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Age-related Contribution of Lp(a) with Coronary Artery Calcification in Patients with Acute Coronary Syndrome: a Potential Role of Metabolic Disorder in Calcified Plaque

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Lp(a) and coronary artery calcification (CAC) have recently been reported as predictors of plaque instability, but this is surrounded by much controversy. We investigated the influence of Lp(a) and CAC compared other acute coronary syndrome (ACS) risk factors. 698 patients diagnosed with at least minimal coronary artery obstructive disease from a coronary angiography were randomly selected using SPSS.

Lp(a), other lipid profiles and past histories were checked, and CAC semi quantitatively graded on stored fluoroscopic images. The prevalence of CAC was significantly higher in the ACS than the non-ACS group (38.0% vs. 29.9%, p=0.026). The serum level of Lp(a) (26.89± 30.64 vs. 20.85 ± 21.63, p<0.01) and prevalence of positive Lp(a) (>35 mg/dl) was higher in the ACS group (24% vs. 15.7%, p<0.01). The risk of ACS was higher in the patients with both CAC and elevated an Lp(a) than in those with only one (OR: 2.16, p=0.009, 95% CI; 1.213 - 3.843 vs. OR: 1.79, p<0.001, 95% CI; 1.300 - 2.456). The risk of ACS was increased 1.451 times (p=0.040, 95% CI; 1.071 - 2.071) in patients with CAC and 1.648 times (p=0.014, 95% CI; 1.107 - 2.455) in patients with a Lp(a)>35 mg/dl. In the younger patients (<60 years), the Lp(a), but not the CAC, was an independent risk factor for ACS (OR=2.248, p=0.005, 95% CI; 1.281-3.943). In the older patients (> 60 years), CAC, but not the Lp(a), was an independent risk factor (OR=1.775, p=0.021, 95% CI; 1.090 - 2.890). Both the Lp(a) and CAC were risk factors for ACS, and they had a synergistic effect on its development. In the younger Lp(a), and the older CAC, was the more potent risk factor for ACS, respectively.

Key Words: Acute coronary syndrome, Lp(a), coronary artery calcification.

INTRODUCTION

Coronary calcium is a part of atherosclerosis, and its levels relate to the extent of atherosclerosis, but its correlation with plaque instability is still controversial.[1-3] The Lipoprotein(a) [Lp(a)] molecule consists of a low density lipoprotein particle linked to apoprotein(a) [apo(a)]. Apo(a) is a glycoprotein of variable size,[4] which shares remarkable structural homology with plasminogen.[5-7] Lp(a) has been implicated in the regulation of the expression of plasminogen activator inhibitor-1 in endothelial cells, and has been shown to inhibit endothelial cell surface fibrinolysis, attenuate plasminogen binding to platelets and bind to plaque matrix components.[8-10] Therefore, Lp(a) is an atherogenic, and thrombogenic, lipoprotein, which has been implicated in the pathogenesis of acute coronary syndromes (ACS). It is also associated to inflammatory reactions, including the recruitment of macrophage.[11] With its potential role in atherothrombosis, Lp(a) is thought to be a risk factor for coronary artery calcification (CAC), and plays a role in the instability of plaque in calcified lesions. However, a previous study

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reported there was no significant correlation between CAC and Lp(a),[12] although there have been no studies on the synergistic effects of these two risk factors on plaque instability.

This study investigated whether CAC and Lp(a) were independent risk factors for ACS, and looked at their age related effects on ACS.

MATERIALS AND METHODS

Subjects

The subjects were randomly selected by sampling of the patients referred for coronary angiography, due to chest pains or other clinically suspected CAD, between January 1997 and November 2000. The study groups consisted of 698 patients with at least minimal coronary artery obstructive disease (minimal disease: 29.5%, 1-vessel disease: 28.7%, 2-vessel disease: 17.9%, 3-vessel disease: 22.3%, left main disease: 1.6%). The subjects were divided into two groups, those with, or without, ACS. Patients with unstable angina, an acute or old MI and post MI angina, were included in the ACS group (Table 1).

The following three criteria may be said to be unstable angina pectoris: 1) newly onset (<2 months) severe and/or frequent angina (3 episodes per day); (2) accelerating angina, i.e., those with chronic stable angina who developed frequent, severe, prolonged angina, or that precipitated by less exertion than previously; (3) angina at rest. For unstable angina group, the MB fraction of creatinine kinase (CK-MB) and Troponin-T levels were within normal range. The average age, sex and levels of major CAD risk factors of the two groups are detailed in Table 1.

Table 1. Clinical Characteristics of Patients, and the Results of Laboratory Data and Coronary Artery Calcification Measurements

	Total (n=698)	Non ACS (n=364)	ACS (n=334)	*p*-value
CAC (+), %(n)	33.8% (225/666)*	29.9% (103/345)	38.0% (122/321)	0.026
G1	36.9% (83)	36.9% (38)	36.9% (45)	
G2	49.8% (112)	46.6% (48)	52.5% (64)	
G3	13.3% (30)	16.5% (17)	10.6% (13)	
Lp(a) mg%	23.74 ± 26.48	20.85 ± 21.63	26.89 ± 30.64	0.003
Positive Lp(a)	19.6% (137)	15.7%(57)	24.0%(80)	0.006
Male (%)	63.3% (442)	56.3% (205)	71.0% (237)	<0.001
Age (years)	59.35 ± 9.79	59.68 ± 9.45	58.99 ± 10.15	0.348
LDL (mg/dl)	125.60 ± 36.82	124.57 ± 35.17	126.68 ± 38.50	0.484
Hypertension, %(n)	47.7% (333)	51.4% (187)	43.7% (146)	0.051
DM, %(n)	22.8% (159)	23.9% (87)	21.6% (72)	0.488
Smoking, %(n)	43.0% (298)	32.8% (119)	60.1% (179)	0
Obesity, %(n)	5.6% (39)	6.0% (22)	5.1% (17)	0.603
Angiography, %(n)				
Minimal	29.5% (206)	44.8% (163)	12.9% (43)	
1VD	28.7% (200)	21.7% (79)	36.2% (121)	
2VD	17.9% (125)	13.7% (50)	22.5% (75)	
3VD	22.3% (156)	17.9% (65)	27.7% (91)	
Left main	1.6% (11)	1.9% (7)	1.2% (4)	

Obesity: BMI > 30kg/m^2.
ACS, Acute Coronary Syndrome.
Continuous variables are expressed as mean ± SD.
*In 666 patients, CAC was defined and in the others, CAC was undetermined.

Coronary angiography and calcification detection

Coronary angiography was performed using the standard Judkin's technique. All subjects had undergone digital cardiac fluoroscopy for the detection of CAC. Digital fluoroscopy was performed with a 60° left anterior oblique projection, while the patient held their breath for between 2 and 5 seconds. The fluoroscopic images were digitized, on-line, and processed using a digital cardiac imaging unit (Philips Medical Systems; Integris II). The pixel matrix format was 512 × 512. A mask image was acquired over 5 frames immediately prior to a run of between 15 and 20 frames at 15 frames/second. A cardiologist, blinded to clinical and angiographic data, visually interpreted the fluoroscopic studies, and identified any presence of calcification in the major epicardial arteries. Two independent observers reviewed the images, and semi-quantitatively evaluated them using the following visual grading system; grade 0- no calcific deposit in the arteries, grade 1- scanty and discrete calcific deposit, grade 2- definite, but discrete calcific deposits, and grade 3- containing calcific deposit throughout most of the proximal 2 cm of the arteries. CAC was defined as definite CAC at a culprit lesion.

Blood sampling and lipid analyses

Fasting venous blood samples were collected into EDTA tubes. Standardized enzymatic methods were used to analysis the serum total cholesterol, HDL cholesterol and triglycerides. The LDL cholesterol was calculated using the Friedewald equation. The Lp(a) was analyzed for in freshly isolated sera by electroimmunodiffusion, using the IgG-fraction of specific rabbit anti-Lp(a)- antisera, from Behringwerke (Marburg, Germany), with a cut-off point for a positive result of 35 mg/dl.

Statistical analysis

Independent sampled t- and chi-square test analyses were performed to examine differences in the demographic data, including the major risk factors for CAD between the ACS and non-ACS groups. Obesity was defined as a body mass index (BMI) over 30 kg/m^2.

To determine the significant and independent risk factors for unstable angina, all risk factors were analyzed by multivariate analyses. Included risk factors were as follows: age, Lp(a), hypertension, smoking, diabetes (DM), BMI and presence of CAC.

RESULTS

Comparison of patients' characteristics between two groups

The average age of the patients was 59.35 ± 9.79 years, with 442 (63.3%) male and 256 (36.7%) female subjects. In 666 patients, CAC was determined. The prevalence of coronary artery calcification (CAC) was 33.8% (n=225/666). CAC was more frequent in patients with ACS than in those without (38.0% vs. 29.9%, p=0.026), but there was no significant difference in the severity of CAC. The serum Lp(a) levels (26.89 ± 30.64 vs. 20.85 ± 21.63, $p<0.01$), and prevalence of positive Lp(a) (>35 mg/dl), were higher in the ACS group (24.0% vs. 15.7%, $p<0.01$). The prevalence of males and smokers were significantly higher in the ACS group (Table 1).

Analysis of risk factors for coronary artery calcification

The patients with CAC were older than those without (63.25 ± 9.06 vs. 57.57 ± 9.54, $p<0.001$). Furthermore, the frequencies of male (68.9% vs. 62.8%, p=0.04) and DM (32.7% vs. 19.4%, $p<0.01$) patients were higher in the CAC group. From a binary logistic multiple regression analysis, age (OR=1.075, $p<0.001$), male sex (OR=1.773, p=0.011) and DM (OR=2.102, $p<0.001$), were independent risk factors. The serum Lp(a) level was higher in the CAC group, but had no statistical significance (26.99 ± 31.92 vs. 22.41 ± 23.80 mg/dl, p=0.058). From a binary multiple regression analysis, the Lp(a) level was an independent risk factor for CAC (OR=1.006, p=0.045, 95% CI; 1.000-1.013), but, when the patients were divided into two groups according to their Lp(a) levels, with the cut off level of 35 mg/dl, a high Lp(a) level

was not an independent risk factor for CAC (OR=1.256, p=0.289) (Table 2). 36.9% (n=83/225) of CAC group was grade 1, 49.8% (n=112/225) was grade 2, and 13.3% (n=30/225) was grade 3 (Table 1). There was no significant difference in the Lp(a) level according to the severity of CAC (grade 1; 27.2 ± 38.5, grade 2; 25.6 ± 24.0, grade 3; 32.9 ± 38.8 p=0.546, One way ANOVA).

Analysis of risk factors for acute coronary syndrome

A positive Lp(a) (>35 mg/dl) was associated with an odds ratio of 1.648 (p=0.014, 95% CI; 1.107 - 2.455), and the presence of CAC was associated with an odds ratio of 1.451 (p=0.04, 95% CI; 1.071 - 2.071), for ACS. In smokers the risk of ACS was 2.168 times higher than in non-smokers (p<0.01, 95% CI; 1.473 - 3.191) (Table 3).

Synergistic effect of CAC and Lp(a) on acute coronary syndrome

In patients with a CAC and an elevated Lp(a)(> 35 mg/dl) the risk of ACS was increased as much as 2.16 times (p=0.009, 95% CI; 1.213 - 3.843) that of patients without CAC and an elevated Lp(a). However, for the cases with only CAC or an elevated Lp(a), the risk of ACS was increased as much as 1.79 times (p<0.001, 95% CI; 1.300 - 2.456), indicating a potential synergistic effect of elevated Lp(a) and CAC on the development of ACS.

Table 2. Comparison of Factors Associated with Coronary Artery Calcification

	OR	p-value	95% C.I.
Age, year	1.075	<0.001	1.054 - 1.097
Lp(a), mg/dl	1.006	0.045	1.000 - 1.013
Male sex	1.773	0.011	1.140 - 2.756
DM	2.102	<0.001	1.417 - 3.121
Obesity	0.692	0.368	0.310 - 1.544
Hypertension	0.904	0.583	0.631 - 1.295
Smoking	1.217	0.357	0.801 - 1.850

Binary logistic multiple regression.
OR, Odds ratio; C.I., Confidence interval; Obesity, BMI > 30 kg/m^2.

Table 3. Analysis of Relative Risk Factors for Acute Coronary Syndrome

	OR	p-value	95.0% C.I.
Age	0.996	0.665	0.979 - 1.014
Coronary calcium	1.451	0.04	1.071 - 2.071
Lp(a)	1.648	0.014	1.107 - 2.455
Hypertension	0.81	0.21	0.583 - 1.126
Male	1.126	0.561	0.755 - 1.679
Smoking	2.168	< 0.001	1.473 - 3.191
DM	0.901	0.589	0.616 - 1.317
Obesity	1.056	0.875	0.535 - 2.082

Binary logistic multiple regression.
OR, Odds ratio.

Changes of weight of risks according to aging

In the younger age group (≤ 60 years old), CAC was not an independent risk factor for ACS, but Lp(a) was, a significant independent risk factor for ACS (OR=2.248, p=0.005, 95% CI; 1.281-3.943). Conversely, in the older age group (>60 years old), CAC increased the risk of ACS independently (OR= 1.775, p=0.021, 95% CI; 1.090 - 2.890), but Lp(a) did not influence the risk of ACS significantly (Fig. 1 and Table 4).

DISCUSSION

From our study, both the Lp(a) and CAC were significant and independent risk factors of acute coronary syndrome. The Lp(a) was a more potent risk factor in the younger subjects, and CAC was a more potent risk factor in the older patients, with synergistic effects on ACS.

Recent studies have suggested that ACS, including myocardial infarction and unstable angina, usually arises from the disruption of mildly stenosed atherosclerotic lesions.[13,14] Postmortem studies have reported that the mildly stenosed are

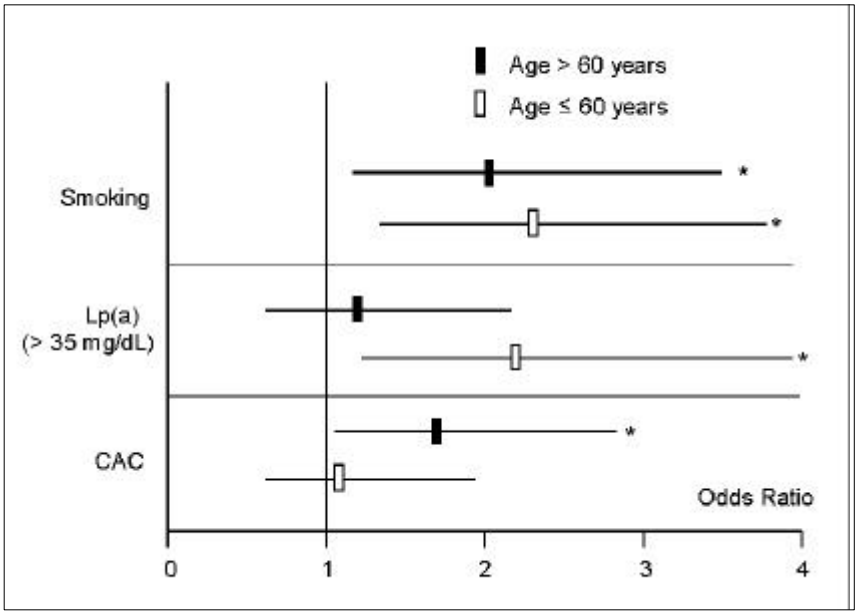

Fig 1. Changes of relative risks for ACS according to age. *p< 0.01. CAC, Coronary artery calcification.

Table 4. Comparison of Relative Risks for ACS According to Age

	Age ≤ 60 years			Age > 60 years		
	OR	p-value	95.0% C.I.	OR	p-value	95.0% C.I.
Coronary calcium	1.158	0.572	0.696 - 1.927	1.775	0.021	1.090 - 2.890
Lp(a)	2.248	0.005	1.281 - 3.943	1.183	0.574	0.658 - 2.126
Hypertension	0.78	0.281	0.496 - 1.225	0.89	0.639	0.547 - 1.448
Male	1.148	0.64	0.644 - 2.044	1.101	0.736	0.630 - 1.924
Smoking	2.272	0.002	1.335 - 3.865	2.007	0.02	1.117 - 3.605
DM	1.169	0.556	0.694 - 1.969	0.681	0.185	0.386 - 1.202
Obesity	1.461	0.436	0.563 - 3.792	0.729	0.546	0.261 - 2.036

Binary logistic multiple regression.
OR, Odds ratio.

more frequently disrupted, and the vulnerability of plaque is associated with the inflammation and thinning of the fibrous cap at the shoulder of the plaque.[15,16] Some studies have reported that CAC has a stabilizing force of the plaque with this mechanism. However, recent clinical studies have reported CAC be a risk factor for ACS.[17,18] It has been suggested that CAC does not increase the risk of plaque rupture, as it does not weaken the plaque's resistance to hoop stresses. If anything, CAC should increase the resistance to circumferential hoop stresses. However, instability is expected to be induced by calcium deposits through dramatically increased solid shear stresses along the sharp interface, where the pulsating, compliant, soft tissue meets the mineral. This interface is known as a site of plaque rupture during balloon angioplasty,[19] and previous studies have suggested that CAC is more likely a feature of advanced obstructive coronary atherosclerosis. Therefore, increasing CAC is likely to be related to an increased atherosclerosis burden, and a risk of cardiovascular events.

Coronary calcium is intimately associated with coronary atherosclerotic plaque development. The use of electron-beam computed tomography (EBCT), for accurate quantitative measurements, has led to an increased interest in understanding the clinical importance of coronary calcium, particularly in terms of its ability to identify unstable coronary plaques underlying clinically ACS. Histopathological studies have demonstrated that calcium is a frequent feature of ruptured plaques, but the presence, or absence, of calcium does not allow for reliable distinction between unstable or stable plaques. This issue is complicated by the lack of a prospective definition of "unstable". A plaque rupture is sometimes found in apparently healthy subjects and in patients with a clinically stable disease. Coronary atherosclerosis is a systemic coronary disease process. Imaging of coronary calcium, although unable to identify a localized unstable plaque, can potentially identify the more clinically pertinent "unstable patient". Almost all patients with a recent ACS have measurable coronary calcium, because moderate-to-advanced coronary plaque disease is already present, although an obstructive disease is frequently not. Prospective studies have demonstrated that extensive coronary calcium, detected by EBCT, is associated with a significantly increased incidence of subsequent myocardial infarction, need for revascularization and coronary death. The incremental prognostic value of coronary calcium, compared to that of risk factor assessment, remains to be fully defined. The occurrence of an ACS is determined by many factors other than from the extent of an atherosclerotic plaque disease. Large prospective trials, on the general population, are needed to define the subgroups that will benefit most from a quantitative assessment of coronary calcium.[20]

Many studies have reported a relationship between Lp(a) and coronary heart disease (CHD). Data from 3,103 women in the Framingham Heart Study showed that elevated Lp(a) was a strong, independent predictor of myocardial infarction, intermittent claudication, cerebrovascular disease and total coronary heart disease.[21] However, other studies that have shown a lack of association between Lp(a) and CHD.[12,22] In short, Lp(a) has a weak correlation with early CHD, but a strong correlation with the severe disease involving a plaque rupture and thrombotic event. Perhaps the lack of association betwAeen Lp(a) and the markers of early CHD could be explained by Lp(a) acting substantially through its antifibrinolytic activity. On reviewing a previous study, Lp(a) was found to have a different action on CHD that related to age. Bostom, et al. reported that elevated plasma Lp(a) was an independent risk factor for the development of premature CHD, as measured by the cardiac events in 2,191 young to middle aged men.[23] Conversely, Simon et al. reported that Lp(a) was not significantly increased in 1,202 male and 1,512 female CHD subjects > 60 year.[24] Similarly to previous studies, we found that Lp(a) was a more potent risk factor for ACS in patients < 60 years. This is related with increment of age, where other risks for increasing ACS and their relative potency may be decreased.

Farzaneh-far, et al. suggested that apoptosis of either vascular smooth muscle cells or macrophage was a crucial initiating event in vascular calcification, and that once an initial nucleation site had been established, apatite crystal growth can occur.[25] Mitochondria, lipids and collagen are

thought to promote this crystal growth. Previous studies suggested that Lp(a) may be an attractant of macrophages in atheromatous plaques.[11,26-28] Furthermore, it has an association with smooth muscle cell proliferation.[29] Therefore, Lp(a) may promote the initiation of calcification, and as a kind of lipoprotein, it is thought to be a promoting factor of crystal growth. In these mechanisms, we hypothesized that Lp(a) is a risk factor for CAC. However, in two previous clinical studies, no correlation between CAC and Lp(a) was proved.[12,30] From our study, we found a tendency for an increased risk of CAC with higher levels of Lp(a), but only with a weak statistical significance (p=0.058).

In atherosclerosis, intimal macrophages and vascular smooth muscle cells express both collagenous (collagen type I and IV) and noncollagenous bone matrix proteins (matrix gamma carboxyglutamate protein, osteopontin, osteonectin, osteoglycin and bone morphogenic protein). The association of intimal calcification with lipids, apoptotic cells and matricellular proteins, suggests that the intimal calcification is an active, rather than a degenerative process.[31,32] Some evidence raises concern over the role of warfarin in cardiovascular calcification. The small protein matrix, GLA protein (MGP), is thought to serve as an inhibitor of soft tissue calcification, possibly through an inhibitory interaction with BMP-2.19 GLA proteins, including coagulation cascade factors, which unusual have a post-translational carboxylation of certain glutamic acid residues, a modification thought to be important in its function. The carboxylase responsible for this modification is vitamin K dependent. Because warfarin interferes with vitamin K-dependent enzymes, it is theoretically possible that treatment with it, or dietary vitamin K deficiency, may increase the risk of vascular calcification by reducing the mineral-inhibitory activity of MGP.[33] Atherosclerotic processes inhibit the synthesis and/or activity of gamma-glutamic carboxylase, which potentially explains why atherosclerotic arteries contain only about 30% of the carboxylase activity found in normal arterial segments.[34] Recent studies have demonstrated that atherosclerosis involves cells with a special embryonic lineage.[35,36] CAC can be expected, not merely to be a direct consequence of atherogenesis, but rather as the presence of specific determinants, independent of the central processes active in plaque formation.[12] Therefore, the presence of calcification may be a marker of the increased collection of inflammatory cells, and a predictor for ACS. The increased risk of ACS with CAC in older subjects suggest that it may have a role in the occurrence of ACS in a time course manner.

In this study, cigarette smoking was significant risk factor for ACS in both the younger and older age groups. In the Framingham cohort, cigarette smoking was the most powerful risk factor in young women (<45 years). Data from the Framingham report have showed significantly higher fibrinogen levels in the smoking group.[37] Meade, et al. also reported that clotting time and platelet aggregation were increased in the smoking group.[38] Most importantly, cigarette smoking appears to damage the endothelium, decreasing the synthesis of prostacyclin and/or its release, thus favoring platelet aggregation.[39] Therefore, our result was compatible with the previous reports relating to ACS and smoking.

In the present study, we did not use EBCT for the measurement of calcification, which is a potential limitation. The present study indicated that ACS, with CAC fluoroscopically, corresponded with endoluminal vascular lesions to definite angiographic culprit lesions.

In conclusion, Lp(a) and CAC acted as independent risk factors for ACS in an age related manner, and had a synergistic effect on the development of ACS. In the younger subjects, elevated plasma Lp(a) was a independent risk for ACS, and in the older subjects, CAC was a independent risk for ACS. Therefore, Lp(a) and CAC may be good predictors of ACS in the younger and older subjects, respectively.

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