Insulin Resistance as a Predictor of the Late Catch-up Phenomenon After Drug-Eluting Stent Implantation

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Background: Percutaneous coronary intervention (PCI) is an effective treatment for patients with ischemic heart disease. In particular, restenosis is suppressed after drug-eluting stent (DES) implantation. However, several problems remain. Previously, we reported neointimal proliferation after DES implantation, which was associated with insulin resistance (IR). The aim of the present study was to clarify whether IR is associated with mortality and major adverse cardiac and cerebrovascular events (MACCE) after 1st-generation DES implantation.

Methods and Results: We researched the clinical records of 109 patients who had undergone elective PCI and DES implantation between May 2007 and December 2010. We segregated these patients according to the value of the homeostasis model assessment of IR (HOMA-IR) into Group P ($n=63$; HOMA-IR ≥ 2.5 , positive) and Group N ($n=46$; HOMA-IR < 2.5 , negative), and examined the relationship between HOMA-IR and MACCE. The observation period was 7.4 ± 1.6 years. There were no differences between the 2 groups in the occurrence of all-cause death, cardiac death, restenosis, myocardial infarction, stroke, heart failure, or stent thrombosis. However, the late catch-up phenomenon was significantly more common in Group P than in Group N (12.7% vs. 2.2% $P=0.048$).

Conclusions: IR is a useful predictor of the late catch-up phenomenon after DES implantation, and improvement of IR may help to prevent the phenomenon. (*Circ J* 2016; **80**: 657–662)

Key Words: Drug-eluting stents; Insulin resistance; Late catch-up phenomenon

Percutaneous coronary intervention (PCI) has been widely confirmed as an effective treatment strategy for patients with ischemic heart disease. However, despite the development of new drug-eluting stents (DES) that may decrease the rate of restenosis, several problems remain, such as stent thrombosis and the late catch-up phenomenon. Insulin resistance (IR) is associated with hypertension, glucose intolerance, obesity, and dyslipidemia, all of which are established risk factors for coronary artery disease (CAD).^{1–3} IR is associated with an increased incidence of cardiovascular disease, even before the onset of diabetes mellitus (DM).^{4,5} Previously, we reported neointimal proliferation after DES implantation that was associated with IR.⁶ In addition, even in patients undergoing hemodialysis, which is one of the strongest predictors for cardiovascular events, DM is an independent predictor of long-term adverse events after DES implantation.⁷ Therefore, there seems to be much room for improvement of dia-

betic treatment. The aim of the present study was to clarify whether IR is associated with mortality and major adverse cardiac and cerebrovascular events (MACCE) after DES implantation.

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Methods

Study Design

We studied 109 patients who had undergone elective PCI and DES implantation between May 2007 and December 2010. All patients in whom stenting was successful gave informed consent to participate in the study. Coronary angiography (CAG) was carried out in all patients using AXIOM Artis dBC (SIEMENS Company Inc, Erlangen, Germany), and PCI was performed for lesions with significant stenosis. Lesions were

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Table 1. Baseline Characteristics of Study Patients Undergoing Elective PCI and DES Implantation

	Group P (n=63)	Group N (n=46)	P value
Age (years)	64.8±8.1	69.4±9.1	0.407
Sex (M/F)	47/16	37/9	0.475
Risk factors			
Hypertension (n, %)	42 (66.7)	31 (67.4)	0.937
Systolic blood pressure (mmHg)	138.4±25.5	134.7±23.5	0.445
Diastolic blood pressure (mmHg)	68.6±11.4	69.2±12.8	0.799
Diabetes mellitus (n, %)	15 (23.8)	7 (15.2)	0.270
Fasting glucose (mg/dl)	121.3±22.3	106.2±18.0	<0.001
HbA1c (%)	5.8±0.8	5.7±1.0	0.784
HOMA-IR	7.1±4.8	1.7±0.5	<0.001
Dyslipidemia (n, %)	39 (61.9)	26 (56.5)	0.572
LDL-cholesterol (mg/dl)	112.7±34.9	113.9±32.9	0.854
HDL-cholesterol (mg/dl)	49.4±11.4	52.0±14.8	0.310
Triglyceride (mg/dl)	144.5±60.0	135.1±47.5	0.372
Smoking (n, %)	31 (49.2)	20 (43.5)	0.554
Family history (n, %)	11 (17.5)	5 (10.9)	0.337
Drug treatment			
ACEI or ARB	40 (63.5)	31 (67.4)	0.673
Statin	42 (66.7)	31 (67.4)	0.937
β-blocker	19 (30.2)	14 (30.4)	0.975
Ca-channel blocker	29 (46.0)	18 (39.1)	0.472
Sulfonylurea	3 (4.8)	3 (6.5)	0.691
α-glucosidase	6 (9.5)	2 (4.3)	0.205
Biganide	3 (4.8)	2 (4.3)	0.919

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; DES, drug-eluting stent; PCI, percutaneous coronary intervention.

classified according to the modified American College of Cardiology (ACC)/American Heart Association (AHA) grading system (types A, B1, B2, and C).

All patients were taking aspirin (100mg/day), ticlopidine hydrochloride (200mg/day) or clopidogrel sulfate (75mg/day). They received a heparin (5,000 IU) bolus intravenously before the PCI in the absence of contraindications. Drug treatment of risk factors (eg, hypertension, dyslipidemia, DM) was provided as appropriate, but we excluded patients who were using pioglitazone hydrochloride or insulin, and/or who had a fasting glucose >200 mg/dl.

The HOMA-IR index is based on the levels of fasting glucose and plasma insulin. We used it as an index of IR,^{8,9} as calculated:

$$[\text{HOMA-IR} = \text{fasting glucose (mg/dl)} \times \text{plasma insulin } (\mu\text{U/ml}) / 405]$$

In Japanese subjects, IR is considered to be present when the HOMA-IR index is >2.5.¹⁰ Therefore, we divided the patients according to the value of the index into a Group P (HOMA-IR ≥2.5, positive) and a Group N (HOMA-IR <2.5, negative). All patients were implanted with a 1st-generation DES (sirolimus-eluting stent or paclitaxel-eluting stent). The luminal diameter of the coronary artery and the degree of stenosis were measured before dilatation and after intervention, and again after 8 months of follow-up. Restenosis was defined as a stenosis of ≥50% of the luminal diameter. After enrollment, all patients had individualized, optimized therapies, including medication and lifestyle changes to reduce risk factors for CAD according to the AHA/ACC guidelines.^{11,12}

All patients were followed up in the hospital or by visiting a physician's office every month, and were encouraged to adhere to the lifestyle changes and diet recommendations. After follow-up CAG, all patients were seen monthly in the hospital or until one of the following events occurred: death, cardiac death, myocardial infarction, stroke, heart failure, stent thrombosis, late catch-up phenomenon. Late catch-up phenomenon was defined as ischemia-driven target lesion revascularization (TLR), except for stent thrombosis after the 8-month follow-up CAG. Patients underwent CAG after the 8-month follow-up CAG whenever their periodic exercise test was interpreted as positive, or if they developed new-onset chest pain. The time to the first event was evaluated prospectively. The cause of death was determined from hospital records. All endpoint data were checked for accuracy, consistency, and completeness of follow-up by several investigators without knowledge of the patients' baseline characteristics. Additional information was obtained from the physicians as needed. Several other investigators were responsible for checking all data, for running the analysis, and for the security of the data files. The study was approved by the institutional review boards.

Statistical Analysis

Data are expressed as mean±SD. Comparisons between groups were performed by the Mann-Whitney U test for continuous variables and by the Chi-square test for categorical variables. Kaplan-Meier analysis of event-free survival during follow-up was performed with stratification of patients based on the change in IR. All analyses were performed using the StatView

Table 2. Angiographic Characteristics of Study Patients Undergoing Elective PCI and DES Implantation

	Group P (n=63)	Group N (n=46)	P value
Stented coronary vessel			0.891
LAD	37	25	
LCX	7	4	
RCA	18	16	
LMT	1	1	
No. of diseased vessels			0.651
1	18	17	
2	23	15	
3	22	14	
AHA type			
B2-C (n, %)	42 (66.7)	30 (65.2)	0.875
Stent			
SES/PES	52/11	39/7	0.755
Stent diameter (mm)	3.04±0.32	3.11±0.31	0.379
Total stent length (mm)	31.2±18.0	31.7±22.0	0.931

LAD, left anterior descending; LCX, left circumflex; LMT, left main trunk; PES, paclitaxel-eluting stent; RCA, right coronary artery; SES, sirolimus-eluting stent. Other abbreviations as in Table 1.

Table 3. Rates of Restenosis and MACCE in Study Patients Undergoing Elective PCI and DES Implantation

	Group P (n=63)	Group N (n=46)	P value
Restenosis (n, %)	8 (12.7)	4 (8.7)	0.509
Mortality (n, %)	8 (12.7)	1 (2.2)	0.050
MACCE events (n, %)			
Cardiac death	3 (4.8)	1 (2.2)	0.478
Myocardial infarction	2 (3.2)	1 (2.2)	0.753
Stroke	2 (3.2)	1 (2.2)	0.753
Heart failure	3 (4.8)	0 (0.0)	0.133
Stent thrombosis	1 (1.6)	0 (0.0)	0.391
Late catch-up phenomenon	8 (12.7)	1 (2.2)	0.048

MACCE, major cardiac and cerebrovascular events. Other abbreviations as in Table 1.

Computer package, version 5.0 (SAS Institute Inc, Cary, NC, USA). $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Group P consisted of 63 patients, and Group N of 46 patients. The observation period was 7.43 ± 1.62 years.

Clinical Characteristics of the Patient Population (Table 1)

There were no differences between the groups in age, sex, body mass index, hypertension, DM, dyslipidemia, current smoking status, or family history. There were no differences between the groups in systolic blood pressure, diastolic blood pressure, hemoglobin A1c (HbA1c), low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, or plasma triglycerides. There were also no differences between them in medications for hypertension, dyslipidemia, or DM (angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium-channel blockers, sulfonylurea, alpha-glucosidase, and biguanide).

CAG Characteristics of the Patient Population (Table 2)

There were no differences between the 2 groups in lesion-

related variables, number of diseased vessels, the ACC/AHA grading system, stent diameter, total stent length, or type of DES implanted (sirolimus-eluting stent and paclitaxel-eluting stent).

Success Rate

PCI was successful in all patients. There were no procedure-related complications (acute stent thrombosis, stent fracture, stent deployment of failure, etc).

Restenosis, Mortality and MACCE Rates (Table 3, Figure)

Restenosis rate after 8 months was 12.7% in Group P, and 8.7% in Group N. This difference was not statistically significant. There were no differences between the groups in the occurrence of restenosis, death, cardiac death, myocardial infarction, stroke, heart failure, or stent thrombosis. However, the late catch-up phenomenon was significantly more common in Group P than in Group N (12.7% vs. 2.2%, $P = 0.048$).

Discussion

We found no significant differences between the 2 study groups in the rates of death, cardiac death, myocardial infarction, stroke, heart failure, or stent thrombosis. However, the

Figure. Kaplan-Meier curves based on insulin resistance of mortality and major adverse cardiac and cerebrovascular events (**A**: mortality, **B**: cardiac death, **C**: cardiac infarction, **D**: stroke, **E**: heart failure, **F**: stent thrombosis, **G**: late catch-up phenomenon). There were no differences between the groups in the occurrence of death, cardiac death, stroke, myocardial infarction, heart failure, or stent thrombosis. However, the late catch-up phenomenon was significantly more common in the positive group of insulin resistance than in the negative group ($P=0.048$).

late catch-up phenomenon rate was significantly greater in Group P than in Group N. Stent implantation per se causes persistent inflammation of the tissues around the stent, because the stent is a foreign material and it continually stretches the vascular wall.¹³ The findings in this study suggested that neointimal tissue proliferation through inflammation might be promoted by IR even after DES implantation in the long-term.

IR and MACCE

IR is affected by several factors that are associated with ischemic heart disease.^{1,2} IR affects renin activity and causes hypertension,¹⁴ is associated with the abnormalities of lipoprotein metabolism found in hypertriglyceridemia,¹⁵ and is an independent risk factor for atherosclerosis.¹⁶ In this way, IR contributes to the initiation and progression of atherosclerosis, and is associated with increases in the rates of myocardial infarction and cardiac death.^{4,17} However, the relationship between outcomes after DES implantation and IR is not clear. The present study found that IR was not associated with MACCE after DES implantation, possibly because patients with uncontrolled DM (fasting glucose >200 mg/dl) were excluded, as a consequence of which IR could not contribute to the clinical endpoints.

IR and the Late Catch-up Phenomenon

The rate of the late catch-up phenomenon in Group P was significantly greater than in Group N. The late catch-up phenomenon is a late restenosis occurring beyond 1 year. PCI causes laceration and dissection of the coronary vessel wall, which recovers by rebuilding neointimal tissue. Restenosis is caused by excessive proliferation of smooth muscle cells as neointimal tissue.^{18,19} This proliferative process of smooth muscle progresses excessively in patients with a high level of IR. Under such conditions, mitogen-activated protein kinase is activated,²⁰ which in turn stimulates smooth muscle cell proliferation in the vessel wall.²¹ Inoue et al reported that high IR caused coronary artery endothelial cell dysfunction,²² which might also promote excessive smooth muscle cell proliferation in the vessel wall.

DES can reduce intimal hyperplasia in stented segments compared with bare-metal stents (BMS).²³ However, the time course of restenosis for these 2 types of stent may be different. A serial angiographic study found that after BMS implantation, intimal hyperplasia peaked during the first 6 months, and lumen enlargement occurred from 6 months to 3 years after index stent implantation.²⁴ In contrast, Byrne et al reported that ongoing late lumen loss beyond 8 months after the procedure was observed in angiographic data during 2 years of follow-up in 1,331 patients treated with DES.²⁵ Nakagawa et al reported that in their 3-year follow-up data of the J-Cypher registry, the TLR rate after sirolimus-eluting stent implantation was 5.5% at 1 year, 8.1% at 2 years, and 10.0% at 3 years.²⁶ Considering the results of our study, these TLR rates might increase in patients affected by IR. Others have reported that the late catch-up phenomenon might be associated with stent fracture and/or hemodialysis.^{27,28} However, the late catch-up phenomenon in our study did not include any stent fracture and/or hemodialysis patients. IR in this study was associated with only the late catch-up phenomenon, not restenosis at 8 months after DES implantation. Although a DES can suppress acute phase inflammation strongly after stent implantation, it can also promote late-stage inflammation.²⁹ Therefore, the small sample size and strong inflammatory suppression by the DES in the acute phase made the restenosis rate in Group P nearly equal to that in Group N, whereas the high rate of IR in Group

P promoted late-stage inflammation after DES implantation, which progressed to the late catch-up phenomenon. Therefore, it might be important to improve IR after DES implantation.

A recently developed new generation of DES has excellent outcomes compared with 1st-generation DES.^{30,31} However, there are many patients around the world in whom a 1st-generation DES was implanted and they are now living normal daily lives. Therefore, we need to treat patients with a 1st-generation DES carefully for a long time, taking into consideration any change in IR.

Future Strategy for Restenosis

DES have been widely used in recent years. Although the restenosis rate after PCI has decreased, restenosis still occurs. The present study showed that IR may contribute to neointimal tissue proliferation after DES implantation. It is known that insulin has both growth-promoting and protective vascular effects in vivo. Breen et al showed that insulin increases neointimal growth after arterial injury.³² In clinical studies, Hoffmann et al showed no significant differences in the occurrence of major adverse cardiac events between BMS and DES in patients with metabolic syndrome.³³ Metabolic syndrome is characterized by high IR, but Hoffmann et al did not evaluate IR. Our data show that the high IR group had a greater rate of the late catch-up phenomenon. Thus, an imbalance of insulin might promote endothelial dysfunction. In future, reducing IR may prevent the late catch-up phenomenon in patients who are given a DES.

Lately, pioglitazone hydrochloride has been used in diabetic patients and it was reported that the drug could improve IR and reduce the occurrence of cardiovascular events.³⁴ However, IR is not limited to patients with DM. Therefore, we suggest that treatment of IR in the early phase in any patient may reduce the occurrence of the late catch-up phenomenon.

Study Limitations

There are 3 limitations in this study. First, this was a single-center non-randomized study. The relatively small number of patients limits the power of the study. Furthermore, the patients were evaluated only in the early postoperative period. Another study involving long-term follow-up of a larger number of patients is required to confirm our findings. Second, the HOMA-IR index cannot be calculated in patients using pioglitazone hydrochloride or insulin, and/or who have a fasting glucose >200 mg/dl. Therefore, another index of IR is necessary in such patients. Additionally, the evaluation of HOMA-IR at 8-month follow-up and the degree of change in HOMA-IR between baseline and 8-month follow-up would be important in addition to the baseline level. We have also analyzed the data of HOMA-IR at 8-month follow-up, and found there was no significant difference from the HOMA-IR data at baseline. These findings suggest there is room for improvement in the treatment of IR. Third, 2nd-generation DES are replacing 1st-generation DES worldwide, and patient outcomes have improved. However, even 2nd-generation DES provide non-uniform neointimal suppression in DM patients compared to non-DM patients.³⁵ Therefore, further study of the late catch-up phenomenon after 2nd-generation DES implantation is also needed in patients with and without IR.

Conclusions

We suggest that IR promotes the late catch-up phenomenon after DES implantation. Accordingly, improvement of IR may help to prevent the phenomenon.

Conflict of Interest

We have no conflicts of interest to declare in relation to this work.

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