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Levels of Lipoprotein(a), Apolipoprotein B, and Lipoprotein Cholesterol Distribution in IDDM: Results From Follow-up in the Diabetes Control and Complications Trial

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Abstract

Levels of lipoprotein (a) [Lp(a)], apolipoprotein (apo) B, and lipoprotein cholesterol distribution using density-gradient ultracentrifugation were measured as part of a cross-sectional study at the final follow-up examination (mean 6.2 years) in the Diabetes Control and Complications Trial. Compared with the subjects in the conventionally treated group (n = 680), those subjects receiving intensive diabetes therapy (n = 667) had a lower level of Lp(a) (Caucasian subjects only, median 10.7 vs. 12.5 mg/dl, respectively; P = 0.03), lower apo B (mean 83 vs. 86 mg/dl, respectively; P = 0.01), and a more favorable distribution of cholesterol in the lipoprotein fractions as measured by density-gradient ultracentrifugation with less cholesterol in the very-low-density lipoprotein and the dense low-density lipoprotein fractions and greater cholesterol content of the more buoyant low-density lipoprotein. Compared with a nondiabetic Caucasian control group (n = 2,158), Lp(a) levels were not different in the intensive treatment group (median 9.6 vs. 10.7 mg/dl, respectively; NS) and higher in the conventional treatment group (9.6 vs. 12.5 mg/dl, respectively; P less than 0.01). No effect of renal dysfunction as measured by increasing albuminuria or reduced creatinine clearance on Lp(a) levels could be demonstrated in the diabetic subjects. Prospective follow-up of these subjects will determine whether these favorable lipoprotein differences in the intensive treatment group persist and whether they influence the onset of atherosclerosis in insulin-dependent diabetes.

Keywords

Adolescent; Adult; African Continental Ancestry Group; Apolipoproteins B; Blood Glucose; Cholesterol; Cholesterol; LDL; Diabetes Mellitus; Type 1; Diabetes Mellitus; Type 1; European Continental Ancestry Group; Female; Follow-Up Studies; Hemoglobin A; Glycosylated; Humans; Hypoglycemic Agents; Longitudinal Studies; Male; Probability; Reference Values; Sex Characteristics; Triglycerides

The leading cause of death for patients with insulin-dependent diabetes mellitus (IDDM) is coronary artery disease (CAD) [1,2]. Current guidelines have sought to reduce morbidity and mortality from CAD in IDDM patients by improving glycemic control and addressing traditional risk factors for heart disease, such as smoking, hypertension, and hypercholesterolemia [3]. Low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol have been studied extensively in patients with IDDM, and recently, levels of triglyceride and LDL cholesterol were shown to be reduced by intensive diabetes treatment, although HDL cholesterol levels were unchanged [4]. Other lipoproteins and apolipoproteins are associated with an increased risk of CAD in the general population, including elevations in lipoprotein (a) [Lp(a)] [5], small dense LDL [5–7], and apolipoprotein (apo) B [8,9], but these risk factors have been less well characterized in individuals with IDDM.

Lp(a) is formed by a molecule of a carbohydrate-rich protein named apo(a) linked by a single disulfide bond to the apo B of an LDL-like lipoprotein. Like LDL, Lp(a) is thought to be atherogenic. Because of the structural homology of apo(a) to plasminogen, it is also thought to have thrombogenic properties. This potential combination of proatherogenic and prothrombotic properties has led to a surge of research into the role of Lp(a) in atherosclerosis. In several case-controlled and prospective studies consisting primarily of white men with at least one preexisting cardiac risk factor, such as a family history of heart disease or an elevated LDL cholesterol level, an increased Lp(a) level has been shown to be an independent risk factor for CAD [5,10,11].

Because up to 91 percent of the variability in plasma Lp(a) levels between individuals has been attributed to the apo(a) isoform [5,12], the contribution of age, sex, diet, and exercise to Lp(a) levels is thought to be small. Lp(a) levels have been shown to be higher in familial hypercholesterolemia [13], chronic renal failure [14–19], and nephrotic syndrome [20–25], and lower levels have been reported in cirrhosis [26]. How Lp(a) levels might be affected by IDDM and its complications and whether Lp(a) contributes to CAD [27,28] in this population remain controversial. Some investigators found elevated Lp(a) levels in subjects with IDDM compared with normoglycemic control subjects [29,30], while others have not [31–34]. Several studies of IDDM subjects have shown that Lp(a) levels increase with worsening glycemic control [35–40], although other studies have not [29,33,41,42]. Finally, earlier studies showed a direct correlation between the degree of proteinuria and increasing Lp(a) levels in subjects with IDDM [43–46], but more recent studies have not [31,42,47]. Many of the above studies were performed on small numbers of patients and had brief follow-up periods.

LDL characteristics, including size, density, and composition, appear to influence the risk for coronary atherosclerosis. In cross-sectional studies, small (as measured by gradient gel electrophoresis) and dense (as measured by density-gradient ultracentrifugation [DGUC]) LDLs have been associated with an increased risk of CAD defined by angiography and/or myocardial infarction [7]. In a previous study comparing IDDM subjects with normal control subjects, a significant decline of the LDL flotation rate and an increase in the cholesterol concentration of the dense LDL fraction (LDL3) were shown in the diabetic group [48] even though total LDL cholesterol levels were similar in both groups.

The Diabetes Control and Complications Trial (DCCT) was a multicenter randomized controlled clinical trial designed to determine whether an intensive treatment regimen would affect the appearance or progression of early microvascular and neurological complications in patients with IDDM compared with conventional therapy [49]. The DCCT demonstrated that intensive diabetes therapy delays the onset and slows the progression of retinopathy, nephropathy, and neuropathy in patients with IDDM [50]. Plasma Lp(a), apo B, and cholesterol distribution in various lipoprotein fractions using DGUC were measured as part of a cross-sectional ancillary study of the DCCT during the 1992 annual examination. These

measurements provide an opportunity to compare these lipids and apolipoproteins in individuals with IDDM who differ by degree of glycemic control and renal dysfunction and to determine how they compare with a nondiabetic control population.

RESEARCH DESIGN AND METHODS

Study design

The methods and trial design of the DCCT have been described elsewhere [49]. Briefly, it was a multicenter trial of 1,441 patients with IDDM who were 13–39 years of age at baseline, randomly assigned to receive conventional or intensive diabetic therapy for an average follow-up of 6.5 years. The study population included two separate cohorts, a primary prevention cohort and a secondary intervention cohort. The primary prevention cohort had IDDM for 1–5 years, no retinopathy, and albuminuria of less than 40 mg/24 h at baseline. The secondary intervention cohort had IDDM for 1–15 years, minimal to moderate nonproliferative retinopathy, and albuminuria of less than 100 mg/24 h at baseline. Subjects were excluded if they had a total cholesterol level greater than 3 SD above the mean for sex and age, as defined by the Lipid Research Clinics Population Studies Data Book [51], or calculated LDL cholesterol levels greater than 190; if they had a body weight greater than 30 percent above their ideal body weight as defined by the 1983 Metropolitan Life Insurance norms [52]; and if they had major electrocardiographic abnormalities, a clinical history of coronary heart disease, or symptoms of peripheral vascular disease.

For this study, serum for Lp(a), apo B, and lipoprotein distribution as measured by DGUC was taken only once at the final follow-up visit. Only those subjects ($n = 1,347$) who had measurements of kidney function (albuminuria, creatinine clearance, and serum creatinine), fasting lipids (triglycerides, total cholesterol, and HDL cholesterol), and body measurements (body mass index and weight-to-hip ratio) performed at the same time the serum was taken were included in the analysis. Of 1,378 patients who had samples available for DGUC measurement, those not included were 11 who died, 25 who were on inactive status, and the remainder for whom collection of data was incomplete (P.A.C., personal communication).

Mean follow-up in this study was 6.2 years. Of the 1,347 subjects included in Lp(a) analysis, 1,299 were Caucasians and 48 were members of ethnic minorities. Because of known differences in the distribution of Lp(a) levels between African-Americans and Caucasians [12], Lp(a) data for the African-Americans from the DCCT were analyzed separately. Lp(a) values in the few remaining minority subjects are presented separately.

Subjects from a multicenter longitudinal study (Coronary Artery Risk Development in Young Adults [CARDIA] study) who were recruited from the general population between 1985 and 1986 [12] (2,158 Caucasians and 2,007 African-Americans) were used as a control group in analysis of the Lp(a) results. These young adults were 18–30 years of age at the time of recruitment, and Lp(a) measurements were performed during the third follow-up examination (1990–1991). Exclusion criteria at entry were limited to only those subjects who had significant disease or disability that prohibited them from participating in the study: blindness, muteness, deafness, mental retardation, or inability to walk on a treadmill. Some baseline characteristics of this control group are shown in Table 1 [53].

Lp(a) protein, apo B concentration, and DGUC profile. Blood was drawn from the subjects after an overnight fast. After the plasma was separated and stored briefly at -20 degrees C, it was placed on dry ice and sent immediately to the DCCT Central Biochemistry Laboratory, where it was stored at -70 degrees C before being routed on dry ice to the Northwest Lipid Research Laboratories in Seattle.

Lp(a) mass was determined using a double monoclonal antibody-based enzyme-linked immunosorbent assay (ELISA) as reported [54]. Fresh-frozen plasma from individuals with various apo(a) isoforms and Lp(a) concentrations covering the 10th to the 90th percentile of Lp(a) distribution were used as quality controls in the assay. Five quality controls and 34 samples were analyzed in duplicate in each ELISA plate. The within-assay coefficient of variation (CV), determined by 35 measurements of each of the five quality control samples, ranged from 2.3 to 4.0 percent while the between-assay CV ranged from 4.0 percent to 6.9 percent. Apo B levels were measured by a highly standardized nephelometric system calibrated with the World Health Organization International Reference Material for apo B [55].

Lp(a) values for the control group were previously reported [12] in terms of the total protein component of Lp(a). In the majority of the published clinical studies, Lp(a) values have been reported in terms of total Lp(a) mass (protein, lipid, and carbohydrate components). Therefore, to facilitate the comparison of the control Lp(a) values with those reported in other clinical studies, we elected to report Lp(a) concentrations from the control group in terms of whole Lp(a) lipoprotein mass using the conversion formula $\text{Lp(a) mass} = \text{Lp(a) protein} \times 2.6$.

Lipoprotein cholesterol distribution was determined by nonequilibrium DGUC using a modification of a previously described technique [56] and a Beckman VTI-65 rotor. Plasma (1 ml) was mixed with 1.5 ml of NaCl (density 1.006) and 1.5 ml of KBr (density 1.21) for a final density of 1.080 g/ml and overlaid with 9.5 ml of NaCl (density 1.006). Samples were ultracentrifuged for 70 min at 65,000 rpm ($w^2t = 1.95 \times 10^{11}$) at 10 degrees C to separate the lipoproteins by flotation characteristics. An Isco fractionator (model 184) was used to drain the tubes from the bottom at a flow rate of 1.0 ml/min. Thirty-eight 0.35-ml fractions were then collected using a Pharmacia fraction collector. The cholesterol content in each fraction was measured using a cholesterol assay kit (Boehringer Mannheim, Indianapolis, IN). The variance of this technique was evaluated by repeat determination of a single sample stored at -70 degrees C for 12–24 months Figure 1. Relative flotation rates were determined by dividing the fraction number containing the peak LDL cholesterol from the DGUC profile by the total number of fractions collected. The CV of relative flotation rates for the 15 repeat DGUC spins is 3.6 percent.

Total cholesterol, triglyceride, and HDL cholesterol levels from the final DCCT follow-up were determined after an overnight fast of at least 8 h on the same day as the sample for the present study was drawn [4]. LDL cholesterol was calculated using the Friedewald equation: $\text{LDL cholesterol} = \text{total cholesterol} - (\text{HDL cholesterol} + \text{triglycerides}/5)$. HbA_{1C}, serum creatinine, and urinary albumin excretion were also measured at final follow-up as previously described [49].

Statistical analysis

Lp(a) results were analyzed using the Kolmogorov-Smirnov test and the Kruskal-Wallis analysis of variance by ranks. Results were considered significant if P less than 0.05. chi square analysis was used to determine differences in percentage of each group with Lp(a) levels greater than 30 mg/dl. Roughly 80 percent of a Caucasian population's Lp(a) values will fall below 30 mg/dl [12]; values above this level have been suggested to correlate significantly with increased CAD in the general population [57]. R values for correlations were determined using Sigmaplot for Windows (version 1.01), and the corresponding P values were determined using Statistix for DOS, version 2.0. Kruskal-Wallis analysis of variance by ranks and Spearman rank order correlations were used in analysis of the effect of age and duration of therapy on Lp(a) levels.

To adjust for differences in total cholesterol levels between subjects, the cholesterol content in each fraction measured from the DGUC is expressed as the percentage of cholesterol

distribution. This is calculated by adding up the cholesterol in all fractions from a subject and then expressing the result for each fraction as the cholesterol in each fraction divided by the total cholesterol multiplied by 100. Included is the 95 percent confidence interval (CI).

As a way of detecting differences in cholesterol distribution between groups of subjects, the mean cholesterol levels in each fraction were compared and reported along with the 95 percent CI as a difference plot [58]. As an example, to compare the cholesterol distribution between treatment groups, this difference plot may be interpreted as follows: if the mean cholesterol value in a fraction is the same between the groups, then the difference is zero; if the mean cholesterol value in a fraction is higher in the intensively treated group compared with that in the conventionally treated group, the difference is a positive number; and if the mean cholesterol value in a fraction is lower in the intensively treated group compared with that in the conventionally treated group, the difference is a negative number. Error bars represent the 95 percent CI for the difference between the two groups of each fraction, and significance occurs when the CI does not cross the zero line [58].

LDL cholesterol and apo B levels were adjusted to the average age at follow-up (33 years old) using regression plots. Adjustment for the cholesterol content and apo B levels in Lp(a) used the following formulas: LDL cholesterol adjusted for Lp(a) cholesterol = LDL cholesterol – $0.31 \times \text{Lp(a) cholesterol}$ [59]; total apo B adjusted for Lp(a)-apo B = total apo B – $0.184 \times \text{Lp(a)}$ [60].

Because of their skewed distribution, triglyceride levels and albumin excretion rates were natural log-transformed before analysis of means using a t test assuming equal variance.

RESULTS

LDL cholesterol and apo B. Apo B and LDL cholesterol levels were lower at follow-up in the intensive diabetes therapy group before adjustment for age and the contribution of apo B and cholesterol from Lp(a) Table 2. These differences remained after adjusting for age alone. After additional adjustment for the cholesterol and apo B content of Lp(a) (see METHODS), apo B remained significantly lower in the intensively treated group but LDL cholesterol did not. Although unadjusted baseline LDL cholesterol levels of men and women were identical, at follow-up the unadjusted LDL cholesterol reduction in the intensively treated group was entirely due to reduced LDL cholesterol in the women (2.77 mmol/l in the intensive group vs. 2.92 mmol/l in the standard group, $P = 0.01$). LDL cholesterol between the men in each treatment group, however, was not different at follow-up (2.95 vs. 2.97 mmol/l, $P = 0.74$).

Lp(a)

For the Caucasian subjects, Lp(a) was distributed in a skewed fashion, as has been described in other Caucasian populations [12] Figure 2. Median Lp(a) levels were significantly lower in the intensively treated group and the nondiabetic control group compared with the conventionally treated group (10.7 and 9.6 vs. 12.5 mg/dl, respectively) Table 3. Both men and women in the intensively treated group showed significantly lower Lp(a) levels at follow-up when compared with similar groups from the conventionally treated subjects (data not shown). The median Lp(a) in the intensively treated group was not significantly different from that in the nondiabetic control group. If subjects within each treatment group were analyzed according to whether they had been included in the primary or secondary intervention group, Lp(a) levels did not differ (data not shown). Lp(a) levels were not correlated with HbA_{1c} within either treatment group Figure 3 and Figure 4.

To assess whether Lp(a) levels may have been affected by the age of the subject or their duration in the study, subjects were grouped in quintiles by age at the final visit and the duration (in

years) between baseline and follow-up measurements. The same analysis was then done after the subjects were further divided into intensive and conventional treatment groups. No significant differences or trends could be shown for age or duration in the study on Lp(a) levels for any of the groups (data not shown).

The effect of renal dysfunction on Lp(a) levels was not remarkable Table 4. If subjects are grouped according to the amount of albuminuria (less than 40, 40–299, and greater or equal to 300 mg/24 h) [50], only the difference between the Lp(a) levels of the conventional and intensively treated groups with normal albumin excretion rates (less than 40 mg/24 h) remained significant. Within each treatment group, levels of Lp(a) increased but were not significantly different as a function of worsening albuminuria. If the treatment groups are stratified by the level of creatinine clearance (less than 1.17 vs. 1.17 ml [bullet] s sup -1 [bullet] 1.73 m sup -2 or more) [50], again no difference in Lp(a) levels was detected between the treatment groups or within each group.

The percentage of subjects with Lp(a) levels greater than 30 mg/dl is similar in the conventional treatment group (27 percent), the intensively treated group (24 percent), and the control group (23 percent) (NS).

Lp(a) levels in the African-American population were closer to a Gaussian distribution, with a mean of 47.9 mg/dl and a median of 49.9 mg/dl. These levels were higher than in the African-American nondiabetic control population (mean 33.9 mg/dl, median 30.2 mg/dl, $P = 0.02$) but were not significantly different when compared between treatment groups.

Lp(a) results from the remaining 19 ethnic minority subjects are included for comparison Table 5.

DGUC

The distribution of cholesterol in the lipoproteins of each treatment group is remarkably similar Figure 5. To demonstrate small but significant differences in these distributions, a difference plot was generated for the cholesterol levels in each fraction Figure 6. This difference plot shows significantly lower cholesterol levels in the very-low-density lipoprotein (VLDL) fractions (fractions 31–38) and in the more dense LDL fractions (fractions 7–11) of the intensively treated group compared with those of the conventionally treated group. Significantly higher cholesterol levels are present in the more buoyant LDL fractions (fractions 12–18) of the intensively treated group. A trend can be seen toward lower cholesterol content in the intermediate-density lipoprotein (IDL) fractions (fractions 19–30) in the intensively treated group, although this did not reach statistical significance.

The different effects of intensive treatment on cholesterol distribution in women and men, similar to results for LDL cholesterol, were determined by generating difference plots to compare the women and men after stratification by treatment group Figure 7 and Figure 8. As shown in Figure 7, intensively treated women had more cholesterol distributed in the buoyant LDL and less in the denser LDL, without significant differences in the VLDL, IDL, or HDL fractions compared with the conventionally treated women. Intensively treated men Figure 8 had less cholesterol in the VLDL and IDL fractions and more cholesterol in buoyant LDL fractions but no changes in cholesterol levels in dense LDL or HDL fractions compared with the conventionally treated group.

DISCUSSION

The purpose of this study was to determine the effect of intensive diabetes therapy on several of the nontraditional lipoprotein risk factors for CAD in IDDM patients. Since these results

represent cross-sectional data obtained at follow-up and baseline levels were not measured, we cannot state unequivocally that the differences between these groups are the result of their treatment group assignment. Despite this limitation, we believe that given the large numbers in each treatment group, the well-controlled randomization at baseline, the highly significant improvement in the primary endpoint of glycemic control in the intensively treated group, and the nearly perfect follow-up of all the subjects, these two groups represented ideal populations in which to study this question.

The adjusted apo B level [for age and Lp(a)-apo B] in the intensively treated group was slightly, although significantly, lower than the level in the conventionally treated group. The adjusted LDL cholesterol was the same between the groups. Since each LDL particle contains only one molecule of apo B, the ratio of LDL cholesterol to apo B can be used as a rough estimate of LDL size. When the LDL cholesterol-to-apo B ratio is higher, it implies an enrichment of cholesterol in each LDL particle, making it more buoyant. That the intensively treated group had more buoyant LDL particles was confirmed by DGUC in that the difference plot showed an increase in cholesterol in the more buoyant LDL fractions and less cholesterol in the denser LDL subfractions when compared with the conventionally treated group. In addition, cholesterol was lower in the VLDL and IDL fractions of the intensively treated group, although this was significant only in the VLDL fractions. Thus, the intensive treatment group showed favorable differences in the cholesterol composition of the lipoprotein particles when compared with the conventionally treated group. Moreover, these favorable lipoprotein particle changes occurred in both sexes, with men showing less cholesterol in VLDL and IDL and increased cholesterol in buoyant LDL and women showing increased cholesterol in buoyant LDL and less cholesterol in dense LDL.

In subjects with IDDM, Lp(a) levels have been reported to be the same as or higher than those in a control population [29–34,63]. Conclusions as to the effect of improved glycemic control on Lp(a) levels have also varied [29,33,35–42]. At follow-up in the DCCT, Caucasian subjects who received conventional treatment had significantly higher levels of Lp(a) than both the subjects who received intensive treatment and those in a nondiabetic control population. In addition, Lp(a) levels in those subjects receiving intensive diabetic therapy did not differ from those of this control population. Further analysis showed that the Lp(a) levels were significantly lower (to a similar degree) in men and women from the intensively treated group than in the men and women of the conventionally treated group. Therefore, the lower levels of Lp(a) in the intensive treatment group do not account for the gender effect seen for total LDL cholesterol as noted above.

Linear regression coefficients between Lp(a) and HbA_{1c} were generated to test the hypothesis that the differences in Lp(a) levels seen between the treatment groups were related to improved glycemic control. In this study, however, a significant correlation between Lp(a) levels and HbA_{1c} could not be detected. Because Lp(a) levels may vary up to 1,000-fold based solely on apo(a) isoforms, it is possible that a true association between Lp(a) levels and HbA_{1c} may be masked by this large genetically determined variation. Thus, examining Lp(a)-HbA_{1c} relationships according to apo(a) isoforms may reveal an association between Lp(a) levels and glycemic control.

Other influences on Lp(a) levels that may have accounted for the differences seen between treatment groups were considered. Apo(a) isoforms are a major contributor to Lp(a) levels in the general population. Since the apo(a) isoform distribution in IDDM patients of Northern European descent is not different from that of normal subjects from the same background [32,34], an increase in subjects with isoforms associated with higher Lp(a) levels in this diabetic population is unlikely. It is also unlikely that the DCCT randomization resulted in more subjects who have isoforms with higher Lp(a) levels in the conventional than in the intensive treatment

group. Isoform analysis of these subjects is currently in progress to address these possibilities. Puberty has also been noted to affect Lp(a) levels [64]. At entry into this study, the average age of the subjects was the same in both groups (27 years of age) and each treatment group had a similar number of subjects less than 17 years of age.

Because of the size of the treatment groups, small differences in the Lp(a) levels could be detected between them, it should be noted, however, that the median Lp(a) level in the conventionally treated group is still very close to that of the general control population, and neither the treatment group nor the control group had a greater percentage of subjects with levels of greater than 30 mg/dl, a level some feel is predictive of an increased risk of CAD [57].

Intense interest has centered on the effect of proteinuria and renal failure on Lp(a) levels. In subjects with IDDM and proteinuria, Lp(a) levels have been reported to be either increased or unchanged [31,42–47]. Several studies of patients with nephrotic syndrome and/or renal failure from various causes have failed to demonstrate a difference in Lp(a) levels in subjects with IDDM compared with in subjects with other causes of renal dysfunction [20,29,65]. In the present study, most of the subjects had a normal creatinine clearance (greater than 1.17 ml [bullet] s sup-1 [bullet] 1.73 m sup-2) and level of albuminuria (less than 40 mg/24 h). In those who did develop renal dysfunction, Lp(a) levels were not different between the treatment groups. Likewise, within each treatment group, Lp(a) levels were not different with increasing albuminuria or decreasing creatinine clearance. Because Lp(a) levels have been shown to be elevated in patients with nephrotic-range proteinuria and renal failure, the most likely explanation for our results is that the small numbers of subjects with severe renal complications in the DCCT did not allow a significant trend to be shown.

African-American subjects with diabetes had a less skewed distribution and higher levels of Lp(a) than the Caucasian diabetic patients, paralleling the Lp(a) levels reported in a nondiabetic African-American population [12] that served as the control group for this study. Lp(a) levels in the African-American subjects were higher than in the control group but did not differ between treatment groups. Although the African-American subjects did not have more severe proteinuria or worse creatinine clearances than the Caucasian subjects, they did have a higher mean HbA_{1c} (data not shown) at follow-up. This difference in glycemic control may in part explain these results, although the number of African-American subjects in the DCCT was much smaller than that of the Caucasian group and limits the conclusions that can be drawn.

In summary, Lp(a) (Caucasian subjects only) and apo B levels were lower, the cholesterol content in buoyant LDL was higher, and the cholesterol content in the dense LDL and VLDL fractions in the intensively treated diabetic patients was lower compared with those in subjects receiving conventional therapy. The intensive diabetic therapy group (Caucasian subjects only) had Lp(a) levels not significantly different from those of a normal Caucasian population. Correlation of Lp(a) levels with HbA_{1c} after separation according to the apo(a) phenotype will need to be performed to determine whether Lp(a) levels fluctuate with glycemic control. Proteinuria and reduced creatinine clearance did not affect Lp(a) levels, but because of the small number of subjects affected by severe renal disease in the DCCT, continued follow-up may yet bear out differences in Lp(a) levels in subgroups of subjects with renal dysfunction. Lp(a) levels in the African-American subjects were higher than in a control group but did not differ between treatment groups.

The follow-up period reported here was too short and there were too few events related to atherosclerotic disease to determine whether these differences in lipoprotein levels are clinically significant. Prospective follow-up of this group will be vital in determining whether

these differences persist and whether these favorable lipoprotein changes as a result of intensive therapy alter the progression of CAD in these IDDM patients.

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Glossary

apo	apolipoprotein
CAD	coronary artery disease
CI	confidence interval
CV	coefficient of variation
DCCT	Diabetes Control and Complications Trial
DGUC	density-gradient ultracentrifugation
ELISA	enzyme-linked immunosorbent assay
IDDM	insulin-dependent diabetes mellitus
IDL	intermediate-density lipoprotein
HDL	high-density lipoprotein
LDL	low-density lipoprotein
Lp(a)	lipoprotein (a)
VLDL	very-low-density lipoprotein

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Figure 1.
Mean distribution of lipoprotein cholesterol across nonequilibrium DGUC (line) and 1 SD (bars) of 15 repeat runs on a single sample stored at -70 degrees C for 12–24 months

Figure 2. Frequency distribution histogram of Lp(a) levels in 1,299 Caucasian IDDM patients (A) and 2,158 Caucasian control subjects (B).

Figure 3. Relationship between Lp(a) level and HbA_{1c} in the Caucasian subjects of the conventionally treated group (n = 653). $r = 0.052$; $P = 0.18$.

Figure 4. Relationship between Lp(a) level and HbA_{1c} in the Caucasian subjects of the intensively treated group (n = 646). $r = 0.022$; $P = 0.59$.

Figure 5.

Distribution of lipoprotein cholesterol across nonequilibrium density-gradient ultracentrifugation of the conventionally treated group [open bullet] (n = 698) and the intensively treated group [bullet] (n = 680). HDL is located in fractions 0–6, LDL in fractions 7 to approximately 18, IDL in fractions 19–30, and VLDL in fractions 31–38.

Figure 6.

Difference plot comparing the mean cholesterol levels of each fraction from the DGUC for differences from 0, with 95 percent CI (bars), between the intensively and conventionally treated groups. The fractional location of each of the lipoprotein classes (VLDL, IDL, LDL, and HDL) is the same as in Figure 3.

Figure 7.

Difference plot comparing the mean cholesterol levels of each fraction for differences from 0, with 95 percent CI (bars), for intensively treated women ($n = 323$) versus conventionally treated women ($n = 315$). The location of each of the lipoprotein classes (VLDL, IDL, LDL, and HDL) is the same as in Figure 3.

Figure 8.

Difference plot comparing the mean cholesterol levels of each fraction for differences from 0, with 95 percent CI (bars), for intensively treated men ($n = 357$) versus conventionally treated men ($n = 383$). The location of each of the lipoprotein classes (VLDL, IDL, LDL, and HDL) is the same as in Figure 3.

Table 1

Characteristics of the nondiabetic control group used in Lp(a) analysis

	Caucasian		African-American	
	Men	Women	Men	Women
<i>n</i>	1,171	1,307	1,157	1,480
Glucose at entry (mmol/l)	4.7 (4.66–4.73)	4.5 (4.46–4.54)	4.7 (4.65–4.75)	4.5 (4.43–4.56)
Total cholesterol (mmol/l)	4.55 (4.50–4.60)	4.55 (4.51–4.59)	4.55 (4.50–4.60)	4.61 (4.57–4.65)
Triglycerides (mmol/l)	1.02 (0.98–1.06)	0.79 (0.77–0.81)	0.80 (0.77–0.83)	0.72 (0.70–0.74)
Weight (kg)	77.0 (76.3–77.7)	62.8 (62.1–63.5)	76.9 (76.0–77.8)	69.2 (68.2–70.2)

Data are means (95% CI).

Characteristics of DCCT study patients

Table 2

	Treatment group		P value
	Conventional	Intensive	
<i>n</i>	680	667	—
Average age at beginning (years)	27 (26.5–27.5)	27 (26.5–27.5)	NS
HbA _{1c} (%)	9.2 (9.1–9.3)	7.3 (7.2–7.4)	<0.00001
Triglyceride (mmol/l)	0.98 (0.93–1.03)	0.90 (0.86–0.94)	0.007
Apo B (mg/dl)	86 (84–88)	83 (81–85)	0.01
Apo B (mg/dl) adjusted for age	85 (83–87)	82 (80–84)	0.01
Apo B (mg/dl) adjusted for age, Lp(a)–apo B	81 (79–83)	79 (77–81)	0.05
LDL cholesterol (mmol/l)	2.95 (2.89–3.01)	2.87 (2.82–2.92)	0.05
LDL cholesterol (mmol/l) adjusted for age	2.95 (2.89–3.01)	2.87 (2.82–2.92)	0.03
LDL cholesterol (mmol/l) adjusted for age, Lp(a)–cholesterol	2.77 (2.71–2.83)	2.71 (2.66–2.76)	0.12
Creatinine clearance (ml · s ^{−1} · 1.73 m ^{−2})	2.03 (1.99–2.07)	2.03 (1.99–2.07)	NS
Albumin excretion rate (mg/24 h)	78 (41–115)	30 (15–450)	2 × 10 ^{−6}
Insulin dosage (units · kg ^{−1} day ^{−1})	0.65 (0.63–0.67)	0.71 (0.69–0.73)	0.001
Body mass index (kg/m ²)	25 (24.7–25.2)	27 (26.7–27.3)	1 × 10 ^{−14}

Data are means (95% CI) and represent values at follow-up unless otherwise specified.

Table 3
Comparison of Lp(a) levels between Caucasian subjects in treatment and control groups

Treatment group	n	Median	Mean	SD	25th %	75th %
Conventional	653	12.5 ^{*,†}	22.0	23.9	4.9	33
Intensive	646	10.7 [‡]	18.5	19.8	4.2	26.8
Caucasian control subjects	2,158	9.6	18.2	19.2	4.4	27.8

Results are expressed in mg/dl. Lp(a) results were analyzed using the Kolmogorov-Smirnov test and Kruskal-Wallis analysis of variance by ranks.

^{*} $P = 0.03$, conventional vs. intensive treatment group.
[†] $P < 0.01$, conventional vs. control group.
[‡] NS intensive vs. conventional treatment group.

Table 4

Lp(a) levels according to albumin excretion rate and creatinine clearance in Caucasian subjects

Table 5

Lp(a) levels in other minority groups

Treatment group	Albumin excretion rate (mg/24 h)			Creatinine clearance (ml · s ⁻¹ · 1.7 · m ⁻²)	
	<40	40–299	≥300	<1.17	≥1.17
Conventional	12.7* (570)	10.1 (65)	11.2 (18)	15.1 (12)	12.5 (641)
Intensive	10.7 (598)	15.1 (41)	4.9 (7)	10.1 (8)	10.7 (638)

Data are medians in mg/dl (n). n = 653 and 646 for conventional and intensive groups, respectively.

* P < 0.02 conventional vs. intensive groups, otherwise NS for all values within and between each treatment group.