Plasma Lipoprotein(a) Levels Are Not Influenced by Glycemic Control in Type 1 Diabetes

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OBJECTIVE — To determine the influence of glycemic control improvement with intensive therapy on lipoprotein(a) [Lp(a)] concentrations in type 1 diabetic patients.

RESEARCH DESIGN AND METHODS — A total of 105 poorly controlled type 1 diabetic patients (60 men, 45 women) without diabetic complications participated in a longitudinal study performed in a tertiary referral center, to compare lipid, lipoprotein, and Lp(a) levels before and after 3 months of intensive therapy with multiple insulin doses. Lp(a) levels were measured by the Terumo method. Differences between the two periods were assessed by the paired *t* test and Wilcoxon's test.

RESULTS — After 3 months of intensive therapy, all patients exhibited improved glycemic control. HbA_{1c} decreased from 8.9 ± 2.4 to 6.5 ± 1.6% ($P < 0.0001$), being ≤6% in 47% of patients. However, although a more favorable lipoprotein profile was obtained, no changes in Lp(a) concentrations were observed in the whole group of patients (16.7 ± 17.3 vs. 17.2 ± 17.7 mg/dl) or in patients with baseline Lp(a) levels above 30 mg/dl (47.1 ± 14.8 vs. 47.4 ± 18.9 mg/dl) or below 30 mg/dl (9.6 ± 7.3 vs. 10.2 ± 6.7 mg/dl). In addition, patients reaching HbA_{1c} ≤6 or >6% presented similar Lp(a) levels (19.7 ± 18.0 vs. 15.0 ± 17.4 mg/dl), and changes in Lp(a) did not correlate with those observed in HbA_{1c}.

CONCLUSIONS — These data demonstrate that the improvement of glycemic control does not influence plasma Lp(a) concentrations in type 1 diabetic patients independently of baseline Lp(a) levels and the degree of glycemic control.

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The risk of cardiovascular disease is increased in patients with type 1 diabetes, and this excess of risk cannot totally be attributed to conventional risk factors (1–3). Another possible factor that is potentially implicated, and the subject of recent and extensive studies, is lipoprotein(a) [Lp(a)].

Lp(a) has been identified as an independent risk factor for atherosclerotic vascular disease in the general population (4–7). The link between atherosclerosis and Lp(a) may be the striking homology between apolipoprotein(a) and plasminogen (7–9). The presence of Lp(a) in atherosclerotic plaques is further evidence of its potential role in atherogenesis (10).

Results of studies assessing Lp(a) levels in type 1 diabetic patients are inconsistent, showing either normal (11–18) or increased levels (19–22). The most controversial area concerning Lp(a) and type 1 diabetes is whether there is a relationship between Lp(a) levels and glycemic control. Although some studies indicated that Lp(a) levels increase with worsening glycemic control (13,23–28), others have failed to confirm it (14,16,19–21,29,30). Most protocols that investigate this issue have been cross-sectional (13,14,16,19–21,23–30), and available longitudinal studies have included a small number of patients followed for a brief period (24,28,29). The Diabetes Control and Complications Trial's (DCCT) cross-sectional comparison at the final evaluation revealed that both control subjects and type 1 diabetic patients receiving intensive therapy displayed lower plasma Lp(a) levels than did patients receiving conventional treatment (22). However, Lp(a) levels did not correlate with HbA_{1c} under any treatment. On the basis of the contradictory results and in order to resolve this question, we examined the effect of 3-month improved glycemic control on Lp(a) concentrations in a group of 105 poorly controlled type 1 diabetic patients.

RESEARCH DESIGN AND METHODS

Patients

The study population consisted of 105 type 1 diabetic patients (60 men, 45 women) recruited from the diabetes clinic on the basis of their deficient glycemic control and the absence of chronic diabetic complications. The diagnosis of type 1 diabetes was based on World Health Organization criteria (31). None of the patients had retinopathy, albumin excretion rate ≥20 μg/min or serum creatinine ≥120 μmol/l, or macrovascular complications. Furthermore, none of the patients were taking any drug (other than insulin) or presented with any disease known to affect lipoprotein metabolism. All patients were included in an intensive insulin therapy regimen, with regular insulin before main meals and intermediate insulin before dinner or at bedtime. Patients received an isocaloric diet, providing 50–55% carbohydrate and 30–35% fat, and they underwent a specific diabetes education program. All patients were

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Abbreviations: DCCT, Diabetes Control and Complications Trial; Lp(a), lipoprotein(a).

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

Table 1—*Effect of improved glycemic control on plasma lipoprotein(a), lipids, and lipoproteins in 105 type 1 diabetic patients*

	Before	After 3 months	*P*
HbA_{1c} (%)	8.9 ± 2.4	6.5 ± 1.6	<0.0001
Fructosamine (μmol/l)	452 ± 125	349 ± 90	<0.0001
BMI (kg/m²)	22.45 ± 3.24	22.50 ± 4.72	NS
Total cholesterol (mmol/l)	4.79 ± 0.88	4.29 ± 0.88	<0.05
HDL cholesterol (mmol/l)	1.17 ± 0.33	1.33 ± 0.33	<0.01
LDL cholesterol (mmol/l)	3.15 ± 0.90	2.70 ± 0.71	<0.0001
VLDL cholesterol (mmol/l)	0.45 ± 1.15	0.27 ± 0.31	<0.05
Triglyceride (mmol/l)	1.40 ± 2.43	0.83 ± 0.50	<0.01
Lipoprotein(a) (mg/dl)	16.7 ± 17.3	17.2 ± 17.7	NS
Lipoprotein(a) ≥30 mg/dl (%)	19	16	NS

Data are means ± SD, unless otherwise indicated.

instructed for self-monitoring of blood glucose 4 or more times per day and were visited in the outpatient unit every 2–4 weeks. The study was approved by the Ethics Committee in the hospital, and all the patients gave informed consent.

Laboratory analysis

Blood samples were obtained, after a fast of at least 10 h, from all type 1 diabetic patients at baseline. A second laboratory assessment was carried out 3 months later, after registered improvement of glycemic control (decrease in HbA_{1c} ≥1%). Serum samples were stored at −80°C before the Lp(a) assay was done.

Glucose was determined by an automated enzymatic method and fructosamine by a colorimetric method, using glycated albumin as a pattern of the reaction (Boehringer Mannheim, Mannheim, Germany; reference range: 205–285 μmol/l). HbA_{1c} was measured by high-performance liquid chromatography (Hi-Auto A_{1C} HA-8121 Analyzer; Dic-Kioto, Kyoto, Japan; reference range: 3.7–5.5%; intra- and interassay coefficients of variability: 3.2 and 5.5, respectively). Cholesterol and triglyceride were determined by standard enzymatic methods (Boehringer Mannheim) adapted to a RA-XT autoanalyzer (Technicon Instruments, Tarrytown, NY). HDL cholesterol, LDL cholesterol, and VLDL cholesterol were determined using a combined ultracentrifugation-precipitation method recommended by the Lipid Research Clinics Laboratory (32).

Lp(a) levels were measured by an enzyme-linked immunoassay technique using a monoclonal anti-Lp(a) antibody (Terumo Medical, Elkton, MD). The intra- and interassay coefficients of variation were 6.4 and 7.8%, respectively.

Statistical analysis

All data are expressed as means ± SD. $P < 0.05$ was considered significant. Triglyceride, VLDL cholesterol, and Lp(a) were logarithmically transformed to improve skewness. Paired *t* test and Wilcoxon's test were used to analyze changes in the lipid profile and in glycemic control. Pearson's correlation coefficient was used to determine the relationship between changes in glycemic control and log-transformed Lp(a) levels.

RESULTS — Table 1 shows glycemic control, BMI, lipid, lipoprotein, and Lp(a) levels before and after 3 months of intensive therapy with multiple insulin doses. A significant improvement of glycemic control was obtained as assessed by fructosamine and HbA_{1c} levels, without changes in BMI. All patients exhibited improved glycemic control (mean HbA_{1c} decrement was 2.4 ± 2.5%), with HbA_{1c} ≤6% in 47% of patients. The improvement of glycemic control was accompanied by a decrease in total cholesterol, triglyceride, VLDL cholesterol, and LDL cholesterol, as well as an increase in HDL cholesterol. However, no changes in Lp(a) concentrations were observed, and changes in Lp(a) levels did not correlate with those observed in fructosamine, HbA_{1c}, and BMI. Moreover, when patients with baseline Lp(a) levels above or below 30 mg/dl were studied separately, Lp(a) levels also remained unchanged after glycemic control improvement (Table 2, Fig. 1). The lack of change in Lp(a) levels after the improvement of glycemic control was observed in patients with an HbA_{1c} decrement either ≥2% (n = 46; 19.4 ± 16.8 vs. 20.1 ± 17.4 mg/dl) or <2% (n = 59; 14.4 ± 17.5 vs. 14.8 ± 17.7 mg/dl). Finally, patients reaching HbA_{1c} ≤6% (mean HbA_{1c} 5.3 ± 0.5%) or >6% (mean HbA_{1c} 7.7 ± 1.3%) presented similar Lp(a) levels (19.7 ± 18 vs. 15.0 ± 17.4 mg/dl).

CONCLUSIONS — Results of the DCCT (33) have shown that improved glycemic control in type 1 diabetic subjects delays the onset and slows the progression of diabetic retinopathy, nephropathy, and neuropathy. However, macrovascular disease remains the most common cause of morbidity and mortality in diabetic patients, and the St. Vincent Declaration has called for systematic screening and reduction of risk factors of macrovascular disease in such patients (34).

Researchers have postulated that Lp(a) may explain, in part, the increased risk of vascular disease associated with diabetes that exists after the adjustments for conventional risk factors. However, results of studies assessing Lp(a) concentrations in the general diabetic population, and especially in type 1 diabetic patients, are controversial, and the role of Lp(a) in atherogenesis in diabetic patients is still unknown.

Based on the association between glycemic control and Lp(a) levels in some cross-sectional studies and earlier longitudinal studies in type 1 diabetic patients, poor glycemic control has been proposed as one of the causes of high plasma Lp(a) levels in diabetic patients through an unknown mechanism. However, the relationship between glycemic control and plasma lipoprotein(a) levels in diabetes, especially in type 1 diabetic subjects, has not been fully

Table 2—*Lp(a) levels before and after the improvement of glycemic control in type 1 diabetic patients with baseline Lp(a) levels above and below 30 mg/dl*

	Lp(a) ≥30 mg/dl (n = 20)		Lp(a) <30 mg/dl (n = 85)	
	Before	After	Before	After
HbA_{1c} (%)	9.1 ± 2.3	5.9 ± 1.4	8.9 ± 2.4	6.7 ± 1.6
Lp(a) (mg/dl)	47.1 ± 15	47.4 ± 19	9.6 ± 7	10.2 ± 7

Data are means ± SD.

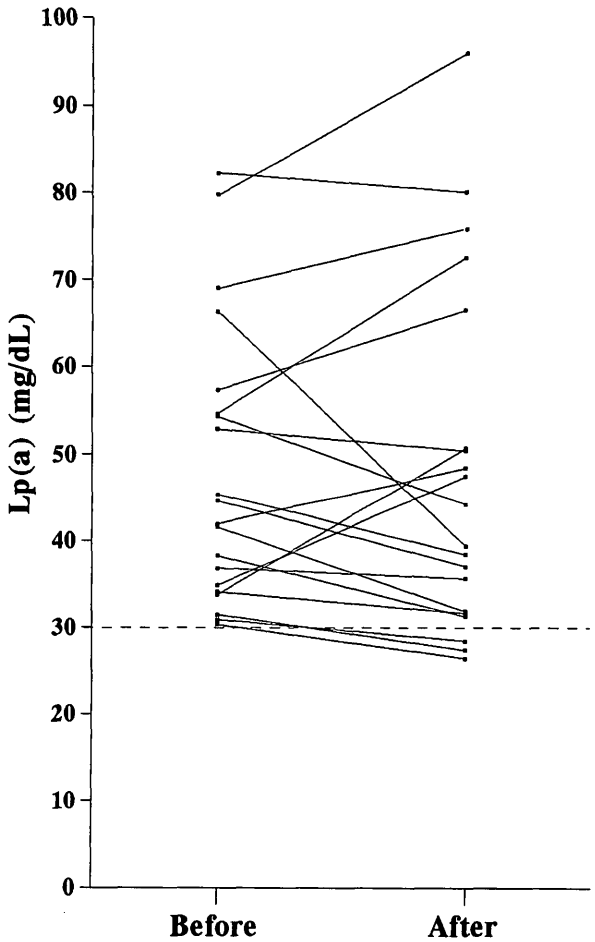

Figure 1—*Individual levels of Lp(a) before and after the improvement of glycemic control in 20 type 1 diabetic patients with baseline Lp(a) levels ≥30 mg/dl.*

clarified. In cross-sectional studies of type 1 diabetic subjects, Lp(a) levels have been reported to be positively related to HbA_{1c} (13,23,25–27). In contrast, findings obtained by our group (30) and others (14,16,19–21) show no relationship between Lp(a) levels and the degree of glycemic control. Finally, Purnell et al. (22) found higher Lp(a) levels in patients receiving conventional therapy compared with patients receiving intensive therapy, although Lp(a) levels showed no correlation with HbA_{1c} in either treatment group. These conflicting data may be attributed, at least in part, to the limitations of cross-sectional studies. Therefore, well-designed longitudinal studies were required to clarify the relationship between glycemic control and Lp(a) in type 1 diabetes. To our knowledge, only two studies have examined the effect of the improvement of glycemic control on Lp(a) levels in type 1 diabetic subjects. A significant reduction in plasma Lp(a) levels has been reported 3 weeks after improvement of glycemic control in 10 type 1 diabetic subjects with high levels of Lp(a) by Bruckert et al. (24) and in 12 type 1 diabetic subjects by Haffner et al. (28). In the present study, plasma Lp(a) levels did not decrease when glycemic control was considerably improved by intensive therapy, despite significant improvement of other lipid parameters, as reported by other authors (35,36). Moreover, the lack of change in Lp(a) levels was independent of baseline Lp(a) levels, of the degree of glycemic control improvement measured by the decrement of HbA_{1c}, and of the degree of glycemic control reached. Interestingly, these findings are consistent with previous studies carried out by our group and others in subjects with type 2 diabetes investigated 21 days (n = 12) (37), 30 days (n = 54) (38), 3 months (n = 60) (39), and 6 months (n = 54) (40) after the improvement of glycemic control. In addition, Ritter et al. (29) did not find a significant effect of a mild improvement of glycemic control in nine type 1 and nine type 2 diabetic subjects. Possibly, discrepancies in the effect of improved glycemic control on Lp(a) levels in both type 1 and type 2 diabetic subjects may be explained either by the small number of patients included or by the brief duration of some studies (12,24,29,37). In our study, the sample size was large (n = 105), and patients were highly selected on the basis of their deficient glycemic control and absence of late diabetic complications. In addition, the duration of the study was sufficient on the basis of both the fractional catabolic rate of Lp(a) (41,42) and the assessment of diabetes control using HbA_{1c}. Furthermore, a marked improvement of glycemic control was obtained (mean HbA_{1c} decrement was 2.36 ± 2.5%) without associated changes in other clinical characteristics, such as BMI, that may potentially affect Lp(a) levels (43). Finally, although the method used to measure Lp(a) (Terumo method) reflects not only the change in the concentration of Lp(a) in terms of moles per deciliter but also variations in the genetically determined size of apolipoprotein(a), the proportion of Lp(a) measurement related to molar concentration did not cause influence, because the study was performed before and after in the same patients. Thus, we believe that the lack of response of Lp(a) levels to the improvement of glycemic control may not be attributed to these methodological issues.

In conclusion, our findings revealed that a marked improvement in glycemic control by intensive therapy with multiple insulin doses does not influence plasma Lp(a) levels in type 1 diabetic patients, independent of baseline Lp(a) levels and the degree of glycemic control improvement. These findings suggest that glycemic control and plasma Lp(a) concentrations are not related in type 1 diabetic patients.

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