Lipoprotein(a) Concentrations in Non–Insulin-Dependent Diabetes Mellitus and Borderline Hyperglycemia: A Population-Based Study

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The objective of the study was to compare lipoprotein(a) [Lp(a)] concentrations in population-based samples of individuals with non–insulin-dependent diabetes mellitus (NIDDM), borderline hyperglycemia, and normoglycemia. From 2,740 male Italian Telephone Company employees aged 40 to 59 years participating in a health screening, we selected all those with NIDDM (n = 100) plus a random sample of 950 nondiabetic individuals. Diabetes was defined as fasting plasma glucose (FPG) of at least 140 mg/dL or current use of hypoglycemic drugs. Among nondiabetic individuals, 854 were defined as normoglycemic (FPG < 115 mg/dL) and 95 were defined as borderline hyperglycemic (115 < FPG < 140 mg/dL). Lp(a) level was measured on frozen plasma by enzyme-linked immunosorbent assay. Lp(a) concentrations were similar in people with NIDDM, borderline hyperglycemia, and normoglycemia: 11.2 ± 14, 14.1 ± 20, and 13.9 ± 18 mg/dL, respectively (F = 1.03). Accordingly, the proportion of subjects with Lp(a) levels of at least 30 mg/dL was comparable in the three groups (12%, 15%, and 14%; $\chi^2 = 3.95$, $P = .41$). Results were not confounded by differences in age, body mass index (BMI), waist to hip ratio, plasma lipids, alcohol consumption, physical activity, and use of drugs. Furthermore, within the diabetic group Lp(a) levels were not significantly different for those on diet only versus those on oral agents (10.8 ± 14.1 *v* 11.7 ± 14.7, $P = .7$) or for people with FPG of at least 180 as compared with people with FPG less than 180 mg/dL (9.9 ± 12.8 *v* 11.5 ± 14.8, $P = .5$). These findings were confirmed when the distribution of Lp(a) (>30 mg/dL) was analyzed. No correlation was found between Lp(a) levels and FPG ($r = .030$, P = NS) in the whole study group. In conclusion, Lp(a) levels are similar in individuals with NIDDM, borderline hyperglycemia, and normoglycemia. Furthermore, Lp(a) is not influenced by type of hypoglycemic treatment or blood glucose level, and Lp(a) concentrations are not related to glycemia in the total study population.

THE RISK OF CORONARY heart disease is increased twofold to fourfold in diabetic patients as compared with nondiabetic subjects; this excess risk is not fully explained by increased levels of major established cardiovascular risk factors.[1-4] The hypothesis has been put forward that other, less well-studied factors might play an important role. Relatively recent studies have indicated lipoprotein (a) [Lp(a)] as a strong independent predictor of coronary heart disease in nondiabetic populations.[5-7] Thus, increased plasma levels of Lp(a) might partly account for the extraordinary proneness to cardiovascular disease observed in diabetics. However, data on Lp(a) and diabetes are still conflicting.[8-13] Partly as a result of the small sample size of most of the studies or because clinic-based samples were studied and distinction was not always made between insulin-dependent diabetes mellitus (IDDM) and non–insulin-dependent diabetes mellitus (NIDDM) patients,[8] it remains unproven whether Lp(a) is increased in diabetic patients as a whole or in subgroups of patients. Furthermore, little is known about Lp(a) in people with minor degrees of hyperglycemia, who share with diabetics an increased risk for coronary heart disease.[14]

The purpose of this study was to compare Lp(a) concentrations in large, population-based samples of individuals with NIDDM, borderline hyperglycemia, and normoglycemia. We also examined the relationship of Lp(a) concentration to degree of hyperglycemia and type of hypoglycemic treatment.

SUBJECTS AND METHODS

A working population of 2,740 male employees of the Italian Telephone Company aged 40 to 59 years participated in a health screening. It was planned to perform Lp(a) analysis for all those who met diagnostic criteria for diabetes plus a random sample of approximately 1,000 people who did not meet these criteria and were therefore defined as nondiabetic. In this latter group, people were selected to participate in the Lp(a) study on the basis of their identification code using a computer-generated list of random digits.

NIDDM was defined as fasting plasma glucose (FPG) of at least 140 mg/dL or current use of medications for diabetes. One hundred six subjects, representing all those who met these criteria within the screened population, were selected for study. Among diabetics, six subjects were taking insulin and were excluded from the analyses. Nine hundred forty-nine nondiabetic participants were also studied, among whom those with FPG less than 115 mg/dL were defined as having normoglycemia (n = 854) and those with FPG of at least 115 mg/dL and less than 140 mg/dL were considered to have borderline hyperglycemia (n = 95).

Venous blood specimens were obtained after 12 to 14 hours of fasting. Plasma glucose, plasma total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were measured immediately after blood sampling by dry-chemistry methods using an Ektachem DT-60 analyzer (Eastman Kodak, Rochester, NY).[15,16] With this method, the day-to-day coefficient of variation ranged from 3.5% for glucose to 6.5% for triglycerides. Low-density lipoprotein (LDL) cholesterol level was calculated by the formula reported by Friedwald et al[17] in subjects with plasma triglycerides less than 400 mg/dL. Lp(a) concentrations were measured on fasting plasma specimens that had been stored at −70°C for an average of 1 year, using an enzyme-linked immunoab-

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sorbent assay. The antibodies used in this assay included all known isoforms of Lp(a), and no cross-reactivity with plasminogen is reported. The detection limit of the method is 1 mg/dL. In the data, values less than that limit (found in 1% of the study population) were recorded as 1 mg/dL. Intraassay and interassay coefficients of variation for Lp(a) in our laboratory were 9% and 12%, respectively.

Medical history, alcohol consumption, physical activity during leisure time, and intake of drugs were determined by questionnaire. Anthropometric measurements (height, weight, and waist and hip circumference) were taken with subjects in light indoor clothes and without shoes. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. For calculation of waist to hip ratio, the smallest circumference of the waist and the thickest part of the hip in the standing position were measured. Blood pressure was measured with a standard mercury sphygmomanometer in the supine position after 10 minutes of rest. The mean of two measurements was used in the analyses.

Statistical Analyses

The data are expressed as the mean ± SD unless otherwise specified. Triglyceride and Lp(a) concentrations were not normally distributed, and they were therefore log-transformed to reduce skewness; logarithms of these variables were used in all parametric significance testing, and original values are shown in tables and the figure. Comparisons between groups were performed with ANOVA and unpaired *t* test. Covariance analysis was performed to adjust for confounders. Differences between proportions were tested by χ^2 analysis. Correlation between Lp(a) levels and other variables was assessed by the Pearson coefficient test. A two-tailed *P* value less than .05 was considered significant. All statistical calculations were performed with SPSS.[18]

RESULTS

Table 1 shows clinical characteristics of the participants by glycemic status. Diabetic patients were older than the normoglycemic and hyperglycemic group. As expected, NIDDM patients and subjects with borderline hyperglycemia were more obese than the normoglycemic group. Furthermore, systolic and diastolic blood pressures were significantly higher in hyperglycemics and diabetics, as was the percentage of people on antihypertensive drugs. The percentage of subjects for whom alcohol consumption exceeded 50 g/d was similar in the three groups. The proportion of physically active subjects was too small to permit statistical analysis (1%, 2%, and 4%, respectively, in NIDDM, hyperglycemic, and normoglycemic participants).

Table 1. Clinical Characteristics (mean ± SD) of Study Subjects by Glycemic Status

Characteristic	Normoglycemia	Borderline Hyperglycemia	NIDDM
No. of subjects	854	95	100
Age (yr)	46.1 ± 5.2	46.4 ± 5.0	50.1 ± 5.9†
BMI (kg/m²)	26.1 ± 2.9	27.2 ± 3.4	27.9 ± 3.3†
Waist to hip ratio	0.97 ± 0.07	0.98 ± 0.05	0.99 ± 0.05*
Fasting glucose (mg/dl)	98.5 ± 8.6	122.1 ± 6.4	173.0 ± 53.0†
Blood pressure (mm Hg)			
Systolic	136.4 ± 17.0	139.5 ± 14.8	144.4 ± 19.1†
Diastolic	88.2 ± 10.8	90.8 ± 10.3	90.1 ± 11.9*
Antihypertensive treatment (%)	6.5	11.2	17.7*
Alcohol intake > 50 g/d (%)	2.3	2.1	2.0

*$P < .05$, ANOVA.
†$P < .001$, ANOVA.

Table 2. Plasma Lipids and Use of Lipid-Lowering Drugs by Glycemic Status (mean ± SD)

Parameter	Normoglycemia	Borderline Hyperglycemia	NIDDM
No. of subjects	854	95	100
Total cholesterol (mg/dL)	203.9 ± 38.7	207.2 ± 37.1	210.9 ± 45.5
LDL cholesterol (mg/dL)	128.4 ± 39.3	129.9 ± 35.0	121.7 ± 51.0
HDL cholesterol (mg/dL)	45.0 ± 13.3	45.4 ± 14.1	41.9 ± 14.2
Triglycerides (mg/dL)	142.7 ± 76.6	159.3 ± 82.7	196.7 ± 112.5†
Lipid-lowering drug (%)	2.2	1.1	6.0*
Lp(a) (mg/dL)	13.9 ± 18.4	14.1 ± 19.6	11.2 ± 14.1

*$P < .05$, χ^2.
†$P < .001$, ANOVA.

Table 2 shows the lipid profile and percentage of lipid-lowering drug users by glycemic status. NIDDM patients had higher plasma triglycerides and slightly but nonsignificantly lower plasma HDL cholesterol as compared with the other two groups. Total cholesterol and LDL cholesterol were not significantly different in the three groups. Conversely, the proportion of subjects under treatment with lipid-lowering drugs was significantly higher in the diabetic group ($\chi^2 = 6.15$, $P < .05$). No significant difference was observed in mean Lp(a) concentrations between normoglycemic, hyperglycemic, and diabetic people (13.9 ± 18.4 *v* 14.1 ± 19.6 *v* 11.2 ± 14.1, respectively; $F = 0.96$, $P = .4$).

After adjusting for differences in age, BMI, and triglycerides by covariance analysis, mean Lp(a) levels were still remarkably similar in individuals with normoglycemia, borderline hyperglycemia, and NIDDM (13.91, 14.89, and 13.52 mg/dL, respectively; $F = 1.746$). The same was observed when the analysis was repeated after excluding people on antihypertensive drugs to account for possible effects of these drugs on Lp(a) levels.

Even if none of the participants were receiving nicotinic acid (the only lipid-lowering drug reported to reduce Lp(a) concentration[19]), the analysis was also performed after excluding subjects on lipid-lowering treatment and the findings remain much the same: no differences in mean Lp(a) concentrations were observed between diabetic, borderline hyperglycemic, and normoglycemic subjects (12.2 ± 15.7, 14.1 ± 19.7, and 14.1 ± 18.6, respectively; $F = 0.34$, $P = .7$); if anything, Lp(a) concentration was lower in diabetics.

A graph showing the distribution of Lp(a) values in the three groups is reported in Fig 1. It shows that the proportion of subjects with elevated Lp(a) levels—≥30 mg/dL, the concentration at which a substantial increase in coronary heart disease risk is reported to occur—was similar in normoglycemic, borderline hyperglycemic, and

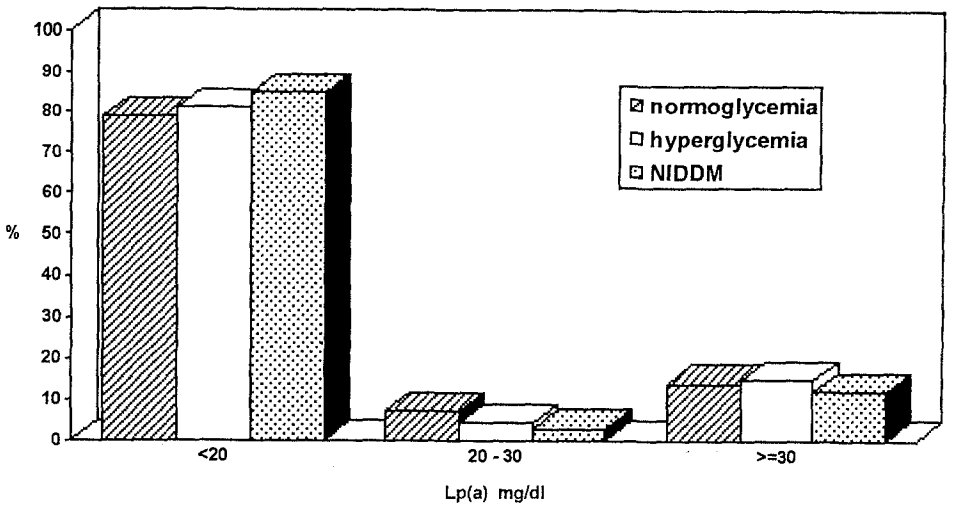

Fig 1. Distribution of Lp(a) concentrations by glycemic status (n = 1,049). $\chi^2 = 3.95$, $P = .41$.

diabetic subjects (14%, 15%, and 12%, respectively; $\chi^2 = 3.5$, $P = .41$).

Table 3 shows mean Lp(a) levels and the proportion of subjects with Lp(a) levels of at least 30 mg/dL by type of treatment and by level of glycemia in diabetic patients. No differences in mean Lp(a) levels were observed between patients treated with oral hypoglycemic agents or with diet only. Lp(a) concentrations of at least 30 mg/dL were more frequently observed in patients taking oral hypoglycemic agents (15.4% *v* 11%), but this difference did not achieve the conventional level for statistical significance ($\chi^2 = .49$, $P = .78$). No difference in mean Lp(a) values or in the percentage of subjects with elevated Lp(a) levels was observed between NIDDM subjects with FPG less than 180 mg/dL and those with FPG of at least 180 mg/dL (11.5 ± 14.8 *v* 9.9 ± 12.8, P = NS, and 12% *v* 13%, $\chi^2 = 1.4$, $P = .5$, respectively).

The correlation analysis performed in the whole study population showed, as expected, that Lp(a) levels correlated positively and significantly with total cholesterol and LDL cholesterol, but no correlation was found between Lp(a) levels and both plasma triglycerides and fasting blood glucose concentrations (Table 4).

DISCUSSION

These data indicate that neither individuals with NIDDM nor those with borderline hyperglycemia have elevated Lp(a) levels as compared with normoglycemic individuals. Furthermore, no relationship exists between blood glucose and plasma Lp(a) levels in the total study population.

Table 3. Mean Levels and Distribution of Lp(a) by Type of Treatment and by Fasting Blood Glucose Levels in NIDDM Patients (n = 100)

	Type of Treatment		Fasting Blood Glucose	
Parameter	Diet	Oral Agents	< 180 mg/dL	≥ 180 mg/dL
No. of subjects	74	26	69	31
Lp(a) (mg/dL)	10.8 ± 14.1	11.7 ± 14.7	11.5 ± 14.8	9.9 ± 12.8
Lp(a) ≥ 30 mg/dL (%)	11	15	12	13

Data on Lp(a) in diabetics are still conflicting; some investigators have reported high Lp(a) values in diabetic patients.[8-11] The sample size in this study is larger than in the majority of earlier studies conducted in whites, and therefore, lack of power is an unlikely explanation for the negative finding we have obtained. Possible alternative explanations for the discrepancies between results of our study and others include the fact that a distinction was not always made between IDDM and NIDDM in previous studies.[8,20] There are in fact indications that Lp(a) behaves differently in these two subgroups of patients, with higher values observed in IDDM.[21-23] An additional confounder might be represented by diabetic complications. Elevated Lp(a) levels have been reported in IDDM patients with microalbuminuria.[24,25] Although this finding has not been confirmed in NIDDM patients to date,[26] it is not possible to rule out an effect of early diabetic nephropathy on Lp(a) values in this group of patients. It is reasonable to suppose that in many studies performed on clinic-based samples of diabetic patients, more severely diseased people were investigated than those included in the present study. This hypothesis is confirmed by the fact that our results fully agree with indications coming from the Multinational Monitoring of Determinants and Trends in Cardiovascular Disease (MONICA) project and results from the San Antonio Heart Study, the only other studies conducted in unselected samples of NIDDM subjects.

Lp(a) levels are strongly genetically determined and are poorly influenced either by dietary measures or by hypolipidemic drugs.[27-30] However, the relationship between Lp(a) concentration and degree of metabolic control or type of

Table 4. Correlation Coefficients Between Lp(a) Levels and Metabolic Variables in the Study Subjects (n = 1,049)

Variable (mg/dL)	*r*	*P*
Total cholesterol	.1118	.001
LDL cholesterol	.1234	.001
HDL cholesterol	.0306	NS
Triglycerides	−.0718	NS
Fasting glucose	−.0298	NS

hypoglycemic treatment is not clear as yet.[20,31-34] Our data indicate that there is no relation between blood glucose and Lp(a) within the whole range of glucose values. Furthermore, within the diabetic group, Lp(a) levels do not vary according to degree of hyperglycemia and type of hypoglycemic treatment (ie, diet only *v* diet plus oral agents). It has been found that insulin-treated type II diabetic patients have higher levels of Lp(a) as compared with non–insulin-treated patients.[35] Unfortunately, this study does not include insulin-treated patients and therefore does not permit us to explore this issue.

As for people with minor degrees of hyperglycemia, few data are available. Of the two other studies published, one shows higher Lp(a) levels in people with impaired glucose tolerance than in controls and the other reports similar plasma levels in the two groups.[36,37] Once again, lack of power can be ruled out as a possible explanation for the negative finding of this study. Alternative explanations include differences in methodology—ie, we did not perform a glucose tolerance test, and therefore the group we studied does not meet the current definition for impaired glucose tolerance—and differences in selection criteria for the participants—ie, one of these studies[36] was restricted to people with a previous myocardial infarction.

In conclusion, no relation was found in this study between diabetes, borderline hyperglycemia, and Lp(a); also, no relation was found between glycemia and Lp(a) values either in the whole study group or in the diabetic group. Although caution is needed in extrapolating these results to more severely diseased subgroups of NIDDM patients such as those on insulin and those with overt or incipient diabetic nephropathy, these data do not support the idea that increased Lp(a) levels substantially contribute to the excess coronary heart disease risk observed in NIDDM subjects and people with minor degrees of hyperglycemia.

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