Journal of Cardiology 61 (2013) 113–116

Contents lists available at SciVerse ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Impact of insulin resistance on 1-year clinical outcomes in non-diabetic patients undergoing percutaneous coronary intervention with drug-eluting stents

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ARTICLE INFO

Article history:
Received 18 May 2012
Received in revised form 31 July 2012
Accepted 22 August 2012
Available online 16 November 2012

Keywords:
Insulin resistance
Drug-eluting stent

ABSTRACT

Background: Insulin resistance (IR) is known to be a risk factor for coronary artery disease (CAD). We aimed to evaluate the impact of IR on 1-year clinical outcomes in non-diabetic CAD patients who underwent percutaneous coronary intervention (PCI) with drug-eluting stents (DESs).
Methods and results: A total of 229 consecutive non-diabetic CAD patients treated with DESs were enrolled. Study population was divided into IR group [homeostasis model assessment (HOMA) index ≥ 2.5, $n = 54$] and non-IR group (HOMA index < 2.5, $n = 175$). Baseline clinical and procedural characteristics were similar between the groups except higher incidence of high-sensitivity C-reactive protein and lower incidence of multivessel disease as the target vessel in the non-IR group. There was a trend toward longer restenosis lesion length in the IR group at 6 months angiographic follow up but composite major clinical outcomes up to 1 year were similar between the two groups.
Conclusions: Despite worse trend in angiographic outcomes in the IR group (HOMA index ≥ 2.5), it was not translated into worse 1-year major clinical outcomes following PCI with DESs as compared to the non-IR group.

Introduction

Insulin resistance (IR) is defined as decreased sensitivity and responsiveness to metabolic action of insulin to target organs. In 1936 Himsworth suggested the first concept of IR [1]. He found some diabetic patients who required more doses of insulin for blood sugar control. He differentiated types of diabetes into insulin sensitive and insulin insensitive. IR with hyperinsulinemia is known to be associated with hypertension, glucose intolerance, obesity, and dyslipoproteinemias of low high-density lipoprotein cholesterol (HDL-C) levels or hypertriglyceridemias, which are well-known risk factors for coronary artery disease (CAD) [2].

There are some reports that high fasting-insulin level and IR are also associated with in-stent restenosis in nondiabetics [3] and studies have shown that IR is an independent predictor of early restenosis after coronary stenting [4].

However, the impact of IR on major clinical outcomes following percutaneous coronary intervention (PCI) in the drug-eluting stent (DES) era is largely unknown.

Therefore we conducted this study to evaluate the impact of IR on 1-year major clinical outcomes in non-diabetic CAD patients undergoing PCI with DESs.

Methods

Study population

We performed a retrospective observational analysis of 229 consecutive non-diabetic patients with CAD who underwent PCI with DESs from January 2004 to June 2009 at the Cardiovascular Center, Korea University Guro Hospital, Seoul, Korea. We excluded patients

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http://dx.doi.org/10.1016/j.jjcc.2012.08.022

who were newly diagnosed with diabetes, treated for diabetes, and those who had high fasting glucose (>125 mg/dL) or glycated hemoglobin A1c level (>6.5%).

Patients' baseline demographic characteristics, clinical characteristics, medical history, and procedural data were collected. One-year major clinical outcome data were collected by interviewing at outpatient clinic, telephone interview, and interviewing at the time of routine 6-month follow-up coronary angiography. All patients gave informed consent according to a protocol approved by the Ethics Committee in Korea University Guro Hospital.

Blood sample and biochemical investigation

Blood sampling was done before PCI at fasting state in routine stable PCI. In cases of ST-elevation myocardial infarction (STEMI) undergoing primary PCI or non-STEMI undergoing early invasive strategy, blood sampling was done next day early in the morning following adequate fasting. Samples were collected from venous blood after overnight fasting and blood chemistry was performed. Fasting plasma glucose and insulin were measured and other parameters including the concentrations of serum total cholesterol, triglyceride, HDL-C, low-density lipoprotein cholesterol (LDL-C), creatinine, and high-sensitivity C-reactive protein (hsCRP) were measured. Insulin resistance was calculated by the homeostasis model assessment of insulin resistance (HOMA-IR), proposed by Matthews et al., whose formula was: HOMA-IR (mg/dL × U/mL) = fasting glucose (mg/dL) × fasting insulin (U/mL)/405 [5]. There were no reports of standard of insulin resistance at HOMA index in Koreans. We used 2.5 as a cut-off point for the analysis; HOMA index ≥ 2.5 was defined as IR group and HOMA index < 2.5 was defined as insulin sensitive group [6].

Percutaneous coronary intervention

Coronary angiography was performed by either femoral or radial approach. Interventional procedure included percutaneous transluminal balloon angioplasty and subsequent DES implantation. PCIs were performed after administration with weight-adjusted bolus of unfractionated heparin (UFH, 70–100 U/kg) or combined administration of low molecular weight heparin (LMWH) and reduced dose of UFH (50 U/kg) during the procedure. During the procedure, patients received UFH to maintain the activated clotting time >250 s. Loading doses of aspirin (200–300 mg) and clopidogrel (300 or 600 mg) were administered before the procedure and followed by aspirin (100 mg/day) and clopidogrel (75 mg/day) after procedure and these dual antiplatelets were maintained at least for 1 year. GP IIbIIIa blocker use was dependent on physician's discretion. Thrombus aspiration was done using Thrombuster II catheter (Kaneka, Osaka, Japan) or Export catheter (Medtronic, Minneapolis, MN, USA) if there were significant angiographic visible thrombi in the target lesion before stenting. After successful wiring to the target lesion, predilation was performed using 2.0–2.5 mm diameter balloons and then stent was deployed. The type of DES was left to the operating physician's choice. Routine angiographic follow up was done at six to nine months after stent implantation.

Study endpoints

Study endpoints were death (cardiac and non-cardiac deaths), non-fatal myocardial infarction, repeat revascularization, and composites of major adverse cardiac events (MACEs) at 1 year. Myocardial infarction included Q-wave myocardial infarction and non-Q-wave myocardial infarction. Revascularization included target lesion revascularization (TLR), target vessel revascularization (TVR), and non-target vessel revascularization (non-TVR). TLR-MACE was defined as the composite of cardiac death, Q-wave myocardial infarction and TLR. TVR-MACE was defined as the composite of total death, any myocardial infarction, and TVR. All MACE (total MACE) was defined as the composite of total death, any myocardial infarction, and any revascularization (TLR, TVR, and non-TVR).

At 6–9 months, routine angiographic follow up was strongly recommended and a variety of angiographic parameters including % restenosis, restenosis lesion length, binary restenosis, restenosis type, late loss, and follow up minimal luminal diameter (MLD) were evaluated between the two groups.

Table 1
Baseline clinical and laboratory characteristics.

Variable, n (%)	IR (n = 54 pts, 23.6%)	Non-IR (n = 175 pts, 76.4%)	p-Value
Male	39 (72.2)	130 (74.3)	0.860
Age, years	63.2 ± 12.4	64.0 ± 11.6	0.616
Current smoking	26 (49.1)	91 (52.6)	0.754
Hypertension	38 (70.4)	99 (56.6)	0.082
Dyslipidemia	9 (16.7)	37 (21.1)	0.563
Prior myocardial infarction	0 (0.0)	2 (1.1)	1.000
Prior CABG	0(0)	1(0.6)	1.000
Prior PCI	4 (7.4)	12 (6.9)	1.000
UA	21 (38.9)	86 (49.1)	0.213
STEMI	3 (5.6)	19 (10.9)	0.302
NSTEMI	9 (16.7)	18 (10.3)	0.229
Total cholesterol (mg/dL)	178.2 ± 47.6	173.4 ± 41.9	0.847
Triglyceride (mg/dL)	137.1 ± 74.9	133.1 ± 86.3	0.941
HDL-cholesterol (mg/dL)	44.0 ± 12.0	44.9 ± 12.9	0.403
LDL cholesterol (mg/dL)	117.6 ± 41.4	112.9 ± 37.1	0.436
Insulin (μm/mL)	18.2 ± 34.8	4.7 ± 2.7	0.002
Glucose (mg/dL)	106.2 ± 12.0	99.5 ± 13.2	0.474
HbA1c (U/mL)	5.8 ± 0.4	5.7 ± 0.6	0.258
HOMA-IR (mg/dL × U/mL)	3.6 ± 1.1	1.1 ± 0.7	0.000
Creatinine (mg/dL)	0.9 ± 0.3	1.0 ± 0.8	0.566
hs CRP (mg/L)	5.4 ± 12.9	13.1 ± 34.8	0.015

Data are mean ± SD or number (%). IR, insulin resistance; CABG, coronary artery bypass graft; Hb, hemoglobin; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; hs CRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein; PCI, percutaneous coronary intervention; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; UA, unstable angina.

Statistical analysis

All statistical analyses were performed using SPSS 17.0 (Statistical package for the social sciences, SPSS-PC Inc., Chicago, IL, USA). Continuous variables were expressed as means ± standard deviation and were compared using Student's t-test. Categorical data were expressed as percentages and were compared using chi-square statistics or Fisher's exact test. p-Value of 0.05 was considered statistically significant.

Results

A total 229 patients were enrolled, the mean age was 63.8 years, and 73.8% (169/229) were male. Twenty-four percent (54/229) of the patients had IR (HOMA index ≥ 2.5, IR group) and 76% (175/229) patients were insulin sensitive (HOMA index < 2.5, non-IR group).

Between the IR and the non-IR groups, there were no significant differences in cardiovascular risk factors including hypertension, dyslipidemia, and smoking. The concentration of insulin was significantly higher in the IR group compared to the non-IR group. Other laboratory parameters including serum creatinine and individual lipid profiles were not different between the two groups except high sensitivity CRP which was higher in the non-IR group (Table 1). Regarding the lesion locations, the non-IR group had