Hyperinsulinemia as a Risk Factor for Restenosis After Coronary Balloon Angioplasty

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The present study evaluated whether hyperinsulinemia is a predictor of restenosis after coronary balloon angioplasty in 69 patients who underwent elective coronary balloon angioplasty; patients were excluded if they were known diabetics being treated with insulin. Quantitative coronary angiography was performed before and after angioplasty and at follow-up. Restenosis was defined as the presence of $\geq 50\%$ stenosis at follow-up. Plasma insulin responses before, 30, 60, and 120 min after 75 g glucose load (OGTT) were measured. Plasma insulin levels were higher in patients with restenosis than in patients without restenosis. Minimal lumen diameter at follow-up was smaller, and percent diameter stenosis at follow-up was higher and late loss was greater in the highest sum of insulin levels during OGTT (insulin) quartile (0.95 ± 0.15 vs 1.47 ± 0.09 mm, $p=0.005$; 66.3 ± 5.8 vs $40.5 \pm 3.3\%$, $p=0.0003$; 0.90 ± 0.15 vs 0.49 ± 0.08 mm, $p=0.02$). Even after adjustment for coronary risk factors and administration of angiotensin converting enzyme inhibitors, the association of hyperinsulinemia with restenosis leads to the conclusion that hyperinsulinemia is a strong risk factor for restenosis. (*Jpn Circ J* 2001; 65: 947–952)

Key Words: Coronary heart disease; Hyperinsulinemia; Restenosis

Although the introduction of new devices for angioplasty and improvements in the balloon technique have reduced complications during the procedure, restenosis after percutaneous coronary angioplasty (PTCA) remains a serious problem. Neointimal hyperplasia caused by smooth muscle cell (SMC) proliferation and migration, regulated by various growth factors, has been suggested as the main mechanism of restenosis¹

Some studies^{2,3} have shown that insulin stimulates the proliferation of arterial SMC and increases vascular cell mitogenesis and protein synthesis, particularly matrix proteins such as type IV collagen.⁴ Aortic SMC proliferation after endothelial injury was promoted in the obese Zucker rat model, which is characterized by early spontaneous development of hyperinsulinemia and insulin resistance.⁵ Moreover, insulin sensitizing agents, the thiazolidinediones, inhibit SMCs proliferation and migration in a rat balloon injury model⁶

However, an association with hyperinsulinemia and restenosis after PTCA is controversial and only a few studies^{7,8} have shown a positive association. Rabbani et al showed a negative association between hyperinsulinemia and restenosis after excimer laser angioplasty.⁹ The aim of the present study was to evaluate whether hyperinsulinemia is a predictor of restenosis after PTCA.

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Methods

Subjects

We previously reported our findings from a randomized, multicenter clinical restenosis trial with cilazapril in patients with coronary artery disease.¹⁰ In brief, of 128 patients (94 males) who underwent successful coronary balloon angioplasty, 69 (48 males; mean age, 64 years) were enrolled if they had undergone an oral glucose tolerance test (OGTT) and their quantitative coronary angiography (QCA) findings were available. Patients were excluded if they had been diagnosed as diabetic and were being treated with insulin.

Informed consent was obtained from all patients participating in this study.

PTCA Procedure and Quantitative Coronary Angiography Analysis

All patients received a bolus of 10,000 IU heparin intravenously and 5 mg of isosorbide dinitrate intracoronary. Angiography was performed before and immediately after PTCA and at follow-up 6 months after successful PTCA, but was performed earlier if clinically indicated. Off-line QCA was conducted using CARDIO 500 (Kontron Instruments, Inc, Everett, MA, USA) with the view revealing the highest degree of stenosis. All angiographic analyses were performed at a core hospital whose staff did not have access to the clinical findings. Reference diameter (RD), minimal lumen diameter (MLD), and percent diameter stenosis (%DS) were calculated. Late loss was defined as the difference between MLD after PTCA and follow-up MLD. Restenosis was defined as the presence of $\geq 50\%$ stenosis at follow-up. Patients were considered to have restenosis when the %DS of the main culprit lesion was more than 50% at follow-up if they had undergone multi-lesion angioplasty. The main culprit lesion was defined as

Table 1 Clinical Characteristics

	Restenosis (n=31)	No restenosis (n=38)	p value
Age (years)	64.7±1.5	63.2±1.3	0.44
Males (%)	77.4	63.2	0.20
Previous myocardial infarction (%)	48.4	44.7	0.76
Hypertension (%)	58.1	52.6	0.65
Diabetes mellitus (%)	12.9	31.6	0.07
History of smoking (%)	45.2	39.5	0.63
ACE inhibitor administration (%)	32.3	57.9	0.04
Total cholesterol (mg/dl)	202.4±7.4	219.4±6.8	0.10
Triglycerides (mg/dl)*	115.5 (106.9–124.8)	133.0 (123.9–142.8)	0.18
HDL cholesterol (mg/dl)	42.6±2.0	44.3±1.8	0.54
LDL cholesterol (mg/dl)	137.8±8.3	149.7±7.6	0.29
Fasting glucose (mg/dl)	93.9±4.8	100.2±4.4	0.34
30 min glucose (mg/dl)	155.8±6.4	155.3±5.8	0.96
60 min glucose (mg/dl)	179.7±9.4	179.8±8.3	0.99
120 min glucose (mg/dl)	146.8±12.5	159.5±11.0	0.45
Fasting insulin (μU/ml)*	7.7 (6.8–8.6)	6.8 (6.2–7.6)	0.45
30 min insulin (μU/ml)*	49.1 (42.7–56.5)	30.9 (27.2–35.1)	0.02
60 min insulin (μU/ml)*	70.5 (61.9–80.3)	48.2 (42.8–54.2)	0.04
120 min insulin (μU/ml)*	58.6 (50.2–68.5)	44.9 (39.0–51.6)	0.21
insulin (μU/ml)*	201.2 (179.3–225.7)	144.9 (130.6–160.8)	0.04

Values are given as means±SE, (95% confidence intervals), or percentages. *Values are back-transformed from log transformations. insulin is the sum of fasting, 30 min, 60 min, and 120 min insulin levels.

the lesion that had a larger RD or a higher %DS before angioplasty. If we could not decide on a culprit lesion with these criteria, we chose the lesion that had a greater difference between the RD and the MLD before angioplasty.

Blood Sampling

Before PTCA, blood samples were obtained in the morning after a 12-h fast to measure the fasting levels of total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides by enzymatic methods. Low-density lipoprotein (LDL) cholesterol was calculated using Friedewald's formula. Plasma glucose insulin concentrations were measured before, 30, 60, and 120 min after an oral challenge with 75 g glucose (OGTT). The homeostasis model insulin resistance index (HOMA index) was calculated using the formula: fasting plasma glucose (mg/dl) × fasting plasma insulin (μU/ml)/405.¹¹ Plasma glucose was measured by the glucokinase method, and insulin was measured by a radioimmunoassay.

Statistic Analysis

Values are expressed as means±SE. Differences between the means of the 2 groups were evaluated with a Student's 2-tailed t-test. Logarithmic transformations of triglycerides and insulin were performed because these variables showed a skewed distribution in all statistical analyses including these variables as continuous variables. They were reconverted to their original form before presentation. Analysis of covariance was used to assess the relationship between the %DS, MLD at follow-up, late loss and hyperinsulinemia adjusted for age, gender, previous myocardial infarction, administration of angiotensin converting enzyme (ACE) inhibitors, coronary risk factors, RD before PTCA, and MLD immediately after PTCA. Contingency tables of quartiles of insulin concentrations in individuals were compared by chi-square or Fisher's exact test. Logistic regression was used to calculate the relative risk ratio (RR) and 95% confidence intervals (CI) for the association between restenosis and hyperinsulinemia. Additional analyses were adjusted for age, gender, previous myocardial

infarction, and coronary risk factors, including hypertension, dyslipidemia, smoking, and diabetes mellitus (DM). Statistical analyses were carried out using the SAS program (JMP3.0). A level of $p<0.05$ was considered statistically significant.

Results

Patient's Characteristics

The study population consisted of 69 patients with 76 vessels and 90 lesions. Of the 69 patients with initially successful PTCA, 31 (45%) developed restenosis (Table 1). There were no significant differences between the 2 groups with regard to age, gender, incidence of hypertension, dyslipidemia, previous myocardial infarction, or history of smoking. The prevalence of DM tended to be higher in patients without restenosis than in those with restenosis. A greater number of patients without restenosis were receiving ACE inhibitors. Serum levels of total cholesterol, triglycerides, HDL cholesterol, and plasma glucose levels before and after glucose load were not different between the 2 groups. However, plasma 30-min and 60-min insulin levels after glucose load and the sum of insulin levels during OGTT (insulin) were significantly higher in patients with restenosis than in those without restenosis ($p<0.05$). Plasma fasting and 120-min insulin levels were slightly higher in patients with restenosis, but not significantly.

Hyperinsulinemia and Restenosis

Restenosis rates and the relative risks for restenosis by quartiles of insulin levels are shown in Table 2. The restenosis rate was significantly higher in the highest quartile of 30 min, 60 min, and insulin than in the 3 lower quartiles, and tended to be higher in the highest quartile of fasting insulin. When restenosis was evaluated in terms of vessels or lesions, both restenosis per vessel and that per lesion were associated with hyperinsulinemia (Table 3).

In a multivariable prediction model that includes age, gender, previous myocardial infarction, administration of

Table 2 Rates and Relative Risks for Restenosis in Relation to Insulin Concentrations

	$\mu\text{U/ml}$	(n)	Restenosis		
			Rate (%)	Relative risk (95% CI), p value Quartile 4 vs Quartiles 1–3	p value for trend
Fasting insulin					
Quartile 1	<4.7	(17)	41.2	1.71 (0.98–3.92), 0.06	0.07
Quartile 2	4.7–	(17)	52.9		
Quartile 3	7.3–	(18)	22.2		
Quartile 4	10.9–	(17)	64.7		
30 min insulin					
Quartile 1	<21.3	(17)	41.2	2.48 (1.37–4.94), 0.005	0.02
Quartile 2	21.3–	(17)	29.4		
Quartile 3	41.0–	(18)	33.3		
Quartile 4	72.2–	(17)	76.5		
60 min insulin					
Quartile 1	<33.6	(17)	44.4	1.83 (1.06–3.33), 0.04	0.14
Quartile 2	33.6–	(17)	29.4		
Quartile 3	63.6–	(18)	37.5		
Quartile 4	102.0–	(17)	66.7		
120 min insulin					
Quartile 1	<32.8	(17)	35.3	1.45 (0.84–2.58), 0.19	0.52
Quartile 2	32.8–	(17)	47.1		
Quartile 3	56.2–	(18)	38.9		
Quartile 4	86.7–	(17)	58.8		
insulin					
Quartile 1	<113.0	(17)	41.2	3.10 (1.65–6.77), 0.001	0.004
Quartile 2	113.0–	(17)	29.4		
Quartile 3	174.4–	(18)	27.8		
Quartile 4	256.3–	(17)	82.4		

insulin is the sum of fasting, 30 min, 60 min, and 120 min insulin levels. CI, confidence interval.

Table 3 Restenosis Rate at Follow-up Angiography

	Q 1–3 insulin		Q 4 insulin		p value
	Total	Restenosis (%)	Total	Restenosis (%)	
Patients (n)	52	17 (32.7)	17	14 (82.4)	0.0004
Vessels (n)	56	17 (30.4)	20	14 (70.0)	0.002
Lesions (n)	63	18 (28.6)	27	14 (51.9)	0.03

insulin is the sum of fasting, 30 min, 60 min, and 120 min insulin levels. Q, quartile.

Table 4 Quantitative Angiographic Analysis

	1–3 Quartile insulin (n=52)	Highest Quartile insulin (n=17)	p value
<i>RD (mm)</i>			
Before PTCA	2.72±0.10	2.70±0.17	0.91
After PTCA	2.67±0.08	2.60±0.14	0.65
Follow-up	2.52±0.09	2.65±0.16	0.47
<i>MLD (mm)</i>			
Before PTCA	0.83±0.05	0.58±0.10	0.02
After PTCA	1.96±0.06	1.85±0.10	0.35
Follow-up	1.47±0.09	0.95±0.15	0.005
<i>%DS</i>			
Before PTCA	70.3±1.6	78.1±2.9	0.02
After PTCA	25.3±1.8	29.0±2.4	0.32
Follow-up	40.5±3.3	66.3±5.8	0.0003
Late loss (mm)	0.49±0.08	0.90±0.15	0.02

Values are given as means±SE. insulin is the sum of fasting, 30 min, 60 min, 120 min insulin levels. RD, reference diameter; PTCA, percutaneous transluminal coronary angioplasty; MLD, minimal lumen diameter; DS, diameter stenosis.

ACE inhibitors, and coronary risk factors, including hypertension, dyslipidemia, smoking, DM, the highest quartile of insulin was associated with restenosis (risk ratio=3.43, 95% CI 1.51–9.57, $p<0.01$). Administration of ACE inhibitors prevented restenosis.

HOMA Index and Restenosis

The HOMA index was not different between the patients with and without restenosis (2.21 ± 0.27 vs 2.04 ± 0.24). The distribution of restenosis rates along quartiles of the HOMA index detected no obvious trend (from first to last quartile, percentage of restenosis: 47.3%, 35.3%, 31.3%, 58.8%).

Table 5 Quantitative Angiographic Analysis

	insulin		p value
	Quartiles 1–3	Quartile 4	
<i>Nondiabetic patients</i>	(n=37)	(n=16)	
MLD at follow-up (mm)	1.43±0.10	0.90±0.15	0.006
%DS at follow-up	42.5±4.0	67.7±6.1	0.001
Late loss (mm)	0.63±0.10	0.92±0.15	0.10
Restenosis (%)	35.1	87.5	0.002
<i>Single lesion angioplasty</i>	(n=39)	(n=9)	
MLD at follow-up (mm)	1.46±0.11	0.84±0.23	0.02
%DS at follow-up	40.8±4.1	69.8±8.5	0.004
Late loss (mm)	0.47±0.10	0.97±0.22	0.04
Restenosis (%)	30.8	77.8	0.009

Values are given as means±SE or percentages. insulin is the sum of fasting, 30 min, 60 min, 120 min insulin levels. RD, reference diameter; MLD, minimal lumen diameter; DS, diameter stenosis.

The risk ratio for restenosis comparing patients in the highest HOMA index with those in the combined 3 lower quartiles was 1.53 (95% CI, 0.88–2.73). In nondiabetic patients, the risk ratio was 4.08 (95% CI, 1.67–17.93).

Quantitative Coronary Angiography Analysis

Quantitative angiographic findings along quartiles of insulin levels are shown in Table 4. There were no significant differences in RD, MLD after PTCA, and %DS after PTCA between the 2 groups. MLD before PTCA was smaller and %DS before PTCA was higher in the highest insulin quartile than in the combined 3 lower quartiles. MLD at follow-up was smaller, and %DS at follow-up was higher and late loss was greater in the highest insulin quartile. The %DS at follow-up was higher in the highest insulin quartile than in the combined 3 lower quartiles after adjustment for %DS before angioplasty (65.8±6.6 vs 40.7±3.4%, $p=0.006$) and after adjustment for MLD before angioplasty (64.8±6.3 vs 41.4±3.5%, $p=0.002$).

After adjustment for age, gender, previous myocardial infarction, administration of ACE inhibitors, coronary risk factors, RD before PTCA, and MLD after PTCA, %DS at follow-up was 57.2±7.6 in the highest insulin quartile and 37.7±3.8 in the other group ($p=0.01$), MLD at follow-up tended to be smaller, and late loss tended to be greater in the highest insulin quartile (1.24±0.18 vs 1.55±0.09 mm, $p=0.09$; 0.69±0.18 vs 0.37±0.09 mm, $p=0.08$).

Hyperinsulinemia and Restenosis in Nondiabetic Patients or Who Underwent the Single-Lesion PTCA Procedure (Table 5)

In a subgroup of nondiabetic patients (n=53), MLD at follow-up was smaller, %DS was higher, and late loss tended to be greater in patients with the highest insulin quartile than in the other group. The highest insulin quartile showed a higher restenosis rate (87.5%) and was associated with restenosis (risk ratio=3.59; 95% CI, 1.74–9.53, $p=0.002$). Further adjustments for age, gender, previous myocardial infarction, administration of ACE inhibitors, and coronary risk factors, gave a risk ratio of 4.95 (95% CI, 1.72–21.3, $p=0.01$).

After adjustment for age, gender, previous myocardial infarction, administration of ACE inhibitors, coronary risk factor, RD before PTCA, and MLD after PTCA, MLD at follow-up tended to be smaller, %DS at follow-up tended to be higher, and late loss tended to be greater in the highest insulin quartile (1.02±0.19 vs 1.41±0.10, $p=0.08$; 60.2±8.1 vs 43.4±4.5, $p=0.09$; 0.96±0.19 vs 0.58±0.10, $p=0.08$).

In a subgroup of patients (n=48) who underwent the single-lesion PTCA procedure, MLD at follow-up was smaller, %DS was higher, and late loss tended to be greater in patients with the highest insulin quartile than in the other group. The highest insulin quartile had a higher restenosis rate (77.8%) and was associated with restenosis (risk ratio=2.81; 95% CI, 1.28–7.64, $p=0.02$). Further adjustments for age, gender, previous myocardial infarction, administration of ACE inhibitors, and coronary risk factors, gave a risk ratio of 3.96 (95% CI, 1.48–24.3, $p=0.02$).

After adjustment for age, gender, previous myocardial infarction, administration of ACE inhibitors, coronary risk factor, RD before PTCA, and MLD after PTCA, MLD at follow-up was smaller, %DS at follow-up was larger, and late loss was greater in the highest insulin quartile (0.82±0.23 vs 1.45±0.11 mm, $p=0.01$; 78.9±9.2 vs 42.2±4.3, $p=0.0003$; 1.10±0.23 vs 0.46±0.11 mm, $p=0.008$).

Discussion

The findings of the present study demonstrated that hyperinsulinemia is a strong independent risk factor of restenosis after angioplasty, as reported by a few other studies.^{7,8} One study has reported a negative association between hyperinsulinemia and restenosis after PTCA in patients with DM.⁹ The present study population included patients with DM, but even after excluding them, a positive association between hyperinsulinemia and restenosis remained (Table 5). The HOMA index as a measure of insulin resistance was also associated with restenosis in nondiabetic patients.

Diabetes Mellitus and Restenosis

Several studies have demonstrated that diabetes is a strong predictor of restenosis after successful balloon angioplasty^{12,13} or stent implantation^{14–16} but others^{17,18} have not. Recently, Asakura et al demonstrated that restenosis was significantly more frequent in poorly controlled diabetic patients compared with moderately or well-controlled diabetic patients or nondiabetic subjects.¹³ Most patients with DM in the present study population were moderately or well controlled, which might explain the reason for the lack of an effect on restenosis. Potential factors promoting restenosis in diabetic patients are elevated glucose or insulin levels.¹⁹

Hyperinsulinemia and Restenosis

The mechanisms of restenosis are not fully understood,

but some causal factors have been reported: platelet aggregation;²⁰ elastic recoil;²¹ thrombus formation;²² SMC proliferation and migration;²³ extracellular matrix production;^{22,24} spasm;²⁵ and vascular remodeling.²⁶ Most of these mechanisms are associated with insulin action in part.

Hyperinsulinemia is associated with increased plasminogen activator inhibitor 1 activity²⁷ and its gene expression;²⁸ thereby attenuating fibrinolysis, which may contribute to acceleration of thrombus formation. Proliferation and migration of SMCs is promoted by increased insulin levels; insulin-like growth factor 1 (IGF-1) is a potent mitogen and induces directed migration of arterial SMCs.²⁹ Although insulin itself is not a potent mitogen,²⁹ it can stimulate the expression of IGF-1,³⁰ and is associated with increased extracellular matrix proteins.⁴ Vasospasm of the dilated coronary segment is frequently accompanied by restenosis;²⁵ and loss of the endothelium-derived relaxing factor, nitric oxide caused by endothelial denudation, promotes vasospasm, platelet aggregation, and SMC proliferation.^{31,32} Hypersecretion of insulin may therefore contribute to the pathogenesis of severe coronary vasospasm and increase susceptibility to restenosis,^{33–35} although the relation of vasospastic angina to restenosis is still unclear.

Endothelin-1 (ET-1) is a potent vasoconstrictor and mitogenic peptide produced by the vascular endothelium, and insulin stimulates ET-1 secretion³⁶ and its gene expression.³⁷ Vascular remodeling, the main mechanism of restenosis, is an active process of structural alteration that involves changes in at least 4 cellular processes: cell growth, cell death, cell migration, and production or degradation of extracellular matrix.²⁶ Several growth factors, including platelet-derived growth factors, transforming growth factors, and IGF-1, regulate the growth of vascular cells involved in remodeling.²⁶ However, it is unclear whether hyperinsulinemia is associated with it.

Hyperinsulinemia, Dyslipidemia, Coronary Atherosclerosis, and Restenosis

Insulin resistance and compensatory hyperinsulinemia enhance hepatic very-low-density lipoprotein-triglyceride secretion,³⁸ which results in increased serum triglycerides and decreased HDL cholesterol concentrations. Furthermore, Haffner et al³⁹ suggest that hyperinsulinemia is predictive of an increase in triglycerides and a decrease in HDL cholesterol concentrations. Two additional lipid abnormalities described in hyperinsulinemic individuals are small dense LDL particles and accentuation of postprandial large triglyceride-rich particles,^{40,41} and these lipid abnormalities may contribute to the development of coronary atherosclerosis and restenosis. In the present study, the levels of HDL cholesterol tended to be lower, and the levels of triglycerides slightly higher, and the levels of total cholesterol and LDL cholesterol were slightly lower in the hyperinsulinemic group, but not significantly.

Some studies^{42,43} have suggested that hyperlipidemia may be associated with increased restenosis, but a large clinical trial⁴⁴ indicated that there was no association between hyperlipidemia and restenosis. Levels of total cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol were not associated with restenosis in the present study.

Study Limitations

Although this trial was a multicenter, prospective, randomized study, the major limitations of the present study

were that it was not specifically designed to address the relationship between restenosis after angioplasty and hyperinsulinemia and our study group was small. To compensate for these limitations, we conducted the serial QCA measurements in a blinded manner at a core hospital.

Conclusions

Plasma insulin levels were higher in patients with restenosis than in patients without restenosis. MLD at follow-up was smaller, and %DS at follow-up was higher and late loss was greater in patients with hyperinsulinemia. Even after adjustment for coronary risk factors and administration of ACE inhibitors, an association of hyperinsulinemia to restenosis remained. These findings indicate that hyperinsulinemia is a strong independent risk factor for restenosis.

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