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Relationship Between Preheparin Lipoprotein Lipase Mass Concentration in Serum and Bare Metal Stent Restenosis

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Abstract

Objectives. Insulin resistance or inflammation is known to be related with lipoprotein lipase activity and these factors are also closely associated with the pathogenesis of bare-metal stent restenosis. This study examined the relationship between preheparin lipoprotein lipase protein(preheparin LpL mass)concentration in serum and bare-metal stent restenosis.

Methods. A total of 121 lesions in 112 patients who underwent bare-metal stent implantation using NIR stent or S660/670 stent were examined. Subjects were divided into two groups(N group; patients with normal preheparin LpL mass concentration, $n = 50$ or L group; patients with low preheparin LpL mass concentration, $n = 71$)according to the mean levels of preheparin LpL mass concentration(male 39.3 ng/m*l*, female 50.6 ng/m*l*).

Results. There were no differences in percutaneous coronary intervention or angiographical characteristics. The L group had a significantly higher incidence of restenosis rate and target lesion revascularization than the N group(N group vs L group: 8.0% vs 42.3%, $p < 0.0001$; 8.0% vs 33.8%, $p = 0.0008$, respectively). Homeostatic model assessment of insulin resistance as a marker of insulin resistance and high sensitive C-reactive protein concentration were significantly higher in the L group than the N group. Multiple regression analysis showed that only low preheparin LpL mass concentration was an independent factor for restenosis(t value $= 3.6$, $p = 0.0005$).

Conclusions. Preheparin LpL mass concentration is closely associated with bare-metal stent restenosis and preheparin LpL mass concentration may be an important marker for the selection of bare-metal stent or drug-eluting stent.

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Key Words

■**Stent** ■**Restenosis** ■**Angiography** ■**Lipoproteins (lipoprotein lipase)** ■**Insulin (resistance)**

INTRODUCTION

Coronary stent implantation is well established as a useful technique for resolving myocardial ischemia by relieving coronary artery stenosis, and drug-eluting stents significantly reduce restenosis, which has been the main problem of stenting.[1,2] However, drug-eluting stents have unresolved problems such as cost, long-term safety, and the prolonged administration of anti-platelet drugs.[3,4] Insulin resistance[5−8] and inflammation[9,10] are well-known major risk factors for bare-metal stent restenosis. Recent clinical investigations have reported a small amount of lipoprotein lipase(LpL) protein in serum or plasma without heparin injection(preheparin LpL mass),[11−15] and we confirmed

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that low preheparin LpL mass concentration was closely associated with coronary atherosclerosis.[16–18] LpL production is decreased in patients with insulin resistance,[19] and there may be a relationship between LpL activity and inflammation.[20,21] Therefore, if preheparin LpL mass concentration expresses LpL activity *in vivo*, low preheparin LpL mass concentration may reflect insulin resistance or inflammation *in vivo*, and consequently may provide a predictive factor for bare-metal stent restenosis.

This study examined the relationship between preheparin LpL mass concentration and bare-metal stent restenosis.

SUBJECTS AND METHODS

Patient population

This study investigated successful cases of bare-metal stent implantation using the NIR stent (Boston Scientific) or S660/670 stent (Medtronic) for 121 de novo lesions in 112 patients, who underwent 6-month follow-up coronary angiography, between December 2001 and January 2004 at Toho University School of Medicine, Sakura Hospital. All patients underwent preheparin LpL mass concentration measurement in the serum before stenting. Patients with acute coronary syndrome, low left ventricular ejection fraction (estimation by ultrasonic echocardiography was $< 40\%$), renal failure (serum creatinin concentration was $\geq 2\,mg/dl$), ≥ 2 stents in one lesion, and left main coronary trunk lesion were excluded. No patient with chronic total occlusion was observed in this study. Subjects were divided into two groups: N group (patients with normal preheparin LpL mass concentration, $n = 50$) or L group (patients with low preheparin LpL mass concentration, $n = 71$) based on the mean levels of preheparin LpL mass concentration (male 39.3 ng/ml, female 50.6 ng/ml) in this study. Before the study, informed consent to perform percutaneous coronary intervention (PCI) and laboratory analysis was given by all participants.

Procedure of stent implantation

PCI was performed by the transfemoral or transbrachial approach using a standard technique. Immediately before PCI, patients received an initial bolus of heparin (10,000 U) and intracoronary administration of nitroglycerin. PCI was performed by plain balloon angioplasty, followed by stent implantation. After successful stent delivery, balloon dilation at high pressure was applied to achieve the optimal result, which was defined as residual stenosis of less than 10% of luminal diameter without major in-hospital adverse cardiac events (death, myocardial infarction, coronary intervention, or coronary artery bypass surgery). Heparin and nitroglycerin infusions were continued for 24 hr after stenting.

Quantitative coronary angiography

Coronary angiograms were obtained before, immediately after, and 6 months after stenting, and were reviewed by an unbiased angiographer without knowledge of the preheparin LpL mass concentration. For quantitative analysis, end-diastolic cine-frames were selected from angiographic views demonstrating the maximal degree of stenosis, and were matched before, immediately after, and 6 months after stenting. Using a cine-video converter, views were analyzed using a quantitative coronary angiography analysis system (Heart Analysis Database System, Medical Soft Support Center Corp). Guiding and diagnostic catheters were used as the calibration standard to measure the reference diameter, minimal lumen diameter, percentage diameter stenosis and lesion length. Acute gain was defined as increased minimal lumen diameter immediately after stenting, and late loss as decreased minimal lumen diameter at follow up. Angiographic restenosis was defined as stenosis of $\geq 50\%$ diameter at the end of follow up.

Determination of blood samples

Blood samples were drawn in the morning after overnight fast. Total cholesterol and triglyceride concentrations were measured enzymatically using a kit, and high density cholesterol was measured by the selective inhibition method. Low density cholesterol was calculated by the Friedwald formula (total cholesterol − high density cholesterol − triglyceride/5).[22] Plasma glucose concentration was measured using the glucose oxidase method and serum insulin concentration was measured using the enzyme immunoassay method. The high sensitive C-reactive protein (hs-CRP) concentration was measured using the immunonephelometry method.

Estimation of coronary risk factors

Coronary risk factors were estimated for sex,

Table 1 Baseline clinical characteristics

	N group (n=50)	L group (n=71)	p value
Number of patients	48	64	
Preheparin LpL mass (ng/m*l*)	51.7±10.7	34.3±6.0	<0.0001
Age (yr)	65.9±9.0	64.3±10.0	NS
Male/female	36/14	59/12	NS
Coronary risk factors			NS
Hypertension	24(48)	32(45)	
Diabetes mellitus	6(12)	22(31)	0.01
Obesity (BMI≥25)	18(36)	33(46)	0.04
Smoking	24(48)	38(54)	NS
Family history of IHD	8(16)	10(14)	NS

Continuous values are mean±SD. ( ) : %.
LpL=lipoprotein lipase; BMI=body mass index; IHD=ischemic heart disease.

age, hypertension, diabetes mellitus, obesity, smoking, family history of ischemic heart disease, serum lipid concentrations, insulin resistance and inflammation. Hypertension was defined as patients with systolic pressure ≥ 140 mmHg and/or diastolic pressure 90 mmHg or under antihypertensive treatment. Diabetes mellitus was defined as a history of diabetes mellitus or fasting blood glucose levels ≥ 126 mg/d*l*. Obesity was defined as a body mass index ≥ 25. Smoking was defined as positive if there was a current or past history of cigarette smoking. Family history of ischemic heart disease was considered positive if angina pectoris and/or myocardial infarction were present in grandparents, parents, and siblings. The homeostatic model assessment of insulin resistance [HOMA-IR; serum glucose concentration (mg/d*l*) × serum insulin concentration (μU/m*l*)/405] has been reported as a simple and reliable insulin resistance marker;[23] so we calculated HOMA-IR as a marker of insulin resistance in this study. hs-CRP concentration was measured as a marker of inflammation *in vivo*.

Preheparin LpL mass assay

Preheparin LpL mass concentration was measured by the sandwich enzyme-linked immunosorbent assay using a specific monoclonal antibody against LpL, as described previously,[3] using a kit from Daiichi Pure Chemicals. In this assay system, a linear response was observed from 5 to 400 ng/m*l*. The within-run coefficient of variation was 2.8%. The between-day coefficient of variation was 4.3%.

Statistical analysis

A commercially available statistical software program (Stat View-J 5.0; HULINKS Inc.) was used for all statistical analyses. Data are expressed as mean ± standard deviation. Between-group comparisons were performed using Student's *t*-test or Mann-Whitney *U* test. Multivariate analysis was performed using multiple regression analysis. A p value of less than 0.05 was considered significant.

RESULTS

Baseline clinical characteristics

Patient characteristics are shown in **Table 1**. There were no differences in coronary risk factors such as age, sex, incidence of hypertension, smoking and family history of ischemic heart disease between the two groups. On the other hand, patients with diabetes mellitus and obesity were more frequently detected in the L group than in the N group. Blood sample data are shown in **Table 2**. Total cholesterol and LDL-cholesterol concentrations were almost identical in the two groups. However, triglyceride concentration, HOMA-IR and hs-CRP concentration were significantly higher in the L group than in the N group. Inversely, HDL-cholesterol concentration was significantly lower in the L group.

Angiographic results

Angiographic characteristics are shown in **Table 3**. There were no significant differences in the PCI procedure or baseline coronary angiographic characteristics, and minimal lumen diameter or acute

Table 2 Comparisons of serum parameters

	N group (n=50)	L group (n=71)	p value
Total cholesterol (mg/d*l*)	185.4±28.7	192.8±35.0	NS
LDL-cholesterol (mg/d*l*)	114.7±27.8	117.5±38.0	NS
Triglyceride (mg/d*l*)	113.9±42.1	144.2±62.0	0.003
HDL-cholesterol (mg/d*l*)	48.0±11.0	42.3±11.0	0.01
FBS (mg/d*l*)	107.6±17.5	115.7±30.2	NS
IRI (μU/m*l*)	6.6±3.5	10.0±9.8	0.02
HOMA-IR	1.8±1.1	2.9±3.0	0.02
hs-CRP (mg/*l*)	1.1±1.5	1.7±1.6	0.0002
Administration of statin	25(50)	36(51)	NS

Continuous values are mean±SD. ( ) : %.
LDL=low-density lipoprotein; HDL=high-density lipoprotein; FBS=fasting blood sugar; IRI=immunoreactive insulin; HOMA-IR=homeostasis assessment insulin resistance; hs-CRP=high sensitive C-reactive protein.

Table 3 Angiographic characteristics

	N group (n=50)	L group (n=71)	p value
Target vessel			
LAD	30(60)	40(56)	NS
RCA	13(26)	15(21)	NS
LCX	7(14)	16(23)	NS
ACC/AHA type			
A/B1/B2/C	7/20/15/8	6/37/21/7	NS
Stent type			
NIR	18(36)	16(23)	NS
S660/670	32(64)	55(77)	NS
Stent size (mm)	3.1±0.5	3.1±0.5	NS
2.5/3.0/3.5/4.0	9/25/9/7	21/25/20/5	NS
Stent length (mm)	17.7±5.0	17.3±5.0	NS
≤10	3(6)	4(6)	NS
≥20	14(28)	17(24)	NS
Final balloon pressure (atm)	12.0±2.0	12.0±2.0	NS
RD (mm)	2.9±0.5	2.9±0.5	NS
Pre MLD (mm)	0.6±0.4	0.6±0.4	NS
Pre%DS (%)	78.7±13.6	78.8±14.6	NS
Lesion length (mm)	14.1±5.0	13.2±4.0	NS
Post MLD (mm)	2.7±0.6	2.7±0.5	NS
Acute gain (mm)	2.1±0.7	2.1±0.6	NS
Follow up MLD (mm)	2.2±0.7	1.5±1.0	0.0001
Late loss (mm)	0.5±0.5	1.2±0.9	<0.0001

Continuous values are mean±SD. ( ) : %.
LAD=left anterior descending coronary artery; RCA=right coronary artery; LCX=left circumflex artery; ACC/AHA=American College of Cardiology/American Heart Association; RD=reference diameter; MLD=minimum lumen diameter; DS=diameter stenosis.

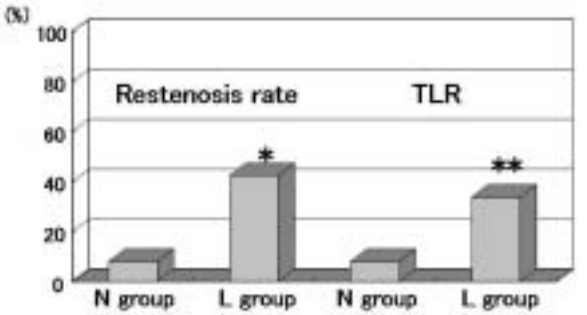

Fig. 1 Relationship between preheparin lipoprotein lipase mass concentration and restenosis
$^{*}p < 0.0001$, $^{**}p = 0.0008$.
L group had a significantly higher incidence of restenosis rate (N group vs L group: 8.0% vs 42.3%) and target lesion revascularization (N group vs L group: 8.0% vs 33.8%) than the N group.
TLR = target lesion revascularization.

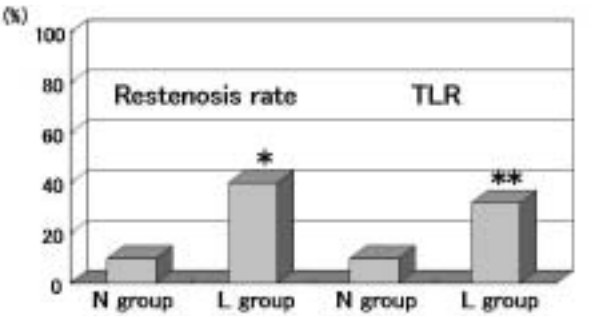

Fig. 2 Relationship between preheparin lipoprotein lipase mass concentration and restenosis in patients without 2.5 mm sized stents
$^{*}p = 0.0009$, $^{**}p = 0.01$.
L group had a significantly higher incidence of restenosis rate (N group vs L group: 9.8% vs 40.0%) and target lesion revascularization (N group vs L group: 9.8% vs 32%) than the N group.
Abbreviation as in Fig. 1.

gain immediately after stenting between the two groups. However, the minimal lumen diameter 6 months after stenting was significantly smaller, and, late loss was significantly higher in the L group. Comparisons of the restenosis rate and target lesion revascularization in the two groups are shown in **Fig. 1**. The L group had a significantly higher restenosis rate and target lesion revascularization than the N group. Small stents are closely associated with restenosis. Therefore, we analyzed only patients without 2.5 mm stents, but the L group still had a significantly higher restenosis rate and target lesion revascularization than the N group as shown in **Fig. 2**.

Results of multiple regression analysis

Restenosis was significantly related with low preheparin LpL mass concentration, reference diameter, diabetes mellitus and hs-CRP concentration. There was no significant relationship with serum lipid concentrations, HOMA-IR and other coronary risk factors, and angiographical data. We performed multiple regression analysis for five factors related with restenosis (reference diameter, diabetes mellitus, hs-CRP concentration and low preheparin LpL mass concentration) and stent type. Only low preheparin LpL mass concentration was an independent factor for restenosis as shown in **Table 4**.

DISCUSSION

The present study found that patients with low preheparin LpL mass concentration had a high restenosis rate or target lesion revascularization although there were no differences in PCI procedure or baseline coronary angiographic characteristics. Furthermore, multiple regression analysis showed that only low preheparin LpL mass concentration was an independent factor for restenosis, which was a subordinate factor.

Relationship between insulin resistance, inflammation and preheparin LpL mass concentration

Insulin resistance is often associated with dyslipidemia such as mild hypertriglyceridemia or low high-density lipoprotein-cholesterolemia, obesity and glucose intolerance.[24–26] In this study, patients with low preheparin LpL mass concentration had these abnormal clinical data associated with insulin resistance, and significantly high HOMA-IR as a marker of insulin resistance. Therefore, we interpret these results as showing that low preheparin LpL mass concentration in patients with stent implantation reflects insulin resistance. However, there was no relationship between restenosis and HOMA-IR, even though preheparin LpL mass concentration was significantly related with restenosis. HOMA-IR is a useful and reliable marker of insulin resistance *in vivo* and stent restenosis may be related to insulin resistance using HOMA-IR.[7,8] However, our results indicate that preheparin LpL mass concentration is a more useful predictive factor for bare-metal stent restenosis than HOMA-IR, even though both markers reflect insulin resistance *in vivo*.

Table 4 Results of multiple regression analysis

	Standard regression coefficient	*t* value	*p* value
Explanatory factor			
Low preheparin LpL mass	0.32	3.6	0.0005
Diabetes mellitus	0.16	1.8	—
Reference diameter	−0.11	−1.3	—
Stent type	0.08	0.8	—
hs-CRP	0.07	0.7	—
Subordinate factor			
Restenosis (Yes=1, No=0)			

R^2=0.20, *F* value=5.4, p=0.002(n=121).
Multiple regression analysis examined four factors including low preheparin LpL mass concentration for the relationship with restenosis (reference diameter, diabetes mellitus, hs-CRP concentration and low preheparin LpL mass concentration) and stent type. Only preheparin LpL mass concentration was an independent variable for restenosis.
Low preheparin LpL mass was defined as less than the mean level of preheparin LpL mass concentration (female 50.6 ng/m*l*, male 39.3 ng/m*l*).
Abbreviations as in Tables 1, 2.

Peroxisome proliferator-activated (PPAR) receptor, PPAR-α or PPAR-γ, in the vascular wall may be associated with inflammation and involved in the pathogenesis of restenosis.[27−29] The link between LpL activity, PPAR-α activation and decreased LpL activity was associated with subsequent downstream effects of PPAR-α, including anti-inflammatory responses,[30] and troglitazone, PPAR-γ activator, increased preheparin LpL mass concentration.[31] Therefore, the link between preheparin LpL mass concentration and hs-CRP concentration may reflect the inflammation caused by decreased PPAR-ligand in coronary artery vessels.

In this study, patients with restenosis had significantly high hs-CRP concentration, indicating that inflammation has an important role in bare metal stent restenosis, at least in patients with low preheparin LpL mass concentration. However, multiple regression analysis showed that only low preheparin LpL mass concentration was an independent factor for restenosis among all factors, including hs-CRP concentration. Therefore, we suggest that low preheparin LpL mass concentration in patients with bare-metal stent restenosis affects factors other than inflammation.

Other factors of preheparin LpL mass concentration as a cause of bare-metal stent restenosis

Nitric oxide (NO) activity affects coronary endothelial function, and has an important role in the pathogenesis of stent restenosis because it decreases the migration and proliferation of vascular smooth muscle cells to attenuate the binding of inflammatory cells to the vascular wall, and inhibits thrombosis by reducing platelet adhesion and aggregation.[32] LpL is reported to increase NO synthetic production and consequentially increase NO production in cultured macrophages.[33] We previously reported that low preheparin LpL mass concentration was closely associated with coronary endothelial dysfunction, estimated by intracoronary administration of acetylcholine,[34] suggesting that low preheparin LpL mass concentration reflects decreased NO in coronary artery vessels, supporting preheparin LpL mass concentration as a predictor of bare-metal stent restenosis.

LpL gene polymorphism is associated with coronary atherosclerosis.[35,36] Recently, examination of the relationship between restenosis, which included about 70% stent use, and LpL gene polymorphism showed that LpL Ser447Ter genotyping may lead to better risk stratification for restenosis.[37] Therefore, low preheparin LpL mass concentration in patients with restenosis may express abnormal LpL gene polymorphism such as decreased LpL Ser447Ter genotyping. However, we did not examine the relationship between preheparin LpL mass concentration and LpL gene polymorphism, so further studies are needed for confirmation.

Strategy for stent implantation by preheparin LpL mass concentration

Plain cut-off levels of preheparin LpL mass concentration could be useful for planning coronary stent implantation. In this study, we divided the subjects into two groups by the mean value of preheparin LpL mass concentration, men, 39.3 ng/m*l* and women, 50.6 ng/m*l*. In another study, we confirmed that the mean values in patients with coronary artery disease were almost the same both in men[16,17,34] and women (unpublished data). Therefore, we recommend values of 40 ng/m*l* for men and 50 ng/m*l* for women for stent implantation in future studies and daily practice. With these cut-off levels, we have two important strategies for stent implantation. First, we can select drug-eluting stent for patients below the cut-off levels and bare-metal stent for those above the cut-off levels. Consequently, we will have good cost benefit and long-term safety. Second, if we perform bare-metal stent implantation for patients less than the cut-off levels for some reason, we also need to increase the preheparin LpL mass concentration immediately. Pioglitazone, an insulin sensitizer, or pitavastatin, a statin, increased LpL activity or preheparin LpL mass concentration.[38−40] These drugs may also reduce intimal proliferation in place of stent implantation.[41,42] Unfortunately, we had no patients taking pioglitazone or pitavastatin in this study. However, good results could be achieved by increasing preheparin LpL mass concentration if these drugs were used aggressively for bare-metal stents. To clarify this hypothesis, further studies are needed to examine the relationship between bare-metal stent restenosis and the effect of these drugs on preheparin LpL mass concentration.

Study limitations

This study has a few important limitations. First, our data sample size is relatively small and we did not select bare-metal stent or drug-eluting stent based on preheparin LpL mass concentration. Therefore, a large number of patients are needed to clarify the significance of preheparin LpL mass concentration as a marker for stent selection from the viewpoint of restenosis rate, cost and safety. Second, we only assessed restenosis by coronary angiography, not by intravascular ultrasound study, which should be analyzed for intimal proliferation in place of stent implantation. Third, we should examine in more detail the low expression of preheparin LpL mass concentration, especially the relationship with genes. Despite these limitations, our data indicate that preheparin LpL mass concentration in serum is closely associated with bare-metal stent restenosis, and preheparin LpL mass concentration may be an important marker for the selection of bare-metal stent or drug-eluting stent.

CONCLUSIONS

Preheparin LpL mass concentration is closely associated with bare-metal stent restenosis and preheparin LpL mass concentration may be one of the important markers when we select bare-metal stent or drug-eluting stent.

要　約

ヘパリン静注前血清リポ蛋白リパーゼ濃度とベアメタルステント再狭窄の関連

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目　的: 近年，感度の良いリポ蛋白リパーゼ蛋白量の測定法の開発によって，ヘパリン静注前の血中に酵素活性を持たないリポ蛋白リパーゼ蛋白(preheparin LpL mass)が存在することが明らかになり，さらに我々は以前，血清preheparin LpL mass濃度の低下が重視すべき冠危険因子であることを報告した．一方，インスリン抵抗性や炎症は，リポ蛋白リパーゼの活性の低下と関係していることが知られているが，これらの因子はまた，ベアメタルステント再狭窄の病態に密接に関係している．そこで今回，ベアメタルステント再狭窄と血清preheparin LpL mass濃度との関連について検討した．

方　法: ベアメタルステント(NIRもしくはS670/660 stent)を留置し6ヵ月後の確認造影を行いえた112症例121病変を対象とした．本研究の平均値のpreheparin LpL mass濃度によりN群(正常preheparin LpL mass濃度群; 50病変)およびL群(低preheparin LpL mass濃度群; 71病変)の2群(カット

オフ値: 男性39.3ng/m*l*，女性50.6ng/m*l*）に分け比較検討した．

結　果: 冠動脈形成術の手技や病変部の血管造影所見に差は認められなかったが，L群はN群に比べて有意に高い再狭窄率や再血行再建率を示した（N群vs L群: 8.0% vs 42.3%，$p < 0.0001$; 8.0% vs 33.8%, $p = 0.0008$）．一方，インスリン抵抗性の指標であるHOMA-IRや高感度C反応性蛋白はN群に比べてL群で有意に高値であったが，重回帰分析の結果，低preheparin LpL mass血症のみが，従属変数である再狭窄率に対する独立した寄与因子として選択された（t値＝3.6，$p = 0.0005$）．

結　論: 血清preheparin LpL mass濃度はベアメタルステント再狭窄と密接な関係を有し，ベアメタルステントと薬物溶出ステントを選択する際の有用な指標になりうる可能性が示唆された．

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