Lipoprotein(a) as a Risk Factor for Cardiovascular Mortality in Type 2 Diabetic Patients

A 10-year follow-up study

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Although patients with type 2 diabetes have a high risk of death from cardiovascular disease (CVD), the traditional risk factors do not fully explain this excess of mortality. In this regard, it would be of great interest to assess the role of nontraditional risk factors such as lipoprotein(a) in cardiovascular mortality in diabetic patients.

Danesh et al. (1), in a meta-analysis including the prospective studies published before 2000, concluded that there was a clear association between lipoprotein(a) and CVD in the general population. Further prospective reports have demonstrated that lipoprotein(a) is an independent predictor of the development of CVD (2–5). However, little data exist on the clinical importance of lipoprotein(a) in the diabetic population. We herein report a prospective study to evaluate the relationship between lipoprotein(a) levels and cardiovascular mortality in type 2 diabetic patients of Caucasian origin.

RESEARCH DESIGN AND METHODS

— One hundred twenty-two consecutive type 2 diabetic outpatients of Caucasian origin attending the outpatient diabetic unit of a university hospital between April and May of 1993 were enrolled for a 10-year prospective study. To avoid the possible transient increase of lipoprotein(a) after starting insulin treatment (6), all patients in whom insulin treatment was initiated in the months before the study were excluded. Patients with renal failure were also excluded. To assess evidence of macroangiopathy, we used the World Health Organization (WHO) protocol, which includes a detailed questionnaire and a 12-lead electrocardiogram (7,8). By the end of the study, data were available from 100 patients. Of these, 29 had died (23 from CVD).

Metabolic parameters were evaluated in venous blood drawn after overnight fasting. Lipoprotein(a) was measured by enzyme-linked immunosorbent assay using a monoclonal lipoprotein(a) antibody technique (Macra Terumo, Newark, DE).

Statistical analysis

The Student's *t* test for continuous variables and the χ^2 test for categorical variables were used. In view of their skewed distribution of lipoprotein(a), triglycerides and albumin excretion rate results were logarithmically transformed. Correlations were studied by linear regression analysis. The event studied was death from vascular disease, e.g., coronary heart disease (CHD) or stroke event. Curves of event-free survival were estimated by the Kaplan-Meier method. To further explore the variables independently associated with cardiovascular mortality (dependent variable), a logistic regression analysis was performed taking into account lipoprotein(a), age, sex, BMI, smoking habit, HbA_{1c}, creatinine, albumin excretion rate, LDL cholesterol, HDL cholesterol, triglycerides, and the presence of hypertension, macroangiopathy, and retinopathy (independent variables). In the present study, the cutoff point was lowered to 20 mg/dl because this enabled us to obtain a sufficient cohort of patients (top quarter) at risk of cardiovascular mortality due to lipoprotein(a) levels. The data were analyzed with SPSS.

RESULTS

— The clinical characteristics and cardiovascular risk factors at baseline for patients in the study are shown in Table 1. During follow-up total mortality was 29% ($n = 29$), and 23 of 29 (79.3%) diabetic patients died due to CVD (18 from CHD and 5 from stroke). The lipoprotein(a) concentration was higher in patients who died from CVD (median 15.5 mg/dl [range 0.5–75]) than those who remained alive or those who died from non-CVD causes (6 mg/dl [0.5–85], $P = 0.03$). The coefficient of correlation between baseline lipoprotein(a) and final lipoprotein(a) performed in the subjects who were still alive at the end of follow-up ($n = 71$) was 0.88 ($P < 0.001$).

In the cross-sectional statistical analysis at the beginning of the study, diabetic patients with macroangiopathy had higher lipoprotein(a) concentrations than those without macroangiopathy (Table 1). There were no differences at baseline in the classic cardiovascular risk factors between patients with high (≥20 mg/dl) or low (<20 mg/dl) concentrations of lipoprotein(a) except for total cholesterol (Table 1). Among patients with serum lipoprotein(a) ≥20 mg/dl, 38.4% ($n = 10$)

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Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; WHO, World Heath Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Univariate analyses comparing clinical features at baseline according to both lipoprotein(a) concentration and cardiovascular mortality*

	Lipoprotein(a) ≥20	Lipoprotein(a) <20	*P*	Group A	Group B	*P*
n	26	74		23	77	
Age (years)	59.1 ± 11	61.3 ± 10	0.36	65.3 ± 9	59.4 ± 10	0.02
Sex (M/F)	12/14	27/47	0.04	9/14	30/4	0.81
BMI (kg/m^2)	27.1 ± 3.4	29 ± 5.3	0.08	29 ± 4	28.5 ± 5	0.66
Smoking habit	3 (11.5)	9 (12.1)	0.62	4/19	8/69	0.55
Hypertension	10 (38.4)	31 (41.9)	0.47	14/9	27/50	0.04
Dyslipemia	14 (53.8)	34 (45.9)	0.32	13/10	35/41	0.34
Total cholesterol (mg/dl)	253 ± 60	225 ± 46	0.02	244 ± 63	229 ± 48	0.28
HDL cholesterol (mg/dl)	52 ± 10	52 ± 14	0.83	50 ± 14	52 ± 13	0.63
LDL cholesterol (mg/dl)	162 ± 38	138 ± 46	0.21	151 ± 34	148 ± 55	0.86
Triglycerides (mg/dl)	149 (62–718)	148 (56–1,826)	0.82	146 (62–616)	148 (56–1,826)	0.53
Apoprotein A1 (mg/dl)	169 ± 32	159 ± 30	0.16	160 ± 36	162 ± 30	0.77
Apoprotein B (mg/dl)	155 ± 39	138 ± 46	0.11	149 ± 44	140 ± 45	0.46
Lipoprotein(a) (mg/dl)	27 (20–85)	5.5 (0.5–19.5)	—	15.5 (0.5–75)	6 (0.5–85)	0.03
Diabetes duration (years)	10.5 ± 8.5	10.3 ± 7.9	0.90	11.1 ± 9.2	10.2 ± 7.7	0.64
HbA_{1c} (%)	7.9 ± 2	8.1 ± 1.7	0.65	8.6 ± 1.7	7.8 ± 1.7	0.07
Creatinine (mg/dl)	1.04 ± 0.3	1.01 ± 0.2	0.59	1 ± 0.3	1 ± 0.19	0.48
Albumin excretion rate (μg/min)	5.1 (1–500)	6.4 (0.5–550)	0.14	9.4 (1–90)	5.1 (0.5–550)	0.41
Retinopathy	11 (42.3)	29 (39.2)	0.47	13 (57)	27 (35)	0.10
Nephropathy	11 (42.3)	20 (27)	0.11	12 (52)	19 (25)	0.02
Neuropathy	8 (30.7)	19 (25.7)	0.39	11 (48)	16 (21)	0.02
Macroangiopathy	14 (53.8)	22 (29.7)	0.02	14 (61)	22 (29)	0.005
CHD	7 (27)	15 (20)		13 (57)	9 (12)	
Stroke	6 (23.1)	4 (5)		5 (22)	6 (8)	
Peripheral arterial disease	5 (19)	9 (12)		8 (35)	8 (10)	

Data are means ± SD, median (range), or *n* (%). Group A: patients deceased due to CVD. Group B: patients alive or deceased due to non-CVD causes.

died of CVD during the study, whereas only 17.5% of patients ($n = 13$) with lipoprotein(a) <20 mg/dl died of CVD ($P = 0.03$). The survival rate from cardiovascular events calculated by means of Kaplan-Meier curves showed that it was lower in those patients in whom lipoprotein(a) was ≥20 mg/dl (log-rank test = 5.1, $P = 0.02$). The logistic regression analysis showed that both lipoprotein(a) concentration (log transformed) and the presence of macroangiopathy at baseline were independent risk factors for cardiovascular mortality (risk ratio 6.7 [1.3–20], $P = 0.018$ and 5.4 [1.3–27.9], $P = 0.017$, respectively). Furthermore, a lipoprotein(a) level ≥20 mg/dl was independently associated with a more than sixfold greater risk of cardiovascular mortality (6.6 [1.6–26.8], $P = 0.008$).

CONCLUSIONS — In this prospective study, we found for the first time that lipoprotein(a) concentration is an independent risk factor for cardiovascular mortality in type 2 diabetic patients. Although lipoprotein(a) serum concentration >30 mg/dl has generally been considered a cardiovascular risk factor, in the present study the cutoff point of 20 mg/dl was selected because it was the lowest lipoprotein(a) level that allowed us to identify those diabetic patients at risk for cardiovascular mortality.

To our knowledge there are only three prospective studies in which the predictive value of lipoprotein(a) on CVD in the diabetic population has been evaluated (9–11). Hiraga et al. (9) demonstrated that lipoprotein(a) was an independent risk factor for CVD in Japanese type 2 diabetic patients. However, the follow-up was short, and plasma lipoprotein(a) was semiquantified by a rapid electrophoretic method that only discriminates high from low serum lipoprotein(a) at 20 mg/dl. Abu-Lebdeh et al. (10), using a similar method of lipoprotein(a) measurement, found no relationship between lipoprotein(a) and CVD. This study was performed in a cohort of type 2 diabetic patients with a short duration of diabetes (one-third were enrolled within 1 year of diagnosis of diabetes) and without CVD at baseline. By contrast, in our study a large percentage of patients (36%) presented macroangiopathy at baseline, the mean duration of diabetes was 10.4 ± 8.1 years, and lipoprotein(a) was assessed by enzyme-linked immunosorbent assay. All of these differences could explain, in part, why these authors did not find a relationship between lipoprotein(a) and CVD. In this regard, it should be noted that the deleterious effect of lipoprotein(a) on CVD is higher in subjects with other risk factors (2,3). Finally, the study published by Simons et al. (11) was performed in elderly patients. It has been shown that the impact of elevated lipoprotein(a) on CHD appears to decrease with age (12). Therefore, the lack of relationship between lipoprotein(a) and CHD observed by these authors could be due to this selection bias.

Our findings suggest that the assessment of lipoprotein(a) concentration could contribute to the identification of diabetic patients with high risk of death due to CVD. However, only patients at-

tending the outpatient clinic of a hospital (high-risk patients) have been included, and, therefore, one should be cautious about extrapolating our results to the general type 2 diabetic population. In addition, this study was not controlled for treatments that could influence cardiovascular mortality. With these caveats in mind, it is proposed that in those patients in whom lipoprotein(a) is ≥20 mg/dl, a strict follow-up to achieve the goals recommended by the American Diabetes Association should be a priority. Further studies to evaluate whether the treatment of cardiovascular risk factors in diabetic patients with high lipoprotein(a) should be more aggressive than currently recommended are needed. In addition, studies including a larger cohort of diabetic patients and control subjects for treatments influencing survival are necessary to confirm the findings of the present report.

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