Lipoprotein(a) in Diabetic Patients and Normoglycemic Relatives in Familial NIDDM

GILBERTO VELHO, MD, PHD
DANIELLE ERLICH, MD, PHD
ELISABETH TURPIN, PHD
DOMINIQUE NÉEL, MD, PHD
DANIEL COHEN, MD, PHD
PHILIPPE FROGUEL, MD, PHD
PHILIPPE PASSA, MD

OBJECTIVE— To compare lipoprotein(a) levels in diabetic patients and normoglycemic relatives in familial NIDDM and to assess whether Lp(a) is a risk factor for myocardial infarction in this population.

RESEARCH DESIGN AND METHODS— We compared 577 patients and 261 normoglycemic relatives from 189 NIDDM multiplex families with 49 unrelated healthy individuals. Of the 577, 23 patients with previously documented myocardial infarction were further analyzed as a separate group.

RESULTS— Lp(a) concentrations in diabetic patients, normoglycemic relatives, and the control group were not significantly different. Variance of Lp(a) in a given individual could not be accounted for by any clinical or biological parameter, but was strongly related to the mean Lp(a) value in his or her family. Diabetic patients with previous myocardial infarction (and their relatives) had significantly higher levels of Lp(a) than patients without coronary heart disease complaints.

CONCLUSIONS— Lp(a) concentration in familial NIDDM was not related to the degree of glucose intolerance, but presented a strong familial aggregation. High Lp(a) levels seem to be an independent risk factor for myocardial infarction in this NIDDM cohort.

FROM THE HUMAN POLYMORPHISM STUDY CENTER (C.E.P.H.); AND THE ENDOCRINOLOGY DEPARTMENT AND THE LABORATORY OF BIOCHEMISTRY, LIPIDS AND PROTEINS UNIT, HOSPITAL SAINT LOUIS, PARIS, FRANCE.

ADDRESS.CORRESPONDENCE AND REPRINT REQUESTS TO GILBERTO VELHO, MD, PHD, CENTRE D'ÉTUDE DU POLYMORPHISME HUMAIN, 27 RUE JULIETTE DODU, 75010 PARIS, FRANCE.

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Lp(a), LIPOPROTEIN(A); NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; MI, MYOCARDIAL INFARCTION; IGT, IMPAIRED GLUCOSE TOLERANCE; BHFPG, BORDERLINE HIGH FASTING PLASMA GLUCOSE; CHD, CORONARY HEART DISEASE; WHO, WORLD HEALTH ORGANIZATION; CV, COEFFICIENT OF VARIATION; ANOVA, ANALYSIS OF VARIANCE; BMI, BODY MASS INDEX; SBP, SYSTOLIC BLOOD PRESSURE; DBP, DIASTOLIC BLOOD PRESSURE; WHR, WAIST-TO-HIP RATIO; OR, ODDS RATIO; HDL, HIGH-DENSITY LIPOPROTEIN; apoA-I, APOLIPOPROTEIN A-I; apoB, APOLIPOPROTEIN B; apo(a), APOLIPOPROTEIN(A); IDDM, INSULIN-DEPENDENT DIABETES MELLITUS; CI, CONFIDENCE INTERVAL.

Lp(a) is considered a major independent risk factor for CHD (1,2). NIDDM patients have an increased risk of cardiovascular disease compared with nondiabetic control subjects, which is not fully explained by the profile of other known atherogenic factors (3,4). To address the question of whether Lp(a) is a risk factor in a population characterized by familial NIDDM, we compared plasma Lp(a) concentrations in family members presenting with chronic hyperglycemia (individuals having either overt diabetes mellitus IGT, or BHFPG) and in normoglycemic relatives with the levels obtained in unrelated healthy individuals. Furthermore, we compared Lp(a) concentrations observed in hyperglycemic individuals with previously documented MI and in patients without previous history of MI. Data from relatives of these two subgroups of patients were also compared.

RESEARCH DESIGN AND METHODS

— Clinical and biological information was obtained from 189 multiplex NIDDM families, collected all over France through a multimedia campaign from 1990 to 1992 (5). This population was originally recruited for the study of the genetic determinants of NIDDM and constitutes a unique cohort of familial diabetes. Families had at least two affected individuals, which were either siblings or from two generations. These individuals presented with either diabetes mellitus or IGT as defined by WHO (6) or BHFPG. BHFPG was defined as fasting plasma glucose >6.1 but <7.8 mM in two separate measurements (with a 2-h post–oral 75-g glucose load plasma glucose <7.8 mM) and represents values >2 SD above the mean of the normal population (7). Individuals were considered normoglycemic when presenting with fasting plasma glucose <6.1 mM in the absence of hypoglycemic medication. In ~50% of the individuals in the normoglycemic group (139 of 261), normal glucose tolerance was fur-

Table 1—*Clinical profile of affected individuals, normoglycemic relatives, and control group*

	n	Age (yr)	BMI (kg/m^2)	Sex (M/F)	Status: BHFPG n (%)	Status: IGT n (%)	Status: Diabetes mellitus n (%)	Duration of diabetes (yr)	Plasma glucose (mM)
Affected subjects	577	59 ± 14	27.1 ± 4.6	285/292	90 (15.6)	60 (10.4)	427 (74)	11 ± 10	8.8 ± 3.4
Normoglycemic relatives	261	57 ± 12	24.5 ± 3.5	89/172					5.2 ± 0.5
Control group	49	38 ± 14	23.3 ± 5.6	33/16					5.0 ± 0.4

Data are means ± SD. Plasma glucose are values after an overnight fast.

ther confirmed by an oral glucose tolerance test. Detailed clinical data were obtained from both the participants and their physicians by standard questionnaires.

For these analyses, the population was composed of 577 affected white individuals and 261 normoglycemic relatives (Table 1). A control group was composed of 49 unrelated normoglycemic white individuals with no diabetic relatives. Controls were recruited from healthy individuals who consulted the Hospital Saint Louis in 1991 as outpatients. No attempt was made to perfectly match diabetic patients and control subjects for age or sex because these parameters do not seem to be implicated in the variance of Lp(a) in any of the three groups. Of the 577 affected individuals, 23 were reported by their physicians to have had documented MI before the beginning of the study (6 ± 4 yr). This information was confirmed by a telephone interview with the patients and/or the physicians. All of these patients had typical symptoms of MI and were admitted to a hospital during the event with clinical, biological, and electrocardiographic evidence of MI. CHD was documented by angiography in 6 patients. Three patients survived and 2 patients died after a second episode of MI. All but 1 of these patients were on drug therapy during the ongoing study. Medication included β-adrenergic blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, digoxin, amiodarone, aspirin, dipyridamole, and coumarin anticoagulants.

Lp(a) was assayed by immunonephelometry (8) using sheep anti-Lp(a) antibodies (Immuno-France, Paris), which were checked not to cross-react with plasminogen. The maximum intra-assay CV and interassay variability were, respectively, 8.5 and 12%. To avoid interference of high levels of triglycerides in the assay, the turbidity of the plasma was checked by measuring the absorbance at 650-nm wavelength. When it was superior to 0.150 the plasma was discarded, and the patient was excluded from the study (n = 6 cases).

Statistical analysis

Data are expressed as means ± SD, unless stated otherwise. Mean value of Lp(a) for each family was computed taking into account the individual values of both diabetic and normoglycemic individuals. Duration of diabetes in the text and the tables refers to patients with diabetes, IGT, and BHFPG. Data were compared with the nonparametric Mann-Whitney U test and Kruskal-Wallis test when comparing two or three groups, respectively. Student's t test and ANOVA were conducted after logarithmic transformation of Lp(a) concentration. Qualitative traits were analyzed by contingency table χ^2 tests. Simple and stepwise linear regression analyses were used to evaluate interactions between Lp(a) levels and other clinical and biological variables. Univariate and multivariate stepwise logistic regression analyses were performed to evaluate the association of clinical and biological parameters with the risk of MI. Statistics were calculated with the Systat software package (9).

RESULTS — The clinical profile of the affected individuals, normoglycemic relatives, and control group is shown in Table 1. The distribution of Lp(a) concentration did not have a Gaussian pro-

Table 2—*Lp(a) profile of affected subjects, normoglycemic relatives, and control group*

	Lp(a) (mg%)*	Lp(a) (mg%)†
Affected subjects	27.2 ± 19.3	21.0
Normoglycemic relatives	27.1 ± 18.2	20.0
Control group	23.1 ± 15.1	18.0
Statistical significance	P = 0.38 (NS)	

Statistics are Kruskal-Wallis test.
*Data are means ± SD.
†Data are medians.

Table 3—*Clinical and biological profile of affected subjects with or without previous MI*

	n	AGE (YR)	BMI (KG/M^2)	SEX (M/F)	DURATION OF DIABETES (YR)	FASTING PLASMA GLUCOSE (MM)	FASTING PLASMA INSULIN (MU/L)
WITH MI	23	64 ± 10	27.2 ± 4.5	14/9	16 ± 10	10.1 ± 3.6	19 ± 10
WITHOUT MI	425	58 ± 13	27.1 ± 4.6	209/216	11 ± 10	8.6 ± 3.3	15 ± 10
STATISTICAL SIGNIFICANCE		$P = 0.028$	$P = 0.97$	$P = 0.38$	$P = 0.011$	$P = 0.029$	$P = 0.064$

Data are means ± SD. Two-hour plasma glucose and insulin values after a 75-g oral glucose load. Statistics are contingency table χ^2 analysis for sex and Mann-Whitney *U* test for other parameters.

file and was skewed toward lower values: the mean value of Lp(a) was higher than the median in the three groups (Table 2). When data were analyzed with the nonparametric Kruskal-Wallis test, Lp(a) concentration was not significantly different in affected individuals and in normoglycemic relatives compared with the control group. Neither did ANOVA after normalization of data by logarithmic transformation show significant differences between groups ($P = 0.4$). Similar results were obtained when individuals with BHFPG and IGT were excluded from the affected group (data not shown) or compared as a separate group. Lp(a) concentrations were, respectively, 26.9 ± 20.5, 25.3 ± 17.9, and 26.1 ± 17.5 mg/dl in diabetic, IGT, and BHFPG individuals (Kruskal-Wallis $P = 0.94$; ANOVA after log transformation, $P = 0.97$).

Simple linear regression analysis with either Lp(a) or log Lp(a) as the dependent variable and fasting or 2-h post–oral glucose load plasma glucose as the independent variable was computed. The percentage of the variance of Lp(a) that could be accounted for by the values of fasting glucose was 0.1% ($P = 0.69$) for the affected individuals, 0.2% ($P = 0.49$) for the normoglycemic relatives, 0.1% ($P = 0.85$) for the control group, and 0.1% ($P = 0.49$) for the three groups together. Similarly, the 2-h post–oral glucose load plasma glucose had a negligible influence on the variance of Lp(a): 0.1% ($P = 0.7$) for the affected individuals, 2% ($P = 0.04$) for the normoglycemic relatives, and 0.3% ($P = 0.35$) for both groups together. Statistically nonsignificant results were obtained with log Lp(a) as the dependent variable.

No correlation of Lp(a) concentration with other clinical and biological parameters was observed with a stepwise linear regression analysis, either in the affected individuals, the normoglycemic relatives, or both groups together (data not shown). The parameters taken into account include age, BMI, WHR, sBP and dBP, fasting and 2-h post–oral glucose load plasma glucose and insulin, total cholesterol, HDL cholesterol, triglycerides, apoA-I, apoB, and creatinine. However, 45% of the variance of Lp(a) in affected and normoglycemic individuals could be accounted for by the mean value of Lp(a) calculated for each family, when this parameter was considered an independent variable ($P < 0.01$). No sex-related differences were found in any of the three groups.

Plasma Lp(a) concentration in the subgroup of affected individuals with previous MI was significantly higher than in patients without previous MI ($P = 0.016$; Table 3). A significant difference between the two groups was confirmed after logarithmic transformation of Lp(a) concentration ($P = 0.014$). Patients with previous MI were older and had a longer duration of diabetes than those without previous MI (Table 3). They also had a more severe form of chronic hyperglycemia: 96% (all but 1) had overt diabetes mellitus versus 73% ($P = 0.051$) and were treated more often with hypoglycemic drugs or insulin (91% vs. 65%; $P = 0.028$). Fasting and 2-h post–oral glucose load plasma glucose were also significantly higher in the MI group (Table 3). Furthermore, patients with previous MI had a higher prevalence of neuropathy (39 vs. 9%; $P = 0.0001$) and proliferative retinopathy (20 vs. 10%; $P = 0.009$). Sex distribution, smoking habits, sBP and dBP, fasting and 2-h post–oral glucose load plasma insulin, triglycerides, total cholesterol, apoA-I, apoB, and creatinine were not significantly different in the two groups (Table 3 and data not shown). HDL cholesterol was lower in the MI group: 1.13 ± 0.29 vs. 1.29 ± 0.36 mM ($P = 0.019$).

Regression analyses, with cardiovascular status as the categorical dependent variable (MI versus without MI), were performed to evaluate a possible association of clinical and biological parameters with the risk of MI. In a first approach, univariate regression analyses were performed; parameters introduced as independent variables included sex, age, BMI, WHR, smoking habits, duration of diabetes, sBP and dBP, and fasting plasma glucose, insulin, triglycerides, total cholesterol, HDL cholesterol, apoA-I, apoB, creatinine, and Lp(a). Parameters with a $P < 0.4$ level of significance on univariate analysis were entered into a stepwise multiple logistic regression

Table 3—*Continued*

2-H PLASMA GLUCOSE (MM)	2-H PLASMA INSULIN (MU/L)	Lp(a) (MG%)	apoA-I (MG%)	apoB (MG%)	TRIGLYCERIDES (MM)	TOTAL CHOLESTEROL (MM)	HDL CHOLESTEROL (MM)
17.5 ± 7.1	44 ± 29	36.1 ± 23.0	157 ± 19	141 ± 30	1.99 ± 1.15	6.01 ± 1.15	1.13 ± 0.29
9.6 ± 4.4	50 ± 35	26.1 ± 19.5	167 ± 26	130 ± 29	1.53 ± 0.75	5.85 ± 1.06	1.29 ± 0.36
$P = 0.007$	$P = 0.85$	$P = 0.016$	$P = 0.059$	$P = 0.13$	$P = 0.081$	$P = 0.43$	$P = 0.019$

analysis (Table 4). An association between Lp(a) values and the risk of MI was observed, with OR of 1.02. When log Lp(a) was introduced in the computations instead of Lp(a), this association was much stronger, with OR of 8.03. Age was also a statistically significant parameter with OR of 1.07. Although not statistically significant ($P = 0.09$), a trend toward an association between log insulin and the risk of MI was observed. Statistically significant association of MI with duration of diabetes, fasting plasma glucose, triglycerides, HDL cholesterol, apoA-I, and apoB levels was excluded (Table 4). Similarly, log transformation of these parameters yielded statistically nonsignificant results (data not shown).

Lp(a) levels in either hyperglycemic or normoglycemic relatives of patients with previous MI were also significantly higher than levels in other hyperglycemic and normoglycemic individuals (Table 5). Analysis after normalization of data by logarithmic transformation yielded similar conclusions with higher statistical significance.

CONCLUSIONS— Lp(a) concentration in NIDDM patients was found to be increased in several studies (10–12), but the relationship between Lp(a) levels and glucose tolerance is controversial. In contrast, in a group of subjects with well-controlled NIDDM, Lp(a) concentration was reported not to be increased compared with nondiabetic control subjects (13). Haffner et al. (12) reported increased concentrations of Lp(a) in NIDDM subjects compared with normoglycemic control subjects, but these elevated levels did not decline with improved metabolic control. However, in a recent publication, the same group reported that NIDDM patients and nondiabetic subjects who participated in a population-based study had similar Lp(a) concentrations (14). Duration of diabetes and level of fasting glycemia were not significantly related to Lp(a) concentration in that cohort.

In this population characterized by familial NIDDM, we could not find any significant differences in Lp(a) concentration when comparing affected individuals and normoglycemic relatives with unrelated normoglycemic controls. Lp(a) levels were not related to the degree of glucose intolerance, because no differences were observed between individuals with BHFPG, IGT, or overt diabetes mellitus. Moreover, Lp(a) variance was independent of the values of fasting or post–glucose load plasma glucose. The only parameter closely related to the Lp(a) concentration in a given individual was the mean value of Lp(a) observed in his or her relatives, suggesting that in these families Lp(a) is mostly under genetic control. In this regard, Boerwinkle et al. (15) reported that in healthy caucasians, 41.9% of the variability of Lp(a) levels could be accounted for by the apo(a) glycoprotein polymorphisms, which are genetically transmitted. Similarly, in this latter study, association of Lp(a) levels with other lipid or lipoprotein levels was weak or absent. Furthermore, in a recent study, the same group compared plasma Lp(a) levels in siblings who shared zero, one, or two apo(a) genes that were identical by descent. The apo(a) gene was estimated to be responsible for >90% of the interindividual variation in plasma Lp(a) levels (16).

These results contrast with those

Table 4—*Stepwise multiple logistic regression analysis of risk factors for MI*

	OR	95% CI	P
Lp(a)	1.02	1.01–1.04	0.032
LOG Lp(a)	8.03	1.63–39.62	0.031
AGE	1.07	1.02–1.12	0.024
FASTING GLUCOSE	1.06	0.93–1.20	0.43
FASTING INSULIN	1.04	0.99–1.08	0.16
LOG FASTING INSULIN	10.40	0.94–114.95	0.09
TRIGLYCERIDES	1.52	0.82–2.81	0.21
HDL CHOLESTEROL	0.39	0.05–3.19	0.42
apoA-I	0.30	0.03–3.48	0.38
apoB	1.40	0.23–8.47	0.73
DURATION OF DIABETES*	1.03	0.99–1.08	0.18

*Duration of diabetes refers to BHFPG, IGT, and diabetes mellitus.

Table 5—*Lp(a) profile in relatives of patients with or without previous MI*

	Lp(a)					
	Hyperglycemic individuals		Normoglycemic individuals		All	
	n	mg%	*n*	mg%	*n*	mg%
Relatives of patients with MI	50	31.6 ± 20.9	29	36.7 ± 26.5	79	33.5 ± 21.9
Relatives of patients without MI	504	26.3 ± 19.6	232	25.9 ± 17.1	736	26.2 ± 18.8
Statistical significance						
Lp(a)		$P = 0.05$		$P = 0.0071$		$P = 0.0015$
Log Lp(a)		$P = 0.035$		$P = 0.004$		$P = 0.0008$

Data are means ± SD. Statistics are Mann-Whitney *U* test for Lp(a) and Student's *t* test for log Lp(a).

obtained in IDDM patients, in whom Lp(a) concentration was shown to be higher than in control subjects (12,17,18), to be positively related to levels of GHb (18), and to decrease significantly with improved metabolic control (17). However, normal Lp(a) concentrations and apo(a) isoforms reported in IDDM patients without diabetic nephropathy (19). Note that Lp(a) was found to be increased in patients with severe proteinuria regardless of its etiology (20). The causes for these differences between NIDDM and IDDM patients remain to be determined.

Although Lp(a) is a well-established risk factor for CHD (1,2,21), very few data concerning NIDDM patients are available. A recent work by Haffner et al. (22) concluded that there was no association between Lp(a) levels and CHD mortality in NIDDM patients. In our population characterized by familial NIDDM, Lp(a) levels were significantly higher in diabetic individuals with a documented previous episode of MI than in diabetic individuals with no complaints of CHD. Normoglycemic and hyperglycemic relatives of these patients with MI shared the trend for significantly higher levels of Lp(a).

The results of this study suggest that high levels of Lp(a) might be an independent risk factor for MI in familial diabetes. Indeed, Lp(a), after log transformation, was independently and strongly associated with the risk of MI (OR of 8.03) in a stepwise multiple logistic regression analysis. Furthermore, a stepwise linear regression analysis in this population showed no relation of Lp(a) variance with other clinical and biological parameters. Note, however, that patients with previous MI had a more severe form of glucose intolerance and lower levels of HDL cholesterol than patients with no CHD complaints.

Two limitations of this study should be emphasized: the first one concerns the coronary status of the group of patients without CHD complaints, because we did not routinely perform electrocardiogram exercise tests, myocardial scintigraphy, or coronary angiography to exclude silent CHD, which was reported to be frequent in NIDDM patients (23). The second one is related to the small number of diabetic individuals in the group with CHD complaints.

In conclusion, Lp(a) levels do not correlate with the degree of glucose tolerance in a population characterized by familial NIDDM. High Lp(a) levels might be an independent risk factor of MI in this population. However, prospective longitudinal studies in larger NIDDM cohorts are required to confirm the predictive value of Lp(a) as a determinant of CHD.

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