Differential Association of Serum Lipids with Diabetic Retinopathy and Diabetic Macular Edema

Rehab Benarous,[1] *Muhammad B. Sasongko,*[1,2] *Salmaan Qureshi,*[1] *Eva Fenwick,*[1] *Mohamed Dirani,*[1] *Tien Y. Wong,*[1,3] *and Ecosse L. Lamoureux*[1,3]

Purpose. To assess the association of serum lipids with diabetic retinopathy (DR), diabetic macular edema (DME), and macular thickness in adults with diabetes.

Methods. Diabetic patients aged ≥18 years were prospectively recruited from specialized eye clinics in Melbourne, Australia. Fasting total-C (cholesterol), triglyceride, HDL-C, non-HDL-C, and LDL-C were assessed. DR was graded from fundus photographs and classified into mild, moderate, severe nonproliferative, and proliferative DR and separately graded for the presence of DME, including clinically significant macular edema (CSME). Macular thickness was assessed using optical coherence tomography (OCT).

Results. A total of 500 participants (median age, 65 years) were examined. DR, DME, and CSME were present in 321 (66.2%), 149 (33.0%), and 68 (15.0%) patients, respectively. Serum lipid levels were not related to DR or DME. In multivariate models adjusted for traditional risk factors and lipid medications, persons with higher total-, LDL-, and non-HDL-C were more likely to have CSME (odds ratio of 1.54, 1.49, and 1.63 per 1-SD increase, respectively; all $P < 0.05$). No association was found for serum lipids with macular thickness, as assessed by OCT. The pattern of these associations remained similar in both type 1 and type 2 diabetes, although it was statistically significant only in type 2 diabetes.

Conclusions. Serum lipids are independently associated with the CSME, but not with DR, mild or moderate DME, or macular thickness. These data reflect the different impact of hyperlipidemia in the pathogenesis of DR and DME and may explain the discrepancies in previous studies. (*Invest Ophthalmol Vis Sci.* 2011;52:7464–7469) DOI:10.1167/iovs.11-7598

Diabetic retinopathy (DR) is one of the most common microvascular complications of diabetes.[1,2] Diabetic macular edema (DME), which can occur at any stage of DR, is now the major cause of vision loss and the target of a range of new therapies, such as intraocular administration of anti-vascular endothelial growth factor treatments.[3]

Although landmark studies have shown that intensive glycemic and blood pressure control can substantially reduce the onset and progression of DR,[4,5] the contribution of lipids to the pathogenesis of DR and DME has been less clear.[6–8] Previous studies have shown a stronger association of serum lipids with DME than DR, per se,[9,10] yet the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study reported the benefits of fenofibrate in slowing the progression of DR,[11] although this trial did not specifically evaluate the effect of fenofibrate on DME.

The relationship of lipids with DR and DME deserves further investigation for two reasons. First, only one study has reported the detailed assessment of the association of serum lipids with DR and DME severity[9] and only two reports have examined this relationship specifically with proliferative diabetic retinopathy (PDR) or the more severe spectrum of macular edema, clinically significant macular edema (CSME).[10,12] Second, no study has examined whether lipids have an effect on objective measurement of early retinal pathology, such as macular thickness quantified using optical coherence tomography (OCT).[13]

Thus, we prospectively recruited a large clinical sample of diabetic patients with the spectrum of DR and DME and investigated the association of serum lipids, including serum total cholesterol, triglycerides (TGs), LDL-C, HDL-C, and non-HDL-C with the presence and severity of DR, DME, and macular thickness (determined by OCT), in patients with type 1 and 2 diabetes.

Methods

Study Population

Five hundred English-speaking adults with diabetes (391 type 2, 79.5%) aged 18 years or older were prospectively recruited from general and specialized eye clinics at the Royal Victorian Eye and Ear Hospital, Victoria, Australia, from March 2009 to July 2010 as part of the Diabetes Management Project. All participants were free of significant hearing and cognitive impairment and lived independently in the community. Written informed consent was obtained from all participants. The study was approved by the Human Research and Ethics Committee and adhered to the tenets of the Declaration of Helsinki.

Assessment of Diabetic Retinopathy

DR was graded from two-field fundus photographs (CR6-45NM, Canon Inc., Tokyo, Japan), according to the modified Airlie House classification system. We categorized the severity of DR as no DR (Early Treatment of Diabetic Retinopathy Study [ETDRS] levels 10–15), mild nonproliferative DR (NPDR; level 20), moderate NPDR (levels 31–43), severe NPDR (levels 53–60), and PDR (levels 61–80).

DME was graded from stereoscopic fundus photographs and was confirmed by OCT. DME was considered present if there was some

From the [1]Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, Melbourne, Victoria, Australia; the [2]Department of Ophthalmology, Faculty of Medicine, Gadjah Mada University, Yogyakarta, Indonesia; and the [3]Singapore Eye Research Institute, National University of Singapore, Singapore.

Supported by Australian Research Council (ARC) Linkage Grant LP0884108. The Centre for Eye Research Australia receives operational infrastructure support from the Victorian Government.

Submitted for publication March 21, 2011; revised May 22, 2011; accepted May 24, 2011.

Disclosure: **R. Benarous**, None; **M.B. Sasongko**, None; **S. Qureshi**, None; **E. Fenwick**, None; **M. Dirani**, None; **T.Y. Wong**, None; **E.L. Lamoureux**, None

Corresponding author: Ecosse L. Lamoureux, Principal Research Fellow, Department of Ophthalmology, University of Melbourne, 32 Gisborne Street, East Melbourne 3002, Victoria, Australia; ecosse@unimelb.edu.au.

visible retinal thickening or hard exudates in the posterior pole. If present, DME was further classified as mild (retinal thickening or hard exudate distant from the macula), moderate (retinal thickening or hard exudate approaching the center of the macula), or CSME (retinal thickening within a circle of 1-mm diameter at the center of the macula).

Assessment of Macular Thickness

OCT (Stratus Model 3000; Carl Zeiss Meditec Inc., North Ryde, NSW, Australia) was used to measure macular thickness. Fast macular scans with retinal map analyses were performed for both eyes. Four measurements were recorded: (1) central macular thickness (CMT), defined as the central circular zone of 1 mm diameter of the scan; (2) inner macular thickness (IMT), defined as the mean retinal thickness within the central 3 mm surrounding the central circular zone; (3) outer macular thickness (OMT), defined as the mean retinal thickness within the central 6 mm surrounding the central circular zone; and (4) total macular volume (TMV). Right eye measurement was used for this analysis (Pearson correlation for right and left >0.5).

Blood and Urine Chemistry

Fasting (≥8 hours) blood samples were collected for analysis of blood glucose, glycated hemoglobin (GHb), and lipids (total-, HDL-, and LDL-C [cholesterol] and triglycerides). Fasting plasma glucose and serum lipids including total, HDL-C and triglycerides, were estimated with a chemistry analyzer (Modular P; Roche Diagnostics; Mannheim, Germany). Non-HDL-C was calculated by subtracting HDL-C from total-C. The Friedewald formula was used to calculate LDL-C, if plasma triglyceride concentrations were less than or equal to 4.5 mmol/L (400 mg/dL). In participants with triglyceride concentrations >4.5 mmol/L, LDL-C measurements were not calculated.

A 50-mL midstream urine sample was collected into 50-mL specimen containers, to determine the albumin creatinine ratio (ACR). All blood and urine analyses were performed at Melbourne Pathology (Melbourne, Australia), with individual results electronically delivered through a password-protected program. The laboratory is accredited to the International Standard ISO15189 (Medical Laboratories) and is certified by NATA (National Association of Testing Authorities).

Assessment of Other Risk Factors

Each participant underwent a comprehensive assessment that included a range of clinical, biochemical, and anthropometric measurements and a series of validated questionnaires on lifestyle, diet, psychosocial factors, and quality of life. Key covariates included age, sex, duration of diabetes (years), diabetic medication use, use of antihypertensive medications, use of lipid-lowering medications, GHb level (percentage), blood pressure (mm Hg), body mass index (BMI; kilograms divided by height in meters squared), waist circumference (WC; in centimeters), ACR, and smoking status

Statistical Analysis

Participants' characteristics with and without DR, DME, and CSME were compared by using the χ^2 statistic for proportions, and a *t*-test or Mann–Whitney U test for means or median (Intercooled STATA version 10.1 for Windows; StataCorp., College Station, TX). Serum lipids were assessed categorically (in quintiles) and continuously (per standard deviation change). The four measures of macular thickness were as-

Table 1. Participant's Characteristics According to Diabetic Retinopathy and Macular Edema Presence

	DR		DME		CSME	
	Absent	**Present**	**Absent**	**Present**	**Absent**	**Present**
***Characteristics* (%)**						
n (%)	171 (34.8)	321 (65.2)	302 (66.9)	149 (33.0)	383 (84.9)	68 (15.0)
Male	57.5	71.7	61.2	76.5*	65.8	69.1
Current smoker	12.1	9.7	10.9	9.52	10.5	10.5
Use of insulin	22.2	53.6†	37.0	55.0*	39.9	60.3*
Use of oral hypoglycemic agent	70.6	73.6	72.6	74.5	70.5	88.1*
Use of lipid-lowering medication						
Statins	10.3	8.2	9.2	12.3	11.5	13.4
Fenofibrate	8.0	9.0	7.3	7.10	5.5	7.2
Use of anti-hypertensive medication	26.5	23.2	22.1	29.5	24.02	27.94
Characteristics, Mean (SD)						
Age, y	68.0 (17.0)	63.0 (15.0)*	64.9 (12.6)	61.9 (11.5)*	64.6 (12.0)	60.2 (11.1)*
BMI, kg/m^2	30.5 (6.6)	30.9 (6.0)	33.9 (22.3)	30.5 (12.0)	33.2 (21.0)	30.3 (6.1)
WC, cm	104.7 (17.5)	107.7 (15.3)	104 (19.8)	103 (20.3)	107 (43.4)	103 (21.6)
SBP, mm Hg	138.6 (18.6)	141.1 (18.9)	139 (18.7)	141 (19.3)	139.7 (18.8)	141 (1963)
Duration of diabetes, y‡	8.0 (9.0)	18.0 (12.0)*	14.5 (11.5)	17.8 (10.2)*	15.5 (11.6)	16.5 (8.2)
GHb, %	7.3 (1.3)	8.0 (1.5)*	7.5 (1.3)	8.1 (1.6)*	7.6 (1.4)	8.3 (1.7)*
CMT, μm	215.5 (38.5)	236.0 (85.0)*	217.0 (50.0)	250.5 (94.1)*	241.9 (78.3)	301.7 (117.9)*
IMT, μm	261.0 (29.9)	279.4 (52.5)*	269.2 (52.5)	288.9 (60.9)*	274.8 (54.7)	323.6 (81.5)*
OMT, μm	228.5 (24.8)	250.9 (43.8)*	239.5 (33.3)	277.5 (52.5)*	244.0 (35.8)	291.9 (62.2)*
TMV, mm^3	6.7 (0.7)	7.5 (1.4)*	6.9 (1.0)	8.0 (1.5)*	7.1 (1.1)	8.4 (1.8)*
Cholesterol, mmol/L	4.8 (1.2)	4.6 (1.3)	4.6 (1.3)	4.7 (1.3)	4.6 (1.2)	5.2 (1.4)*
TGs, mmol/L‡	1.7 (1.0)	1.9 (1.5)	1.8 (1.2)	1.9 (1.3)	1.8 (1.1)	2.1 (1.8)
HDL-C, mmol/L	1.4 (0.5)	1.3 (0.4)†	1.4 (0.4)	1.3 (0.4)	1.3 (0.4)	1.3 (0.5)
Non-HDL-C, mmol/L	3.3 (1.3)	3.3 (1.3)	3.2 (1.3)	3.4 (1.2)	3.2 (1.2)	3.8 (1.3)*
LDL-C, mmol/L	2.5 (1.0)	2.4 (1.1)	2.4 (1.0)	2.6 (1.1)	2.4 (1.0)	2.9 (1.2)*
LDL-C/HDL-C	2.0 (1.4)	1.9 (0.9)	1.8 (1.2)	2.0 (1.0)†	1.8 (1.1)	2.3 (1.1)*
Chol/HDL-C	3.6 (1.4)	3.7 (1.4)	3.5 (1.3)	3.8 (1.3)†	3.5 (1.3)	4.2 (1.5)*

* $P < 0.001$ compared with the absent group.
† $P < 0.05$ compared with the absent group.
‡ Median (IQR).

TABLE 2. Association of Serum Lipids with the Severity of DR

Serum Lipids (Per SD increase)	Mild NPDR OR (95% CI)	Moderate NPDR OR (95% CI)	Severe NPDR OR (95% CI)	PDR OR (95% CI)	P_{trend}
Model 1*					
Cholesterol (1.3), mmol/L	1.00 (0.63–1.59)	0.77 (0.60–0.99)	1.18 (0.79–1.77)	0.86 (0.67–1.10)	0.26
Triglyceride (1.0), mmol/L	1.49 (0.97–2.45)	1.00 (0.75–1.34)	1.09 (0.71–1.67)	1.07 (0.81–1.41)	0.72
HDL-C (1.1), mmol/L	1.02 (0.66–1.58)	0.88 (0.69–1.13)	0.86 (0.51–1.43)	0.93 (0.72–1.20)	0.36
Non HDL-C (1.3), mmol/L	0.99 (0.62–1.59)	0.80 (0.62–1.03)	1.23 (0.83–1.84)	0.87 (0.68–1.12)	0.39
LDL-C (1.3), mmol/L	0.77 (0.46–1.31)	0.77 (0.60–0.98)	1.18 (0.79–1.76)	0.88 (0.69–1.12)	0.38
LDL-C/HDL-C (1.2)	0.82 (0.45–1.47)	0.73 (0.54–0.98)	1.11 (0.78–1.58)	0.88 (0.67–1.16)	0.41
Chol/HDL-C (1.2)	0.88 (0.51–1.52)	0.80 (0.61–1.05)	1.26 (0.84–1.88)	0.99 (0.76–1.27)	0.89
Model 2†					
Cholesterol (1.3), mmol/L	1.02 (0.60–1.74)	0.73 (0.53–1.01)	1.16 (0.72–1.86)	0.79 (0.57–1.11)	0.20
Triglyceride (1.0), mmol/L	1.55 (0.97–2.47)	1.02 (0.71–1.48)	1.12 (0.69–1.83)	1.16 (0.81–1.66)	0.48
HDL-C (1.1), mmol/L	0.97 (0.61–1.56)	0.89 (0.67–1.19)	0.90 (0.51–1.56)	0.90 (0.66–1.24)	0.34
Non HDL-C (1.3), mmol/L	1.05 (0.61–1.80)	0.76 (0.55–1.05)	1.22 (0.76–1.96)	0.83 (0.59–1.16)	0.33
LDL-C (1.3), mmol/L	0.75 (0.41–1.36)	0.69 (0.50–0.95)	1.06 (0.67–1.70)	0.76 (0.55–1.06)	0.14
LDL-C/HDL-C (1.2)	0.86 (0.48–1.55)	0.66 (0.46–0.96)	1.09 (0.69–1.75)	0.85 (0.59–1.21)	0.41
Chol/HDL-C (1.2)	0.93 (0.51–1.70)	0.74 (0.53–1.04)	1.30 (0.81–2.07)	1.03 (0.74–1.43)	0.64

* Model 1: age- and sex-adjusted.

† Model 2: model 1 plus duration of diabetes, GHb, systolic BP, BMI, and use of oral hypoglycemic drugs, insulin, and lipid lowering agents.

sessed as continuous variables. Normality was checked, and data were transformed as appropriate. Person data were used for DR, DME, and CSME based on the worse eye. Multinomial and ordinal logistic regression models were performed to assess associations between serum lipids and severity of DR (mild, moderate, severe NPDR, and PDR) or DME (mild, moderate, and CSME). A binomial logistic regression model was used to assess the association between serum lipids and CSME. Association between serum lipids and macular thickness was examined using generalized linear models. We initially adjusted for age and sex (model 1) and additionally for diabetes duration, GHb, SBP, BMI, use of diabetes medications, use of lipid-lowering medications, and insulin usage (model 2). Covariates included in the models were either categorical or continuous (per standard deviation changes for age, SBP, and BMI; per year for diabetes duration; and per percent for GHb level).

RESULTS

Of the 500 participants, 436 (87.2%) had type 2 and 64 (12.8%) had type 1 diabetes. Among 492 with gradable fundus photographs, 321(65.2%) had any DR and 171 (34.8%) had no signs of DR. In those with DR, 22 (4.5%) had mild NPDR, 139 (28.3%) had moderate NPDR, 26 (5.3%) had severe NPDR, and 134 (27.2%) had PDR. Of those with DR, 149 (33.0%) and 68 (15.1%) had DME and CSME, respectively. The participants' characteristics stratified for DR, DME, or CSME status are shown in Table 1. Participants with DR and DME were younger, had a longer duration of diabetes, and had higher GHb and increased macular thickness and volume (all $P < 0.001$) than did those without. Serum lipid levels were similar in persons with DR or DME compared with those without. However, total-, non-HDL-, and LDL-C were significantly higher in participants with CSME than in those without CSME (all $P < 0.001$).

Table 2 shows the association of serum lipids with DR severity. After adjustment for age and sex (model 1), serum lipids were not associated with increasing severity of DR (Table 2).

Table 3 shows the association of serum lipids with the severity of DME. Except for LDL-C which was associated with increasing severity of DME ($P_{trend} = 0.02$), no other lipid measure was

TABLE 3. Association of Serum Lipids with the Severity of DME

Serum Lipids (Per SD Increase)	Mild DME OR (95% CI)	Moderate DME OR (95% CI)	CSME OR (95% CI)	P_{trend}
Model 1*				
Cholesterol (1.3), mmol/L	0.90 (0.63–1.29)	0.81 (0.54–1.19)	1.41 (1.09–1.82)	0.08
Triglyceride (1.0), mmol/L	0.92 (0.62–1.37)	0.79 (0.49–1.29)	1.11 (0.86–1.43)	0.72
HDL-C (1.1), mmol/L	1.02 (0.70–1.50)	0.96 (0.64–1.42)	1.04 (0.78–1.38)	0.94
Non HDL-C (1.3), mmol/L	0.89 (0.61–1.29)	0.81 (0.55–1.21)	1.40 (1.10–1.81)	0.07
LDL-C (1.3), mmol/L	0.89 (0.61–1.29)	0.85 (0.58–1.26)	1.50 (1.17–1.93)	0.02
LDL-C/HDL-C (1.2)	0.96 (0.64–1.46)	0.75 (0.46–1.22)	1.34 (1.04–1.71)	0.06
Chol/HDL-C (1.2)	0.96 (0.66–1.39)	0.76 (0.49–1.18)	1.41 (1.08–1.84)	0.08
Model 2†				
Cholesterol (1.3), mmol/L	0.74 (0.45–1.09)	0.84 (0.52–1.18)	1.50 (1.08–1.96)	0.07
Triglyceride (1.0), mmol/L	0.96 (0.59–1.48)	0.78 (0.48–1.25)	1.00 (0.74–1.36)	0.77
HDL-C (1.1), mmol/L	0.79 (0.49–1.27)	0.88 (0.57–1.37)	1.18 (0.86–1.62)	0.60
Non HDL-C (1.3), mmol/L	0.77 (0.46–1.14)	0.79 (0.51–1.21)	1.41 (1.04–1.90)	0.10
LDL-C (1.3), mmol/L	0.69 (0.45–1.09)	0.83 (0.55–1.25)	1.55 (1.15–2.09)	0.06
LDL-C/HDL-C (1.2)	0.88 (0.54–1.45)	0.74 (0.44–1.26)	1.37 (1.06–1.77)	0.05
Chol/HDL-C (1.2)	0.94 (0.61–1.46)	0.75 (0.46–1.22)	1.43 (1.04–1.97)	0.10

* Model 1: age- and sex-adjusted.

† Model 2: model 1 plus duration of diabetes, GHb, systolic BP, BMI, and use of oral hypoglycemic drugs, insulin, and lipid- lowering agents.

associated (model 1). However, after adjustment for traditional risk factors and lipid-lowering medications, the association between serum lipids and DME lost its significance (P_{trend} = 0.06; Table 3).

Table 4 shows the associations of serum lipids with CSME. After adjustment for age and sex, per SD increase in total-C (odd ratio [OR], 1.45; 95% confidence interval [CI], 1.13–1.86; P = 0.003), non-HDL-C (OR, 1.45; 95% CI, 1.13–1.86; P = 0.003), LDL-C (OR, 1.54; 95% CI, 1.21–1.98; P = 0.001), LDL-C/HDL-C (OR, 1.37; 95% CI, 1.07–1.75; P = 0.014), and total-C/HDL-C (OR, 1.46; 95% CI, 1.13–1.89; P = 0.004) were strongly associated with having CSME. These associations persisted after further adjustment for duration of diabetes, GHb, SBP, BMI, and use of insulin, oral hypoglycemia, and lipid-lowering medications. Stratification of these results by sex and diabetes type showed that our findings were similar for the women and the men, or in type 1 and type 2 diabetes, except for non-HDL-C with regard to having CSME. However, these associations were only significant in type 2 diabetes (Supplementary Tables S4–S6, http://www.iovs.org/lookup/suppl/doi:10.1167/iovs.11-7598/-/DCSupplemental).

No serum lipid measure was associated with any of the macular thickness parameters (Supplementary Table S2, http://www.iovs.org/lookup/suppl/doi:10.1167/iovs.11-7598/-/DCSupplemental).

TABLE 4. Association of Serum Lipids with CSME

Serum Lipids	At Risk (*n*)	Model 1 OR (95% CI)	*P*	Model 2 OR (95% CI)	*P*
Cholesterol, mmol/L					
1st quintile, ≤3.5	97	1.00		1.00	
2nd quintile, 3.6–4.2	95	1.41 (0.53–3.73)		1.06 (0.38–3.30)	
3rd quintile, 4.3–4.7	100	1.21 (0.45–3.24)		1.36 (0.46–3.96)	
4th quintile, 4.8–5.6	92	2.56 (1.02–6.40)		4.34 (1.57–12.0)	
5th quintile, ≥5.7	83	2.88 (1.12–7.12)	0.006*	3.48 (1.26–9.64)	0.001*
Per SD (1.3) increase		1.45 (1.13–1.86)	0.003	1.54 (1.15–2.07)	0.003
Triglyceride, mmol/L					
1st quintile, ≤1.0	110	1.00		1.00	
2nd quintile, 1.1–1.4	95	1.38 (0.55–3.47)		1.28 (0.45–3.64)	
3rd quintile, 1.5–1.8	85	2.78 (1.19–6.52)		2.60 (1.00–6.74)	
4th quintile, 1.9–2.5	92	1.66 (0.68–4.05)		1.72 (0.64–4.61)	
5th quintile, ≥2.6	84	1.72 (0.70–4.20)	0.21*	1.47 (0.53–4.08)	0.37*
Per SD (1.1) increase		1.14 (0.89–1.47)	0.30	1.04 (0.78–1.40)	0.74
HDL-C, mmol/L					
1st quintile, ≤1.0	100	1.00		1.00	
2nd quintile, 1.1–1.2	101	1.11 (0.49–2.51)		1.11 (0.44–2.81)	
3rd quintile, 1.3–1.4	85	1.28 (0.55–3.01)		1.46 (0.56–3.76)	
4th quintile, 1.5–1.7	94	1.37 (0.60–3.14)		1.29 (0.50–3.32)	
5th quintile, ≥1.8	84	0.94 (0.36–2.43)	0.84*	1.33 (0.46–3.84)	0.52*
Per SD (1.0) increase		1.04 (0.79–1.38)	0.77	1.21 (0.89–1.65)	0.22
Non HDL-C, mmol/L					
1st quintile, ≤2.1	94	1.00		1.00	
2nd quintile, 2.2–2.7	94	2.82 (0.95–8.32)		1.74 (0.52–5.78)	
3rd quintile, 2.8–3.2	96	2.27 (0.75–6.85)		1.99 (0.63–6.26)	
4th quintile, 3.3–4.1	88	3.37 (1.14–9.92)		3.64 (1.18–11.2)	
5th quintile, ≥4.2	92	4.82 (1.72–13.5)	0.003*	4.95 (1.63–15.1)	0.001*
Per SD (1.4) increase		1.45 (1.13–1.86)	0.003	1.49 (1.11–1.99)	0.007
LDL-C, mmol/L					
1st quintile, ≤1.6	97	1.00		1.00	
2nd quintile, 1.7–2.0	107	3.13 (0.98–9.96)		3.82 (1.14–12.8)	
3rd quintile, 2.1–2.4	77	3.18 (0.93–10.9)		2.32 (0.59–9.03)	
4th quintile, 2.5–3.2	83	4.29 (1.33–13.8)		5.38 (1.61–17.9)	
5th quintile, ≥3.3	86	6.63 (2.15–10.5)	0.001*	8.02 (2.42–26.5)	<0.001*
Per SD (1.4) increase		1.54 (1.21–1.98)	0.001	1.63 (1.22–2.19)	<0.001
LDL-C/HDL-C					
1st quintile, ≤1.1	95	1.00		1.00	
2nd quintile, 1.2–1.5	92	1.49 (0.45–4.92)		1.20 (0.35–4.12)	
3rd quintile, 1.6–2.0	84	3.14 (1.07–9.24)		2.39 (0.74–7.72)	
4th quintile, 2.1–2.6	100	3.81 (1.32–10.9)		3.18 (1.04–9.78)	
5th quintile, ≥2.7	78	5.26 (1.82–15.2)	<0.001*	4.89 (1.54–15.5)	0.001*
Per SD (1.2) increase		1.37 (1.07–1.75)	0.014	1.41 (1.10–1.82)	0.008
Chol/HDL-C					
1st quintile, ≤2.5	97	1.00		1.00	
2nd quintile, 2.6–3.1	99	2.20 (0.71–6.75)		1.39 (0.42–4.66)	
3rd quintile, 3.2–3.8	86	3.95 (1.37–11.4)		3.08 (1.00–9.53)	
4th quintile, 3.9–4.7	91	2.83 (0.94–8.53)		2.47 (0.76–8.08)	
5th quintile, ≥4.8	92	5.59 (1.97–15.9)	0.001*	4.78 (1.51–15.1)	0.003*
Per SD (1.2) increase		1.46 (1.13–1.89)	0.004	1.49 (1.09–2.03)	0.012

Model 1: age- and sex-adjusted.

Model 2: model 1 plus duration of diabetes, GHb, systolic BP, BMI, and use of oral hypoglycemic drugs, insulin, and lipid-lowering agents.

* *P* for trend.

Discussion

In this large clinical sample of adults with diabetes, we found that serum lipids were not associated with the presence and severity of DR, mild or moderate DME, or macular thickness. In contrast, serum lipids (total-C, LDL-C, non-HDL-C, LDL-C/HDL-C, and total-C/HDL-C) were independently associated with CSME, after adjustment for traditional DR risk factors and lipid-lowering medications.

The lack of association of serum lipids with both the presence and severity of DR in this study is compatible with previous data from the Multi-ethnic Study of Atherosclerosis (MESA), which show no association between serum lipids, including total-C, LDL-C, and HDL-C and DR,[7] and the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab).[14] On the contrary, our findings of an association between serum lipids and CSME confirm previous reports that have specifically evaluated this endpoint.[9,10] For example, data from the Diabetes Control and Complication Trial (DCCT)[4] demonstrated that LDL-C and total-C/HDL-C were associated with increased risk for developing CSME. Recent evidence from the Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetic Study also demonstrated that patients with CSME, but not DME, had elevated total-, non HDL-, and LDL-C.[10]

The association between serum lipids and CSME is biologically plausible.[9] Several proposed mechanisms discussed in earlier reports include the direct involvement of serum lipids in endothelium dysfunction[15,16] which subsequently result in the breakdown of the blood retinal barrier leading to exudation of serum lipids and lipoproteins to intercellular space in the retina.[10,17] However, although DR and CSME share some similar pathogenesis, our study demonstrated that the association of serum lipids with DR was different from that with CSME. Whereas serum lipids were not associated with DR, in contrast, we found strong associations with CSME.

We speculate that serum lipids may have a strong influence only in the severe forms of diabetic microvascular eye endpoint. In support of this, our data showed that serum lipids were not associated with macular thickness and volume in this population. These findings may provide additional insight that serum lipids are involved in the pathogenesis of DME only via exudation of lipids through damaged retinal vasculature, which occurs at a later stage, but may not cause direct injury to the endothelium and consequent damage to the blood–retinal barrier, which can occur at an earlier stage.[18,19] Consistent with this hypothesis, a previous study found that there was no association between serum lipids and development of retinopathy in nondiabetics,[20] indicating the importance of existing damage in retinal vasculature for lipids to exhibit their harmful effect on the retina. Future work is obviously needed in this area.

Our study findings have clear clinical implications. The difference in the association of serum lipids with DR and CSME suggests that hyperlipidemia may have a different impact on those disorders. We have speculated that serum lipids are involved in the later, more severe stages than in earlier stages; thus, dyslipidemia may have a more direct impact on CSME than on DR. This finding may help to explain the discrepancy in previous studies and suggests that lipid-targeting therapies may show more benefit in slowing the progression to the severe stage than in preventing the development of DR. This notion is supported by the data from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) and ACCORD-Eye trials, which showed that the use of lipid-lowering medication slowed the progression of DR, but was not related to incident DR.[11,21] These two studies were, however, large prospective clinical trials, and information about the impact of lipid-lowering therapy on DME and CSME has not been presented. This area of research needs to be further investigated in the future.

Our study's strengths include the large clinical sample of diabetic patients with differing levels of DR, the assessment of DR by grading retinal photographs according to standardized protocols, assessment of DME by OCT, detailed and comprehensive clinical examination, and a patient sample with typical characteristics of other diabetic populations, with DR showing strong associations with duration of diabetes and GHb level, which support the generalizability of our findings. However, some limitations are also noted. First, the cross-sectional nature of the study did not allow us to assess the temporal sequence of these associations. Second, DR was graded from two-field instead of seven-field retinal photographs, as were used in large clinical trials such as the ETDRS. This method may have underestimated the presence of DR. However, since we did not find any association with DR, grading of two-field photographs is unlikely to have affected our findings. Third, there is a possibility of selection bias due to patients with resolved CSME after treatment being categorized as non-CSME. However, during the recruitment process, we also carefully reviewed and obtained detailed medical history, and we did not find such cases. Therefore, a selection bias in this regard was unlikely to occur. Finally, due to the small number of patients with type 1 diabetes in this study, no distinction was made between types 1 and 2 diabetes in the primary analysis. However, stratification for types 1 and 2 diabetes did not substantially change our findings (Supplementary Tables S4–S6, http://www.iovs.org/lookup/suppl/doi:10.1167/iovs.11-7598/-/DCSupplemental).

In conclusion, we have shown that serum lipids were largely associated with CSME, but not with the severity of DR, milder forms of DME, or subclinical macular thickness, suggesting a differential impact of dyslipidemia in the pathogenesis of DR and CSME. These findings may explain discrepancies found in previous studies and suggest that differing hyperlipidemia therapies targeting at DR and CSME are needed.

References

1. Cheung N, Mitchell P, Wong YT. Diabetic retinopathy. *The Lancet.* 2010;376(9735):124–136.
2. Klein R, Klein BE. Are individuals with diabetes seeing better?—a long-term epidemiological perspective. *Diabetes.* 2010;59:1853–1860.
3. Ciulla TA, Amador AG, Zinman B. Diabetic retinopathy and diabetic macular edema. *Diabetes Care.* 2003;26(9):2653–2664.
4. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med.* 1993;329(14):9.
5. Matthews D, Stratton I, Aldington S, Holman R, Kohner E. Risks for progression of retinopathy and vision loss related to tight blood pressure control in type 2 diabetes mellitus: UKPDS 69. *Arch Ophthalmol.* 2004;122:1631–1640.
6. Wong TY, Cheung N, Tay WT, et al. Prevalence and risk factors for diabetic retinopathy: the Singapore Malay Eye Study. *Ophthalmology.* 2008;115:1869–1875.
7. Wong TY, Klein R, Islam FM, et al. Diabetic retinopathy in a multi-ethnic cohort in the United States. *Am J Ophthalmol.* 2006;141:446–455.
8. Sasongko BM, Wong YT, Nyugyn TT, et al. Serum apolipoprotein AI and B are stronger predictors of diabetic retinopathy than traditional lipids. *Diabetes Care.* 2011;34(2):474–479.
9. Miljanovic B, Glynn RJ, Nathan DM, Manson JE, Schaumberg DA. A prospective study of serum lipids and risk of diabetic macular edema in type 1 diabetes. *Diabetes.* 2004;53(11):2883–2892.
10. Raman R, Rani PK, Kulothungan V, Rachepalle SR, Kumaramanickavel G, Sharma T. Influence of serum lipids on clinically signif-

icant versus nonclinically significant macular edema: SN-DREAMS Report number 13. *Ophthalmology.* 2010;117:766–772.

11. The ACCORD study group and the ACCORD Eye Study Group. Effects of medical therapies on retinopathy progression in type 2 diabetes. *N Engl J Med.* 2010;363:233–244.
12. Rema M, Premkumar S, Anitha B, Deepa R, Pradeepa R, Mohan V. Prevalence of diabetic retinopathy in urban India: The Chennai Urban Rural Epidemiology Study (CURES) Eye Study, I. *Invest Ophthalmol Vis Sci.* 2005;46(7):2328–2333.
13. Massin P, Girach A, Erginay A, Gaudric A. Optical coherence tomography: a key to the future management of patients with diabetic macular oedema. *Acta Ophthalmol Scand.* 2006;84(4): 466–474.
14. Tapp RJ, Shaw JE, Harper CA, et al. The prevalence of and factors associated with diabetic retinopathy in the Australian population. *Diabetes Care.* 2003;26(6):1731–1737.
15. Landmesser U, Hornig B, Drexler H. Endothelial dysfunction in hypercholesterolemia: mechanisms, pathophysiological importance, and therapeutic interventions. *Semin Thromb Hemost.* 2000;26(5):529–538.
16. Schalkwijk CG, Stehouwer CDA. Vascular complications in diabetes mellitus: the role of endothelial dysfunction. *Clin Sci.* 2005; 109(2):143–159.
17. Chowdhury T, Hopkins D, Dodson PM, Vafidis GC. The role of serum lipids in exudative diabetic maculopathy: is there a place for lipid lowering therapy? *Eye* 2002;16(6):689–693.
18. Antcliff RJ, Marshall J. The pathogenesis of edema in diabetic maculopathy. *Semin Ophthalmol.* 1999;14(4):223–232.
19. Cunha-Vaz J, Faria de Abreu JR, Campos AJ. Early breakdown of the blood-retinal barrier in diabetes. *Br J Ophthalmol.* 1975;59(11): 649–656.
20. Klein R, Sharrett AR, Klein BEK, et al. The association of atherosclerosis, vascular risk factors, and retinopathy in adults with diabetes: The Atherosclerosis Risk in Communities Study. *Ophthalmology.* 2002;109(7):1225–1234.
21. Keech AC, Mitchell P, Summanen PA, et al. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. *Lancet.* 2007;370(9600): 1687–1697.