Differing Associations of Lipid and Lipoprotein Disturbances With the Macrovascular and Microvascular Complications of Type 1 Diabetes

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OBJECTIVE — Cardiovascular disease (CVD) is increased in patients with type 1 diabetes, but lipid and lipoprotein patterns remain favorable. In contrast, nephropathy is associated with an adverse distribution. We compared the associations and predictive power of lipid and lipoprotein disturbances with these complications.

RESEARCH DESIGN AND METHODS — A nested case-control study from the EURODIAB cohort of 140 case subjects with evidence of at least one complication and 84 control subjects with no complications were analyzed. Conventional and unconventional lipid and lipoprotein fractions, including apolipoprotein (apo)-A1, lipoprotein (Lp)-A1, LpA1/A2, apoB, and LDL particle size were measured centrally.

RESULTS — CVD was only associated with increased LDL cholesterol (3.6 vs. 3.0 mmol/l, $P = 0.02$). In contrast, albuminuria was associated with elevated cholesterol, triglyceride, LDL, and apoB and with diminished LDL particle size. No disturbances in HDL and related lipoproteins were noted. In normoalbuminuric patients, CVD was not associated with any significant changes in lipids. CVD in macroalbuminuric patients was associated with increased triglyceride level (2.37 vs. 1.07 mmol/l, $P = 0.001$; $P = 0.02$ for CVD/albuminuria interaction) and LDL cholesterol (5.4 vs. 3.3 mmol/l, $P = 0.005$; $P = 0.004$ for interaction). Independent associations were observed for total cholesterol and for LDL particle size and albuminuria.

CONCLUSIONS — Abnormalities in lipid and lipoprotein disturbances are more closely related to albuminuria than to CVD in patients with type 1 diabetes. Measurement of conventional parameters provide sufficient risk information. ApoB and LDL particle size offer limited extra information. HDL metabolism remains undisturbed in the presence of complications. These changes reflect associations with glycemic control, which is the key to understanding lipid and lipoprotein disturbances.

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A paradox of type 1 diabetes is that although in patients with this condition mortality from cardiovascular disease (CVD) is three- to sixfold that of the general population (1), lipid and lipoprotein patterns are generally favorable. In patients with well-controlled type 1 diabetes, cholesterol, triglyceride, and LDL levels are similar to or lower than those in the general population, whereas HDL cholesterol levels are normal or increased (2,3). In the presence of coronary heart disease, although triglyceride, LDL, and VLDL cholesterol levels are increased and HDL cholesterol levels are lower than in those without heart disease (4,5), these and associated lipid and lipoprotein disturbances do not seem to be disadvantageous enough to explain this elevated risk for CVD (4,6,7).

In contrast, however, lipoprotein patterns are much more adversely affected by diabetic nephropathy (8–10), and changes can be observed even at the microalbuminuric stage (11,12). The reasons for such marked changes occurring with nephropathy, but to a much lesser extent with CVD, are unclear. There are indications that lipoprotein abnormalities in type 1 diabetes are caused, in part, by poor glycemic control (13). In addition, renal excretion of lipoprotein molecules may contribute to the poor profiles observed in association with albuminuria (14,15).

The interaction between CVD and nephropathy in terms of their association with lipid and lipoprotein disturbances has not been well explored, and the etiology of these disturbances is mainly uncertain. Furthermore, associations with retinopathy have been conflicting, and a better understanding of alterations associated with retinopathy may provide valuable etiologic clues (16–19).

The optimal lipid and lipoprotein predictors of subsequent coronary heart disease events remain unclear. Total cholesterol has been the main target for risk

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Abbreviations: AER, albumin excretion rate; apo, apolipoprotein; CVD, cardiovascular disease; Lp, lipoprotein; SRE, standardized regression effect.

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

assessment and treatment, but it is increasingly clear, particularly for type 2 diabetes, that triglyceride, perhaps via its association with small dense LDL, may be a more useful marker (20,21). Recently, there also have been indications that the apolipoproteins may be seriously deranged in the presence of complicated diabetes and may independently predict future events (22). Furthermore, trial data in the nondiabetic population suggest that on-treatment apolipoprotein (apo)-B and apoA1 may be even better predictors of subsequent events than more conventional measures (23). There are few data on these markers in patients with type 1 diabetes, and no previous study has assessed these measures simultaneously to compare their relative importance.

We therefore studied the associations between lipid and lipoprotein alterations and the microvascular and macrovascular complications of type 1 diabetes and explored their interactions. We also assessed the extent to which possible etiologic factors, such as glycemic control, could account for such disturbances. Finally, we determined whether measuring unconventional lipoprotein parameters in addition to traditional markers added useful predictive information. For this analysis, we used a nested case-control study approach from the EURODIAB Prospective Complications Study.

RESEARCH DESIGN AND METHODS

Patient population

Baseline investigations for the EURODIAB IDDM Complications Study were performed between 1989 and 1991 on 3,250 patients with type 1 diabetes, defined as a diagnosis made before 36 years of age and need for continuous insulin therapy within 1 year of diagnosis (24). Patients were recruited from 31 centers in 16 European countries and were aged between 15 and 60 years. These patients were invited back for reexamination an average of 6–8 years after the baseline investigations. Of the original 3,250 patients, 437 could not be contacted because their center had dropped out of the study, 8 violated the protocol from the baseline examination, and 101 died. Of the remaining 2,604 patients, 1,880 (72%) were reexamined.

Assessment of complications

At both baseline and reexamination, complication status was measured using the same standardized protocol, as described previously, including a questionnaire (24). Height, weight, and waist-to-hip ratio were measured, and resting blood pressure was recorded (5). Retinal photographs were taken according to the EURODIAB protocol (25). Slides were developed and graded by the Retinopathy Grading Center at the Hammersmith Hospital of Imperial College, London, U.K., by graders masked to all information about the patients except the identity numbers (25). Two 24-h urine specimens were collected, after testing for infection, for measurement of albumin excretion rate (AER) (26). The presence of CVD was defined as history of a cardiovascular event, including myocardial infarction, angina, coronary artery bypass graft or stroke, or major Q waves on electrocardiography (Minnesota codes 1.1 or 1.2) (5).

Measurement of lipids and lipoproteins

Aliquots of blood samples, fasting if possible, were sent to central laboratories for analysis. Measurements included total cholesterol, HDL cholesterol, and triglyceride (27,28). Only fasting values for triglyceride were used in these analyses. LDL cholesterol was calculated according to the Friedewald formula (29). The reference range for the HbA_{1c} assay was 4.2–6.2% (30).

Serum apoA1 and apoA2 concentrations were measured by an immunoturbidimetric method with commercially available kits (Boehringer Mannheim, Mannheim, Germany) (31). The concentration of LpA1 particles was quantified using a differential electroimmunoassay with hydrated agarose gels containing monospecific antibodies against apoA1 and apoA2 (Sebia, France) as previously described (31). This method directly quantifies the LpA1 particles as the concentration of apoA1 in these particles. The concentration of LpA1:A2 is then calculated by subtracting the concentration of LpA1 particles from the immunoturbidimetrically measured total of apoA1 in the serum. The interassay variations for these assays were 3.5, 2.1, and 7.3% for apoA1, apoA2, and LpA1, respectively. The concentration of apoB was measured by an immunochemical assay (Orion Diagnostica, Espoo, Finland). The interassay coefficient of variation was 4.9%.

LDL peak particle diameters were determined on linear 1-mm-thick 2–10% gradient gels. The vertical slab gels were run in the Bio-Rad Mini-Protean II electrophoresis cell (Bio-Rad, Richmond, CA) in a cooled room at +4°C. Preelectrophoresis (20 min at 30 V) and electrophoresis (18 h at 125 V) were performed by using Tris-glycine buffer pH 8.3 (0.024 mol/l Tris and 0.192 mol/l glycine). Serum samples were stored in −80°C and diluted with sample buffer containing 0.6 mol/l Tris pH 8.3, 8% sucrose, and 0.035% bromphenol blue; 10 μl diluted sample was applied to each well. Gels were stained with newly filtered Sudan Black B lipid stain (0.3% Sudan Black B and 1% Zn-acetate in 30% methanol, 30% 2-propanol) for 1 h and destained with 30% 2-propanol for 24 h. Gels were kept in 5% acetic acid for 4–6 h and dried with the Bio-Rad GelAir Drying System for 4 h. Two isolated LDL samples were used as a size reference on each gel. LDL was isolated by ultracentrifugation and dialyzed against 0.9% NaCl containing 0.01% EDTA; 8% of sucrose was added to the dialyzed LDL. The particle size of two standard samples was measured by electron microscopy. The median diameter of the LDL particles was calculated by measuring the diameters of at least 100 LDL particles from the electron microscopy photograph. The calculated mean diameters of LDL standards were 27.9 and 23.9 nm. In addition, one control sample was applied on each gel. Dried gels were photographed with a Kodak Digital Science DC120 camera (Eastman-Kodak, Rochester, NY) and analyzed with a Kodak Digital Science Electrophoresis Documentation and Analysis System 120 (Eastman-Kodak). The mean particle diameter of the major LDL peak was determined by comparing the mobility of the sample with the mobility of the calibrated LDL preparations run on each gel. In addition, a control serum sample was run on each gel to measure the intergel coefficient of variation, which was 1.4%.

Design of nested case-control study

This analysis is based on a nested case-control study of all patients who were reexamined and for whom aliquots of serum from the follow-up examination could be stored at −80°C within a few

Table 1—*Risk factors for complications by case/control status (adjusted for age and sex)*

	Control subjects	Cases	*P*
n	84	140	
Age (years)	35.9 ± 1.1	40.9 ± 0.8	0.0003
Duration of diabetes (years)	15.1 ± 0.9	24.4 ± 0.7	0.0001
HbA_{1c} (%)	7.3 ± 0.2	8.9 ± 0.1	0.0001
Systolic blood pressure (mmHg)	118 ± 2	127 ± 2	0.001
Diastolic blood pressure (mmHg)	74 ± 1	76 ± 1	0.2
Height (cm)	170 ± 0.7	169 ± 0.5	0.1
Weight (kg)	69.9 ± 1.1	71.1 ± 0.9	0.3
BMI (kg/m^2)	24.1 ± 0.4	24.9 ± 0.3	0.05
Waist circumference (cm)	83.4 ± 1.2	86.9 ± 0.9	0.02
Hip circumference (cm)	97.6 ± 1.0	97.6 ± 0.7	1.0
Waist-to-hip ratio	0.86 ± 0.01	0.90 ± 0.01	0.04

Data are means ± SEM.

hours of collection until they were analyzed centrally. Cases had to have at least one complication from retinopathy, nephropathy, CVD, and neuropathy at follow-up. Because CVD was a rare event, all patients with this condition were selected first. Then, all patients with either proliferative retinopathy or macroalbuminuria were added. Finally, all patients with microalbuminuria and background retinopathy were selected. This supplied 140 case subjects. Control subjects included all patients who had no complications at follow-up ($n = 84$).

Statistical analysis

Mean values of continuous risk factors by complication status were compared using regression techniques with adjustment for age. Models were then repeated using adjustment for duration of diabetes, and results were found to be the same as those adjusted for age, so the original models were maintained. The following lipid parameters required log transformation for analysis: fasting triglyceride, LDL cholesterol, apoB, and LpA1.

Standardized regression effects for risk factors that were continuous variables were calculated by multiplying the β-estimate from logistic regression models by the standard deviation of that variable; in this case, all log-transformed variables were not converted back to antilogarithms. This allows the direct comparison of the degree of importance of each variable in accounting for the risk of each complication. Multivariate models were restricted to those individuals for whom data on all included risk factors were complete. The bulk of the missing data were due to the number of patients for whom fasting triglyceride level was not recorded at baseline.

All analyses were stratified by sex in the first instance; because there were no appreciable differences, only combined data are presented here.

RESULTS — At follow-up, compared with the control subjects, the mean age of the case subjects was 5 years older and the duration of diabetes was 9 years longer. Glycated hemoglobin and resting systolic blood pressure were also higher in case subjects, who also had a greater degree of general and central obesity (Table 1).

Although conventional lipid parameters were more adverse in subjects with CVD than in those without CVD, these only reached statistical significance for LDL (3.6 vs. 3.0 mmol/l, $P = 0.02$) (Table 2). HDL cholesterol and associated parameters, in particular, showed little difference in subjects with and without CVD.

More distinct disturbances were observed by albuminuric status. Total cholesterol, triglyceride, LDL cholesterol, and apoB levels were higher and LDL particle size was smaller with worsening albuminuric status (Table 3). Again, HDL cholesterol and associated parameters showed trivial alterations. Findings for retinopathy were similar to those for nephropathy, except that apoA1 was positively associated with worsening retinopathy status but LDL particle size was not (Table 4).

These associations for macrovascular and microvascular disease were adjusted for age and sex. Many lipid parameters are adversely affected by glycemic control, but interestingly, although the correlation coefficients for cholesterol (0.19, $P = 0.007$), triglyceride (0.18, $P = 0.04$), apoB (0.35, $P = 0.0001$), and LDL size (−0.21, $P = 0.003$) were relatively strong, those with parameters of HDL cholesterol, such as HDL itself (−0.14, $P = 0.05$), apoA1 (−0.03, $P = 0.7$), LpA1 (−0.08, $P = 0.2$), and LpA1/A2 (0.10, $P = 0.2$), were weak. When we further adjusted for glycated hemoglobin, the significant difference in LDL cholesterol between case subjects with CVD and control subjects was attenuated to 3.5 vs. 3.1 mmol/l, respectively ($P = 0.05$). All associations with both nephropathy and retinopathy persisted, and all remained statistically significant. The associations between retinopathy and lipid parameters could be confounded by AER. When this was adjusted for, differences persisted but were no longer statistically significant (Table 5).

We then compared lipoproteins between subjects with and without CVD and subjects with and without macroalbuminuria, as lipoprotein disturbances

Table 2—*Lipids and lipoproteins by CVD status (adjusted for age and sex)*

	With CVD	Without CVD	*P*
n	150	55	
Cholesterol (mmol/l)	5.3 ± 0.1	5.5 ± 0.2	0.3
HDL (mmol/l)	1.63 ± 0.04	1.60 ± 0.06	0.5
Triglyceride (mmol/l)	0.93 (0.84–1.03)	1.13 (0.94–1.36)	0.08
LDL (mmol/l)	3.0 ± 0.1	3.6 ± 0.2	0.02
ApoA1 (mg/dl)	1.37 ± 0.04	1.50 ± 0.09	0.2
LpA1 (mg/dl)	66.4 (63.7–69.2)	65.3 (60.8–70.1)	0.7
LpA1/A2 (mg/dl)	82.7 ± 1.6	84.0 ± 2.8	0.7
ApoB (mg/dl)	80.2 (76.6–83.9)	84.8 (78.4–91.7)	0.2
LDL particle size (nm)	27.0 ± 0.1	27.0 ± 0.2	0.9

Data are *n*, mean ± SEM, or geometric mean and 95% CI for log-transformed data.

Table 3—*Lipids and lipoproteins by albuminuric status (adjusted for age and sex)*

	Normoalbuminuria	Microalbuminuria	Macroalbuminuria	*P* for trend
n	139	29	54	
Cholesterol (mmol/l)	5.1 ± 0.1	5.2 ± 0.2	6.0 ± 0.2	0.0001
HDL (mmol/l)	1.65 ± 0.04	1.56 ± 0.08	1.57 ± 0.06	0.3
Triglyceride (mmol/l)	0.86 (0.78–0.95)	1.23 (0.98–1.55)	1.29 (1.08–1.54)	0.0001
LDL (mmol/l)	2.95 ± 0.1	3.06 ± 0.3	3.78 ± 0.2	0.001
ApoA1 (mg/dl)	1.33 ± 0.04	1.43 ± 0.08	1.51 ± 0.07	0.08
LpA1 (mg/dl)	65.7 (63.0–68.6)	66.5 (60.6–72.9)	66.3 (61.9–71.0)	1.0
LpA1/A2 (mg/dl)	82.1 ± 1.6	82.7 ± 3.6	84.9 ± 2.7	0.7
ApoB (mg/dl)	76.2 (72.9–79.7)	81.7 (74.2–90.1)	95.3 (88.6–102.4)	0.0001
LDL particle size (nm)	27.2 ± 0.1	27.0 ± 0.2	26.7 ± 0.1	0.05

Data are means ± SEM or geometric mean and 95% CI for log-transformed data.

were greatest in those with macroalbuminuria (Table 6). Even in patients without CVD, lipid patterns were still disturbed in patients with macroalbuminuria, particularly cholesterol, (5.8 vs. 5.0 mmol/l, $P = 0.01$), triglyceride (1.07 vs. 0.84 mmol/l, $P = 0.05$) and apoB (91.2 vs. 78.7 mg/dl, $P = 0.01$). In patients with CVD, triglyceride and LDL cholesterol levels were particularly elevated in patients with macroalbuminuria compared with subjects without macroalbuminuria. In macroalbuminuric patients, CVD was associated again with elevated triglyceride and LDL cholesterol levels, whereas no differences were observed in subjects with and without CVD or in normoalbuminuric patients. There was a significant interaction between albuminuric and CVD status for triglyceride ($P = 0.02$) and LDL cholesterol ($P = 0.004$), such that these lipid parameters in the presence of the combination of these two complications were far higher than would be anticipated by their levels in the presence of just one of these complications alone.

Standardized regression effects (SREs) were also calculated to compare the strength of the relationships between each lipoprotein and albuminuric status. The only two parameters that remained in the model were total cholesterol (SRE 0.62; 95% CI 0.23, 1.00; $P = 0.003$) and LDL particle size (SRE −0.49; 95% CI −0.84, −0.14; $P = 0.008$). The next strongest SRE was for fasting triglyceride, which was not statistically significant (SRE 0.16; 95% CI −0.26, 0.58; $P = 0.5$).

CONCLUSIONS — We confirm that CVD in patients with type 1 diabetes is associated with only modest lipid and lipoprotein abnormalities (4,6). In contrast, both albuminuria and retinopathy were associated with quite marked disturbances, even in the early stages (11,16). Part, but by no means all, of the association between abnormal lipid and lipoprotein patterns and retinopathy could be accounted for by the association with increased AER.

Generally, comparing subjects with and without complications, the greatest differences were observed for conventional parameters such as total and LDL cholesterol and fasting triglyceride. Additional factors added little to this predictive power. This means that in clinical practice, we do not need to measure unconventional lipid parameters to identify type 1 diabetic patients at increased risk of CVD. The exception to this was nephropathy, in which apoB and LDL particle size were strongly related to AER, even in the normoalbuminuric range. For LDL particle size, this was independent of all other lipid risk factors. In fact, others have shown that although LDL particle size is more favorable in patients with type 1 diabetes compared with a nondiabetic population (2), albuminuria has a striking adverse effect on LDL particle size (10), as we have shown.

It is striking that the parameters associated with HDL cholesterol were poorly related to complication risk, even for CVD. We show that although correlation coefficients for HbA_{1c} and apoB, triglyceride, and LDL particle size were strong, correlations with lipoproteins associated with HDL cholesterol were weak. Others

Table 4—*Lipids and lipoproteins by retinopathy status (adjusted for age and sex)*

	No retinopathy	Background retinopathy	Proliferative retinopathy	*P* for trend
n	110	54	64	
Cholesterol (mmol/l)	5.0 ± 0.1	5.3 ± 0.2	5.9 ± 0.1	0.0001
HDL (mmol/l)	1.67 ± 0.04	1.54 ± 0.06	1.62 ± 0.05	0.3
Triglyceride (mmol/l)	0.84 (0.75–0.95)	1.07 (0.88–1.29)	1.17 (1.02–1.36)	0.02
LDL (mmol/l)	2.87 ± 0.12	2.98 ± 0.20	3.68 ± 0.15	0.002
ApoA1 (mg/dl)	1.31 ± 0.05	1.40 ± 0.06	1.52 ± 0.06	0.04
LpA1 (mg/dl)	66.1 (63.0–69.3)	64.6 (60.2–69.3)	68.0 (63.8–72.3)	0.6
LpA1/A2 (mg/dl)	81.4 ± 1.8	84.5 ± 2.7	84.3 ± 2.4	0.5
ApoB (mg/dl)	73.8 (70.2–77.6)	84.7 (78.6–91.2)	91.9 (86.1–98.1)	0.0001
LDL particle size (nm)	27.1 ± 0.1	27.0 ± 0.2	26.9 ± 0.1	0.3

Data are mean ± SEM, or geometric mean and 95% CI for log-transformed data.

Table 5—*Lipids and lipoproteins by retinopathy status (adjusted for age, sex, HbA_{1c}, and AER)*

	No retinopathy	Background retinopathy	Proliferative retinopathy	*P* for trend
n	110	50	64	
Cholesterol (mmol/l)	5.18	5.17	5.65	0.06
LDL (mmol/l)	3.0	2.9	3.5	0.06
Triglyceride (mmol/l)	0.92	1.07	1.04	0.4
ApoA1 (mg/dl)	1.34	1.38	1.49	0.4

demonstrate that HDL cholesterol is generally high in individuals with type 1 diabetes compared with control subjects, is unaltered in the presence of complications (6,12), and is, therefore, unlikely to account for the enhanced risk of CVD observed in this condition (2,12). Although hepatic lipase activity is preserved and perhaps even enhanced in type 1 diabetes, HDL patterns remain favorable (32). However, elevations in hepatic lipase activity, particularly associated with albuminuria, are also associated with an increase in small, dense LDL (33), itself closely associated with albuminuria in this study.

A further explanation proposed for the striking abnormalities observed with albuminuria is enhanced urinary loss of lipoproteins, which disturbs metabolic pathways (14,15). However, adjustment for AER in the relationship between retinopathy and lipoproteins could not wholly abolish this association either, suggesting that renal loss alone cannot be the whole explanation for adverse lipoprotein patterns in the microvascular complications of type 1 diabetes. However, we and others have shown that abnormal lipid and lipoprotein patterns can independently predict the incidence of both microalbuminuria and retinopathy (34–36), indicating that the direction of causality may differ from that assumed in previous studies. A state of generalized inflammation and endothelial dysfunction at the early stage of diabetes may result in abnormal lipid profiles, which, in turn, could be causally related to both microvascular and macrovascular disease. In support of this is the observation that elevated von Willebrand factor levels can predict the onset of microalbuminuria (37).

In the stratified analysis by CVD and albuminuric status, we showed that there was little difference in lipoprotein patterns in those with macroalbuminuria and no evidence of CVD and those with CVD who were normoalbuminuric. This confirms the profound nature of the changes in lipoprotein patterns that occur with nephropathy. Furthermore, we also demonstrate the enhanced impact of both macroalbuminuria and CVD on lipoprotein patterns, especially for triglyceride and LDL.

Previous studies have provided conflicting findings for each of these complications. Some of the studies examined relatively small numbers of patients and were, therefore, underpowered to detect true associations. Others studies often matched individuals with and without the complication in question by duration of diabetes and/or glycemic control (18,19). However, this may result in a biased comparison, because, in general, patients with complications are likely to have poorer glycemic control and to have had diabetes longer than control subjects. By forcing these populations to be identical for these criteria, at least one group will be unrepresentative of the population from which it came, and the lipoprotein abnormalities observed may be very different from a truly representative population. Our patients were from a representative sample of people with type 1 diabetes across Europe, and our results, therefore, are likely to be generalizable. Furthermore, by not matching for glycemic control, we could assess its impact on lipoprotein profiles and, therefore, how independent these associations are from glycemic control. Finally, previous studies have often ignored the impact of comorbidity; for example, the lipoprotein differences observed in the presence or absence of retinopathy could be confounded by nephropathy. We addressed this problem in two different ways. For retinopathy, we showed that lipoprotein differences persisted when adjusted for AER, although they were no longer statistically significant. We also performed a stratified analysis for albuminuria and CVD to disentangle the separate effects of these complications on lipoprotein parameters.

In conclusion, we show that profound lipid and lipoprotein disturbances

Table 6—*Lipids and lipoproteins stratified by CVD and albuminuric status (adjusted for age, sex, and HbA_{1c})*

	With CVD			Without CVD			*P* for CVD in macroalbuminuria	*P* for CVD in normoalbuminuria
	Macroalbuminuria	Normoalbuminuria	*P*	Macroalbuminuria	Normoalbuminuria	*P*		
n	12	28		35	84			
Cholesterol (mmol/l)	6.1	5.6	0.4	5.8	5.0	0.01	0.7	0.4
HDL (mmol/l)	1.56	1.70	0.4	1.61	1.59	0.8	0.3	0.5
Triglyceride (mmol/l)	2.37	0.94	0.0001	1.07	0.84	0.05	0.001	0.3
LDL (mmol/l)	5.4	3.2	0.003	3.3	2.9	0.2	0.005	0.6
ApoA1 (mg/dl)	162.5	157.8	0.6	153.3	146.0	0.3	0.7	0.2
LpA1 (mg/dl)	68.9	67.7	0.8	68.8	63.7	0.2	0.8	0.5
LpA1/A2 (mg/dl)	91.9	86.8	0.3	81.9	79.8	0.7	0.5	0.2
ApoB (mg/dl)	93.9	87.1	0.5	91.2	78.7	0.01	0.9	0.6
LDL particle size (nm)	26.8	26.9	0.8	26.9	27.1	0.3	0.6	0.4

can be observed at the early stages of both nephropathy and retinopathy in type 1 diabetes and are unlikely to be wholly explained by glycemic control or comorbidity. In contrast, features of HDL metabolism are unaffected by diabetes complications, which may be accounted for by their relatively weak association with glycemic control. We further suggest that lipid disturbances may be etiologically related to microvascular complications, because they are observed so early in the course of disease. We confirm that such disturbances are relatively milder for macrovascular disease but that the combination of nephropathy and CVD has a major impact on lipoprotein profiles. In terms of prediction, it is likely that the measurement of conventional parameters is sufficient to assess risk, and additional parameters make little predictive impact. The question of why lipoprotein changes are so great in association with microvascular compared with macrovascular complications remains unresolved. It is likely, however, that this is related to the relative impact of glycemic control on microvascular as opposed to macrovascular complications. A more detailed examination of lipoprotein changes in association with poor glycemic control, as well as an examination of other pathways, such as those for inflammation and endothelial dysfunction, may be rewarding.

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