Does Lipoprotein (a) Level Have a Predictive Value in Restenosis after Coronary Stenting?

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ABSTRACT

Objectives: Lipid disorders, lipoproteins, diabetes mellitus, and hypertension are the known risk factors for coronary artery diseases; however, their role is unknown in restenosis after coronary stenting. This study aimed to review the role of these factors, particularly lipoprotein (a) or Lp (a), as a predictive factor for restenosis after coronary stenting with Bare Metal Stent.

Methods: In this study, coronary artery stenting was performed on 170 patients. Follow-up was done using coronary angiography in 128 patients, 6 months after conducting angioplasty. Clinical and biochemical characteristics of the patients were collected as prospective method and were compared between the patients with and without restenosis.

Results: Restenosis was seen in 46 patients (35.9%). Fasting blood glucose level (FBG) in patients with restenosis was significantly higher than patients without restenosis (102.3 ± 39 mg/dl vs. 84.5 ± 28.9 [OR: 1.02, 95% CI: 1.00-1.04]). Lp (a) levels (OR: 0.54, 95% CI: 0.26-1.10) and other biochemical markers and clinical variables had no correlation with restenosis.

Conclusions: Lipoproteins and lipids may not be the underlying cause of restenosis but accurate control of diabetes may improve prognosis after elective coronary stenting.

Keywords: Stent, Restenosis, Lipoprotein (a), Lipid, Diabetes.

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INTRODUCTION

Percutaneous transluminal coronary angiography (PTCA) currently is a proved treatment for coronary artery disease. However, despite advances in this technique, angioplasty restenosis is still considered as a long-term complication in 30-45% of the treated coronary stenosis without stenting.[1-4] Although restenosis would decline to lower levels (20-30%) after Bare Metal Stent BMS replacement, yet it is not in a considerable level.[5,6]

Various parameters have been suggested to be effective on restenosis rate after angioplasty; lipoprotein (a) level [Lp (a)] is one of these; a low-density lipoprotein like LDL in which apolipoprotein A (Apo A) is connected to a disulfide through to the apolipoprotein B (Apo B) through a link. Lp (a) is part of a plasminogen family with potentially atherogenic and thrombotic properties.[7,8] Although Lp (a) has been discussed as an independent risk factor for cardiovascular disease,[9,10] its role would be discussed in restenosis after angioplasty.[11-18]

Most previous studies had been conducted retrospectively based on evaluation of stored blood samples and/or patients with recent myocardial infarction. These potential sources were confounding and moreover, heterogeneity of Lp (a) to some extents were the cause of contradictory results in different studies. The present study, as a prospective study, designed

to evaluate the association between Lp (a), blood glucose and clinical characteristics of patient with incidence of restenosis after artery coronary stenting with BMS.

METHODS

A total of 170 patients, from July 2003 to May 2005, who successfully underwent PTCA and elective coronary artery stenting, entered the study. The exclusion criteria included any prohibition to consume anticoagulant drugs, myocardial infarction during past three months, unstable angina, malignancy, rheumatoid arthritis, inflammatory bowel disease or other serious, and severe diseases. A written consent form was taken from the participants before entering the study.

Angiographic evaluation and coronary intervention was performed through a digital angiography system (Advantx LCV, GE Medical System, Milwaukee, WI).[19] Successful angiography was considered as stent replacement into the target lesion along with thrombosis in myocardial infarction aimed to create coronary blood flow grade III (TIMI flow 3) and residual stenosis of less than 50%.

Angiography film of the patients was reviewed by two cardiologists who were unaware of the blood tests. Seven patients had unsuccessful angioplasty and out of the other 163 patients, 128 patients agreed to repeat angiography for follow-up. The second angiographt was conducted approximately six months after the first angioplasty (mean = 5.4 months). Stenosis of more than 50% in target lesion was considered as restenosis. It should be noted that all the patients were followed-up once a fortnight by phone call and the second angiography could be done earlier due to angina or its equivalents.

Clinical and Laboratory Evaluation

The data about age, sex, body mass index (BMI), smoking habit (more than 10 cigarettes per day), history of lipid disorders, and hypertension of the patients were collected. The blood samples, taken from femoral artery sheath exactly before conducting PTCA and after at least 8 hours of fasting, were analyzed to measure fasting blood glucose (FBG), total cholesterol, high- and low-density lipoprotein-cholesterol (HDL-C and LDL-C), triglycerides (TG), Lp (a), Apo A, and Apo B. The patients' serum was centrifuged. Lipids and blood glucose were evaluated by enzymatic-colorimetric methods. Evaluation of Lp (a) was implemented using enzyme linked immunosorbent assay (ELISA) on fresh blood samples. All tests were performed in Isfahan Cardiovascular Research Center's laboratory.

Statistical Analysis

To analyze univariate data, two methods (t-test or Mann-Whitney test) were used when appropriate. Relative frequency between the two groups with and without restenosis was assessed using chi-square test. To determine predictive value of the related variables to restenosis or re-occlusion (re-blockage), multiple logistic regression method was used. It should be noted that due to frequency distribution of Lp (a) toward lower values inclination, logarithmic values of Lp (a) was used in regression analysis. P-value of less than 0.05 was considered as significant. Statistical analysis was conducted using SPSS for Windows (version 11:0, SPSS Inc., Chicago, IL).

RESULTS

The rate of restenosis in 46 out of 128 patients was 35.9 percent. The rate of restenosis is shown in Table 1, based on coronary artery type. Univariate analysis of underlying characteristics and probable risk factors in incidence of restenosis in 128 patients is presented in Table 2. Among the study variables, only FBG was significantly different between the two groups with and without restenosis.

Table 1. The frequency of restenosis incident based on type of the coronary artery

	No-restenosis group (n = 82)	Restenosis group (n = 46)
LAD	58	38
CX	14	2
RCA	4	2
OM	6	4

LAD: Left anterior descending artery; LCX: Left circumflex artery; RCA: Right coronary artery; OMB: Obtuse marginal branch

Furthermore, logistic regression analysis showed that FBG was a predictive factor in incidence of restenosis (OR, 1.02; 95% CI, 1.00-1.04). However, Lp (a) (OR, 0.54; 95% CI, 0.26-1.10) and other serum parameters, as well as demographic characteristics probably did not have any role in predicting in-stent restenosis after PTCA (Table 3).

DISCUSSION

Various studies have shown that neointimal hyperplasia had an essential role in the incidence of coronary artery restenosis after in-stent restenosis.[20] Neointimal proliferation after coronary stenting probably may be stimulated or activated by some of the biochemical mediators, lipids, lipoproteins and blood glucose.

In this study, plasma lipid levels including Lp (a), Apo A, Apo B, total cholesterol, TG and HDL-C had no association with restenosis after PTCA along with Bare Metal stenting. There is a growing body of evidence about the predictive level of Lp (a) in incidence of restenosis.[11-18] Lp (a) is a substance similar to LDL-C containing Apo A and Apo B, which are connected together with a disulfide bond; this combination would competitively inhibit plasminogen binding in thrombolytic system.[21] Moreover, Apo A and Lp (a) both stimulate the proliferation of the smooth vessel walls of the muscles cells,[22] which would raise their probable role in restenosis after coronary artery stenting.

Most previous investigations had many limitations in studying the role of Lp (a) in reviewing

Table 2. Univariate analysis of the demographic characteristics and probable risk factors in restenosis

	Total (n = 128)	No-restenosis group (n = 82)	Restenosis group (n = 46)	P-value
Age (years)	55 ± 9	55 ± 9	53 ± 8	0.15
Male sex (%)	80(62.5)	54(65.9)	26(56.5)	0.34
Diabetes mellitus n(%)	20(15.6)	11(13.4)	9(19.6)	0.45
Hypertension n(%)	21(16.4)	15(18.3)	6(13.0)	0.62
Dyslipidemia n(%)	52(40.6)	34(41.5)	18(39.1)	0.85
Smokers n(%)	22(17.2)	14(17.1)	8(17.4)	1.0
Family history of CAD n(%)	9(7.0)	5(6.1)	4(8.7)	0.72
Body mass index (Kg/m^2)	26.4 ± 3.6	26.3 ± 3.9	26.6 ± 3.0	0.65
Lipoprotein (a) (mg/dl)	44.2 ± 44.7	51.6 ± 50.9	30.9 ± 26.4	0.15
	24.5(1-183)	30(1-183)	21(1-90)	
Apolipoprotein A (mg/dl)	124.5 ± 37.2	121.7 ± 39.0	129.6 ± 33.5	0.25
	122.5(1-216)	122(1-192)	123(74-216)	
Apolipoprotein B (mg/dl)	128.5 ± 41.8	124.6 ± 34.7	135.4 ± 51.9	0.16
	123.5(14-262)	120(63-238)	127(14-262)	
Total Cholestrol (mg/dl)	221 ± 57	216 ± 56	231 ± 57	0.16
	208(138-439)	208(145-405)	215(138-439)	
HDL-Cholestrol (mg/dl)	37.5 ± 8.9	37.9 ± 8.5	36.7 ± 9.7	0.44
	37(20-56)	39(24-55)	36(20-56)	
Triglycerides (mg/dl)	197 ± 74	189 ± 73	211 ± 75	0.11
	186(90-447)	180(90-447)	202(111-380)	
Fasting blood glucose	90.8 ± 34.2	84.5 ± 28.9	102.3 ± 39.7	< 0.01
(mg/dl)	85(47-198)	77(47-172)	89(52-198)	

Continuous variables are shown as mean ± standard deviation and median (range)
CAD: Coronary artery disease

Table 3. Multiple logistic regression analysis of the probable risk factors of restenosis incidence

	Odds Ratio (95% CI)	P value
Lipoprotein (a) (mg/dl)	0.54(0.26-1.10)	0.09
Apolipoprotein A (mg/dl)	1.01(0.99-1.03)	0.15
Apolipoprotein B (mg/dl)	0.99(0.97-1.02)	0.78
Total Cholestrol (mg/dl)	1.00(0.98-1.02)	0.83
HDL-Cholestrol (mg/dl)	0.93(0.85-1.00)	0.06
Triglycerides (mg/dl)	0.99(0.98-1.01)	0.43
Fasting blood glucose (mg/dl)	1.02(1.00-1.04)	< 0.01

in-stent restenosis including retrospective review,[12,16] blood sampling after PTCA,[11,12,14,16] admission of the patient with recent myocardial infarction[12,14] and using stored samples [23] and all these factors may affect the Lp (a) level. The present study had none of the mentioned limitations. Therefore, it can be concluded that Lp (a), Apo A and Apo B levels are not reliable predictors for restenosis six months after coronary stenting.

Moreover, it seems that Lp (a) plasma level is associated with the number, intensity and length-extension of the coronary lesions[24,25] while the present study did not analyze neither the role of coronary lesion, nor the procedure-based dependent variables. Therefore, more studies are needed to clarify the entire aspects of this issue. Furthermore, finding evidences about direct effects of Lp (a) on thrombosis, fibrinolysis, or restenosis would be problematic due to methodology and ethical considerations. On the other hand, currently there is no medication available to reduce Lp (a) level which does not change LDL-C level. In this study, similar to many other previous investigations,[11,14,26-28] no predictive value was found for total cholesterol, HDL-C, and TG levels in incidence of restenosis after angioplasty. The association between diabetes and restenosis is documented in some of the previous studies[29-31] while such an association was not found in some of the other studies.[32-34]

In the present study, frequency distribution of restenosis was not statistically significant among the diabetic and non-diabetic patients; however, FBG showed a close association with restenosis after coronary stenting with BMS. This finding might be due to accurate controlling of blood glucose in a group of the patients with diabetes in the present study.[35]

However, it can be concluded that poor control of diabetes can aggravate the prognosis of patients after coronary stenting. Its mechanism of action might be due to an increase in the neointimal hyperplasia caused by stimulatory effect of the growth factors.[29] The role of major cardiovascular risk factors, e.g. age, sex, hypertension and smoking in incidence of restenosis after coronary artery stenting is still controversial.[36-39] Although differences in univariate analysis were not significant in this study, further prospective studies with more accurate quantitative assessment, particularly about the role of hypertension and smoking, is recommended.

It can be concluded that among the known cardiovascular disease risk factors, only blood glucose level can have a predictive value in incidence of restenosis after coronary stenting.

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