Correlation of Serum Lipoprotein(a) with the Clinical Presentation of Thai Coronary Artery Disease Patients

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Abstract

Elevated serum levels of lipoprotein(a) [Lp(a)] confer and increased risk of coronary artery disease (CAD) and have been confirmed as a strong and independent risk factor for this disease. This case-control study was to determine the significance of elevated Lp(a) levels for the existence of CAD by systematically recording cardiovascular risk factors in diagnostic coronary angiography in a group of patients. Two hundred thirty seven consecutive patients (175 men, 62 women, aged 61±10 years) which comprised 24 acute myocardial infarction (AMI), 76 unstable angina (UA) and 137 stable angina (SA) who underwent coronary angiography, were used as cases. One hundred seventy normal healthy volunteers (95 men, 75 women, and aged 58±15 years) were used as controls. Lp(a) concentration were measured by an immunoturbidimetric method (Roche Diagnostics, Switzerland). There was a significant difference between Lp(a) levels in UA compared with the control subjects (44.2±49.0 vs. 27.6±25.3 mg/dL, p = 0.0006). When we compared SA and the control group (35.6±31.3 vs. 27.6±25.3 mg/dL, p = 0.0139) there was a significant difference between these two groups. UA patients also had a significantly higher prevalence of abnormal Lp(a) (>30 mg/dL) compared with the normal healthy control group (43.2% UA vs. 28.8% control, OR = 1.90, 95%CI = 1.08 – 3.32, p = 0.0248). SA patients also had the same finding as UA patients in a higher prevalence of abnormal Lp(a) when compared with the control group (45.2% SA vs. 28.8% control, OR = 2.04, 95%CI = 1.27 – 3.27, p = 0.0028). These data further support the role of Lp(a) in atherosclerotic coronary disease and the pathogenesis of acute coronary syndromes.

Key word : Serum Lp(a), CAD, Thailand

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Lipoprotein(a) [Lp(a)] is considered an independent risk factor for premature cardiovascular disease[1]. Many prospective and case control studies identified elevated levels of Lp(a) as a factor associated with the development of myocardial infarction and the presence of coronary, carotid and peripheral vascular atherosclerosis[2-4]. Lp(a) resembles low density lipoprotein (LDL) in its high cholesterol content and in the presence of 1 molecule of apolipoprotein(apo) B. The additional protein in Lp(a) is called apo(a) and contains a protease domain, a kringle V-like domain, and a variable number of kringle IV repeats, all of which have strong structural homologies to plasminogen[5]. The unique structural features of Lp(a) suggest thrombogenic and atherogenic potential, although the precise mechanism of its action is still uncertain. The pathogenesis of unstable angina is mainly related to plaque disruption, which has been associated with the local activity of macrophages[6]. An apo(a) portion of unoxidized Lp(a) induces monocytes chemotactic activity in human coronary and umbilical vein endothelial cells[7]. Oxidized Lp(a) has been shown to enhance *in vitro* adhesion of human monocytes to cultured endothelial cells. These data indicate that Lp(a) may be an attractant of macrophages in the atheromatous plaque and may lead to progressive luminal obstruction[8]. We hypothesized that Lp(a) may be involved in the process of repetitive rupture and healing of the plaque and the development of a totally occluded coronary artery. The present study investigated this hypothesis by evaluating serum Lp(a) levels in patients with unstable and stable angina.

MATERIAL AND METHOD

Patients and angiographical examination

A study population was 237 patients (175 men, 62 women, with mean age 61±10 years) consecutively underwent coronary angiography. These comprised 24 acute myocardial infarction (AMI), 76 unstable angina (UA) and 137 stable angina (SA). Reasons for the examination were the confirmation of clinically suspected coronary artery disease (CAD) with regard to a percutaneous transluminal coronary angioplasty (PTCA) or a surgical coronary intervention, as well as the exclusion of significant CAD in the presence of unclear cardiac symptoms. Two independent experienced researchers using the conventional base of the number of involved vessels quantified the angiographic findings. One hundred seventy normal healthy volunteers (95 men, 75 women, with mean age 58±15 years) were used as controls. Within the framework of the clinical examination, the patients and the controls were questioned about their family histories. The diagnosis of hypertension was not reached on the basis of sporadically measured blood pressure values, but on the basis of the previous histories, medications and medical records. Likewise, the diagnosis of diabetes mellitus was reached through the evaluation of blood sugar values, daily profiles, the current medication, and the previous histories. Smoking behavior was recorded according to the beginning, the end and the quantity of nicotine consumption.

Measurement of Lipoprotein Levels

Immediately before coronary angiography examinations, blood was taken from the patients after a minimum of 12-h fast for laboratory lipid determination. In controls, blood was also taken after a minimum 12-h fast. Total cholesterol and triglycerides were measured with enzymatic assays and HDL-cholesterol was measured by homogeneous immunoassay (Roche Diagnostics, Switzerland) on a Hitachi autoanalyzer. LDL-cholesterol was calculated with the Friedewald formula. Serum Lp(a) concentrations were measured by the immunoturbidimetric method from Roche Diagnostics, Switzerland.

Statistical Analysis

We used chi-square test and student's *t*-test to evaluate the categorical and continuous variables, respectively. We calculated odds ratios (ORs) plus 95 per cent confidence intervals (CIs) to evaluate the association of AMI, UA and SA with the prevalence of Lp(a) more than 30 mg/dL. EpiInfo software from the Center for Disease and Control (CDC) was used for calculation.

RESULTS

There were no significant differences in demographic, clinical and laboratory values between patients and the control group except patients (AMI, UA and SA) had significantly lowers HDL-cholesterol levels than the control group (Table 1). There was a significant trend of increasing Lp(a) levels: 27 mg/dL for the control group, 35 mg/dL for SA and 44 mg/dL for UA, but in AMI the level of Lp(a) was not significantly high when compared with the con-

Table 1. Demographic data of patients and controls.

	AMI (n=24)	UA (n=76)	SA (n=137)	Control (n=170)
Age	61 ± 12.4	62 ± 9.2	61 ± 10.3	58 ± 17.8
Male gender	17(71)	52(68)	106(77)	95(57)
Diabetes mellitus	12(50)	32(42)	53(39)	48(28)
Hypertension	11(46)	36(47)	74(54)	52(31)
Smoking	10(42)	43(45)	61(45)	73(49)
Total cholesterol (mg/dL)	201 ± 52	216 ± 52	207 ± 45	213 ± 43
Triglycerides (mg/dL)	130 ± 42	159 ± 76	154 ± 81	170 ± 108
HDL-C (mg/dL)	34 ± 9*§	39 ± 11 §	40 ± 10 *§	46 ± 11 §
LDL-C (mg/dL)	140 ± 47	144 ± 45 *	135 ± 39	133 ± 41 *
Lp(a) (mg/dL)	29 ± 26	44 ± 49 ¶	35 ± 31 *	27 ± 25 *¶

* $p < 0.05$; ¶ $p < 0.005$; § $p < 0.0001$

Table 2. The odd ratio and 95% confidence interval of AMI, UA and SA compared with control when Lp(a) level more than 30 mg/dL.

	Lp(a) > 30 mg/dL		
	N (%)	OR (95% CI)	p value
AMI	8/21 (33)	1.65 (0.65 – 4.31)	NS
UA	33/76 (43)	1.90 (1.08 – 3.32)	0.0248
SA	62/137 (45)	2.04 (1.27 – 3.27)	0.0028
Control	49/170 (29)	1	-

Table 3. The odd ratio and 95% confidence interval of one vessel disease compared with two vessel and three vessel disease when Lp(a) level more than 30 mg/dL.

	Lp(a) > 30 mg/dL		
	N (%)	OR (95% CI)	p value
One vessel	40/80 (50)	1.45 (0.72 – 2.92)	NS
Two vessels	22/52 (42)	1.07 (0.55 - 2.10)	NS
Three vessels	41/105 (39)	1.56 (0.87 – 2.81)	NS

trol. UA and SA patients had a significantly higher prevalence of abnormal Lp(a) (> 30 mg/dL) compared with the control group (Table 2). The OR of UA compared with the control was 1.90 and 95% CI = 1.08 – 3.32, p = 0.0248 and the OR of SA compared with the control group was 2.04 and 95% CI = 1.27 – 3.27, p = 0.0028. In the case of AMI there were no significant differences when compared with the control group, OR = 1.65 and 95% CI = 0.65 – 4.31, p > 0.05. A total of 237 CAD patients consisted of 80 patients with one-vessel disease, 52 patients with two-vessel disease and 105 patients with three-vessel disease. The prevalence of Lp(a) more than 30 mg/dL in one-, two- and three-vessel disease are shown in Table 3. There was no significant difference between these groups.

DISCUSSION

The aim of the present study is to report an association between Lp(a) and clinical presentation or the severity of CAD by related to the number of disease vessels. This role of Lp(a) in the develop-

ment of occluded arteries was implied previously by the association of elevated serum Lp(a) with rapid angiographic progression of coronary disease (9). The mechanism of coronary atherosclerosis and occlusion was the incorporation of mural thrombus into the arterial wall leading to increasing luminal obstruction(10). The authors did not document increased serum Lp(a) in patients with single-vessel disease compared with those with two- or three-vessel disease, like some studies and unlike other studies(11,12).

The association of Lp(a) with the clinical syndrome of UA and SA provides additional support for the role of Lp(a) in plaque disruption and intracoronary thrombosis. Dangas G et al previously reported the presence of Lp(a) in human coronary atheroma(12). Lp(a) was found in greater distribution in plaques of patients with unstable compared with stable angina. Our present data demonstrated the association between serum Lp(a) levels and clinical presentation of CAD as previously reported by other investigators(11,13).

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ความสัมพันธ์ระหว่างระดับซีรั่มไลโปโปรตีน(เอ) กับชนิดของผู้ป่วยโรคหลอดเลือด-แดงโคโรนารี่ในประเทศไทย

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การเพิ่มสูงขึ้นของระดับซีรั่มไลโปโปรตีน(เอ) ทำให้อัตราเสี่ยงในการเกิดโรคหลอดเลือดแดงโคโรนารี่เพิ่มขึ้นและถือได้ว่าเป็นปัจจัยเสี่ยงอิสระของโรคนี้ สำหรับประเทศไทยข้อมูลด้านนี้ยังมีการศึกษาน้อยมาก คณะผู้วิจัยจึงทำการศึกษาถึงความสัมพันธ์ระหว่างระดับซีรั่มไลโปโปรตีน(เอ)กับผู้ป่วยโรคหลอดเลือดแดงโคโรนารี่ชนิดต่างๆรวม 237 ราย (ผู้ชาย 175 ราย, ผู้หญิง 62 ราย, อายุเฉลี่ย 61 ± 10 ปี)ที่ทำการตรวจสวนหลอดเลือดหัวใจ ประกอบด้วยผู้ป่วยกล้ามเนื้อ-หัวใจตายเฉียบพลัน (acute myocardial infarction, AMI) 24 ราย ผู้ป่วยเจ็บหน้าอกแบบไม่เสถียร 76 ราย และผู้ป่วยเจ็บหน้าอกแบบเสถียร 137 ราย เปรียบเทียบกับคนปกติจำนวน 170 ราย (ผู้ชาย 95 ราย, ผู้หญิง 75 ราย, อายุเฉลี่ย 58 ± 15 ปี) การตรวจวัดระดับไลโปโปรตีน(เอ) ทำโดยวิธีอิมมูโนเทอบิดดิเมตริก (โรชไดแอกโนสติกส์, สวิตเซอร์แลนด์) พบว่าระดับของซีรั่มไลโปโปรตีน(เอ)ในผู้ป่วยเจ็บหน้าอกแบบไม่เสถียรมีค่าสูงกว่าในคนปกติอย่างมีนัยสำคัญทางสถิติ (44.2 ± 49.0 กับ 27.6 ± 25.3 มก/ดล, พี = 0.0006) ในผู้ป่วยที่มีอาการเจ็บหน้าอกแบบเสถียรพบว่าระดับซีรั่มไลโปโปรตีน (เอ) มีค่าสูงกว่าในกลุ่มคนปกติอย่างมีนัยสำคัญทางสถิติเช่นกัน (35.6 ± 31.3 กับ 27.6 ± 25.3 มก/ดล, พี = 0.0139) เมื่อลองหาอุบัติการณ์ของการมีระดับซีรั่มไลโปโปรตีน(เอ)สูงกว่า 30 มก/ดล ในผู้ป่วยเจ็บหน้าอกแบบไม่เสถียรเทียบกับในกลุ่มอาสาสมัครสุขภาพดีพบว่าอุบัติการณ์ของการมีระดับซีรั่มไลโปโปรตีน(เอ)สูงกว่า 30 มก/ดล มีสูงกว่าอย่างมีนัยสำคัญทางสถิติ (43.2% กับ 28.8%, OR = 1.90, 95%CI = 1.08 – 3.32, พี = 0.0248) ปรากฏการณ์นี้พบเช่นเดียวกันในผู้ป่วยเจ็บหน้าอกแบบเสถียรโดยพบอุบัติการณ์ 45.2% เทียบกับคนปกติ ซึ่งพบเพียง 28.8% (OR = 2.04, 95%CI = 1.27 – 3.27, พี = 0.0028) โดยสรุปคณะผู้วิจัยเชื่อว่าไลโปโปรตีน(เอ)น่าจะมีส่วนในการเกิดภาวะหลอดเลือดแข็งตัวและนำไปสู่การเกิดโรคหลอดเลือดแดงโคโรนารี่ในที่สุดซึ่งแป็นปัญหาที่พบบ่อยในประเทศไทยเช่นเดียวกับประเทศทางตะวันตก

คำสำคัญ : ซีรั่มไลโปโปรตีน(เอ), โรคหลอดเลือดแดงโคโรนารี่, ประเทศไทย

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