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Impact of Insulin Resistance on Post-Procedural Myocardial Injury and Clinical Outcomes in Patients Who Underwent Elective Coronary Interventions With Drug-Eluting Stents

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Objectives This study sought to evaluate the associations between homeostatic indexes of insulin resistance (HOMA-IR) and post-procedural myocardial injury and clinical outcome after a percutaneous coronary intervention (PCI) with a drug-eluting stent.

Background Insulin resistance increases the risk of cardiovascular events. However, the association between insulin resistance and clinical outcome after coronary intervention is unclear.

Methods We evaluated 516 consecutive patients who underwent elective PCI with drug-eluting stents. Blood samples were collected from venous blood after overnight fasting, and fasting plasma glucose and insulin levels were measured. HOMA-IR was calculated according to the homeostasis model assessment. Post-procedural myocardial injury was evaluated by analysis of troponin T and creatine kinase-myocardial band isozyme levels hours after PCI. Cardiac event was defined as the composite endpoint of cardiovascular death, myocardial infarction, and any revascularization.

Results With increasing tertiles of HOMA-IR, post-procedural troponin T and creatine kinase-myocardial band levels increased. In the multiple regression analysis, HOMA-IR was independently associated with troponin T elevation. During a median follow-up of 623 days, patients with the highest tertiles of HOMA-IR had the highest risk of cardiovascular events. The Cox proportional hazard models identified HOMA-IR as independently associated with worse clinical outcome after adjustment for clinical and procedural factors.

Conclusions These results indicated the impact of insulin resistance on post-procedural myocardial injury and clinical outcome after elective PCI with drug-eluting stent deployment. Evaluation of insulin resistance may provide useful information for predicting clinical outcomes after elective PCI. (J Am Coll Cardiol Intv 2012;5:1159–67) © 2012 by the American College of Cardiology Foundation

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Insulin resistance may be a key pathological factor of metabolic syndrome, and it is associated with risk of type-2 diabetes. Impaired insulin signaling, especially in peripheral tissues, is associated with abnormal lipid metabolism, hypertension, thrombogenesis, and atherosclerosis, resulting in increased risk of cardiovascular events (1–5). Several large-scale cohort studies have documented that insulin resistance and hyperinsulinemia are associated with increased risk of cardiovascular events (6–8).

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Patients who underwent percutaneous coronary interventions (PCI) had a higher risk of recurrent cardiovascular events (9). In small cohort studies, it was demonstrated that insulin resistance was associated with neointimal tissue proliferation of coronary stents and progression of de novo coronary lesions in patients receiving hemodialysis (10,11). However, little is known about the impact of insulin resistance on clinical outcome in patients who underwent PCI. In addition, widespread use of drug-eluting stents (DES) has revolutionized coronary interventional practice, and factors associated with outcome in patients who underwent PCI may also change (12,13).

Abbreviations and Acronyms

CI = confidence interval
CK-MB = creatine kinase-myocardial band
DES = drug-eluting stent(s)
HOMA-IR = homeostatic models of insulin resistance
HR = hazard ratio
MI = myocardial infarction
PCI = percutaneous coronary intervention
TnT = troponin T

Periprocedural cardiac biomarker elevation, which was commonly observed after apparent uncomplicated PCI, is now considered to reflect post-procedural myocardial injury/infarction (14). Post-procedural myocardial injury after PCI was also associated with worse clinical outcome. Several patient-related factors, including age, acute coronary syndrome, inflammatory status, and coronary thrombogenicity, are associated with post-procedural myocardial injury (14–16). Several studies have reported that patient-related factors of post-procedural myocardial injury, such as abnormal lipid metabolism, thrombogenicity, and systemic inflammation are also associated with insulin resistance (1,17,18).

Therefore, the aim of this study was to evaluate the impact of insulin resistance on post-procedural myocardial injury and long-term clinical outcomes in patients who underwent elective coronary interventions with DES.

Methods

Study population. A population of 623 consecutive patients who underwent initial elective PCI with DES in Chubu Rosai Hospital from January 2006 to October 2008 was enrolled in this study, which was approved by the hospital ethics committee. All patients had angina, documented myocardial ischemia, or both, and all patients gave their informed consent for participation in this study. Diabetic patients treated with any insulin therapy were excluded because fasting plasma insulin levels, an essential component for the calculation of the homeostatic models of insulin resistance (HOMA-IR), may be affected by insulin therapy. Patients with elevated pre-procedural troponin levels or who underwent angioplasty with atherectomy, bare-metal stents, or balloon angioplasty alone were also excluded. Thus, the study included 516 patients. Data, including baseline patient characteristics, procedural characteristics, and clinical outcomes, were prospectively collected and retrospectively analyzed.

Evaluation of insulin resistance. Blood samples were collected from venous blood after overnight fasting, and fasting plasma glucose and insulin levels were measured. HOMA-IR was calculated according to the homeostasis model assessment as follows: HOMA-IR = fasting insulin (μU/ml) $\times$ fasting glucose (mg/dl)/405 [or fasting glucose (mmol/l)/22.5] (19).

Coronary angiography and PCI. All patients underwent DES implantation with or without pre-dilation. All patients received treatment with antiplatelet agents for at least 24 h before the procedure. Furthermore, 5,000 to 10,000 IU of heparin were administered before stenting, and an additional bolus of 1,000 to 2,000 IU was given every hour if the procedure lasted for more than an hour. No patient received glycoprotein IIb/IIIa receptor inhibitors, which are not approved for use in Japan. Baseline angiography was evaluated by an independent investigator who was not involved in the procedures and was unaware of the final outcomes. A computerized quantitative analysis system (QCA-CMS system, version 6.0.39.0, MEDIS, Leiden, the Netherlands) was employed with the guiding catheter for calibration. All procedures were performed using 6- to 8-F guiding catheters by either the radial or the femoral approach. The operator who was blinded to HOMA-IR levels selected the position and length of the angioplasty and stent implantation according to angiography and conventional intravascular ultrasound findings. We administered clopidogrel (75 to 300 mg/day) or ticlopidine (200 mg/day) to prevent thrombosis after stent implantation in patients who were not already receiving thienopyridine derivatives.

Evaluation of cardiac biomarkers. Blood was sampled before and 18 h after the procedure. Serum troponin T (TnT) was measured using an enzyme immunoassay kit (Roche Diagnostics, Tokyo, Japan). Creatine kinase-myocardial band (CK-MB) isozyme activity was measured using an immunoinhibition assay kit (Sysmex, Kobe, Japan).

Clinical follow-up. Clinical follow-up data were obtained through in-hospital and outpatient medical records or telephone interviews until December 2011. The endpoint was defined as the composite of cardiovascular death,

myocardial infarction (MI), and revascularization, including target lesion revascularization.

MI was defined as the development of signs and/or symptoms suggestive of MI, accompanied by elevation of CK-MB or TnT levels at least 2-fold higher than normal or new significant Q waves in 2 or more contiguous leads. After PCI, MI was defined as an elevation of CK-MB or TnT levels more than 3-fold times the upper limit of normal or new significant Q waves in at least 2 contiguous leads (20). Stent thrombosis was defined by Academic Research Consortium definitions (definite or probably) (21). Target lesion revascularization was defined as reintervention (percutaneous or surgical) for in-stent or in-segment significant stenosis (larger than 75% in angiographic diameter stenosis). New lesion revascularization was defined as revascularization (percutaneous or surgical) for newly developed significant lesions that had been nonsignificant (<75% in angiographic diameter stenosis) at baseline coronary angiography. Ischemia-driven revascularization was defined as revascularization (percutaneous or surgical) for patients with evidence of ischemia (ischemic electrocardiographic change or positive myocardial biomarker) or positive findings of stress test.

Statistical analysis. All normally distributed data are expressed as mean ± SD. Variables that are not normally distributed are expressed as median (interquartile range). A comparison of continuous variables was achieved with the unpaired Student *t* test and of categorical variables by using chi-square analysis or Fisher exact probability test. Comparison of cardiac biomarkers (CK-MB and TnT) was performed using Kruskal-Wallis test and Mann-Whitney *U* test. Linear regression analysis and Spearman rank correlation were performed to assess the association between clinical parameters and increased TnT levels (log-transformed). Successful normalization of TnT after log-transformation was evaluated using Kolmogorov-Smirnov test. To identify predictors of myocardial injury, multiple regression analyses were performed. Event-free survival was

Table 1. Patient Characteristics

	Tertile 1	Tertile 2	Tertile 3	p Value
Age, yrs	72.0 ± 9.0	70.3 ± 8.7	69.7 ± 9.3	<0.01
Male	115 (67.3)	127 (74.7)	117 (68.8)	0.29
Diabetes	78 (45.3)	89 (51.7)	87 (50.6)	0.45
Hypertension	155 (90.1)	158 (91.9)	158 (91.9)	0.80
Dyslipidemia	90 (52.3)	107 (62.2)	101 (58.7)	0.18
Smoking, %	46 (26.7)	34 (19.8)	40 (23.3)	0.31
Previous myocardial infarction	43 (25.0)	36 (20.9)	43 (25.0)	0.58
Acute coronary syndrome	35 (20.5)	36 (20.9)	37 (21.4)	0.98
Body mass index, kg/m^2	22.4 ± 3.1	23.9 ± 2.9	25.0 ± 3.3	<0.01
Systolic blood pressure, mm Hg	138.1 ± 25.6	141.9 ± 21.3	139.4 ± 20.7	0.34
LDL cholesterol, mg/dl	117.5 ± 33.8	118.9 ± 31.1	120.1 ± 36.2	0.78
HDL cholesterol, mg/dl	51.2 ± 13.3	45.1 ± 12.9	44.5 ± 11.5	<0.01
Triglyceride, mg/dl	109.5 (82.0–165.0)	144.5 (102.0–202.0)	171.8 ± 105.1	<0.01
C-reactive protein, mg/l	1.0 (0.3–0.6)	1.0 (0.06–0.35)	8.6 ± 16.6	0.48
Hemoglobin A1c, %	6.1 ± 1.16	6.4 ± 1.41	6.3 ± 1.13	0.16
Estimated GFR, ml/min	62.4 ± 19.1	62.5 ± 24.7	64.3 ± 19.7	0.65
HOMA-IR	0.90 (0.66–1.11)	1.78 (1.53–2.07)	3.72 (2.95–5.54)	<0.01
Fasting insulin, μU/ml	3.6 (2.6–4.6)	6.8 (5.7–7.8)	12.7 (10.3–17.2)	<0.01
Fasting glucose, mg/dl	99.7 ± 21.4	111.3 ± 23.1	132.4 ± 36.5	<0.01
Aspirin	144 (83.7)	148 (86.0)	147 (85.5)	0.83
Thienopyridine derivative	62 (36.0)	77 (44.8)	84 (48.8)	0.05
Statins	87 (50.6)	95 (55.2)	84 (48.8)	0.47
Calcium-channel blocker	76 (44.2)	77 (44.8)	63 (36.6)	0.23
Beta-blockers	58 (33.7)	71 (41.3)	65 (37.8)	0.35
ACE inhibitor or ARB	81 (47.1)	85 (49.4)	86 (50.0)	0.85
Sulfonylurea	33 (19.3)	44 (25.6)	47 (27.2)	0.19
Metformin	6 (3.5)	12 (7.0)	8 (4.7)	0.32
Alpha-glucosidase inhibitors	21 (12.3)	22 (12.8)	19 (11.0)	0.75
Pioglitazone	23 (13.4)	23 (13.4)	15 (8.7)	0.31

Values are n (%), mean ± SD (normally distributed data), or median (interquartile range) (not normally distributed data).

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; GFR = glomerular filtration rate; HDL = high-density lipoprotein; HOMA-IR = homeostatic models of insulin resistance; LDL = low-density lipoprotein.

Table 2. Lesion and Procedural Characteristics

	Tertile 1	Tertile 2	Tertile 3	p Value
Target lesions	210	212	212	
LAD/LCX/RCA/LMT/SVG	85/50/67/8/0	104/57/48/3/0	95/40/69/6/2	0.15
Type B2 or C lesion	118 (56.2)	125 (59.0)	128 (60.4)	0.68
Reference diameter, mm	2.64 ± 0.22	2.64 ± 0.24	2.62 ± 0.26	0.66
Minimal lumen diameter, mm	0.83 ± 0.23	0.86 ± 0.30	0.84 ± 0.25	0.48
Lesion length, mm	17.9 ± 7.93	17.8 ± 7.45	18.1 ± 8.35	0.96
Sirolimus-eluting stent	215	194	212	0.34
Paclitaxel-eluting stent	49	37	43	0.45
Zotarolimus-eluting stent	4	3	2	0.71
Maximum ballooning pressure, atm	16 (14–20)	16.5 (14–20)	16 (15–20)	0.65
Total ballooning time, s	120 (76.3–180)	130 (85–195)	123 (75–168)	0.28
Pre-dilation	152	154	145	0.23
Post-dilation	137	132	136	0.75

Values are n, n (%), mean ± SD (normally distributed data), or median (interquartile range) (not normally distributed data).
LAD = left anterior descending; LCX = left circumflex; LMT = left main trunk; RCA = right coronary artery; SVG = saphenous vein graft.

analyzed using Kaplan-Meier estimation with the log-rank test. The Cox proportional hazards model was used to estimate the contribution of HOMA-IR to the prediction of cardiovascular events during follow-up periods. In multivariate analysis, variables listed in Tables 1 or 2 with a significance level <0.1 in the univariate analysis, age, sex, and conventional coronary risk factors (hypertension, diabetes, body mass index, dyslipidemia, and smoking) were considered candidate variables for inclusion in the multivariate analysis. Post hoc analysis (with Bonferroni correction) was performed for multiple comparisons. Differences were considered significant at $p < 0.05$. All p values were derived from 2-sided significance tests.

Results

Baseline characteristics. Our population was divided into 3 groups in accordance with tertiles of HOMA-IR at baseline as follows: 1) tertile 1—HOMA-IR of <1.32 in 172 patients; 2) tertile 2—HOMA-IR of 1.32 to 2.48 in 172 patients; 3) tertile 3—HOMA-IR of >2.48 in 172 patients. Clinical, angiographic, and procedural parameters of patients, subdivided according to tertiles of HOMA-IR, are summarized in Table 1. There was significant association between increased tertiles of HOMA-IR and age, body mass index, high-density lipoprotein cholesterol, and triglycerides. No difference was observed among the 3 groups in

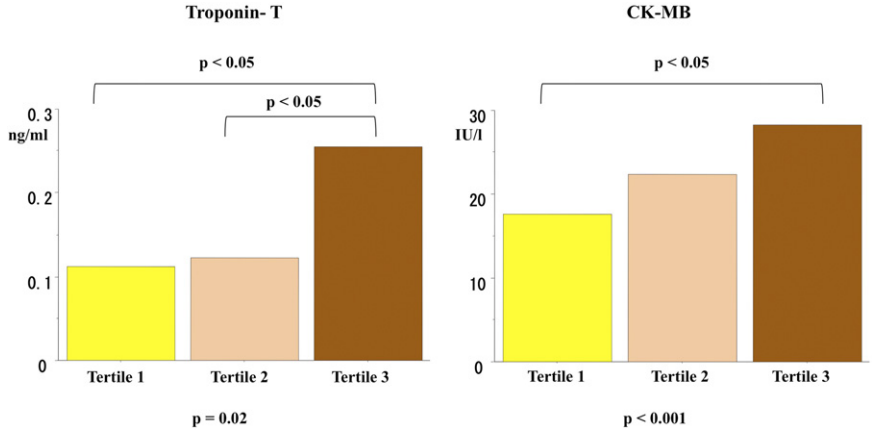

Figure 1. Post-Procedural TnT and CK-MB Levels in Accordance With the Tertiles of HOMA-IR

Troponin T (TnT) and creatine kinase-myocardial band (CK-MB) isozyme significantly increased across tertiles of homeostatic models of insulin resistance (HOMA-IR) (p [trend] < 0.001 and p [trend] = 0.018). Post-procedural TnT levels in tertile 3 patients (0.26 ± 0.47 ng/ml) were significantly higher than those in tertile 1 (0.11 ± 0.22 ng/ml) and tertile 2 patients (0.12 ± 0.26 ng/ml). Post-procedural CK-MB levels in tertile 3 patients (28.2 ± 39.1 IU/l) were higher than were those in tertile 1 patients (17.6 ± 11.5 IU/l).

Table 3. Simple and Multiple-Regression Analysis With Post-Procedural TnT (Log-Transformed)

	Simple Regression		Multiple Regression	
Variable	Coefficient (95% CI)	p Value	Coefficient (95% CI)	p Value
HOMA-IR	0.085 (0.061–0.109)	<0.001	0.012 (0.005–0.018)	<0.001
ACS	0.087 (0.023–0.165)	<0.001	0.104 (0.058–0.150)	<0.001
GFR	−0.214 (−0.156 to −0.273)	0.001	−0.002 (−0.003 to −0.001)	<0.001
Stents, n	0.039 (0.013–0.064)	0.003	0.032 (0.001–0.064)	0.002
Female	0.047 (0.006–0.089)	0.026	0.035 (−0.010–0.075)	0.106
Total ballooning time, s	0.001 (0.000–0.001)	0.004	0.001 (−0.001–0.001)	0.112
Age	0.002 (0.000–0.004)	0.050	0.001 (−0.002–0.003)	0.513

ACS = acute coronary syndrome; CI = confidence interval; TnT = troponin T; other abbreviations as in Table 1.

lesion characteristics, angiographic parameters, and procedural characteristics.

Post-procedural elevation of TnT and CK-MB. We observed that post-procedural TnT and CK-MB levels significantly increased across tertiles of HOMA-IR (p [trend] < 0.001 and p [trend] = 0.018). Post-procedural TnT levels of patients in tertile 3 (0.26 ± 0.47 ng/ml) were significantly higher than those of patients in tertile 1 (0.11 ± 0.22 ng/ml) and tertile 2 (0.12 ± 0.26 ng/ml). Post-procedural CK-MB levels in tertile 3 patients (28.2 ± 39.1 IU/l) were higher than those in tertile 1 patients (17.6 ± 11.5 IU/l) (Fig. 1).

Predictor of post-procedural troponin elevation. The results of simple and multiple regression analyses with post-procedural TnT levels (log-transformed) are given in Table 3. HOMA-IR, total ballooning time, acute coronary syndrome, estimated glomerular filtration rate, number of implanted stents, female sex, and age were significantly associated with post-procedural TnT elevation in the simple regression analysis. HOMA-IR, acute coronary syndrome, glomerular filtration rate, and number of stents were independently associated with post-procedural TnT levels in the multiple regression analysis after adjusting for age, sex, and conventional risk factors.

Clinical outcomes. During the median follow-up of 632.8 days, 28 hard events (cardiac death and nonfatal MI) and 108 total events (hard event and/or any revascularization) occurred. Event-free survival was significantly associated with HOMA-IR tertiles, with worse event-free survival ratios in tertile 3 patients (67.4%; p < 0.001, log-rank test) than in tertile 2 (80.2%) and tertile 1 patients (89.5%) (Fig. 2).

During the follow-up period, coronary angiography was performed in 33 patients presenting with acute coronary syndrome and 306 patients with stable symptoms 302 ± 123 days after the procedure. The incidence of emergency angiography was significantly increased according to increasing tertile of HOMA-IR. No difference was found in incidence of planned angiography among the 3 groups (Table 4).

We observed that the incidence of cardiac death or MI, target revascularizations, revascularizations for new lesions, and ischemia-driven revascularization significantly increased across tertiles of HOMA-IR (p [trend] < 0.001, p [trend] = 0.02, p [trend] < 0.001, and p [trend] < 0.01, respectively). The incidence of cardiac death or MI, target revascularizations, revascularizations for new lesions, and ischemia-driven revascularization were significantly higher in tertile 3 patients than those in tertile 1 and 2 patients were. There was no significant difference in the incidence of stent thrombosis among the 3 groups (Fig. 3).

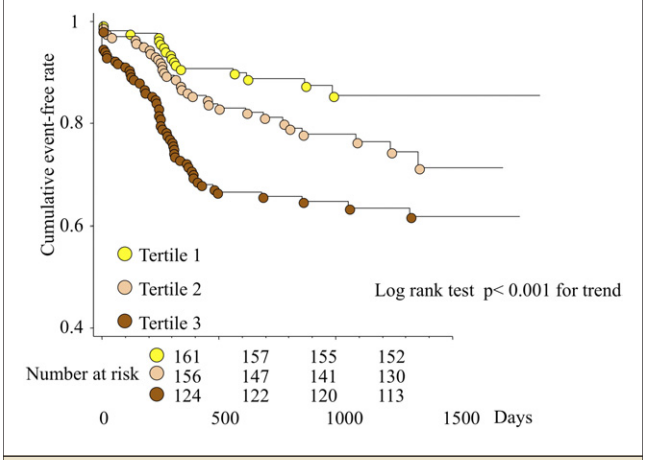

Figure 2. Kaplan-Meier Curves of Event-Free Survival in Accordance With HOMA-IR Tertiles

Event-free survival was significantly associated with homeostatic models of insulin resistance (HOMA-IR) tertiles, with worse event-free survival ratios in tertile 3 patients (67.4%, p < 0.001 log-rank test) than in tertile 2 (80.2%) and tertile 1 patients (89.5%).

Table 4. Coronary Angiography During Follow-Up Period

	Tertile 1	Tertile 2	Tertile 3	p Value
Emergency CAG	4 (2.3)	12 (7.0)	17 (9.9)	0.01
Planned CAG	100 (58.4)	99 (57.6)	107 (61.9)	0.69

Values are n (%).
CAG = coronary angiography.

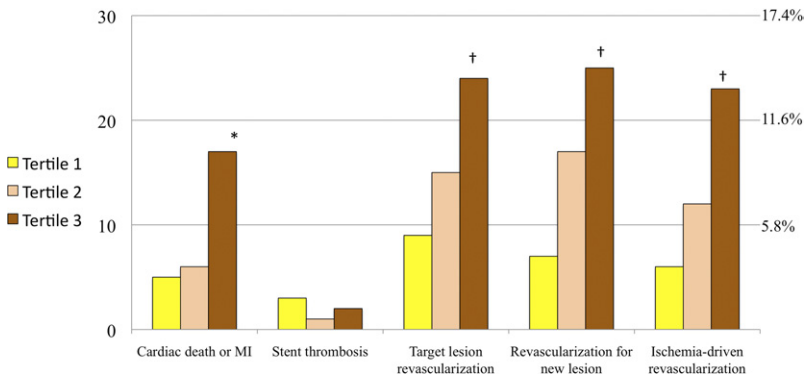

Figure 3. The Number of Cardiac Events During Follow-Up Period

Increasing tertile of homeostatic models of insulin resistance (HOMA-IR) was significantly associated with incidence of death or myocardial infarction (MI), target lesion revascularization, revascularization of new lesion, and ischemia-driven revascularization (p [trend] < 0.001, p [trend] = 0.02, p [trend] < 0.001, and p [trend] < 0.01, respectively).*p < 0.01 between patient with tertile 1 or 2 and those with tertile 3. †p < 0.05 between patient with tertile 1 or 2 and those with tertile 3.

A Cox proportional hazard models adjusted for age, sex, and conventional risk factors showed that HOMA-IR (hazard ratio [HR]: 1.98 per tertile, 95% confidence interval [CI]: 1.51 to 2.61; p < 0.01), number of stents (HR: 1.65, 95% CI: 1.31 to 2.07; p < 0.01), total ballooning time (HR: 1.00, 95% CI: 1.00-1.00; p < 0.01), acute coronary syndrome (HR: 2.04, 95% CI: 1.34 to 3.12; p < 0.01), and maximum ballooning pressure (HR: 0.913, 95% CI: 0.85 to 0.93; p = 0.01) were independently associated with cardiac events (Table 5).

Associations were consistent in subgroups, including male versus female sex (HR per tertile in HOMA-IR: 2.48, 95% CI: 1.75 to 3.52 in men; and HR per tertile in HOMA-IR: 1.18, 95% CI: 0.75 to 1.85 in women), age of 75 years or more versus age of <75 years, diabetes versus without diabetes, hypertension versus without hypertension, acute coronary syndrome versus without acute coronary syndrome, and body mass index of ≥25 versus body mass index of <25 kg/m^2 (Fig. 4). Increasing tertile of HOMA-IR was also an independent predictor of patient without diabetes.

Discussion

The results of this study demonstrated that insulin resistance as estimated by a simple method based on a single fasting blood sampling is associated with post-procedural myocardial injury and increases the risk of cardiovascular events in patients who underwent elective PCI with DES. These associations were independent after adjustment for evaluated factors, including age, sex, conventional risk factors, history of acute coronary syndrome, renal function, and procedural valuables.

Insulin resistance and post-procedural myocardial injury. Even in asymptomatic patients without apparent change on the electrocardiogram, post-procedural elevation of cardiac biomarkers has been associated with worse clinical outcomes. Distal embolism following stent expansion may play an important role in the development of a post-procedural myocardial injury. Recent studies on distal protection devices confirmed the mobilization of plaque material after coronary stenting in patients with stable or unstable angina

Table 5. Results of Cox Proportional Hazard Model Analysis

	Univariate		Multivariate	
Variable	HR (95% CI)	p Value	HR (95% CI)	p Value
HOMA-IR, per tertile	1.887 (1.464–2.433)	<0.001	1.984 (1.510–2.608)	<0.001
Stents, n	1.553 (1.245–1.938)	0.003	1.645 (1.309–2.069)	<0.001
Total ballooning time, s	1.002 (1.000–1.004)	0.039	1.003 (1.001–1.005)	<0.001
ACS	1.780 (1.178–2.691)	0.006	2.040 (1.335–3.118)	0.001
Maximum ballooning pressure, atm	0.953 (0.920–0.988)	0.008	0.913 (0.852–0.979)	0.011

Values are median (interquartile range). This model was adjusted for age and conventional coronary risk factors (hypertension, diabetes, body mass index, dyslipidemia, and smoking).
HR = hazard ratio; other abbreviations as in Tables 1 and 3.

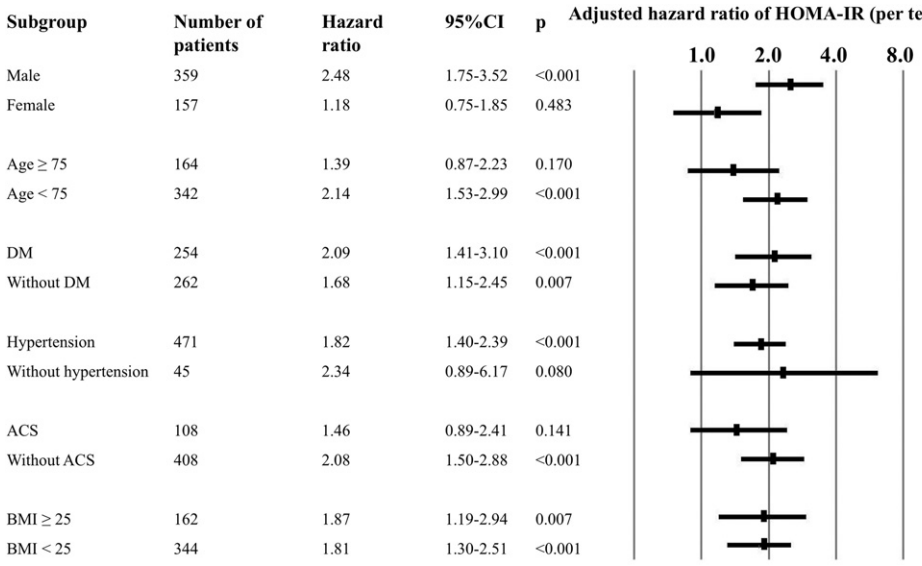

Figure 4. Adjusted HR (95% CI) per Tertile of HOMA-IR for Various Subgroups

ACS = acute coronary syndrome; BMI = body mass index; CI = confidence interval; DM = diabetes mellitus; HOMA-IR = the homeostatic models of insulin resistance.

(22). Several studies using recently developed imaging modalities, such as integrated backscatter intravascular ultrasound, virtual histology, and multidetector computed tomography demonstrated that lipid-rich or necrotic characteristics of coronary plaque within target lesion were strongly associated with post-procedural myocardial injury (23–25). Additionally, it was reported that coronary lesions in patients with increased insulin resistance or metabolic syndrome are associated with more lipid-rich plaque content (26,27). Therefore, it is plausible that lipid-rich or vulnerable plaques characteristics of patients with insulin resistance may be associated with post-procedural myocardial injury and higher risk of cardiovascular events.

Interaction between insulin resistance and other risk factors. It has been suggested that insulin resistance, as well as metabolic syndrome, overlaps type-2 diabetes, which is a known risk factor of cardiac events following PCI and the clustering of other coronary risk factors. There is a possibility that increased risk of cardiovascular events in patients with insulin resistance is attributable to overlap with diabetes or other coronary risk factors. However, multivariate Cox proportional hazards models demonstrated the independent association between HOMA-IR and worse clinical outcome after adjusting for other clinical and procedure-related factors for cardiac events, including diabetes. In contrast to previous reports, patients with diabetes in this study did not have a significantly higher risk of cardiovascular events. There are potential reasons for the relatively lower event rate for diabetic patients in this study. First, we excluded diabetic patients receiving insulin therapy who have higher risk of in-stent restenosis and cardiovascular events than do diabetic patients who were treated with oral agents because of difficulties in measuring and interpreting insulin resistance (28). Second, diabetic patients with multivessel coronary disease or complex lesion characteristics are subject to referral for bypass surgery, and therefore, diabetic patients in this study had lower risk than those in other studies. Third, a relatively small portion of diabetic patients in this study were treated with insulin-producing drugs (sulfonylurea, 24%) compared with nonsulfonylurea drugs (metformin, pioglitazone, and alpha-glucosidase inhibitors, 48%). Beneficial cardiovascular effects of metformin, pioglitazone, and alpha-glucosidase inhibitors were demonstrated in large-scale clinical trials (29–31). Therefore, these medications may contribute to better outcomes in diabetic patients.

Incidence of stent thrombosis. It has been well documented that insulin resistance is associated with increased thrombogenicity that results in coronary thrombosis. A recent report from other registries suggested that diabetes is an independent predictor of stent thrombosis (32). However, because of the relatively small number of cases of stent thrombosis in this study, no association between HOMA-IR tertiles and the rate of stent thrombosis was observed. The relatively lower incidence of stent thrombosis in this study was comparable to that in the larger DES registry in Japan (33).

Study limitations. Among diabetic patients, antidiabetic agents could affect fasting insulin levels differently. We obtained post-procedural blood samples only once, at 18 h

after PCI. In daily practice, it may be impractical to repeatedly collect blood from patients without any apparent complications. However, 100% of the peak TnT elevations and 92% of the peak CK-MB levels were observed 12 to 20 h (mean: 17.9 ± 0.46 h) after the procedure in patients who underwent elective PCI without pre-procedural elevation of cardiac biomarkers (34). Therefore, we evaluated cardiac biomarkers obtained from single blood samples at 18 h after PCI.

In this study, the indication for follow-up angiography of stable patients depends on the attending physician, and planned follow-up angiography was performed in about 60% of the study population. Even today, 3 to 12 months after PCI, follow-up angiography is performed in most stable patients in Japan. There is a concern that follow-up angiography may lead to unnecessary reinterventions in asymptomatic patients (35). However, there was no deference of rate of planned follow-up angiography among each tertile of patients.

Conclusions

In patients who underwent elective PCI, insulin resistance calculated by homeostasis model assessment is an independent predictor of post-procedural myocardial injury and cardiovascular events after PCI with DES.

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REFERENCES

1. Semenkovich CF. Insulin resistance and atherosclerosis. J Clin Invest 2006;116:1813–22.
2. Morisco C, Lembo G, Trimarco B. Insulin resistance and cardiovascular risk: new insights from molecular and cellular biology. Trends Cardiovasc Med 2006;16:183–8.
3. Basili S, Pacini G, Guagnano MT, et al. Insulin resistance as a determinant of platelet activation in obese women. J Am Coll Cardiol 2006;48:2531–8.
4. Schenk S, Saberi M, Olefsky JM. Insulin sensitivity: modulation by nutrients and inflammation. J Clin Invest 2008;118:2992–3002.
5. de Luca C, Olefsky JM. Inflammation and insulin resistance. FEBS Lett 2008;582:97–105.
6. Robins SJ, Rubins HB, Faas FH, et al., for the VA-HIT Investigators. Insulin resistance and cardiovascular events with low HDL cholesterol: the Veterans Affairs HDL Intervention Trial (VA-HIT). Diabetes Care 2003;26:1513–7.
7. Tenenbaum A, Adler Y, Boyko V, et al. Insulin resistance is associated with increased risk of major cardiovascular events in patients with preexisting coronary artery disease. Am Heart J 2007;153:559–65.
8. Lakka HM, Lakka TA, Tuomilehto J, Sivenius J, Salonen JT. Hyperinsulinemia and the risk of cardiovascular death and acute coronary and cerebrovascular events in men: the Kuopio Ischaemic Heart Disease Risk Factor Study. Arch Intern Med 2000;160:1160–8.
9. Hirsh J, Bhatt DL. Comparative benefits of clopidogrel and aspirin in high-risk patient populations: lessons from the CAPRIE and CURE studies. Arch Intern Med 2004;164:2106–10.
10. Takagi T, Akasaka T, Yamamuro A, et al. Impact of insulin resistance on neointimal tissue proliferation after coronary stent implantation: intravascular ultrasound studies. J Diabetes Complications 2002;16:50–5.
11. Nishimura M, Tokoro T, Nishida M, et al. Association of insulin resistance with de novo coronary stenosis after percutaneous coronary artery intervention in hemodialysis patients. Nephron Clin Pract 2008;109:c9–17.
12. Khattab AA, Hamm CW, Senges J, et al., for the German Cypher Registry. Prognostic value of the modified American College of Cardiology/American Heart Association lesion morphology classification for clinical outcome after sirolimus-eluting stent placement (results of the prospective multicenter German Cypher Registry). Am J Cardiol 2008;102:954–5.
13. Shishehbor MH, Goel SS, Kapadia SR, et al. Long-term impact of drug-eluting stents versus bare-metal stents on all-cause mortality. J Am Coll Cardiol 2008;52:1041–8.
14. Herrmann J. Peri-procedural myocardial injury: 2005 update. Eur Heart J 2005;26:2493–519.
15. Bhatt DL, Topol EJ. Does creatinine kinase-MB elevation after percutaneous coronary intervention predict outcomes in 2005? Periprocedural cardiac enzyme elevation predicts adverse outcomes. Circulation 2005;112:906–15, discussion 923.
16. Uetani T, Amano T, Kumagai S, et al. Intracoronary electrocardiogram recording with a bare-wire system: perioperative ST-segment elevation in the intracoronary electrocardiogram is associated with myocardial injury after elective coronary stent implantation. J Am Coll Cardiol Intv 2009;2:127–35.
17. Randriamboavonjy V, Fleming I. Insulin, insulin resistance, and platelet signaling in diabetes. Diabetes Care 2009;32:528–30.
18. Koh KK, Han SH, Quon MJ. Inflammatory markers and the metabolic syndrome: insights from therapeutic interventions. J Am Coll Cardiol 2005;46:1978–85.
19. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–9.
20. Thygesen K, Alpert JS, White HD, for the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. Eur Heart J 2007;28:2525–38.
21. Cutlip DE, Windecker S, Mehran R, et al., for the Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
22. Porto I, Selvanayagam JB, Van Gaal WJ, et al. Plaque volume and occurrence and location of periprocedural myocardial necrosis after percutaneous coronary intervention: insights from delayed-enhancement magnetic resonance imaging, thrombolysis in myocardial infarction myocardial perfusion grade analysis, and intravascular ultrasound. Circulation 2006;114:662–9.
23. Hong YJ, Mintz GS, Kim SW, et al. Impact of plaque composition on cardiac troponin elevation after percutaneous coronary intervention: an ultrasound analysis. J Am Coll Cardiol Img 2009;2:458–68.
24. Uetani T, Amano T, Ando H, et al. The correlation between lipid volume in the target lesion, measured by integrated backscatter intravascular ultrasound, and post-procedural myocardial infarction in patients with elective stent implantation. Eur Heart J 2008;29:1714–20.
25. Uetani T, Amano T, Kunimura A, et al. The association between plaque characterization by CT angiography and post-procedural myocardial infarction in patients with elective stent implantation. J Am Coll Cardiol Img 2010;3:19–28.
26. Amano T, Matsubara T, Uetani T, et al. Abnormal glucose regulation is associated with lipid-rich coronary plaque: relationship to insulin resistance. J Am Coll Cardiol Img 2008;1:39–45.
27. Amano T, Matsubara T, Uetani T, et al. Impact of metabolic syndrome on tissue characteristics of angiographically mild to moderate coronary lesions: integrated backscatter intravascular ultrasound study. J Am Coll Cardiol 2007;49:1149–56.

28. Kumar R, Lee TT, Jeremias A, et al. Comparison of outcomes using sirolimus-eluting stenting in diabetic versus nondiabetic patients with comparison of insulin versus non-insulin therapy in the diabetic patients. Am J Cardiol 2007;100:1187–91.
29. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352:854–65.
30. Dormandy JA, Charbonnel B, Eckland DJ, et al., for the PROactive Investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the proactive study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005;366:1279–89.
31. Chiasson JL, Josse RG, Gomis R, et al., for the STOP-NIDDM Trial Research Group. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. JAMA 2003;290:486–94.
32. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet 2007;369:667–78.
33. Kimura T, Morimoto T, Nakagawa Y, et al., for the j-Cypher Registry Investigators. Antiplatelet therapy and stent thrombosis after sirolimus-eluting stent implantation. Circulation 2009;119:987–95.
34. Miller WL, Garratt KN, Burritt MF, Reeder GS, Jaffe AS. Timing of peak troponin T and creatine kinase-MB elevations after percutaneous coronary intervention. Chest 2004;125:275–80.
35. ten Berg JM, Kelder JC, Suttorp MJ, Verheugt FW, Thijs Plokker HW. Influence of planned six-month follow-up angiography on late outcome after percutaneous coronary intervention: a randomized study. J Am Coll Cardiol 2001;38:1061–9.

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