Lipoprotein (a) Is Increased in Acute Coronary Syndromes (Unstable Angina Pectoris and Myocardial Infarction), but It Is Not Predictive of the Severity of Coronary Lesions

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Summary: Lipoprotein (a) [Lp(a)] concentrations were determined in 365 patients undergoing coronary angiography for stable angina (n = 159), unstable angina (n = 99), recent myocardial infarction (n = 45), and nonischemic heart disease (cardiomyopathy or valvular disease, n = 62, non-IHD). Mean ± SD and median Lp(a) concentrations in stable angina (29.9 ± 29.2; 22 mg/dl) did not differ from those in non-IHD (26.9 ± 26.3; 17), but were significantly lower than in patients with unstable angina (52.7 ± 36.6; 58) and myocardial infarction (44.8 ± 36.4; 34) (p < 0.01). Coronary angiography revealed that 261 patients, including 4 patients in the non-IHD group, had significant (≥ 50%) coronary lesions. Lp(a) was higher in patients with (41 ± 35; 32) than in those without (28 ± 27; 19) angiographic evidence of significant coronary stenosis (p < 0.05) and showed a weak univariate correlation with the angiographic index (Total Score) of the severity of the disease (r = 0.106; p < 0.05). However, in the subgroup of 303 patients with stable/unstable angina or myocardial infarction, Lp(a) was predictive neither of angiographic presence nor of severity of coronary disease. Patients were then ranked according to the Total Score values. Among patients with comparable angiographic severity of coronary artery disease, Lp(a) appeared to be remarkably higher in patients with acute ischemic syndromes (unstable angina, myocardial infarction) than in patients with stable angina. In conclusion, Lp(a) was roughly twice as high in acute (unstable angina, myocardial infarction) than in chronic (stable angina) ischemic syndromes, but there was no difference between chronic stable angina and non-IHD. Serum level determination of Lp(a) made a poor contribution in predicting the extent of coronary artery disease.

Introduction

Lipoprotein (a) [Lp(a)] is a lipoprotein with pro-athero/thrombogenic activities.[1] Lp(a) can transverse the endothelium,[2] interact with the tissue matrix of the arterial wall,[3] and accumulate in atheromatous arteries and vein grafts.[4, 5] It also competes with the bindings of plasminogen to fibrin and inhibits clot lysis induced by tissue plasminogen activator (tPA).[6, 7] Moreover, it induces expression and secretion of PAI-1 from endothelial cells in tissue cultures.[8]

Since coronary ischemic events are the consequence of both the long-lasting process of coronary atherogenesis and the acute development of intracoronary thrombosis, the potential role of Lp(a) in ischemic heart disease (IHD) has aroused considerable interest in the past decade. Studies which have examined the relationship between Lp(a) and angiographically documented coronary lesions estimated the role of Lp(a) to be of the same order of magnitude as low-density lipoprotein (LDL) cholesterol.[9–11] However, these studies did not provide data on the phase of the clinical activity of the disease. Therefore, it is still unknown whether the occurrence of acute coronary syndromes [unstable angina and myocardial infarction (MI)] may have influenced the correlations between the Lp(a) level and coronary atherosclerosis. The purpose of the study was to examine the Lp(a) level relationship with the occurrence of acute ischemic syndromes and with the presence and severity of coronary lesions.

Methods

Patients

The study population consisted in a consecutive series of 365 Caucasian patients undergoing coronary angiography at the Cardiology Unit of the University of Genoa. A total of 303 patients underwent coronary angiography for IHD; these patients had a clinical diagnosis of stable (n = 159) or unstable (n = 99) angina, or had had a recent (< 3 weeks) MI (n = 45).

Patients with previous coronary artery surgery or angioplasty or under treatment with lipid-lowering drugs were not included. The remaining 62 patients (non-IHD group) underwent coronary angiography for reasons other than IHD (cardiomyopathy or valvular disease). Myocardial infarction was diagnosed when prolonged chest pain was accompanied by ST-segment shift >1 mV and when total creatine kinase (CK) was twice the upper limit of the normal range with CK-MB present. Unstable angina consisted of the typical patterns of rest angina, a new onset of angina, or crescendo angina with documented electrocardiographic (ECG) changes, the severity of which led to admission to the Coronary Care Unit. The time that elapsed (mean ± SD) between MI or the last episode of unstable angina and coronary arteriography was 17 ± 3 and 4 ± 4 days, respectively.

Coronary Angiography

Selective coronary angiography was performed by standard techniques with multiple injections of 4–8 ml of iohexol (647 mg/ml) in anteroposterior, right and left oblique views with various cranial and caudal angulations. All angiograms were examined by three observers blinded to the results of lipid and lipoprotein determinations. The luminal percent diameter narrowings were measured with a caliper and calculated by the mean of different measurements. Significant coronary artery disease was defined when narrowings ≥50% were present in one or more major coronary branches. The extent of coronary atherosclerosis (Total Score) was evaluated on the track of the 15-segment coding system of the American Heart Association[12] and calculated as the sum of the maximum narrowing value present in each of the 15 segments.

Lipid and Lipoprotein Determinations

After 12–16 h, overnight fasting-venous blood samples were obtained in the catheterization laboratory before arteriotomy and systemic heparinization. Plasma lipoproteins were separated by preparative ultracentrifugation in a Beckman 50.4 Ti rotor,[13] and cholesterol[14] and triglycerides[15] were assayed by enzymatic methods. Lp(a) concentration was determined in whole plasma with a commercially available enzyme-linked immunosorbent assay [Macra Lp(a)® kit, Terumo Corp., Elkton, Md.] using a monoclonal antibody against apo(a), which does not cross-react against plasminogen, and a second polyclonal antibody directed against the apo(a) portion of Lp(a).[16] The assay was standardized with respect to the mass of the Lp(a) particle. Plasma samples were stored at −80°C and assayed within 2 months of blood drawing. The mean intra- and interassay precisions for Lp(a), expressed as coefficient of variation (%), were 2.7 and 4.2, respectively.

Statistical Analysis

Mann-Whitney and chi-square tests were used when comparing the two groups. For multiple comparisons, analysis of variance was employed, and the significance of differences between groups was determined by Dunnet t-test; logarithmic transformation was applied for variables with a skewed distribution. Nonparametric correlations by Spearman coefficients were adopted for univariate analysis. Multiple stepwise discriminant and regression analyses were performed by standard techniques. Data are given as mean ± SD. A p value <0.05 was considered significant.

Results

Table I reports the demographic and clinical data and the lipid profile of the 365 patients examined in the study. Age, body mass index (BMI) [weight (kg)/height (m²)], hypertensive status, total and LDL cholesterol did not differ between patients with and without IHD. In the non-IHD group, there were more women (p <0.001), and fewer smokers (p < 0.001) than in the IHD group. Triglyceride concentrations were lower and high-density lipoprotein (HDL) cholesterol was higher in non-IHD than in IHD patients (p <0.01).

Lp(a) turned out to be higher in IHD than in non-IHD patients (p = 0.019). As shown in Figure 1, remarkable differences among the four subgroups (non-IHD, stable angina, unstable angina, and MI) were found (p <0.001). Lp(a) in unstable angina and MI was significantly higher than in non-IHD patients (p <0.01). It is worth noting that Lp(a) levels in stable angina did not differ from those in non-IHD, but were significantly lower than those in unstable angina and MI (p < 0.01). Age, gender, BMI, smoking habit, hypertensive status, total cholesterol, and triglyceride concentrations were similar in stable angina, unstable angina, and MI patients. Serum LDL cholesterol levels were 132 ± 30 mg/dl in stable angina, 139 ±

TABLE I   Demographic and clinical data, lipid profile of the 365 patients examined in the study

	non-IHD	IHD
No. of patients	62	303
Women	27 (44%)	52 (17%)
Age (years)	57.2 ± 9.3; 59	58.1 ± 8.8; 59
Old MI	0	122 (40%)
Smoke	23 (37%)	221 (73%)
Hypertension	17 (27%)	121 (40%)
BMI (kg/m2)	24.2 ± 4; 24	25.1 ± 3.1; 25
Cholesterol (mg/dl)	192.1 ± 39.2; 193	197.2 ± 38.1; 195
HDL-C (mg/dl)	43.2 ± 11.9; 42	37.7 ± 11.2; 35
LDL-C (mg/dl)	131.2 ± 36.7; 125	136.1 ± 32.9; 135
Triglycerides (mg/dl)	93.2 ± 43.2; 83	112.9 ± 56.1; 102
Lp(a) (mg/dl)	26.9 ± 26.3; 17	39.5 ± 34.4; 30

Data are given as mean ± SD; median.
Abbreviations: IHD = ischemic heart disease, non-IHD = nonischemic heart disease, MI = myocardial infarction, BMI = body mass index, HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol, Lp(a) = lipoprotein (a).
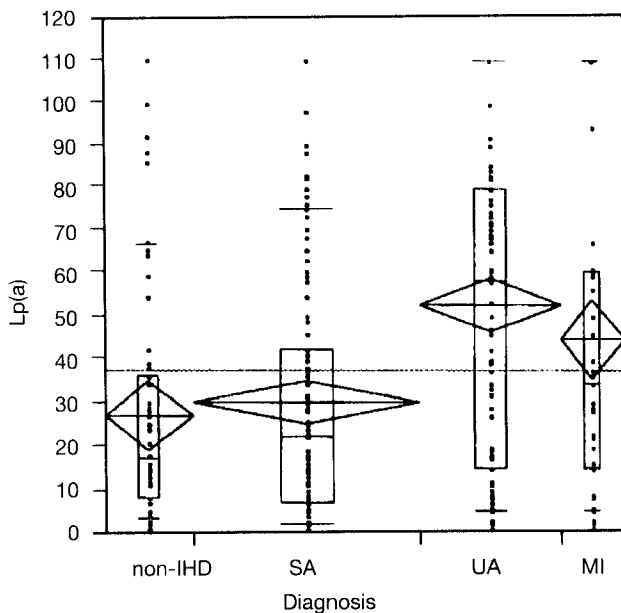
FIG. 1 Lp(a) levels in patients with nonischemic heart disease (non-IHD), stable angina (SA), unstable angina (UA), myocardial infarction (MI). Values are given as a mean with a 95% confidential interval (diamond) and quantiles (the box constitutes the range between the 25 and the 75 percentile; the horizontal line in the box represents the median; the lines outside the box constitute the 10 and 90 percentiles). The width of each study subgroup is proportional to the number of patients included.

32 mg/dl in unstable angina, and 144 ± 40 mg/dl in MI patients ($p < 0.05$), while in the same clinical subsets, HDL cholesterol concentrations were, respectively, 39 ± 11, 36 ± 11, and 34 ± 9 mg/dl ($p < 0.05$). A total of 121 subjects had suffered from MI some time before: the prevalence in the stable (50%), unstable angina (35%), and MI (16%) groups was statistically different ($p < 0.001$).

Multivariate statistical analysis was performed to evaluate which variables, including demographic and clinical data and lipoprotein levels, discriminate among stable angina, unstable angina, and MI patients. Three variables proved to be significantly and independently predictive of the clinical diagnosis: Lp(a) (partial $r^2 = 0.099$, $p < 0.001$), previous MI (partial $r^2 = 0.069$, $p < 0.001$), and HDL cholesterol (partial $r^2 = 0.038$, $p < 0.01$). Lp(a) did not correlate with the other variables listed in Table I; nevertheless, a weak but significant ($p < 0.01$) Spearman rank correlation with total cholesterol ($r = 0.159$) and LDL cholesterol ($r = 0.166$) was noted.

Of the whole population studied, 261 patients had significant coronary lesions at angiography with single- ($n = 107$), double- ($n = 90$), or triple- ($n = 64$) vessel disease. The vast majority ($n = 257$) belonged to the IHD group, while four patients, since they had a clinically latent coronary disease, were apparently non-IHD patients. No angiographic difference, in terms of number of diseased vessels, was noted among patients with stable angina, unstable angina, and MI. Plasma Lp(a) levels were higher in patients with significant coronary lesions ($41 \pm$

35; median 32) than in those without significant coronary lesions (28 ± 27; median 19) ($p < 0.05$), and showed a weak univariate association with the Total Score ($r_s = 0.106$, $p < 0.05$); by multivariate analysis, however, Lp(a) was predictive neither of presence of significant lesion, nor of severity of coronary disease. Considering only patients undergoing coronary angiography for chest pain (IHD subgroup), Lp(a) concentrations were higher in patients with significant coronary lesions (41 ± 34; 32 mg/dl vs. 32 ± 30; 21 mg/dl), but the difference was of no statistical significance and no relationship between Lp(a) and coronary disease severity was found. These patients were then subdivided into acute (unstable angina and MI) and chronic syndromes and ranked according to the severity of coronary lesions. As shown in Figure 2, among patients with comparable coronary lesion severity, Lp(a) appeared to be remarkably higher in those with acute ischemic syndromes.

Discussion

The first result of this study is the strong association between Lp(a) and acute coronary syndromes: patients with unstable angina or MI showed higher concentrations not only in comparison with non-IHD patients but also with regard to the stable angina group; a striking observation was that Lp(a) levels in the stable angina group were not statistically different from those found in non-IHD patients; when patients were scored on the basis of the angiographic findings, we observed that Lp(a) was higher in acute than in chronic coronary syndromes among patients with comparable severity of coronary atherosclerosis. Few studies have previously investigated this aspect with opposite results. Oshima et al.[17] found Lp(a) levels on admission significantly higher in 18 patients with unstable angina than in 18 patients with stable effort angina. On the other hand, Qiu et al.[18] observed similar Lp(a) levels in 60 patients with unstable angina or MI as well as in 64 patients with chronic stable angina.

The second result of the study is that Lp(a) itself is of limited value in predicting the angiographic presence and severity of
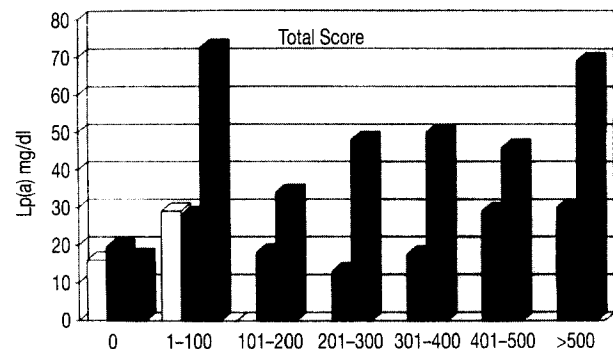

FIG. 2 Lp(a) concentrations (median) in patients divided for clinical diagnoses and ranked by severity of coronary atherosclerosis. □ = non-IHD, ■ = SA, ■ =UA MI. Abbreviations as in Figure 1.

coronary disease. Only in the overall population did plasma Lp(a) concentrations appear to offer a univariate, but not independent, association with the presence and the severity of coronary artery disease. However, in the IHD group, that is, patients with chest pain and/or clinical diagnosis of myocardial ischemia, Lp(a) was not predictive of the coronary anatomy. This result was not completely unexpected. Although the vast majority of studies supports the concept that Lp(a) is a major risk factor for coronary atherosclerosis, there are some investigations that report no difference in Lp(a) concentrations between patients with and without coronary lesions,[19] or among patients with single-, double-, or triple-vessel disease.[19,20]

The mechanisms responsible for the higher level of Lp(a) in acute coronary syndromes are not explained by our data. However, Maeda *et al.*[21] found a transient increase of Lp(a) in the days following acute MI and suggested that Lp(a) behaves as an acute-phase reactant. Acute-phase proteins are known to increase in serum after tissue damage or inflammation and are suspected to play a role in recovery of injury. This does not seem to be applicable to our patients with unstable angina who, by definition, did not present cardiac enzyme release. Furthermore, Oshima *et al.*[17] observed a rise in Lp(a) concentrations uncoupled with changes in the levels of the C-reactive and the alpha1 - antitrypsin acute phase proteins in their unstable angina patients. Pain and psychological stress certainly have a different impact in acute and stable patients and may be a hypothetical source of variation for Lp(a) concentrations. In any case, blood samples for Lp(a) determination were obtained in the catheterization laboratory at the beginning of the procedure. As a result of this modality of blood collection, stable patients were in conditions similar to those patients with clinically more severe conditions. This should have reduced the impact of stress in producing differences between the groups.

Conclusion

Our study shows an important relation between Lp(a) and presence of acute ischemic syndromes. The presence of this connection does not imply a cause-effect relationship. Since Lp(a) was determined after the onset of the acute event, its high levels can be interpreted as secondary to the intracoronary thrombotic process. However, these high levels of Lp(a) in acute coronary syndromes, whether primary or secondary, may be pathogenetically important and related to the clinical outcome. It could also be of interest to assess prospectively whether Lp(a) may be a risk factor for the destabilization of symptoms in stable angina patients.

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