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The prognosis of patients with coronary artery disease complicated by postload hyperinsulinemia ☆

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ABSTRACT

Background: The long-term prognosis of coronary artery disease (CAD) patients with insulin resistance has not been fully examined. In this study, we investigated the influence of postload hyperinsulinemia (PHI) after a 75-g oral glucose tolerance test (OGTT), on the long-term prognosis of CAD patients.
Methods: All study patients were diagnosed as having CAD by coronary angiography. The OGTT was performed for all patients to establish their blood glucose. Measurement of serum insulin was also performed simultaneously. Patients with 2-h insulin level of ≥64 mU/l after the OGTT were included in the postload hyperinsulinemia (PHI) group, and the others were included in the non-PHI group. The prognosis of 208 patients (96 from the PHI group and 112 from the non-PHI group) was retrospectively investigated. Study end points were the composite of death from any cause, unexpected hospitalization for heart failure, new-onset ACS, angina pectoris requiring PCI or CABG, cerebrovascular disease (CVD), and peripheral artery disease (PAD). Variables were compared using Kaplan–Meier analysis and the log-rank tests.
Results: The mean follow-up period was 78.7 months. Cardiovascular events including death were 40.6% in the PHI group and 23.2% in the non-PHI group (log-rank $p = 0.0144$). CVD, PCI, and CABG occurred continuously from early to late stage of follow-up in the PHI group compared with the non-PHI group.
Conclusions: The present study showed that the prognosis of CHD patients with PHI was poor. Thus, it is important to pay attention to these conditions for improving the prognosis of CAD patients.

1. Introduction

The incidence of coronary artery disease (CAD) is approximately three times more likely in diabetes mellitus (DM) patients than in non-DM patients [1]. Because previous studies have found that glucose intolerance occurs in approximately two third of patients with acute myocardial infarction [2], impaired glucose tolerance (IGT) can be considered as a major coronary risk factor. Hyperinsulinemia, one of the conditions of abnormal glucose metabolism, significantly affects atherosclerosis development [3–6]. Cardiovascular complications could develop in DM patients even during the pre- or early stage of diabetes. Many of patients of this status have insulin resistance. However, the prognosis of CAD patients with insulin resistance has not been fully investigated.

In this study, we examined the prognosis of CAD patients with insulin resistance using postload hyperinsulinemia (PHI), which was defined as 2-h serum insulin level of ≥64 mU/l after the oral glucose tolerance test (OGTT).

2. Methods

We investigated the prognosis of 208 CAD patients who were diagnosed with CAD by their first coronary angiography at our hospital between April 2000 and December 2010. CAD included acute coronary syndrome (ACS), stable angina pectoris (SAP), and coronary spastic angina (CSA). ACS was diagnosed by chest pain together with ST segment changes on ECG and angiographically significant coronary artery stenosis or occlusion with thrombus. CSA was angiographically total or subtotal occlusion after an intracoronary infusion of acetylcholine. SAP was angiographically ≥75% coronary artery stenosis according to the American Heart Association (AHA) category. Patients' diabetic conditions were not available on admission, but all had no history of treatment of diabetes. Fasting blood glucose was <126 mg/dl, and blood glucose at any time was <200 mg/dl. All patients underwent a

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Table 1
Characteristics of study patients.

	Non-PHI group (n = 112)	PHI group (n = 96)	p value
Age (yr)	65.3 ± 1.1	64.8 ± 1.2	ns
Male/female	76/36	78/18	p = 0.0284
BMI	23.1 ± 3.0	24.9 ± 3.0	p < 0.0001
Hypertension (%)	49.1	50.0	ns
Smoking (%)	56.3	45.8	ns
LDL-cholesterol (mg/dl)	126.4 ± 54.3	124.1 ± 32.4	ns
HDL-cholesterol (mg/dl)	46.8 ± 14.2	44.4 ± 14.7	ns
Triglyceride (mg/dl)	108.4 ± 52.2	131.6 ± 64.5	p = 0.0051
Lp (a) (mg/dl)	30.6 ± 32.1	25.6 ± 24.9	ns
RLP-cholesterol (mg/dl)	4.26 ± 3.26	5.19 ± 4.12	p = 0.0389
Statin (%)	69.6	64.6	ns

Data are expressed as n (%) or mean ± SD. BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; RLP, remnant-like particle.

75-g OGTT, and plasma glucose and immunoreactive insulin (IRI) levels were measured before and 1 and 2 h after the OGTT.

All patients diagnosed as having glucose intolerance underwent diet therapy, and oral antidiabetic drugs were prescribed for diabetic patients if required. No patient required insulin and had a history of renal or hepatic disease. All study protocols conformed to the requirements of the Declaration of Helsinki.

For ACS patients, height and weight were measured, and blood samples were obtained after 12 h of fasting and when their clinical status was stable, i.e., approximately 2 weeks after admission. For all other patients, height and weight were measured on admission, and blood samples were obtained after 12 h of fasting on their second day of admission. Homeostatic model assessment indices (HOMA-R) were calculated as follows: HOMA-R = [fasting insulin (mU/l) × fasting serum glucose (mg/dl)] / 405 [7]. Those with results ≥1.73 were considered to have insulin resistance [8].

Patients were divided into two groups based on their 2-h insulin level after the OGTT. Those with 2-h insulin levels after the OGTT of ≥64 mU/l were included in the PHI group, and the others were included in the non-PHI group [8].

Study end points were the composite of death from any cause and cardiovascular events including unexpected hospitalization for heart failure, new-onset ACS, coronary artery restenosis after percutaneous coronary intervention (PCI), and new-onset angina requiring PCI or coronary artery bypass graft surgery (CABG), cerebrovascular disease (CVD; transient ischemic attack, cerebral infarction, cerebral hemorrhage, and subarachnoid hemorrhage), and peripheral artery disease (PAD; aortic aneurysm, arteriosclerosis obliterans, and carotid artery stenosis). We retrospectively investigated the last consultation day, event-free period, and details of cardiovascular events. For patients who consulted with other hospitals, we requested information from these hospitals. Patients with follow-up periods of ≤5 years were excluded.

Table 2
Glucose conditions of the two groups.

	Non-PHI group (n = 112)	PHI group (n = 96)	p value
FBS (mg/dl)	90.4 ± 18.0	93.3 ± 11.0	ns
1 h BS (mg/dl)	175.0 ± 57.2	196.9 ± 41.5	p < 0.0001
2 h BS (mg/dl)	155.3 ± 71.6	179.3 ± 51.2	p < 0.0001
Fasting insulin (μIU/ml)	5.4 ± 2.5	9.1 ± 9.3	p < 0.0001
1 h insulin (μIU/ml)	42.4 ± 28.7	89.3 ± 67.1	p < 0.0001
2 h insulin (μIU/ml)	41.3 ± 14.2	119.0 ± 65.5	p < 0.0001
HbA1c (%)	5.7 ± 12	5.7 ± 0.4	ns
HOMA-R	1.44 ± 1.63	1.91 ± 1.27	p = 0.023
Insulin resistance (%)	22.3	42.7	p = 0.0014
Pioglitazone (%)	0	1	ns
Hypoglycemic agents (%)	8.0	4.2	ns

Data are expressed as n (%) or mean ± SD. FBS, fasting blood sugar; BS, blood sugar; HOMA-R, homeostasis model assessment-insulin resistance.

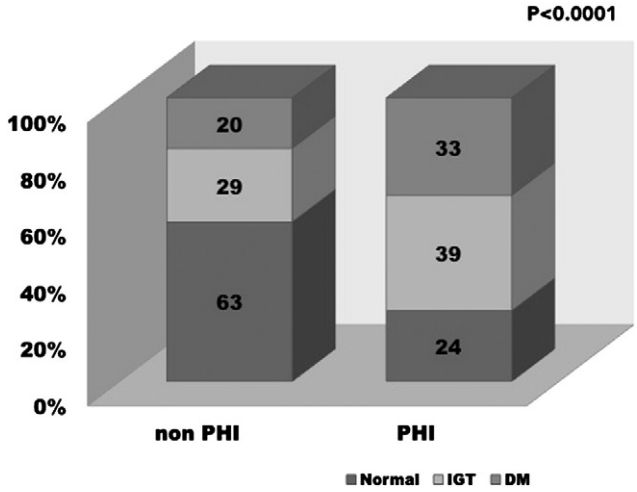

Fig. 1. Comparison of the OGTT results between the two groups. The IGT and diabetes rate were higher in the PHI group than in the non-PHI group.

3. Statistical methods

Statistical results are expressed as a mean ± standard deviation. Data were analyzed using the Student's *t*-test for comparison between the two groups. The Chi-square test was used for all rate comparisons. Cumulative end point-free ratios were analyzed using the Kaplan–Meier method and compared using the log-rank test. Resulting p value of <0.05 was considered statistically significant. Statistical analyses were performed using JMP10 software for Macintosh (SAS Institute Inc., Cary, NC, USA).

4. Results

Clinical characteristic data are shown in Table 1. No significant differences were identified between the groups in terms of age, rate of hypertension, and smoking. Significant lipid result data included remarkably high triglyceride and remnant-like particle cholesterol (RLP-C) values in the PHI group. Low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, Lp (a), and the rate of statin use at admission were not significant. Table 2 shows the result of the OGTT. FBS was not different, but 1- and 2-h BS and three insulin level points were all significantly high in the PHI group compared with the non-PHI group. HOMA-R, rate of insulin resistance, and normal/IGT/DM ratio (Fig. 1) were also significantly high in the PHI group but HbA1c was not. The frequency of use of pioglitazone or

Table 3
Details of cardiovascular events.

	Non-PHI group (n = 112)	PHI group (n = 96)
Death	2	5
Cardiovascular event		
Heart failure	3	2
ACS	7	4
PCI & CABG	6	17
CVD	5	7
PAD	3	4

Data are expressed as n. ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CVD, cerebrovascular disease; PAD, peripheral artery disease.

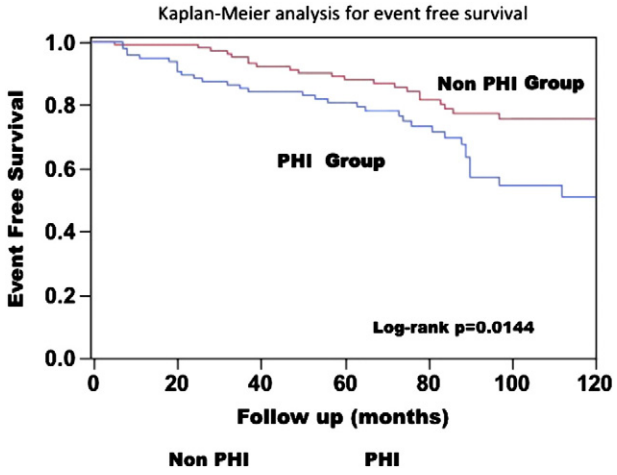

Fig. 2. PHI and 120 month outcome. Kaplan–Meier event-free survival curve.

other hypoglycemic agents after the OGTT did not differ between the groups. Details of cardiovascular events are shown in Table 3. Cardiovascular events occurred in 39 patients, including five deaths, in the PHI group and 26 patients, including two deaths, in the non-PHI group. In particular, the number of patients requiring PCI and CABG was 17 in the PHI group.

Kaplan–Meier survival curves showed that the prognosis was significantly poorer for the PHI group than for the non-PHI group. Incidence event rates were 40.6% and 23.2% in the PHI and non-PHI groups, respectively (log-rank $p = 0.0144$) (Fig.2). In the PHI group, cardiovascular events occurred immediately after initiation of follow-up. In contrast, in the non-PHI group, most events occurred 24 months after the follow-up. This difference was more marked after approximately 90 months. The occurrence of events over time is depicted in Fig. 3. In the non-PHI group, almost all events occurred between 30 and 80 months. However, in the PHI group, events occurred from the early to late stage of follow-up, particularly for those requiring PCI and CABG.

5. Discussion

It has been reported that cardiovascular diseases occur even during the pre- or early stage of diabetes [2], and most of them are complicated by insulin resistance [6]. Therefore, the diagnosis and treatment of insulin resistance are important to prevent cardiovascular disease and improve its prognosis. Although the glucose clamp technique is necessary for an accurate diagnosis of insulin resistance, HOMA-R, which is a simple and easy diagnostic procedure [7], is often generally used. However, even if HOMA-R is within the normal range, many patients with postprandial hyperinsulinemia have been detected. In addition, these patients are believed to have insulin resistance. In this study, almost all patients in the PHI group were in the pre- or early stage of diabetes and had insulin resistance. Patients of vasospastic angina with hyperinsulinemia reportedly have a poor long-term prognosis [9] . Similarly, the results of this study, comprising ACS, SAP, and CSA patients, show that the long-term prognosis of patients with PHI was poor. Kaplan–Meier curves dissociated from the early stage of follow-up and after 80 months. Occurrence of death, heart failure, ACS, and PAD did not differ between the two groups; however, that of CVD, PCI, and CABG was constant from the early stage of follow-up to after 80 months in the PHI group compared with the non-PHI group. It has been reported that insulin resistance is related to the onset of stroke and coronary heart disease [10,11]. In this study, occurrence of CVD, PCI, and CABG led to this difference.

All patients in this study had already developed CAD and were provided treatment for coronary risk factors. It has been reported that the development of cardiovascular events can be reduced with the use of statins in type 2 diabetic patients, even if their diabetes is not well controlled [12]. Although the usage rate of statin was ≥60% in both groups in this study, the prognosis of the PHI group was poor. It is conceivable that insulin resistance led to the development of atherosclerotic disease and adversely affected the prognosis of CAD patients. PHI may be a “residual risk factor” for cardiovascular disease.

In this study, some problems exist in judging the influence of insulin resistance on atherosclerosis. The control levels of coronary risk factors were unknown when the cardiovascular events occurred. In addition, most of the patients in the PHI group were in the pre- or early stage of diabetes. For these patients, diet was the main treatment, and oral

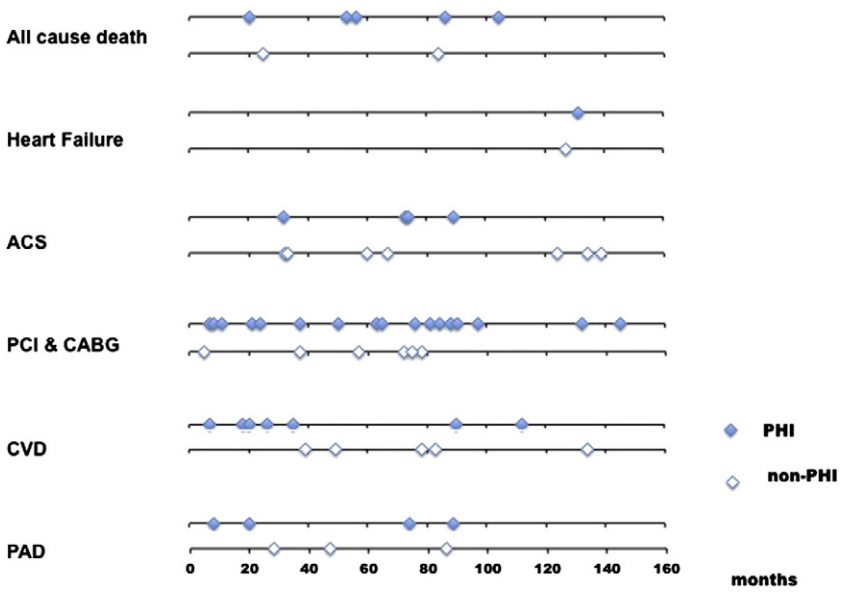

Fig. 3. Time series display of cardiovascular events. ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CVD, cerebrovascular disease; PAD, peripheral artery disease.

antidiabetic drugs were seldom used. Therefore, it may be believed that patients' diabetic conditions worsened when the events occurred. The rate of obesity, triglyceride, and RLP-C levels was significantly high in the PHI group. Therefore, it was believed that many patients had metabolic syndrome in the PHI group. However, we did not measure adiponectin, which is concerned with the progression of atherosclerosis [13,14].

Pioglitazone is an insulin sensitizer used for the treatment of type 2 diabetes. It has been reported that pioglitazone reduced cardiovascular complications in type 2 diabetic patients [15]; however, it does not have applications for prediabetic patients. In addition, some problems have been reported with pioglitazone [16,17]. Therefore, it is difficult to positively recommend this drug to prediabetic patients. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers have an inhibitory effect on new-onset diabetes and an improving effect on insulin resistance [18–22]. Therefore, we believe that these drugs should be prescribed for patients in the pre- or early diabetes if their condition is complicated by hypertension. Diet therapy and weight control have an improving effect on insulin resistance, and as such, they are the basics for treatment of glucose intolerance. UKPDS [23] that provided intensive blood glucose control for patients with new-onset type II diabetes improved the long-term prognosis [24]. However, good results have not yet been reported, even for intensive glucose control for type II diabetic patients who had already been treated [25–27]. The results of this study show that the prognosis of patients complicated with PHI was poor, even if they were in the pre- or early stage of diabetes. It is important to pay attention to patients with PHI, even if their blood glucose is normal, or they have IGT level. However, it is unclear whether intensive control for these conditions improves the prognosis.

Conflict of interest

The authors declare no conflict of interest.

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