Lack of Change of Lipoprotein(a) Levels by the Optimization of Glycemic Control With Insulin Therapy in NIDDM Patients

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OBJECTIVE — To evaluate the effect of glycemic control improvement with insulin therapy on lipoprotein(a) [Lp(a)] levels in patients with NIDDM.

RESEARCH DESIGN AND METHODS — We performed a longitudinal study in a tertiary referral center to compare lipid and Lp(a) levels before and after 3 months of insulin therapy in 60 poorly controlled NIDDM patients (32 men, 28 women). Patients previously treated with oral hypoglycemic agents (n = 50) received one to two insulin doses, and those previously treated with insulin (n = 10) received 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 insulin therapy, HbA_{1c} decreased from 9.6 ± 1.9 to 6.0 ± 1.4% ($P < 0.0005$) in all patients and from 9.1 ± 2.1 to 6.1 ± 2.9% ($P < 0.05$) in patients under multiple insulin doses, being ≤6.0% in 59% of patients. Total triglyceride and VLDL cholesterol levels decreased ($P < 0.01$) and HDL cholesterol increased significantly ($P < 0.0005$). However, no changes in Lp(a) levels were observed in all patients (25.3 ± 25.0 vs 25.7 ± 27.2% mg/dl) and in patients with baseline Lp(a) levels above (63.5 ± 15.5 vs. 65.1 ± 23.1 mg/dl) or below 30 mg/dl (11.5 ± 7.5 vs. 11.5 ± 7.3 mg/dl). In addition, patients reaching HbA_{1c} levels ≤6.0% or >6.0% presented similar Lp(a) levels (26.0 ± 29.1 vs 25.3 ± 25.0 mg/dl). Moreover, no correlations were observed between changes in Lp(a) levels and in the glycemic control parameters.

CONCLUSIONS — This study shows that the improvement of glycemic control by insulin therapy does not influence plasma Lp(a) levels, measured by the Terumo method, in NIDDM patients, independently of baseline values and the degree of glycemic control reached.

The risk of cardiovascular disease is increased in NIDDM patients (1), but the precise reasons for this excess of risk are not known. Lipoprotein(a) [Lp(a)] levels are considered an independent risk factor for coronary heart disease in the general population (2) and in both NIDDM and IDDM patients (3,4). However, results of studies in NIDDM patients are inconsistent, showing normal (5–8), higher (9–12), or even lower (13) Lp(a) levels as compared with nondiabetic subjects. Furthermore, the relationship between glycemic control and Lp(a) levels in NIDDM has not been fully clarified. Most of the information comes from cross-sectional studies (9,14–17) and only a few have evaluated the effect of improving glycemic control on Lp(a) levels in NIDDM patients (7,10–12,18). In this report, we have examined the effect of 3-month improvement of glycemic control with insulin therapy on Lp(a) levels in 60 poorly controlled NIDDM patients reaching near-normal blood glucose control.

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Abbreviations: Lp(a), lipoprotein(a).

RESEARCH DESIGN AND METHODS

Patients

Sixty NIDDM patients (32 men, 28 women) were recruited from the diabetes clinic on the basis of poor glycemic control despite diet plus oral hypoglycemic agents (n = 50) or diet plus insulin (n = 10). Mean age was 60.5 ± 9.7 years, mean BMI 25.7 ± 3.3 kg/m², and mean diabetes duration 8.0 ± 7.9 years. NIDDM was defined according to the National Diabetes Data Group criteria (19). Of the patients, 14 (23%) had nonproliferative retinopathy and 2 (3%) had clinical coronary heart disease. None had albumin excretion rate ≥20 µg/min or creatinine ≥120 µmol/l. In addition, none of the patients were taking any drug (other than insulin) or presented any disease known to affect lipoprotein metabolism. All patients previously treated with oral hypoglycemic agents (n = 50) received NPH insulin at bedtime or before breakfast and dinner. Patients already under insulin treatment (n = 10) received regular insulin before main meals plus ultralente insulin before dinner. All patients were instructed in observing an isocaloric diet, providing 50–55% carbohydrate and 30–35% fat, and in self-monitoring blood glucose two or more times per day. All these patients were visited in the outpatient unit at least every 3–6 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 at least a 10-h fast in all NIDDM patients at baseline and after 3 months of improved glycemic control with insulin therapy (decrease in HbA_{1c} >1%). Serum samples were stored at −80°C before Lp(a) assay. 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-pressure liquid chromatography (Hi-Auto A1c HA-8121 Analyzer; Dic-Kyoto,

Table 1—*Effect of optimized glycemic control on plasma Lp(a), lipid, and lipoproteins in 60 NIDDM patients*

	Before	After 3 months	*P*
HbA_{1c} (%)	9.6 ± 1.9	6.0 ± 1.4	<0.0005
Fructosamine (μmol/l)	409 ± 89	322 ± 69	<0.0005
BMI (kg/m²)	25.7 ± 3.3	26.4 ± 3.1	NS
Total cholesterol (mmol/l)	5.3 ± 1.0 (205.1 ± 38.7)*	5.3 ± 1.0 (205.1 ± 38.7)*	NS
HDL cholesterol (mmol/l)	1.1 ± 0.4 (42.6 ± 15.5)*	1.3 ± 0.4 (50.3 ± 15.5)*	<0.0005
LDL cholesterol (mmol/l)	3.5 ± 0.9 (135.4 ± 34.8)*	3.4 ± 0.8 (131.6 ± 31.0)*	NS
VLDL cholesterol (mmol/l)	0.57 ± 1.0 (22.1 ± 38.7)*	0.45 ± 0.4 (17.4 ± 15.5)*	<0.01
Triglyceride (mmol/l)	1.7 ± 1.0 (150.5 ± 87.5)*	1.4 ± 1.9 (123.9 ± 168.2)*	<0.01
Lipoprotein(a) (mg/dl)	25.3 ± 25.0	25.7 ± 27.2	NS

*Expressed in milligrams per deciliter.

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 an RA-XT autoanalyzer (Technicon Instruments, Tarrytown, NY). HDL, LDL, and VLDL cholesterol levels were determined using a combined ultracentrifugation-precipitation method recommended by the Lipid Research and Clinics Laboratory (20). 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.

Statistics

All data are expressed as mean ± 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 in log-transformed Lp(a) levels.

RESULTS — Table 1 shows glycemic control, lipid, lipoprotein, and Lp(a) levels before and after 3 months of insulin therapy in 60 NIDDM patients. All patients exhibited improved glycemic control (HbA_{1c} decreased >1%), being ≤6% in 59% of patients. The improvement of glycemic control was followed by a decrease in total triglyceride ($P < 0.01$) and VLDL cholesterol ($P < 0.01$), as well as an increase in HDL cholesterol ($P < 0.0005$). However, no changes in total cholesterol, LDL cholesterol, and Lp(a) levels were observed. Moreover, the lack of change in Lp(a) levels after the improvement of glycemic control was observed in NIDDM patients either with baseline levels <30 mg/dl (n = 44, 11.5 ± 7.5 vs. 11.5 ± 7.3 mg/dl) or ≥30 mg/dl (n = 16, 63.5 ± 15.5 vs. 65.1 ± 23.1 mg/dl) (Fig. 1). Furthermore, changes in Lp(a) levels did not correlate with those observed in fructosamine and HbA_{1c}, and patients reaching HbA_{1c} ≤6% presented Lp(a) levels similar to those of patients who did not reach this goal (26.0 ± 29.1 vs. 25.3 ± 25.0 mg/dl). Comparable changes in glycemic control and Lp(a) levels were obtained in 10 patients treated with multiple insulin doses: mean HbA_{1c} decreased from 9.0 ± 2.0 to 6.1 ± 2.9 mg/dl ($P < 0.05$) and mean Lp(a) levels remained unchanged (26.0 ± 29.1 to 24.7 ± 27.2 mg/dl).

CONCLUSIONS — As in the general population, elevated Lp(a) levels (>30 mg/dl) are considered an independent risk factor for cardiovascular disease in NIDDM (3). However, although higher Lp(a) levels have been reported in NIDDM patients (9–12) in recent years, most researchers agree that Lp(a) concentrations are not different from those of nondiabetic control subjects (5–8). Poor glycemic control has been proposed as one of the causes of high plasma Lp(a) levels in diabetic patients through an unknown mechanism and, therefore, optimization of glycemic control

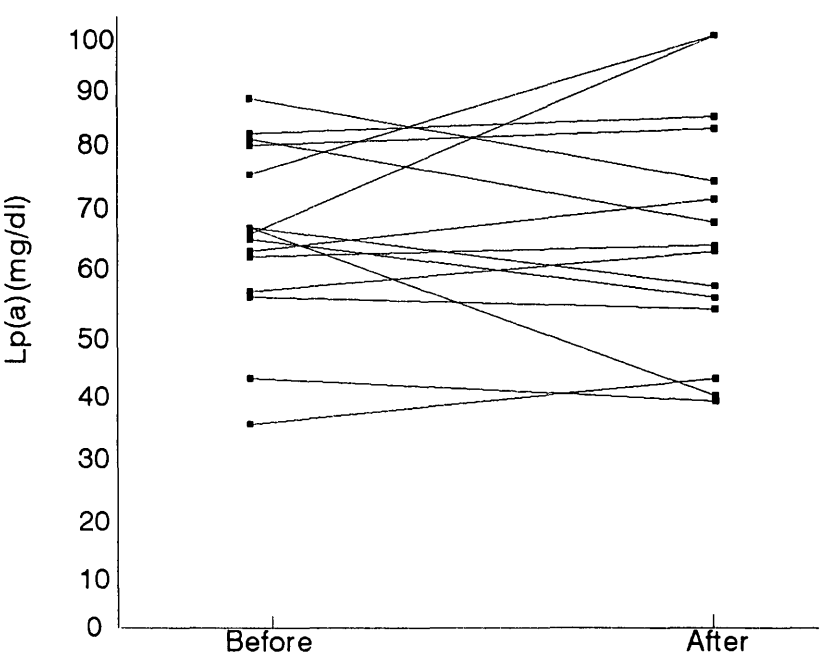

Figure 1—*Lp(a) levels before and after the improvement of glycemic control in NIDDM patients with baseline Lp(a) levels ≥30 mg/dl.*

may prevent the development of macrovascular disease by reducing Lp(a) levels (9,11). This hypothesis is based on the association between glycemic control and Lp(a) levels found in some cross-sectional studies (9) and the reduction of Lp(a) levels observed after the improvement of glycemic control in IDDM subjects (21).

In the present study, plasma Lp(a) levels, independently of baseline levels, did not decrease when glycemic control was markedly improved by insulin therapy in 60 NIDDM patients previously treated with oral hypoglycemic agents or insulin. These findings are consistent with others obtained by our group in 54 IDDM subjects (22) and confirm the findings of previous longitudinal studies performed in NIDDM with a small number of patients (6,12), during a short period of time (6,10), or without achieving an optimization of glycemic control (7,10,12). Nakata et al. (11) reported a slight positive correlation among changes in Lp(a) and HbA_{1c} levels after a 3-month follow-up period. However, this association could be a statistical effect, since mean HbA_{1c} levels before and after the study were identical. Kuusi et al. (7) demonstrated that insulin treatment increased Lp(a) levels in patients with baseline values <30 mg/dl, while those with baseline values ≥30 mg/dl remained unchanged, which was not confirmed by our study. In the present study, the sample size was large enough and the duration of the study was sufficient on the basis of the fractional catabolic rate of Lp(a) and the assessment of glycemic control by HbA_{1c}. Furthermore, a marked improvement of glycemic control was obtained, being nearly normal in most of the patients. In addition, although the method used to measure Lp(a) (Terumo method) reflects not only the changes in the concentration of Lp(a) in terms of moles per deciliter but also variations in the genetically determined size of (a), the portion of the Lp(a) measurement related to molar concentration did not cause influence, since the study was performed before and after in the same patients. Thus, the lack of effect of the improvement of glycemic control on Lp(a) levels cannot be attributed to methodological issues.

In conclusion, this study has shown that improvement of glycemic control by insulin therapy does not influence plasma Lp(a) levels, measured by the Terumo method, in NIDDM patients, independently of baseline values and the degree of glycemic control reached. Therefore, improvement of glycemic control does not decrease the possible risk of cardiovascular disease mediated by Lp(a) levels in NIDDM patients.

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