A Prospective Study of Serum Lipids and Risk of Diabetic Macular Edema in Type 1 Diabetes

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We evaluated the relationships between serum lipid levels and clinically significant macular edema (CSME), hard exudates, and other diabetic retinopathy (DR) end points in a population with type 1 diabetes. We studied data from serum lipids that were measured annually among the 1,441 Diabetes Control and Complications Trial (DCCT) participants. We used proportional hazards regression models to examine the relationship of the cumulative average of lipid levels (total, LDL, and HDL cholesterol, total–to–HDL cholesterol ratio, and triglycerides) with development of CSME, hard exudate, DR progression, and development of proliferative DR (PDR). In models controlling for primary prevention versus secondary intervention subgroup, randomized treatment assignment, HbA_{1c}, and other risk factors, both total–to–HDL cholesterol ratio and LDL predicted development of CSME (rate ratio [RR] for extreme quintiles 3.84, *P* for trend = 0.03 for total–to–HDL cholesterol ratio, and RR 1.95, *P* for trend = 0.03 for LDL) and hard exudate (RR 2.44, *P* for trend = 0.0004 for total–to–HDL cholesterol ratio, and RR 2.77, *P* for trend = 0.002 for LDL). Relationships of lipids with progression of DR and development of PDR were weaker and not significant after adjustment for HbA_{1c}. Higher serum lipids are associated with increased risk of CSME and retinal hard exudate. Lipid-lowering treatment among type 1 diabetic subjects, recommended to prevent cardiovascular disease, may also decrease risk of CSME, an important cause of vision loss. *Diabetes* 53: 2883–2892, 2004

Diabetic retinopathy (DR) is a very common, potentially preventable, long-term complication of type 1 diabetes and the leading cause of acquired loss of vision among working-age adults in Europe and North America (1,2). Most vision loss in diabetes is a result of diabetic macular edema (3), which results after breakdown of the blood retinal barrier. Despite intensive study, current understanding of the pathogenesis of diabetic macular edema remains incomplete. Hyperglycemia is clearly the strongest known risk factor for DR. Nevertheless, whereas intensive glucose lowering was effective in substantially reducing the incidence and progression of retinopathy in the Diabetes Control and Complication Trial (DCCT), there was no statistically significant effect on the incidence of clinically significant macular edema (CSME) during the trial (4). Thus, other factors are likely to play at least a contributory role in the pathogenesis of CSME.

Previous studies have suggested that elevated lipid levels may be an additional risk factor for CSME and related deposition of retinal hard exudate (5–8). However, results have been inconsistent, there are few prospective studies, and it is unclear to what extent some previously observed relationships may have been confounded by the degree of hyperglycemia. Nonetheless, a relationship of lipids with CSME and hard exudate is biologically plausible because elevated lipid levels are associated with endothelial dysfunction, which appears to play an important role in the pathogenesis of DR, particularly in relation to breakdown of blood-retinal barrier (9–11). We therefore examined prospectively the relationship of serum lipids with incidence of CSME and hard exudate in the DCCT cohort.

RESEARCH DESIGN AND METHODS

The DCCT was a multicenter, randomized, controlled clinical trial that tested whether an intensive treatment regimen aimed at achieving blood glucose levels as close to the nondiabetic range as possible would affect the onset and progression of retinal, renal, and neurological complications in type 1 diabetes when compared with conventional treatment (12). The DCCT population consisted of 1,441 subjects aged 13–39 years at study entry, who had a duration of diabetes between 1 and 15 years at randomization. The trial included two subcohorts, and within each subcohort, subjects were randomly assigned to intensive or conventional glycemic control. Inclusion criteria for the primary prevention subcohort were diabetes duration of 1–5 years, no retinopathy by seven-field stereoscopic fundus photography, and albuminuria <28 μg/min (<40 mg/24 h). These criteria were met by 726 subjects. The secondary intervention subcohort included 715 subjects with 1–15 years' duration of diabetes, mild-to-moderate nonproliferative retinopathy, and albuminuria <139 μg/min (<200 mg/24 h). All subjects were recruited from

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CSME, clinically significant macular edema; DCCT, Diabetes Control and Complications Trial; DR, diabetic retinopathy; EDIC, Epidemiology of Diabetes Interventions and Complications; ETDRS, Early Treatment Diabetic Retinopathy Study; PDR, proliferative DR; WESDR, Wisconsin Epidemiological Study of Diabetic Retinopathy.

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TABLE 1
Baseline characteristics of the study population by lipid levels

Lipid characteristics (quintiles)	*n*	Baseline DR	Intensive treatment	Age (years)	HbA_{1c} (%)	Duration (months)	Current smoking	Male sex
Total cholesterol (mg/dl)								
<148	275	44.0	44.4	24.3 ± 6.8	8.4 ± 1.3	65.4 ± 46.3	10.2	61.4
148–165	300	50.0	50.3	26.1 ± 7.0	8.8 ± 1.5	68.7 ± 49.9	16.7	58.7
166–181	276	49.3	54.7	26.9 ± 7.1	8.9 ± 1.5	70.4 ± 49.6	20.7	49.6
182–203	294	49.0	48.3	27.9 ± 6.9	9.0 ± 1.6	68.9 ± 50.6	19.1	47.3
≥204	296	55.4	49.0	28.6 ± 7.1	9.4 ± 1.7	75.2 ± 51.3	25.3	47.3
LDL cholesterol (mg/dl)								
<86	276	42.4	44.2	24.8 ± 6.8	8.5 ± 1.4	64.2 ± 46.6	11.6	55.1
86–99	290	50.3	52.1	26.1 ± 7.0	8.8 ± 1.5	69.3 ± 50.2	16.9	55.5
100–114	289	48.8	51.6	26.6 ± 7.2	8.9 ± 1.6	71.8 ± 50.8	16.6	51.2
115–132	294	50.0	49.3	27.7 ± 6.9	9.0 ± 1.6	68.2 ± 48.2	21.8	48.3
≥133	291	56.4	49.5	28.7 ± 7.0	9.3 ± 1.7	75.3 ± 51.9	24.7	54.0
HDL cholesterol (mg/dl)								
<40	249	55.4	47.4	26.6 ± 6.9	8.9 ± 1.6	71.5 ± 49.4	23.7	75.9
40–45	317	49.8	49.8	25.6 ± 7.4	8.9 ± 1.6	71.0 ± 50.2	19.9	64.0
46–51	275	54.9	51.6	26.4 ± 7.4	9.0 ± 1.5	73.5 ± 48.9	17.1	52.0
52–60	302	46.0	45.0	27.5 ± 6.9	8.8 ± 1.5	68.5 ± 49.3	16.9	45.4
≥61	298	43.3	52.7	27.9 ± 6.6	8.9 ± 1.6	64.8 ± 50.2	15.4	29.9
Total–to–HDL cholesterol ratio								
≤803	289	41.2	49.1	26.7 ± 6.7	8.6 ± 1.5	62.7 ± 47.0	11.1	38.4
2.804 to <3.283	288	44.8	47.2	26.7 ± 7.3	8.6 ± 1.5	66.5 ± 50.5	12.5	50.0
3.283 to <3.777	287	52.3	54.4	26.0 ± 7.2	8.8 ± 1.6	72.6 ± 49.1	19.5	50.9
3.777 to <4.429	288	51.0	50.7	26.5 ± 7.1	9.1 ± 1.7	73.2 ± 50.7	20.1	55.9
≥4.429	289	58.8	45.3	28.1 ± 7.2	9.3 ± 1.7	73.9 ± 50.3	29.1	68.9
Triglycerides (mg/dl)								
<52	279	34.4	48.0	26.7 ± 6.7	8.3 ± 1.3	56.0 ± 44.4	9.7	48.4
52–63	283	49.5	48.4	27.7 ± 6.9	8.7 ± 1.5	72.4 ± 50.9	17.0	49.5
64–76	293	49.8	51.9	26.2 ± 7.3	8.8 ± 1.5	72.4 ± 52.5	12.6	51.2
77–99	294	49.7	49.0	26.9 ± 7.4	9.1 ± 1.6	68.3 ± 48.0	24.5	55.1
≥100	292	64.0	49.3	26.5 ± 7.2	9.5 ± 1.7	79.3 ± 49.3	28.1	59.6

Data are means ± SD or percent. Quintile cut points are based on the distribution of lipids at baseline.

1983 to 1989 and were followed for an average of 6.5 years (range 3–9). Exclusion criteria included total cholesterol >3 SD above the mean for age and sex, LDL cholesterol >190 mg/dl, body weight >30% above ideal, and major electrocardiographic abnormalities, chronic heart disease, or symptoms of peripheral vascular disease. A total of 711 subjects were randomly assigned to receive intensive treatment, which consisted of insulin injections three or more times a day or external insulin pump therapy guided by self-monitoring of blood glucose at least four times per day. Seven hundred thirty participants were assigned to conventional treatment, which included one to two insulin injections a day and daily urine or blood glucose self-monitoring.

Fasting plasma samples after at least an 8-h overnight fast were collected at baseline and annually and sent for lipid analysis on dry ice to the DCCT Central Biochemistry Laboratory, Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis. Serum total and HDL cholesterol and triglyceride concentrations were measured as previously described (4). LDL cholesterol was calculated using the Friedewald equation with VLDL cholesterol concentration assumed to be 20% of the triglyceride concentration (13). The laboratory was certified through the Centers for Disease Control and Prevention Lipid Standardization Program and participated in the quality control program of the College of American Pathologists (4).

HbA_{1c} levels were determined from whole blood using high-performance liquid chromatography in the DCCT Central HbA_{1c} Laboratory (14). Whole-blood samples were collected every 3 months and shipped on wet ice to the lab. For the present analysis, we calculated the mean of all previous quarterly HbA_{1c} measurements for each subject for each 6-month follow-up interval (synchronous with the retinal photography grading, see below). Smoking history was assessed at baseline and then annually using a standardized questionnaire, and we defined smoking status using categories of never, past, and current smoker. Clinical proteinuria was defined as urinary albumin excretion of >139 μg/min using a 4-h standardized urine collection taken annually, and we excluded person-time after that diagnosis was made.

To assess retinopathy, standardized seven-field stereoscopic retinal color photographs were taken by certified photographers at baseline and every 6 months during follow-up. All photographs were mailed to the DCCT Central Ophthalmologic Reading Unit located at the University of Wisconsin, where they were assessed by masked graders in a standardized procedure using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol (15). Distinct retinal lesions such as microaneurysms, hard exudates, and macular edema were quantified and recorded separately. CSME was defined as in the DCCT, using as a standard definition retinal thickening (or hard exudates adjacent to retinal thickening) located within 500 μm of the center of the macula or an area of retinal thickening at least one disc area in size, some of which was within one disc diameter of the center of the macula (16). The grading of the extent of hard exudates was based on comparison with ETDRS standard photographs 3, 4, and 5 according to the following scale: 0, no hard exudate; 1, questionable hard exudate; 2, definite hard exudate but less than that in standard photograph 3; 3, obvious hard exudate equal to or more than that in standard photograph 3 but less than that in standard photograph 5; 4, moderate hard exudate equal to or more than that in standard photograph 5 but less than that in standard photograph 4; 5, severe hard exudate equal to or more than that in standard photograph 4; and 8, unable to grade. For the present analysis, we considered a subject to have developed hard exudate if the grade was "obvious" or higher (levels 3–5) (5). If grading was not technically possible, that eye was excluded from analysis for that follow-up visit. We defined progression of DR as in previous DCCT reports, i.e., as an increase of at least three steps from the ETDRS level at baseline that was sustained for ≥6 months. The time of occurrence was defined as the first of

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TABLE 2
Relationship of serum lipids with the incidence of CSME*

Lipids (quintiles)	No. of events	Univariate model†	HbA_{1c} adjusted†‡	Multivariate model†§
Total cholesterol (mg/dl)				
<148	10	1.0	1.0	1.0
148–165	25	1.55 (0.71–3.38)	1.39 (0.64–3.05)	1.68 (0.69–4.11)
166–181	22	2.53 (1.23–5.21)	2.12 (1.03–4.38)	2.52 (1.08–5.85)
182–203	23	2.44 (1.18–5.06)	1.90 (0.91–3.96)	2.25 (0.95–5.31)
≥204	39	3.35 (1.67–6.73)	2.35 (1.16–4.79)	2.54 (1.10–5.87)
P for trend	—	0.0005	0.02	0.11
LDL cholesterol (mg/dl)				
<86	10	1.0	1.0	1.0
86–99	20	1.27 (0.60–2.72)	1.09 (0.51–2.34)	1.07 (0.47–2.44)
100–114	26	1.62 (0.77–3.38)	1.37 (0.65–2.86)	1.23 (0.55–2.77)
115–132	23	2.27 (1.14–4.52)	1.78 (0.89–3.56)	1.84 (0.86–3.95)
≥133	40	3.03 (1.55–5.92)	2.14 (1.08–4.23)	1.95 (0.92–4.13)
P for trend	—	0.0003	0.008	0.03
HDL cholesterol (mg/dl)				
<40	18	1.0	1.0	1.0
40–45	34	0.96 (0.55–1.67)	1.00 (0.57–1.73)	1.10 (0.62–1.95)
46–51	28	1.20 (0.72–1.99)	1.27 (0.76–2.11)	1.00 (0.57–1.75)
52–60	18	0.93 (0.53–1.62)	1.03 (0.59–1.80)	0.86 (0.47–1.57)
≥61	21	0.61 (0.31–1.21)	0.65 (0.33–1.29)	0.52 (0.24–1.10)
P for trend	—	0.68	0.67	0.80
Total–to–HDL cholesterol ratio				
≤2.803	9	1.0	1.0	1.0
2.804 to <3.283	20	2.12 (0.88–5.12)	2.02 (0.84–4.87)	2.22 (0.87–5.64)
3.283 to <3.777	24	2.60 (1.11–6.05)	2.29 (0.98–5.34)	2.59 (1.03–6.50)
3.777 to <4.429	26	3.19 (1.39–7.28)	2.55 (1.11–5.85)	2.88 (1.17–7.10)
≥4.429	40	4.38 (1.97–9.75)	3.24 (1.45–7.27)	3.84 (1.58–9.36)
P for trend	—	0.002	0.03	0.03
Triglycerides (mg/dl)				
<52	9	1.0	1.0	1.0
52–63	20	2.30 (0.92–5.72)	2.12 (0.85–5.29)	1.93 (0.76–4.87)
64–76	27	2.61 (1.07–6.38)	2.21 (0.90–5.41)	2.23 (0.90–5.51)
77–99	25	3.19 (1.32–7.67)	2.27 (0.93–5.52)	2.57 (1.05–6.30)
≥100	38	3.51 (1.48–8.32)	2.19 (0.91–5.28)	2.17 (0.88–5.35)
P for trend	—	0.03	0.41	0.53

Data are RR (95% CI). *Cumulative average of annual lipid measurements, a quintile's cut points are based on the distribution of lipids at baseline; †adjusted for baseline retinopathy subgroup and randomized treatment assignment; ‡adjusted for HbA_{1c} (cumulative average of quarterly measurements); §multivariate model adjusting for HbA_{1c} (cumulative average of quarterly measurements), age (years), sex, smoking (never, past, and current), and duration of diabetes (months) and excluding person-time after diagnosis of proteinuria.

the two consecutive visits at which the progression by three or more steps was observed.

Statistical analysis. For this analysis, we created five categories of each lipid parameter based on quintiles of the distribution in the total study population at baseline and examined their relationship with incidence of CSME, hard exudate, and progression of DR and PDR. We used proportional hazards regression to estimate the rate ratios (RRs) and 95% CIs for the relationships of each lipid variable with each DR end point with stratification on randomization assignment and baseline retinopathy subcohort. Follow-up was defined as beginning at the date of randomization and continuing until an end point was reached or the last scheduled follow-up visit was concluded, whichever came first. Follow-up in the DCCT was extremely high, with subjects completing 99% of all scheduled follow-up visits (12). As in previous analyses of DCCT data, we used individuals rather than eyes as the unit of analysis. Thus, individuals who developed CSME or hard exudate in only one eye were classified in the same manner as those who may have developed CSME or hard exudate in both eyes. We used cumulatively updated mean lipid measures as a time-varying covariate in models adjusted for the design variables. We then extended these models first to control for HbA_{1c} levels and then additionally for other possible confounders, including age, sex, duration of diabetes, and smoking status. Finally, because the cumulative mean of lipid levels may not represent the most appropriate way to express lipid levels as they relate to retinopathy, we also examined associations of baseline and the most recent lipid values in models for CSME and other DR outcomes.

RESULTS

The mean baseline total and LDL cholesterol levels were 176.4 mg/dl (range 73–312) and 109.7 mg/dl (range 17–242), respectively. These values were obviously influenced by the exclusion of potential volunteers with very elevated cholesterol levels. Mean HDL cholesterol was 50.6 mg/dl (range 21–102), and the mean triglyceride level was 81.3 mg/dl (range 20–701). Relationships of lipids with other demographic and clinical characteristics were generally similar to those previously reported. For example, older subjects tended to have higher total and LDL cholesterol levels (Table 1). Also, mean HbA_{1c} was highest in the top quintile of all lipid measures except for HDL cholesterol. Men tended to have lower total and HDL cholesterol but higher triglycerides and total–to–HDL cholesterol ratio. Both current smokers as well as those with prevalent

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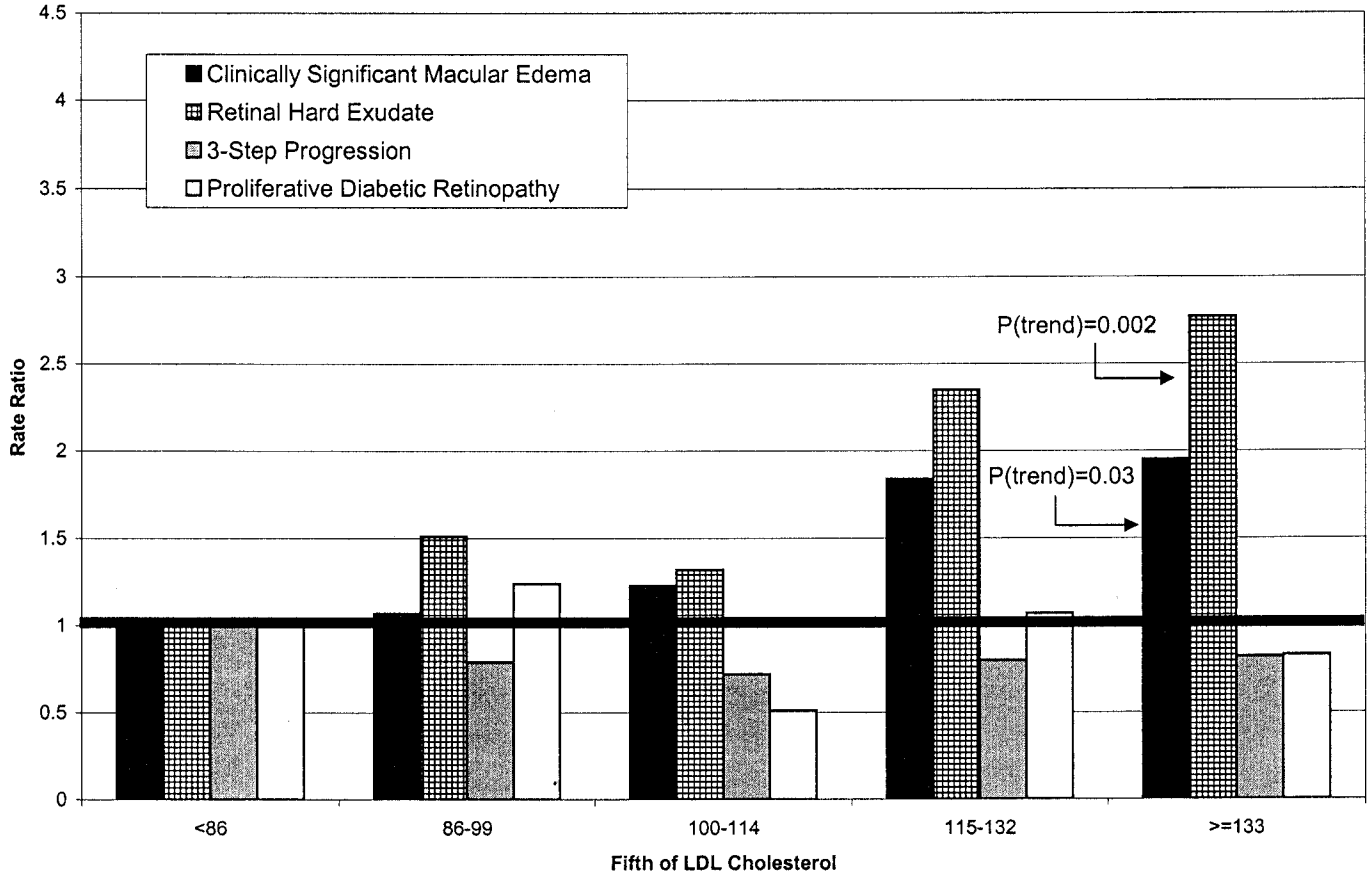

FIG. 1. Relationships of LDL cholesterol with DR end points. Shown are the RRs of CSME (■), retinal hard exudates ([squp]), three-step progression of DR (▨), and PDR (□) per one-fifth of the distribution of serum LDL cholesterol in the DCCT. RRs >1, with a significant *P* value for linear trend, indicate an increased risk with higher serum LDL levels.

retinopathy at baseline were disproportionately represented in the top quintile of triglycerides, total cholesterol, LDL cholesterol, and total–to–HDL cholesterol ratio and the bottom quintile of HDL cholesterol.

For the CSME outcome, models controlling for randomized treatment assignment and primary prevention versus secondary intervention cohorts revealed that compared with those in the lowest quintile of total cholesterol, subjects in the highest quintile had an RR 3.35 (*P* for trend = 0.0005). Similarly, those in the highest quintile of LDL cholesterol had a significant threefold higher risk of CSME (3.03, *P* for trend = 0.0003). HDL cholesterol was not significantly associated with development of CSME (Table 2). In contrast, higher total–to–HDL cholesterol ratio (4.38, *P* for trend = 0.002) and triglycerides (3.51, *P* for trend = 0.03) were associated with an increased risk of CSME in these models. In a second set of models in which we additionally controlled for HbA_{1c}, the associations between lipids and CSME were attenuated; however, significant trends over quintiles of lipids persisted for total cholesterol (top versus bottom quintile, 2.35, *P* for trend = 0.02), LDL cholesterol (2.14, *P* for trend = 0.008), and total–to–HDL cholesterol ratio (3.24, *P* for trend = 0.03). With further adjustment for other possible risk factors for retinopathy, including age, sex, smoking, duration of diabetes, and censoring person-time after diagnosis of proteinuria, LDL cholesterol (1.95, *P* for trend = 0.03) (Fig. 1) and total–to–HDL cholesterol ratio (3.84, *P* for trend = 0.03) (Fig. 2) remained significant predictors of incident CSME.

Models examining lipids and hard exudate are presented in Table 3. In the models controlling for randomized treatment assignment and primary prevention versus secondary intervention subgroup, total cholesterol (RR for top versus bottom quintile, 2.46, *P* for trend = 0.0008), LDL cholesterol (2.93, *P* for trend = 0.001), total–to–HDL cholesterol ratio (2.73, *P* for trend = 0.0003), and triglycerides (3.28, *P* for trend = 0.003) were each significantly associated with hard exudate. Additional control for HbA_{1c} level again attenuated the magnitude of these relationships, but all remained statistically significant. We observed similar findings after adjusting for other potential risk factors (total cholesterol: 2.37, *P* for trend = 0.001; LDL cholesterol: 2.77, *P* for trend = 0.002 [Fig. 1]; total–to–HDL cholesterol ratio: 2.44, *P* for trend = 0.0004 [Fig. 2]; and triglycerides: 3.20, *P* for trend = 0.006).

For the outcome of progression of DR, after controlling for randomized treatment assignment and primary prevention versus secondary intervention cohorts, relationships with total, LDL, and HDL cholesterol were not statistically significant (Table 4). In contrast, there were significant associations with total–to–HDL cholesterol ratio (RR for top versus bottom quintile, 2.38, *P* for trend = 0.004, and triglycerides, 2.64, *P* for trend = 0.0001). However, in models that additionally adjusted for HbA_{1c}, relationships

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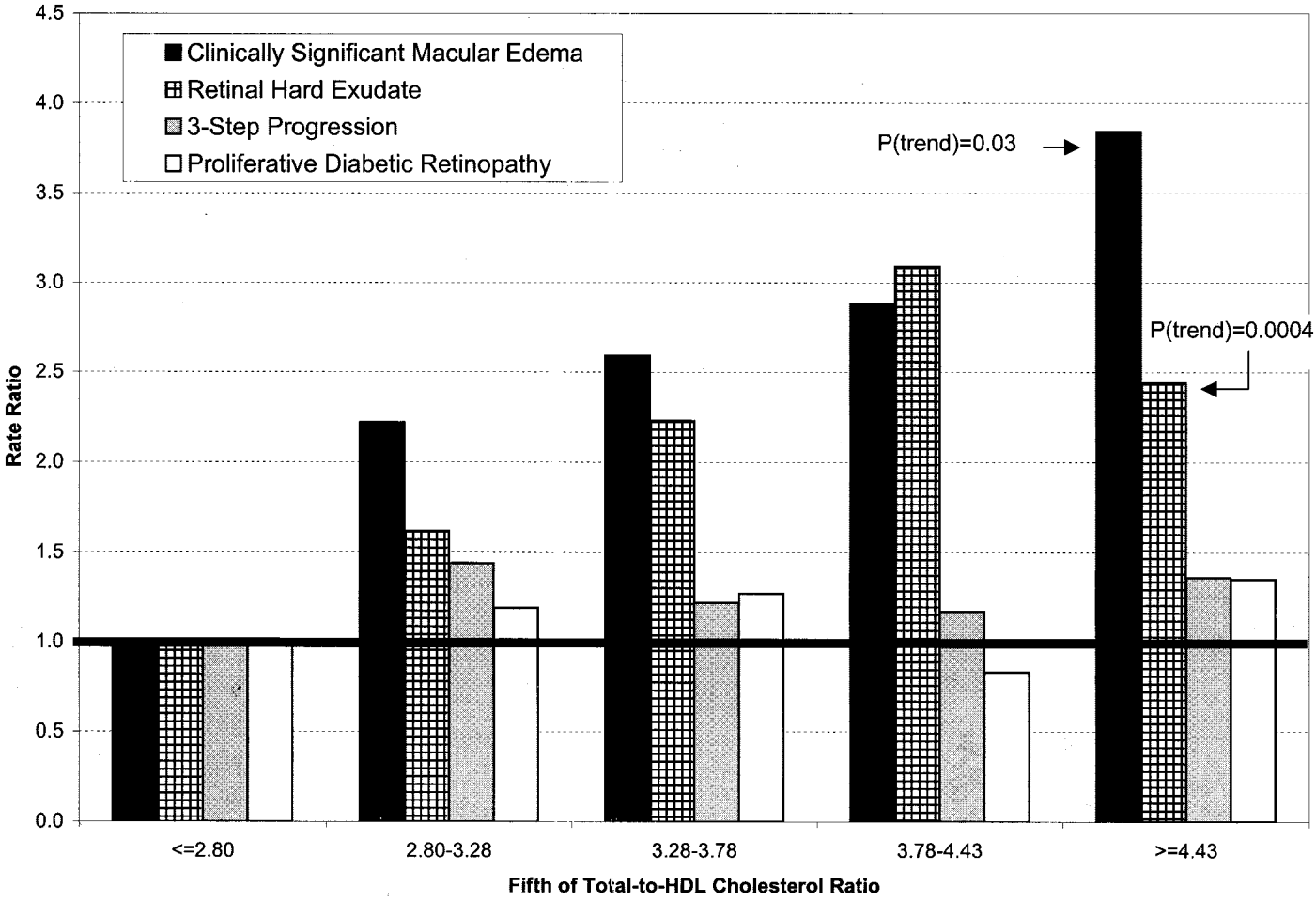

FIG. 2. Relationships of the ratio of total to HDL cholesterol with DR end points. Shown are the RRs of CSME (■), retinal hard exudates ([squp]), three-step progression of DR (▨), and PDR (□) per one-fifth of the distribution of serum LDL cholesterol in the DCCT. RRs >1, with a significant *P* value for linear trend, indicate an increased risk with higher serum total–to–HDL cholesterol ratio.

of triglycerides and total–to–HDL cholesterol ratio were no longer significant.

In examining relationships of lipids with PDR, our initial models showed no association with total, LDL, or HDL cholesterol, but significant associations with total–to–HDL cholesterol ratio (RR for top versus bottom quintile, 2.78, P for trend = 0.03) and triglycerides (3.36, P for trend = 0.02) (Table 5). With adjustment for HbA_{1c}, these associations were no longer significant (total–to–HDL cholesterol ratio: 1.91, P for trend = 0.16, and triglycerides: 1.88, P for trend = 0.23). Adjustment for additional factors further diminished these associations.

In general, results from models of baseline and most recent lipid values were very similar to those from the cumulative average models reported above. For example, in models adjusting for treatment assignment, HbA_{1c}, and other risk factors, there was a significant association between baseline total cholesterol level (RR for top versus bottom quintile, 3.75, P for trend = 0.04), baseline LDL (2.37, P for trend = 0.03), and baseline total–to–HDL cholesterol ratio (2.61, P for trend = 0.03) and CSME. Similarly, the most recent levels of total and LDL cholesterol and total–to–HDL cholesterol ratio were also associated with CSME (data not shown).

Finally, we examined whether any of the lipid parameters was associated with loss of vision. Specifically, in models with an outcome of doubling of the visual angle (equivalent to a decrease of ≥15 letters read correctly on a standard visual acuity chart between baseline and follow-up examinations) and adjusting for treatment assignment, HbA_{1c}, and other risk factors, we found no significant relationship with the cumulative average of any lipid parameter: total cholesterol level (RR for top versus bottom quintile, 1.08, P for trend = 0.88), LDL cholesterol (1.08, P for trend = 0.32), and total–to–HDL cholesterol ratio (0.94, P for trend = 0.30). Of note, the low frequency of this outcome probably limited these analyses.

DISCUSSION

In this, the largest prospective study to date of the relationship of lipids with DR among patients with type 1 diabetes, there was a twofold increased risk of CSME in the highest versus lowest quintile of LDL cholesterol and a fourfold increased risk of CSME in the highest versus lowest quintile of total–to–HDL cholesterol ratio. Similarly, the risk of hard exudate increased more than twofold for subjects in the highest quintile of total cholesterol, LDL cholesterol, or total–to–HDL cholesterol ratio and more than threefold for subjects in the highest quintile of triglycerides. In contrast, no lipid parameters were asso-

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TABLE 3
Relationship of serum lipids with the development of retinal hard exudate*

Lipids (quintiles)	No. of events	Univariate model†	HbA_{1c} adjusted†‡	Multivariate model†§
Total cholesterol (mg/dl)				
<148	19	1.0	1.0	1.0
148–165	39	1.27 (0.70–2.29)	1.22 (0.68–2.21)	1.26 (0.70–2.29)
166–181	32	2.12 (1.23–3.65)	2.03 (1.18–3.50)	1.80 (1.03–3.16)
182–203	38	2.27 (1.32–3.89)	2.14 (1.25–3.68)	2.31 (1.33–4.03)
≥204	48	2.46 (1.44–4.20)	2.23 (1.30–3.83)	2.37 (1.36–4.13)
P for trend	—	0.0008	0.002	0.001
LDL cholesterol (mg/dl)				
<86	21	1.0	1.0	1.0
86–99	32	1.58 (0.87–2.86)	1.52 (0.84–2.75)	1.51 (0.83–2.74)
100–114	41	1.64 (0.90–2.99)	1.57 (0.86–2.86)	1.32 (0.71–2.44)
115–132	35	2.62 (1.51–4.56)	2.45 (1.40–4.26)	2.35 (1.33–4.16)
≥133	47	2.93 (1.69–5.08)	2.68 (1.54–4.66)	2.77 (1.57–4.87)
P for trend	—	0.001	0.003	0.002
HDL cholesterol (mg/dl)				
<40	38	1.0	1.0	1.0
40–45	51	1.40 (0.90–2.17)	1.41 (0.91–2.20)	1.40 (0.89–2.21)
46–51	34	1.10 (0.69–1.74)	1.11 (0.70–1.76)	1.08 (0.66–1.76)
52–60	34	1.22 (0.77–1.92)	1.25 (0.79–1.97)	1.23 (0.76–1.99)
≥61	19	0.81 (0.47–1.38)	0.83 (0.48–1.43)	0.82 (0.45–1.47)
P for trend	—	0.18	0.22	0.18
Total–to–HDL cholesterol ratio				
≤2.803	15	1.0	1.0	1.0
2.804 to <3.283	27	1.77 (0.93–3.36)	1.72 (0.91–3.27)	1.62 (0.85–3.09)
3.283 to <3.777	36	2.30 (1.24–4.26)	2.19 (1.18–4.05)	2.23 (1.19–4.18)
3.777 to <4.429	48	3.22 (1.78–5.83)	2.99 (1.65–5.43)	3.09 (1.68–5.67)
≥4.429	50	2.73 (1.50–4.97)	2.49 (1.37–4.54)	2.44 (1.31–4.57)
P for trend	—	0.0003	0.001	0.0004
Triglycerides (mg/dl)				
<52	13	1.0	1.0	1.0
52–63	31	2.08 (1.01–4.29)	2.06 (1.00–4.25)	2.01 (0.97–4.16)
64–76	37	3.11 (1.56–6.17)	3.01 (1.52–5.98)	3.13 (1.57–6.26)
77–99	43	2.94 (1.47–5.88)	2.74 (1.37–5.48)	3.21 (1.59–6.47)
≥100	52	3.28 (1.67–6.46)	2.91 (1.47–5.75)	3.20 (1.59–6.44)
P for trend	—	0.003	0.02	0.006

Data are RR (95% CI). *Cumulative average of annual lipid measurements, a quintile's cut points are based on the distribution of lipids at baseline; †adjusted for baseline retinopathy subgroup and randomized treatment assignment; ‡adjusted for HbA_{1c} (cumulative average of quarterly measurements); §multivariate model adjusting for HbA_{1c} (cumulative average of quarterly measurements), age (years), sex, smoking (never, past, and current), and duration of diabetes (months) and excluding person-time after diagnosis of proteinuria.

ciated with progression of DR or with PDR after adjusting for HbA_{1c} and other risk factors.

Several previous studies of lipids and DR did not control for HbA_{1c} (7,17–19). In the DCCT (20), as well as in other epidemiological studies, HbA_{1c} was a strong predictor of diabetic macular edema (21). Hyperglycemia is also associated with dyslipidemia, specifically increased levels of total cholesterol and triglycerides, a slight elevation of LDL, but generally little if any change in HDL, resulting in increased total–to–HDL cholesterol ratio (22). Consequently, we think that the potential for confounding demands adjusting for HbA_{1c} to assure that any observed association between lipids and retinopathy is not a spurious finding (23).

Although we observed that adjustment for HbA_{1c} considerably attenuated many of the relationships between lipids and DR end points, several associations persisted. Among previous studies that controlled for HbA_{1c}, higher total cholesterol was positively associated with presence of hard exudate in a cross-sectional analysis of participants with type 1 diabetes in the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) (8). In contrast, in a prospective analysis of type 1 diabetic subjects in the WESDR (24), there was no association of lipids with macular edema after controlling for HbA_{1c} and other risk factors. In a cross-sectional analysis from the ETDRS (6), higher total and LDL cholesterol levels were each associated with severity of hard exudate. Moreover, and similar to our findings, in a prospective analysis of ETDRS data (5), the development of hard exudate was ~50% faster among subjects with elevated baseline levels of total cholesterol and triglycerides and 36% faster among participants with higher baseline levels of LDL compared with participants with normal lipid levels at baseline. In another smaller study (25) of type 1 diabetes, those who had higher cholesterol levels had a 46% higher incidence of macular edema.

In the ETDRS, baseline total cholesterol >240 vs. <200 mg/dl increased the risk of doubling of the visual angle by 50% after 5 years of follow-up (5). Although we did not

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TABLE 4
Relationship of serum lipid levels with progression of DR*

Lipids (quintiles)	No. of events	Univariate model†	HbA_{1c} adjusted†‡	Multivariate model†§
Total cholesterol (mg/dl)				
<148	41	1.0	1.0	1.0
148–165	62	1.10 (0.72–1.67)	0.94 (0.62–1.43)	0.96 (0.62–1.49)
166–181	51	1.28 (0.86–1.90)	1.01 (0.68–1.51)	0.96 (0.63–1.47)
182–203	55	1.10 (0.73–1.67)	0.76 (0.50–1.16)	0.84 (0.53–1.31)
≥204	62	1.71 (1.18–2.49)	1.03 (0.70–1.52)	0.97 (0.64–1.48)
P for trend	—	0.10	0.82	0.42
LDL cholesterol (mg/dl)				
<86	41	1.0	1.0	1.0
86–99	52	0.95 (0.63–1.43)	0.80 (0.54–1.21)	0.79 (0.52–1.21)
100–114	63	0.95 (0.62–1.44)	0.78 (0.51–1.19)	0.72 (0.47–1.12)
115–132	56	1.20 (0.81–1.76)	0.84 (0.57–1.25)	0.80 (0.53–1.20)
≥133	59	1.38 (0.95–2.01)	0.89 (0.61–1.31)	0.82 (0.54–1.23)
P for trend	—	0.12	0.95	0.44
HDL cholesterol (mg/dl)				
<40	54	1.0	1.0	1.0
40–45	67	1.19 (0.83–1.69)	1.24 (0.87–1.76)	1.41 (0.98–2.04)
46–51	54	0.99 (0.69–1.42)	1.04 (0.72–1.49)	1.09 (0.74–1.59)
52–60	50	0.89 (0.61–1.30)	0.99 (0.67–1.45)	1.12 (0.74–1.69)
≥61	46	0.68 (0.45–1.03)	0.70 (0.46–1.06)	0.88 (0.56–1.39)
P for trend	—	0.31	0.34	0.82
Total–to–HDL cholesterol ratio				
≤2.803	36	1.0	1.0	1.0
2.804 to <3.283	46	1.59 (1.02–2.49)	1.48 (0.94–2.32)	1.44 (0.91–2.30)
3.283 to <3.777	61	1.52 (0.96–2.40)	1.29 (0.82–2.05)	1.22 (0.76–1.96)
3.777 to <4.429	56	1.73 (1.11–2.69)	1.38 (0.89–2.16)	1.17 (0.73–1.87)
≤4.429	72	2.38 (1.56–3.61)	1.64 (1.07–2.52)	1.36 (0.86–2.14)
P for trend	—	0.004	0.17	0.58
Triglycerides (mg/dl)				
<52	29	1.0	1.0	1.0
52–63	50	1.14 (0.69–1.88)	1.05 (0.63–1.73)	0.92 (0.55–1.55)
64–76	54	1.51 (0.94–2.41)	1.25 (0.78–2.00)	1.16 (0.72–1.87)
77–99	56	1.79 (1.14–2.83)	1.15 (0.72–1.83)	1.11 (0.69–1.77)
≥100	82	2.64 (1.72–4.05)	1.47 (0.94–2.29)	1.23 (0.78–1.94)
P for trend	—	0.0001	0.10	0.41

Data are RR (95% CI). *Cumulative average of annual lipid measurements, a quintile's cut points are based on the distribution of lipids at baseline; †adjusted for baseline retinopathy subgroup and randomized treatment assignment; ‡adjusted for HbA_{1c} (cumulative average of quarterly measurements); §multivariate model adjusting for HbA_{1c} (cumulative average of quarterly measurements), age (years), sex, smoking (never, past, and current), and duration of diabetes (months) and excluding person-time after diagnosis of proteinuria.

observe any relationship between lipids and vision loss, which was almost nonexistent in the DCCT, results of the present study are similar to those from the ETDRS with regard to hard exudate. This is interesting since ETDRS study participants had mostly type 2 diabetes, were older, and had a duration of diabetes >15 years. More than two-thirds of participants had macular edema at baseline. Moreover, in the ETDRS, the median cholesterol value when compared with the age-stratified distribution of the patients screened by the Lipids Research Clinics Program was at the 75th percentile, compared with approximately the 50th percentile in the DCCT (26). More specifically, ETDRS participants' total cholesterol ranged from 106 to 852 mg/dl, with the mean of 229 mg/dl (27), compared with total cholesterol ranging from 73 to 312 mg/dl, with a mean of 176 mg/dl in the DCCT. Additionally, in the ETDRS, 36% of participants had total cholesterol levels >240 mg/dl compared with <5% in DCCT subjects (28).

Although we did not detect any significant findings for PDR, associations between lipids and PDR have been identified in some previous studies (29–31). It is possible that we failed to identify any associations with PDR because the truncated distribution of lipids in DCCT eliminated subjects with the highest levels that, in light of these other studies, may be associated with increased risk. Moreover, the relatively small number of cases of advanced retinopathy during the DCCT almost certainly reduced our capacity to examine this association. Longer-term follow-up of the DCCT cohort during the Epidemiology of Diabetes Interventions and Complications (EDIC) study should afford the opportunity (32).

The literature regarding effects of lipids on severity or progression of DR overall is less consistent (8,24,29,33–35). Triglycerides were a significant risk factor for presence of DR in two previous cross-sectional studies (29,34). Others failed to find any association with triglycerides, but reported inverse associations between HDL cholesterol and DR (8,35,36). For example, in a recent cross-sectional analysis (36) of EDIC data, consisting of about two-thirds of the initial DCCT cohort, an inverse association between

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TABLE 5
Relationship of serum lipids with incidence of PDR*

Lipids (quintiles)	No. of events	Univariate model†	HbA_{1c} adjusted†‡	Multivariate model†§
Total cholesterol (mg/dl)				
<148	7	1.0	1.0	1.0
148–165	13	1.35 (0.52–3.56)	1.18 (0.45–3.10)	1.28 (0.43–3.89)
166–181	22	3.15 (1.36–7.28)	2.52 (1.08–5.84)	2.26 (0.83–6.15)
182–203	16	1.74 (0.70–4.32)	1.26 (0.50–3.15)	1.30 (0.45–3.81)
≥204	15	2.00 (0.83–4.82)	1.26 (0.52–3.10)	1.12 (0.39–3.26)
P for trend	—	0.23	0.78	0.68
LDL cholesterol (mg/dl)				
<86	7	1.0	1.0	1.0
86–99	12	1.43 (0.63–3.25)	1.18 (0.52–2.68)	1.24 (0.50–3.06)
100–114	21	0.78 (0.30–2.02)	0.61 (0.24–1.60)	0.51 (0.18–1.48)
115–132	14	1.69 (0.77–3.70)	1.19 (0.54–2.64)	1.07 (0.43–2.63)
≥133	19	1.58 (0.71–3.50)	1.01 (0.45–2.28)	0.83 (0.33–2.09)
P for trend	—	0.12	0.48	0.98
HDL cholesterol (mg/dl)				
<40	15	1.0	1.0	1.0
40–45	21	0.80 (0.39–1.64)	0.85 (0.41–1.74)	1.03 (0.47–2.23)
46–51	12	1.28 (0.69–2.39)	1.38 (0.74–2.59)	1.40 (0.70–2.80)
52–60	14	0.86 (0.42–1.75)	0.98 (0.48–2.03)	0.81 (0.35–1.86)
≥61	11	0.59 (0.24–1.41)	0.63 (0.26–1.52)	0.56 (0.21–1.53)
P for trend	—	0.81	0.87	0.98
Total–to–HDL cholesterol ratio				
≤2.803	7	1.0	1.0	1.0
2.804 to <3.283	10	1.84 (0.70–4.84)	1.66 (0.63–4.38)	1.19 (0.44–3.21)
3.28 to <3.777	13	1.77 (0.68–4.61)	1.45 (0.56–3.80)	1.27 (0.48–3.40)
3.777 to <4.429	19	1.75 (0.67–4.56)	1.34 (0.51–3.50)	0.83 (0.30–2.34)
≥4.429	24	2.78 (1.14–6.77)	1.91 (0.78–4.69)	1.35 (0.52–3.49)
P for trend	—	0.03	0.16	0.40
Triglycerides (mg/dl)				
<52	5	1.0	1.0	1.0
52–63	13	2.16 (0.70–6.62)	1.98 (0.64–6.07)	1.42 (0.45–4.48)
64–76	16	2.18 (0.72–6.57)	1.78 (0.59–5.40)	1.30 (0.42–4.06)
77–99	11	2.01 (0.66–6.11)	1.30 (0.42–4.01)	1.09 (0.34–3.44)
≥100	28	3.36 (1.17–9.62)	1.88 (0.64–5.53)	1.21 (0.39–3.72)
P for trend	—	0.02	0.23	0.43

Data are RR (95% CI). *Cumulative average of annual lipid measurements, a quintile's cut points are based on the distribution of lipids at baseline; †adjusted for baseline retinopathy subgroup and randomized treatment assignment; ‡adjusted for HbA_{1c} (cumulative average of quarterly measurements); §multivariate model adjusting for HbA_{1c} (cumulative average of quarterly measurements), age (years), sex, smoking (never, past, and current), and duration of diabetes (months) and excluding person-time after diagnosis of proteinuria.

HDL and the severity of DR was detected ~2–4 years after the end of the DCCT trial. Similarly, in a cross-sectional analysis (8) of participants with type 1 diabetes from the WESDR study, the severity of DR was inversely related to HDL. In contrast to these cross-sectional findings, in 5 years of longitudinal data from the WESDR study, no relationship of HDL or total–to–HDL cholesterol ratio with incidence or progression of any of retinal outcome was shown (24).

Although the current prospective analysis of the DCCT data provide the most systematic and comprehensive analysis of relationships of conventional lipid parameters with DR to date among people with type 1 diabetes, the findings must be interpreted in the context of the study design. Because the study was conducted some time ago, newer more sensitive methods of assessing retinal thickening such as with optical coherence tomography were not available. Future studies using such methods would be of interest (37). Nondifferential misclassification of lipid levels is possible, though this would tend to bias the results toward unity. This problem is also minimized by multiple measurements of lipids. Our analysis of the cumulative average of the lipid measurements may not be the correct specification of the relationship between lipids and DR. However, we also looked at baseline lipid measurement as well as the most recent lipid measurements, and results were very similar to those presented. Residual confounding is always a possibility, but it is unlikely for HbA_{1c} (the most important confounder) in the present study because this was measured repeatedly. In addition, as we made a number of comparisons in the present study, it is possible that some findings were due to chance. The DCCT study population of relatively healthy diabetic volunteers is not representative of all people with type 1 diabetes, so it is uncertain whether these findings are generalizable. In particular, subjects were excluded from the DCCT if they had elevated cholesterol, which may have resulted in some relationships being underestimated or undetected. Finally, we were limited in our analysis to conventional lipid parameters, though recent data from

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the EDIC suggest that lipoprotein particle size and density may also be risk factors (36).

A relationship between lipid levels and macular edema appears to be biologically plausible. High lipid levels are known to cause endothelial dysfunction (38) via a local inflammatory response, with consequent release of cytokines and growth factors, activation of oxygen-sensitive biological changes in vessel walls, increases in LDL oxidation, and quenching of nitric oxide. In turn, endothelial dysfunction in the diabetic vasculature results in blood-retinal barrier breakdown in animal models of DR (9–11), though data are lacking in humans. Moreover, elevated levels of LDL and triglycerides in type 1 diabetes have been linked with higher levels of fluorescent advanced glycation end products, which are hypothesized to play an important role in the pathogenesis of diabetes complications (39).

Diabetic macular edema is an important cause of central vision loss in patients with diabetes (40). Previous studies in the U.S. have estimated the 10-year cumulative incidence of macular edema to be 20.1% and that of CSME to be 13.6% among those with type 1 diabetes and 25.4 and 17.6%, respectively, among people with type 2 diabetes treated with insulin (20). In the ETDRS, macular edema was the second most common cause of severe visual loss (41). The clinical significance of macular edema (4,42) highlights the importance of investigating potentially modifiable risk factors for this condition. These prospective data indicate that elevated serum lipids, particularly total–to–HDL cholesterol ratio and triglycerides, are independent risk factors for both CSME and retinal hard exudate. If indicative of a causal relationship, these data lend additional support to current treatment guidelines recommending aggressive lowering of elevated lipids among diabetic patients. Rigorous lipid control, in addition to its known health benefits in preventing cardiovascular disease, may also lessen ocular morbidity and associated health care costs, thereby potentially improving quality of life and vision among people with type 1 diabetes.

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REFERENCES

1. Aiello LM: Perspectives on diabetic retinopathy. *Am J Ophthalmol* 136: 122–135, 2003
2. Aiello LP, Cahill MT, Wong JS: Systemic considerations in the management of diabetic retinopathy. *Am J Ophthalmol* 132:760–776, 2001
3. Ciulla TA, Amador AG, Zinman B: Diabetic retinopathy and diabetic macular edema: pathophysiology, screening, and novel therapies. *Diabetes Care* 26:2653–2664, 2003
4. Diabetes Control and Complications Trial Group: The effect of intensive diabetes treatment on the progression of diabetic retinopathy in insulin-dependent diabetes mellitus: the Diabetes Control and Complications Trial. *Arch Ophthalmol* 113:36–51, 1995
5. Chew EY, Klein ML, Ferris FL 3rd, Remaley NA, Murphy RP, Chantry K, Hoogwerf BJ, Miller D: Association of elevated serum lipid levels with retinal hard exudate in diabetic retinopathy: Early Treatment Diabetic Retinopathy Study (ETDRS) report 22. *Arch Ophthalmol* 114:1079–1084, 1996
6. Ferris FL 3rd, Chew EY, Hoogwerf BJ: Serum lipids and diabetic retinopathy: Early Treatment Diabetic Retinopathy Study Research Group. *Diabetes Care* 19:1291–1293, 1996
7. Roy MS, Klein R: Macular edema and retinal hard exudates in African Americans with type 1 diabetes: the New Jersey 725. *Arch Ophthalmol* 119:251–259, 2001
8. Klein BE, Moss SE, Klein R, Surawicz TS: The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XIII. Relationship of serum cholesterol to retinopathy and hard exudate. *Ophthalmology* 98:1261–1265, 1991
9. Miyamoto K, Khosrof S, Bursell SE, Rohan R, Murata T, Clermont AC, Aiello LP, Ogura Y, Adamis AP: Prevention of leukostasis and vascular leakage in streptozotocin-induced diabetic retinopathy via intercellular adhesion molecule-1 inhibition. *Proc Natl Acad Sci U S A* 96:10836–10841, 1999
10. Joussen AM, Murata T, Tsujikawa A, Kirchhof B, Bursell SE, Adamis AP: Leukocyte-mediated endothelial cell injury and death in the diabetic retina. *Am J Pathol* 158:147–152, 2001
11. Joussen AM, Poulaki V, Mitsiades N, Kirchhof B, Koizumi K, Dohmen S, Adamis AP: Nonsteroidal anti-inflammatory drugs prevent early diabetic retinopathy via TNF-alpha suppression. *FASEB J* 16:438–440, 2002
12. DCCT Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus: the Diabetes Control and Complications Trial Research Group. *N Engl J Med* 329:977–986, 1993
13. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 18:499–502, 1972
14. DCCT Research Group: The Diabetes Control and Complications Trial (DCCT): design and methodologic considerations for the feasibility phase: the DCCT Research Group. *Diabetes* 35:530–545, 1986
15. Early Treatment Diabetic Retinopathy Study Research Group: Fundus photographic risk factors for progression of diabetic retinopathy: ETDRS report number 12. *Ophthalmology* 98 (Suppl. 5):823–833, 1991
16. Early Treatment Diabetic Retinopathy Study Research Group: Grading diabetic retinopathy from stereoscopic color fundus photographs: an extension of the modified Airlie House classification: ETDRS report number 10. *Ophthalmology* 98:786–806, 1991
17. Kremser BG, Falk M, Kieselbach GF: Influence of serum lipid fractions on the course of diabetic macular edema after photocoagulation. *Ophthalmologica* 209:60–63, 1995
18. Larsson LI, Alm A, Lithner F, Dahlen G, Bergstrom R: The association of hyperlipidemia with retinopathy in diabetic patients aged 15–50 years in the county of Umea. *Acta Ophthalmol Scand* 77:585–591, 1999
19. el Haddad OA, Saad MK: Prevalence and risk factors for diabetic retinopathy among Omani diabetics. *Br J Ophthalmol* 82:901–906, 1998
20. Klein R, Klein BE, Moss SE, Cruickshanks KJ: The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XV. The long-term incidence of macular edema. *Ophthalmology* 102:7–16, 1995
21. DCCT/EDIC Research Group: Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy: The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. *N Engl J Med* 342:381–389, 2000
22. Glasgow AM, August GP, Hung W: Relationships between control and serum lipids in juvenile-onset diabetes. *Diabetes Care* 4:76–80, 1981
23. Robins JM: Data, design, and background knowledge in etiologic inference. *Epidemiology* 12:313–320, 2001
24. Klein BE, Klein R, Moss SE: Is serum cholesterol associated with progression of diabetic retinopathy or macular edema in persons with younger-onset diabetes of long duration? *Am J Ophthalmol* 128:652–654, 1999
25. El-Asrar AM, Al-Rubeaan KA, Al-Amro SA, Kangave D, Moharram OA: Risk factors for diabetic retinopathy among Saudi diabetics. *Int Ophthalmol* 22:155–161, 1998
26. The Lipid Research Clinics: *Population Studies Data Book: The Prevalence Study*. U.S. Department of Health and Human Services, National Institute of Health, 1980, p. 1–115 (NIH publ. no. 80-1527)
27. Chew EY, Ferris FL 3rd, Csaky KG, Murphy RP, Agron E, Thompson DJ, Reed GF, Schachat AP: The long-term effects of laser photocoagulation treatment in patients with diabetic retinopathy: the Early Treatment Diabetic Retinopathy Follow-up Study. *Ophthalmology* 110:1683–1689, 2003
28. ETDRS Study Group: Early Treatment Diabetic Retinopathy Study design and baseline patient characteristics: ETDRS report number 7. *Ophthalmology* 98:741–756, 1991

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29. Sjolie AK, Stephenson J, Aldington S, Kohner E, Janka H, Stevens L, Fuller J: Retinopathy and vision loss in insulin-dependent diabetes in Europe: the EURODIAB IDDM Complications Study. *Ophthalmology* 104:252–260, 1997
30. Porta M, Sjoelie AK, Chaturvedi N, Stevens L, Rottiers R, Veglio M, Fuller JH: Risk factors for progression to proliferative diabetic retinopathy in the EURODIAB Prospective Complications Study. *Diabetologia* 44:2203–2209, 2001
31. Davis MD, Fisher MR, Gangnon RE, Barton F, Aiello LM, Chew EY, Ferris FL 3rd, Knatterud GL: Risk factors for high-risk proliferative diabetic retinopathy and severe visual loss: Early Treatment Diabetic Retinopathy Study report #18. *Invest Ophthalmol Vis Sci* 39:233–252, 1998
32. The DCCT/EDIC Research Group: Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. *JAMA* 287:2563–2569, 2002
33. Cohen RA, Hennekens CH, Christen WG, Krolewski A, Nathan DM, Peterson MJ, LaMotte F, Manson JE: Determinants of retinopathy progression in type 1 diabetes mellitus. *Am J Med* 107:45–51, 1999
34. Ebeling P, Koivisto VA: Occurrence and interrelationships of complications in insulin-dependent diabetes in Finland. *Acta Diabetol* 34:33–38, 1997
35. Kordonouri O, Danne T, Hopfenmuller W, Enders I, Hovener G, Weber B: Lipid profiles and blood pressure: are they risk factors for the development of early background retinopathy and incipient nephropathy in children with insulin-dependent diabetes mellitus? *Acta Paediatr* 85:43–48, 1996
36. Lyons TJ, Jenkins AJ, Zheng D, Lackland DT, McGee D, Garvey WT, Klein RL: Diabetic retinopathy and serum lipoprotein subclasses in the DCCT/EDIC cohort. *Invest Ophthalmol Vis Sci* 45:910–918, 2004
37. Browning DJ, McOwen MD, Bowen RM Jr, O'Marah TL: Comparison of the clinical diagnosis of diabetic macular edema with diagnosis by optical coherence tomography. Ophthalmology 111:712–715, 2004
38. Landmesser U, Hornig B, Drexler H: Endothelial dysfunction in hypercholesterolemia: mechanisms, pathophysiological importance, and therapeutic interventions. *Semin Thromb Hemost* 26:529–537, 2000
39. Galler A, Muller G, Schinzel R, Kratzsch J, Kiess W, Munch G: Impact of metabolic control and serum lipids on the concentration of advanced glycation end products in the serum of children and adolescents with type 1 diabetes, as determined by fluorescence spectroscopy and N_{ϵ}-(carboxymethyl)lysine ELISA. *Diabetes Care* 26:2609–2615, 2003
40. Frank RN: Diabetic retinopathy. *N Engl J Med* 350:48–58, 2004
41. Fong DS, Ferris FL 3rd, Davis MD, Chew EY: Causes of severe visual loss in the early treatment diabetic retinopathy study: ETDRS report no. 24: Early Treatment Diabetic Retinopathy Study Research Group. *Am J Ophthalmol* 127:137–141, 1999
42. White NH, Cleary PA, Dahms W, Goldstein D, Malone J, Tamborlane WV: Beneficial effects of intensive therapy of diabetes during adolescence: outcomes after the conclusion of the Diabetes Control and Complications Trial (DCCT). *J Pediatr* 139:804–812, 2001

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