statistically significant value ($P < .05$).

CEP = composite end point, CI = confidence interval, cTnI = cardiac Troponin I, eGFR = estimated glomerular filtration rate, FBG = fasting blood glucose, HbA1c = glycosylated hemoglobin, HOMA2-IR = Homeostatic Model Assessment 2 for Insulin Resistance, LVEF = left ventricular ejection fraction, MI = myocardial infarction, OR = odds ratio, PCI = percutaneous transluminal coronary intervention, WBC = white blood cells.

Table 3

Risks for hospitalization and 2.5-year composite end points with HbA1c.

	Unadjusted HR (95% CI)	P	Adjusted HR (95% CI)	P
HbA1c				
Hospitalization CEPs	1.456 (1.152–1.840)	.002*	1.512 (1.205–1.897)	.000*
2.5-year CEPs	1.178 (0.976–1.422)	.088	1.216 (1.023–1.445)	.023*
Revascularization	1.450 (1.144–1.838)	.002*	1.540 (1.224–1.938)	.000*
Cardiogenic shock	1.030 (0.652–1.627)	.899	1.065 (0.762–1.489)	.712
Ischemic stroke	1.223 (1.035–1.445)	.018*	1.189 (0.987–1.432)	.068
Major bleeding	0.968 (0.459–2.041)	.932	0.819 (0.369–1.818)	.624
Cardiac death	0.806 (0.520–1.249)	.335	0.864 (0.594–1.257)	.445
Mean HbA1c				
2.5-year CEPs	1.145 (1.022–1.283)	.020*	1.167 (1.044–1.305)	.007*
Revascularization	1.382 (0.931–2.052)	.108	1.268 (1.013–1.587)	.038*
Cardiogenic shock	1.061 (0.872–1.291)	.554	1.050 (0.854–1.291)	.644
Ischemic stroke	1.383 (1.025–1.866)	.034*	1.343 (1.124–1.605)	.001*
Major bleeding	1.152 (0.809–1.640)	.433	1.124 (0.852–1.483)	.408
Cardiac death	1.077 (0.884–1.312)	.462	1.016 (0.814–1.268)	.888

* Statistically significant value ($P < .05$).

CEP = composite end point, CI = confidence interval, HbA1c = lycosylated hemoglobin, HOMA2-IR = Homeostatic Model Assessment 2 for Insulin Resistance, HR = hazard ratio.

Table 4

Risks for hospitalization and 2.5-year composite end points with HOMA2-IR.

	Unadjusted HR (95% CI)	P	Adjusted HR (95% CI)	P
HOMA2-IR				
Hospitalization CEPs	1.228 (0.960–1.571)	.102	1.354 (1.098–1.670)	.005*
2.5-year CEPs	1.077 (0.909–1.276)	.391	1.044 (0.886–1.230)	.607
Revascularization	1.244 (0.931–1.662)	.140	1.289 (0.964–1.724)	.087
Cardiogenic shock	0.948 (0.565–1.591)	.840	0.997 (0.532–1.868)	.993
Ischemic stroke	1.064 (0.824–1.374)	.634	1.029 (0.850–1.246)	.769
Major bleeding	0.859 (0.335–2.203)	.752	0.819 (0.372–1.803)	.620
Cardiac death	0.750 (0.423–1.330)	.325	0.801 (0.448–1.432)	.454
Mean HOMA2-IR				
2.5-year CEPs	1.112 (0.987–1.253)	.081	1.156 (0.957–1.396)	.133
Revascularization	1.143 (0.919–1.422)	.230	1.129 (1.008–1.265)	.036*
Cardiogenic shock	1.044 (0.695–1.568)	.836	1.132 (0.790–1.622)	.499
Ischemic stroke	1.192 (0.972–1.462)	.092	1.276 (1.044–1.560)	.017*
Major bleeding	0.977 (0.405–2.357)	.959	1.131 (0.410–3.120)	.812
Cardiac death	0.850 (0.569–1.270)	.427	0.950 (0.638–1.415)	.801

* Statistically significant value ($P < .05$).

CEP = composite end points, CI = confidence interval, HbA1c = glycosylated hemoglobin, HOMA2-IR = Homeostatic Model Assessment 2 for Insulin Resistance, HR = hazard ratio.

$P = .087$). Preprocedural mean HbA1c was predictive in long-term CEPs (HR = 1.167, 95% CI = 1.044–1.305, $P = .007$). Preprocedural mean HOMA2-IR was associated with revascularization (HR = 1.129; 95% CI = 1.008–1.265; $P = .036$) and ischemic stroke (HR = 1.276; 95% CI = 1.044–1.560; $P = .017$) during the 2.5 year follow-up unlike HOMA2-IR on admission.

3.3. Subgroup Kaplan–Meier survival curves

To further evaluate the prognostic value of glucose metabolism status, a separate survival analysis was performed in patients grouped according to median HbA1c (7.3%) and HOMA2-IR (4.3). Survival curves from the double-low group (group D, n = 54) showed significantly greater prognostic value compared with group A (n = 52, HR = 6.322, 95%CI = 3.268–12.232, $P < .0001$), B (n = 50, HR = 3.417, 95%CI = 1.808–6.458, $P = .0002$), and C (n = 46, HR = 2.399, 95%CI = 1.264–4.555, $P = .0074$). Group C had stronger prognostic value compared to group A (HR = 2.6353, 95%CI = 1.3107–5.2988, $P = .0065$) (Fig. 1, log-rank test for CEPs, overall $P < .0001$). These findings should be interpreted with caution, given the limited number of

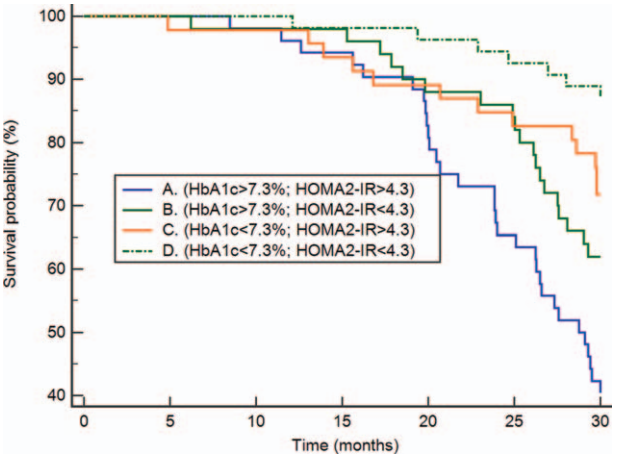

Figure 1. Kaplan–Meier survival curves of CEPs during 2.5-year follow-up in (A) high HbA1c and high HOMA2-IR; (B) high HbA1c and low HOMA2-IR; (C) low HbA1c and high HOMA2-IR; and (D) low HbA1c and low HOMA2-IR groups. CEP = composite end point, HbA1c = glycosylated hemoglobin, HOMA2-IR = Homeostatic Model Assessment 2 for Insulin Resistance.

patients included in each group, and therefore limited statistical power to detect differences in the total cohort.

4. Discussion

This study aimed to investigate the short- and long-term prognostic value of HbA1c and HOMA2-IR after pPCI among patients with DM, NSTEMI, and single contaminant CTO in nonculprit vessels were analyzed. Hyperglycemia induced by acute MI was associated with MI size, area at risk, and salvage[15] and may be associated with increased mortality in patients with and without DM.[16] In patients with DM, NSTEMI, and CTO, HbA1c and HOMA2-IR are useful for determining short-term glucose metabolism state, because glucose on admission may be influenced by diet. Fasting blood glucose may be measured preoperatively or postoperatively in patients. In addition, admission hyperglycemia may be due to the poor glycemic control more so than the stress reaction caused by limited residual myocardium.[17]

Hyperglycemia interrelates with platelet activation, fibrin clot resistance to lysis, and enhanced thrombin formation in patients with acute coronary syndrome.[18] Hyperglycemia can also increase endothelin-1 secretion in endothelial cells which may aggravate MI.[19] HbA1c can be used to determine average blood glucose levels over 2 months[20] and is minimally affected by acute hyperglycemia often observed in MI. Previous evidence has shown chronic glucose dysregulation (ie, HbA1c levels) has strong prognostic value in patients with or without DM after MI.[21,22] Elevated HbA1c is an important determinant of atherosclerosis beyond the risk associated with diagnosed DM.[23] Kassaian et al[24] found more type C lesions in patients with high HbA1c, similar to the results of this study. The ADVANCE study showed intensive glycemic control to lower than 6.5% helped to prevent microvascular complications[25]; insufficient benefit from macrovascular protection was gradually verified by patients without strict glycemic control.[26] HbA1c levels prior to stroke demonstrate a dose–response relationship with poor functional recovery.[27] Finally, HbA1c levels impact the extent of perfusion abnormalities and left ventricular dysfunction.[28]

There is some limited data showing preprocedural HbA1c levels are not associated with severity of CAD[29] and do not predict recurrent cardiovascular events after successful PCI in patients with DM and advanced CAD.[30,31] This study included patients with acute MI, cardiogenic shock, unstable angina pectoris, or stable angina pectoris and therefore less severe coronary lesions. In the present study, it is hypothesized that glucose plays a decisive role for the patient population, which may be reflected by the severe CTO prior to NSTEMI episode.

HOMA2-IR may be used to stratify risk for the recurrence of coronary events in the postinfarction population[32] and predict in-hospital mortality after acute coronary syndrome.[33,34] Previous studies have shown the incidence of adverse cardiac events including mortality rises independently from DM, along with the increase of IR in patients with coronary heart disease.[35,36] IR influences diastolic function among patients with subclinical left ventricular dysfunction and cardiovascular risk factors.[37,38] This may be explained by the decline of circulating endothelial progenitor cells, which have the capacity to repair endogenous vasculature.[39] Patients without DM may suffer acute IR after MI, which is associated with incomplete myocardial reperfusion and impaired coronary microcirculatory function.[40] In the present study, high levels of HOMA2-IR after PCI predicted poor prognosis. Emerging evidence suggests the direct proatherogenic[41] and negative inotropic[42] effect of IR are responsible for the incidence of MACEs. In addition to IR, low insulin secretion appears simultaneously with endothelial dysfunction, enhanced inflammatory response, higher coronary thrombotic burden, and higher short-term mortality after MI.[43]

5. Limitations

The small sample size from 1 hospital limits the ability to apply these results more broadly. Further, it is difficult to obtain subsequent treatment during follow-up of each patient. Some patients may change or strengthen glycemic control scheme. Some patients did not complete 3 subsequent tests, which result in failure to reflect the glucose metabolism status in the same phase for all the patients. Patients were treated according to the norms of the present institution by multiple physicians, which may explain the heterogeneity in the final result. Finally, the infarct size was not assessed to evaluate the severity of basal CTO.

6. Conclusion

High levels of HbA1c and HOMA2-IR in patients with DM may independently predict composite CEPs among NSTEMI patients with single contaminant CTO during hospitalization after pPCI. Moreover, admission and preprocedural HbA1c levels predict long-term prognosis, while preprocedural HOMA2-IR levels are associated with 2.5-year revascularization and ischemic stroke. Better glycemic control and other intervention selection may be beneficial to those patients at risk.

References

[1] Brener SJ, Milford-Beland S, Roe MT, et al. Culprit-only or multivessel revascularization in patients with acute coronary syndromes: an American College of Cardiology National Cardiovascular Database Registry report. Am Heart J 2008;155:140–6.
[2] Montalescot G, Bolognese L, Dudek D, et al. Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes. N Engl J Med 2013;369:999–1010.
[3] Gierlotka M, Tajstra M, Gasior M, et al. Impact of chronic total occlusion artery on 12-month mortality in patients with non-ST-segment elevation myocardial infarction treated by percutaneous coronary intervention (from the PL-ACS Registry). Int J Cardiol 2013;168:250–4.
[4] Hao Y, Lu Q, Li T, et al. Admission hyperglycemia and adverse outcomes in diabetic and non-diabetic patients with non-ST-elevation myocardial infarction undergoing percutaneous coronary intervention. BMC Cardiovasc Disord 2017;17:6.
[5] Ishihara M, Kagawa E, Inoue I, et al. Impact of admission hyperglycemia and diabetes mellitus on short- and long-term mortality after acute myocardial infarction in the coronary intervention era. Am J Cardiol 2007;99:1674–9.
[6] Aronson D, Hammerman H, Kapeliovich MR, et al. Fasting glucose in acute myocardial infarction: incremental value for long-term mortality and relationship with left ventricular systolic function. Diabetes Care 2007;30:960–6.
[7] Selvin E, Marinopoulos S, Berkenblit G, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med 2004;141:421–31.
[8] Wang J, Yan G, Qiao Y, et al. Different levels of glycosylated hemoglobin influence severity and long-term prognosis of coronary heart disease patients with stent implantation. Exp Ther Med 2015;9:361–6.
[9] Zheng J, Cheng J, Zhang Q, et al. Association between glycosylated hemoglobin level and cardiovascular outcomes in diabetic patients after percutaneous coronary intervention. Medicine (Baltimore) 2016;95: e3696.
[10] Samuel VT, Shulman GI. Mechanisms for insulin resistance: common threads and missing links. Cell 2012;148:852–71.

[11] DeFronzo RA, Ferrannini E. Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care 1991;14:173–94.
[12] Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Eur Heart J 2012;33:2551–67.
[13] Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12.
[14] Roffi M, Patrono C, Collet JP, et al. [2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC)]. G Ital Cardiol (Rome) 2016;17:831–72.
[15] Lonborg J, Vejlstrup N, Kelbaek H, et al. Impact of acute hyperglycemia on myocardial infarct size, area at risk, and salvage in patients with STEMI and the association with exenatide treatment: results from a randomized study. Diabetes 2014;63:2474–85.
[16] Savonitto S, Morici N, Cavallini C, et al. One-year mortality in elderly adults with non-ST-elevation acute coronary syndrome: effect of diabetic status and admission hyperglycemia. J Am Geriatr Soc 2014;62: 1297–303.
[17] Turkmen S, Fettser DV, Ozkylych S, et al. [Prediction of severe cardiac complications with the help of myocardial perfusion scintigraphy in patients with residual chronic total occlusion after percutaneous coronary interventions]. Kardiologiia 2013;53:61–7.
[18] Undas A, Wiek I, Stepien E, et al. Hyperglycemia is associated with enhanced thrombin formation, platelet activation, and fibrin clot resistance to lysis in patients with acute coronary syndrome. Diabetes Care 2008;31:1590–5.
[19] Park JY, Takahara N, Gabriele A, et al. Induction of endothelin-1 expression by glucose: an effect of protein kinase C activation. Diabetes 2000;49:1239–48.
[20] Gabbay KH, Hasty K, Breslow JL, et al. Glycosylated hemoglobins and long-term blood glucose control in diabetes mellitus. J Clin Endocrinol Metab 1977;44:859–64.
[21] Gustafsson I, Kistorp CN, James MK, et al. Unrecognized glycometabolic disturbance as measured by hemoglobin A1c is associated with a poor outcome after acute myocardial infarction. Am Heart J 2007;154:470–6.
[22] Cakmak M, Cakmak N, Cetemen S, et al. The value of admission glycosylated hemoglobin level in patients with acute myocardial infarction. Can J Cardiol 2008;24:375–8.
[23] Naito R, Miyauchi K, Ogita M, et al. Impact of admission glycemia and glycosylated hemoglobin A1c on long-term clinical outcomes of non-diabetic patients with acute coronary syndrome. J Cardiol 2014;63:106–11.
[24] Kassaian SE, Goodarzynejad H, Boroumand MA, et al. Glycosylated hemoglobin (HbA1c) levels and clinical outcomes in diabetic patients following coronary artery stenting. Cardiovasc Diabetol 2012;11:82.
[25] Lev EI, Patel RT, Maresh KJ, et al. Aspirin and clopidogrel drug response in patients undergoing percutaneous coronary intervention: the role of dual drug resistance. J Am Coll Cardiol 2006;47:27–33.
[26] Mellbin LG, Malmberg K, Norhammar A, et al. The impact of glucose lowering treatment on long-term prognosis in patients with type 2 diabetes and myocardial infarction: a report from the DIGAMI 2 trial. Eur Heart J 2008;29:166–76.
[27] Lattanzi S, Bartolini M, Provinciali L, et al. Glycosylated hemoglobin and functional outcome after acute ischemic stroke. J Stroke Cerebrovasc Dis 2016;25:1786–91.
[28] Fatima N, u Zaman M, Ishaq M, et al. Impact of glycosylated hemoglobin (HBA1C) on the extent of perfusion abnormalities and left ventricular dysfunction using gated myocardial perfusion imaging and clinical outcomes in diabetic patients. Nucl Med Commun 2013;34:489–94.
[29] Ertem AG, Bagbanci H, Kilic H, et al. Relationship between HbA1c levels and coronary artery severity in nondiabetic acute coronary syndrome patients. Turk Kardiyol Dern Ars 2013;41:389–95.
[30] Lemesle G, Bonello L, de Labriolle A, et al. Prognostic value of hemoglobin A1C levels in patients with diabetes mellitus undergoing percutaneous coronary intervention with stent implantation. Am J Cardiol 2009;104:41–5.
[31] Kauffman AB, Delate T, Olson KL, et al. Relationship between haemoglobin A1C values and recurrent cardiac events: a retrospective, longitudinal cohort study. Clin Drug Investig 2008;28:501–7.
[32] Szepietowska B, McNitt S, Kutyifa V, et al. Insulin resistance predicts the risk for recurrent coronary events in post-infarction patients. Cardiol J 2015;22:519–26.
[33] Sanjuan R, Blasco ML, Huerta R, et al. Insulin resistance and short-term mortality in patients with acute myocardial infarction. Int J Cardiol 2014;172:e269–70.
[34] Lazzeri C, Valente S, Chiostri M, et al. Acute insulin resistance assessed by the homeostatic model assessment in acute coronary syndromes without previously known diabetes. Angiology 2014;65:519–24.
[35] Kitta Y, Nakamura T, Uematsu M, et al. Insulin resistance negatively affects long-term outcome in non-diabetic patients with coronary artery disease after therapies to reduce atherosclerotic risk factors. J Cardiol 2013;62:348–53.
[36] Ausk KJ, Boyko EJ, Ioannou GN. Insulin resistance predicts mortality in nondiabetic individuals in the US. Diabetes Care 2010;33:1179–85.
[37] Novo G, Pugliesi M, Visconti C, et al. Early subclinical ventricular dysfunction in patients with insulin resistance. J Cardiovasc Med (Hagerstown) 2014;15:110–4.
[38] McGuire DK, Gore MO. Insulin resistance and risk for incident heart failure. JACC Heart Fail 2013;1:537–9.
[39] Toda N, Okamura T. Obesity impairs vasodilatation and blood flow increase mediated by endothelial nitric oxide: an overview. J Clin Pharmacol 2013;53:1228–39.
[40] Trifunovic D, Stankovic S, Sobic-Saranovic D, et al. Acute insulin resistance in ST-segment elevation myocardial infarction in non-diabetic patients is associated with incomplete myocardial reperfusion and impaired coronary microcirculatory function. Cardiovasc Diabetol 2014;13:73.
[41] Karrowni W, Li Y, Jones PG, et al. Insulin resistance is associated with significant clinical atherosclerosis in nondiabetic patients with acute myocardial infarction. Arterioscler Thromb Vasc Biol 2013;33:2245–51.
[42] Cadeddu C, Nocco S, Piano D, et al. Early impairment of contractility reserve in patients with insulin resistance in comparison with healthy subjects. Cardiovasc Diabetol 2013;12:66.
[43] Cintra R, Moura FA, Carvalho LS, et al. TCF7L2 polymorphism is associated with low nitric oxide release, endothelial dysfunction and enhanced inflammatory response after myocardial infarction. BBA Clin 2016;5:159–65.