Association Between Plasma Triglycerides and High-Density Lipoprotein Cholesterol and Microvascular Kidney Disease and Retinopathy in Type 2 Diabetes Mellitus

A Global Case–Control Study in 13 Countries

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Background—Microvascular renal and retinal diseases are common major complications of type 2 diabetes mellitus. The relation between plasma lipids and microvascular disease is not well established.

Methods and Results—The case subjects were 2535 patients with type 2 diabetes mellitus with an average duration of 14 years, 1891 of whom had kidney disease and 1218 with retinopathy. The case subjects were matched for diabetes mellitus duration, age, sex, and low-density lipoprotein cholesterol to 3683 control subjects with type 2 diabetes mellitus who did not have kidney disease or retinopathy. The study was conducted in 24 sites in 13 countries. The primary analysis included kidney disease and retinopathy cases. Matched analysis was performed by use of site-specific conditional logistic regression in multivariable models that adjusted for hemoglobin A_{1c}, hypertension, and statin treatment. Mean low-density lipoprotein cholesterol concentration was 2.3 mmol/L. The microvascular disease odds ratio increased by a factor of 1.16 (95% confidence interval, 1.11–1.22) for every 0.5 mmol/L (≈1 quintile) increase in triglycerides or decreased by a factor of 0.92 (0.88–0.96) for every 0.2 mmol/L (≈1 quintile) increase in high-density lipoprotein cholesterol. For kidney disease, the odds ratio increased by 1.23 (1.16–1.31) with triglycerides and decreased by 0.86

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(0.82–0.91) with high-density lipoprotein cholesterol. Retinopathy was associated with triglycerides and high-density lipoprotein cholesterol in matched analysis but not significantly after additional adjustment.

Conclusions—Diabetic kidney disease is associated worldwide with higher levels of plasma triglycerides and lower levels of high-density lipoprotein cholesterol among patients with good control of low-density lipoprotein cholesterol. Retinopathy was less robustly associated with these lipids. These results strengthen the rationale for studying dyslipidemia treatment to prevent diabetic microvascular disease. **(*Circulation*. 2014;129:999-1008.)**

Key Words: diabetes mellitus ■ diabetic retinopathy ■ epidemiology ■ kidney ■ lipids ■ risk factors

Diabetes mellitus is a major cause of microvascular disease, which includes kidney disease and retinopathy and their ultimate consequences, end-stage renal disease and blindness.[1–4] Hyperglycemia and hypertension are major risk factors for the development of microvascular disease.[2,4] Intensive control of blood glucose and blood pressure to, or even beyond, currently recommended targets may provide some additional benefits in the prevention of diabetic microvascular disease but is often impossible to achieve because of the associated risks of hypoglycemia or hypotension.[5,6] Therefore, it is necessary to identify other targets and treatments to make progress in slowing the development of diabetic kidney disease and retinopathy.

Clinical Perspective on p 1008

Most epidemiological studies have found an association between serum triglycerides and diabetic kidney disease, although less consistently for serum high-density lipoprotein cholesterol (HDL-C).[7–21] Results diverged among studies on diabetic retinopathy, especially in multivariable analysis.[4,22–33] In randomized, controlled trials, treatment of patients with type 2 diabetes mellitus with fenofibrate, a peroxisome proliferator–activated receptor-α agonist, reduced the rate of decline in renal function,[25,34] reduced albuminuria, and reduced the requirement for laser treatment of retinopathy.[5,25,34,35] However, it is not clear whether these beneficial effects were caused by improvements in triglycerides or HDL-C or by other biological effects of peroxisome proliferator–activated receptor-α activation.

The objective of the present international study was to determine whether low HDL-C or elevated triglycerides levels are associated with diabetic kidney disease and retinopathy independent of established determinants of microvascular disease in patients with type 2 diabetes mellitus with low-density lipoprotein cholesterol (LDL-C) ≤3.4 mmol/L (130 mg/dL).

Methods

The study used a case–control design in 24 sites in 13 countries. Sites were either hospitals or diabetes clinics. The study was approved by the institutional review boards of the coordinating center and each clinical site.

Population

Case and control subjects were individuals with type 2 diabetes mellitus documented in the medical record, ≥40 years of age, with LDL-C ≤3.4 mmol/L.

Data were compiled from clinical charts. All consecutive charts of patients with type 2 diabetes mellitus who met the selection criteria were processed, and the required parameters were recorded. The methodology was piloted for feasibility assessment at the site in Brussels, Belgium, and included case subjects ascertained from 1990 to 2009 (median visit date May 2006). The chart review period was in 2008 to 2010 for all other sites.

Case Subjects

Case subjects were patients with visits for ≥1 recorded ocular or renal microvascular complication (kidney disease or retinopathy, the latter also including diabetic macular edema). Patients with nondiabetic kidney disease were excluded unless they presented with a known diabetic microvascular complication. Nondiabetic kidney disease was determined by the site's principal investigator from the medical records. The index visit for a case was a complication-related visit to which a lipid panel measured within 6 months could be associated.

Control Subjects

Control subjects were patients with type 2 diabetes mellitus with documented evidence of not having microvascular complications of the kidney and eye as defined below.

Case Definitions

Kidney Disease

Kidney disease was defined as either proteinuria >300 mg/L, albuminuria, or estimated glomerular filtration rate <60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$. Albuminuria was defined as either albumin/creatinine ratio ≥30 μg/mg measured in a single morning urine sample, >20 μg/min in timed overnight urine collections, or >30 mg/24 h in a 24-hour urine collection. Glomerular filtration rate was estimated by the Modification of Diet in Renal Disease formula.

Retinopathy

Retinopathy was defined as laser treatment for diabetic retinopathy; Early Treatment Diabetic Retinopathy Study (EDTRS) staging ≥20 shown by fundus photography; Diabetic Retinopathy Disease Severity Scale 3, 4, or 5 shown by dilated ophthalmoscopy[36]; or maculopathy defined as moderate or severe with the Diabetic Macular Edema Disease Severity Scale,[36] determined by dilated ophthalmoscopy with slit lamp or by biomicroscopy.

Measurements

All data were obtained from reviews of medical records. Fasting samples were obtained from 73% of case subjects and 76% of control subjects. Nonfasting samples were obtained in 10% of case subjects and 8% of control subjects. The remainder, 17% of case subjects and 16% of control subjects, lacked the information. Total cholesterol, HDL-C, LDL-C (measured directly or calculated), and triglycerides were assayed within the 6 months before the date of the index visit. Data obtained included age, sex, duration of diabetes mellitus, body weight, height, ethnicity, history of hypertension, blood pressure, current medical treatment, medications, smoking, cardiovascular diseases, fasting blood glucose, and hemoglobin A_{1c} (HbA_{1c}).

Quality Control

Quality control visits by the Data Coordinating Center team were conducted at 17 of the 24 sites. CMIC, a contract research organization in Japan, monitored the 3 Japanese sites. On-site single entry of data (with programmatic constraints to prevent out-of-range values

and to minimize missing data) was performed with data management software developed for this project.

A 5% random sample of medical charts corresponding to digital study data were requested for review by the data coordinating center; 21 of the study sites complied with the request. Values for participant age, sex, race, LDL-C, triglycerides, HDL-C, and outcome status were checked for concordance between the medical records and the study database. The overall discordance rate was 1.2%. Precision and accuracy of laboratories used by participating sites were assessed (online-only Data Supplement).

Sample Size Determination

Prevalence and incidence statistics derived from the PROCAM study (G. Assmann, written communication, April 8, 2008) were used to obtain a target sample size of 100 case subjects in each clinical site, matched 1:1 with control subjects, which would provide 80% power to identify a relative risk of microvascular complications of 2.0 in any site, assuming a 30% prevalence of dyslipidemia among control subjects.[37,38] Collection of data on additional control subjects, when available, was allowed as a means of increasing power.

Data Analysis

The primary outcome was a diagnosis of kidney disease, retinopathy, or both, according to the protocol. Kidney disease and retinopathy were analyzed as individual outcomes in secondary analyses that included sites that reported ≥10 cases of either event for each site. Multivariable data on all N_1 case subjects and N_2 control subjects was assembled into a distance matrix of dimension $(N_1+N_2)\times(N_1+N_2)$. The optimal partitioning of the full data set into strata that included at least 1 case and 1 control per stratum was determined by use of the Hansen and Klopfer procedure[39] (which in turn uses graph-theoretical optimization procedures attributable to Bertsekas and Tseng); no control was used in >1 stratum. The partitioning is optimal in the sense that no other partition has a smaller sum of within-stratum distances; that is, the groupings together of case and control subjects maximizes the similarities of case subjects to control subjects among all possible groupings. Strata were required to be homogeneous in sex and were formed to minimize the sum of squared Mahalanobis distances over all possible groupings of case and control subjects within sites. Mahalanobis distance was computed based on values of LDL-C, number of years elapsed subsequent to diabetes mellitus diagnosis, and age.

Statistical modeling proceeded along 3 main axes. Case prediction models took several different forms. Most parsimoniously, quintiles of triglycerides and HDL-C were scored 0 to 4, and a single degree of freedom test for trend was used. Separate quintile effects were also estimated to assess adequacy of the linearity assumption. Third, tests of triglycerides and HDL-C effects were conducted marginally (unadjusted); adjusted for statin treatment, hypertension status, and quintile scored HbA_{1c}; and with "mutual" adjustment, in which triglycerides and HDL-C effects were assessed simultaneously. For 1 site, Toronto (2), the hypertension covariate was unavailable, and models for that site excluded this variable.

Statistics were summarized across sites by use of a random effects meta-analysis methodology.[40] Finally, several sensitivity analyses were performed on subsamples of the case subjects and on cases with the 4 specific retinopathy definitions. Results are presented as odds ratio (95% confidence limits). For some subgroups, full covariate adjustment was infeasible owing to data sparseness, and adjustments were limited to feasible variables.

Results

Characteristics of Case and Control Subjects

A total of 2535 case subjects were reported and were matched, within sites and within strata defined by sex, to 3683 control subjects. A total of 2034 strata were formed by the optimal matching procedure. The most common structure for strata was a 1:1 match (1125 such strata were formed), and 92% of strata consisted of 1 or 2 case subjects matched to a group of ≤6 control subjects. Within sites, the median within-stratum age range was computed as a measure of departure from perfect matching on age; its median over all sites was 4.25 years. For duration of diabetes mellitus, the median within-site departure over all sites was 3 years, and for LDL-C level, the median within-site departure over all sites was 0.23 mmol/L. Characteristics of case and control subjects are shown in the Table. The meta-analytic estimates of differences between case and control subjects (denoted Δ) in these characteristics in the matched analyses that were used in the meta-analysis to compute odds ratios (ORs) were very small and not clinically meaningful; for instance, difference in duration of diabetes mellitus was 0.9 years. Information was not available on menopausal status of the women; however, the mean age of the case subjects who were women was 66 years, and 89% were ≥50 years of age.

Kidney disease was present in 1891 case subjects and retinopathy in 1218 case subjects. A total of 574 case subjects had both kidney and eye disease. For the secondary analysis of kidney disease or retinopathy, separately, sites were included that reported ≥10 case subjects. The kidney disease analysis included all 24 sites and 1891 case subjects, whereas the retinopathy analysis included 21 sites and 1202 case subjects. Characteristics of the case and control subjects are shown in the Table, and in each of the sites in Table I in the online-only Data Supplement. Characteristics of the case subjects with diabetic kidney disease and retinopathy were similar.

The primary analysis considered microvascular complication case status, which consisted of a diagnosis of at least 1 of diabetic kidney disease, retinopathy, or maculopathy. Using linear scoring of triglyceride quintiles, the OR for a microvascular complication corresponding to a difference of 1 quintile (≈0.5 mmol/L) was 1.16 (95% confidence interval [CI], 1.11–1.22), including the covariates stated in Methods (Figure 1). Using categorical factors for triglyceride quintile membership, the OR comparing fifth to first quintiles was 1.76 (95% CI, 1.38–2.25). For linear scoring of HDL-C quintiles, the OR for a 1-quintile difference (≈0.2 mmol/L) was 0.92 (95% CI, 0.88–0.96; Figure 1). The OR comparing fifth to first quintiles of HDL-C was 0.73 (95% CI, 0.60–0.90). When the linear quintile scoring model was fit that included triglyceride and HDL-C simultaneously, the OR for a 1-quintile difference of triglyceride was estimated at 1.15 (95% CI, 1.09–1.22) and that for a 1-quintile difference in HDL-C was estimated at 0.96 (95% CI, 0.91–1.01). Site-to-site variability in triglyceride effects was not statistically significant (P=0.22), with 22 of 24 sites yielding OR estimates >1 in the marginal, linear scoring model. Site-to-site variability in the HDL-C effect was also not statistically significant (P=0.42), and 20 of 24 sites yielded OR estimates <1 for this association. Tests for heterogeneity were generally not significant for any of the analyses (see Figure legends).

A planned secondary analysis was the evaluation of the associations of triglycerides and HDL-C with each of the 2 microvascular event types. The OR for a kidney disease complication corresponding to a difference of 1 quintile in triglycerides (≈0.5 mmol/L) was 1.23 (95% CI, 1.16–1.31; Figure 2); the OR estimates were >1.0 in 23 of the 24 sites. Using categorical factors, the OR comparing fifth to first quintiles (2.8

Table. Descriptive Statistics of Case and Control Subjects

	Case Subjects (n=2535)	Kidney Cases (n=1891)	Eye Cases (n=1202)	Control Subjects (n=3683)	Case–Control Difference	*P* (H0: Δ=0)
Demographics						
Male, n (%)	1470 (58)	1153 (61)	649 (54)	2040 (55)	…	…
White/European, %	44	44	41	51	…	…
Age, y, mean (SD)	65 (11)	65 (11)	64 (10)	62 (11)	0.6	<0.01
Diabetes mellitus duration, y, mean (SD)	14 (9)	14 (9)	16 (9)	10 (8)	0.9	<0.01
Lipids, mmol/L, mean (SD)						
Total cholesterol	4.30 (0.92)	4.26 (0.84)	4.36 (1.02)	4.30 (0.83)	0.01*	0.03
LDL-C	2.31 (0.63)	2.28 (0.64)	2.34 (0.62)	2.35 (0.85)	0.0*	0.34
HDL-C	1.20 (0.44)	1.18 (0.46)	1.23 (0.40)	1.26 (0.45)	–0.04*	<0.01
Triglycerides	1.78 (1.14)	1.85 (1.17)	1.72 (1.18)	1.61 (1.20)	0.12*	<0.01
Hemoglobin A_{1c}, %	8.1% (1.7%)	8.0% (1.7%)	8.3% (1.8%)	7.6% (1.6%)	0.46	<0.01
Medication, n (%)						
Fibrate use	195 (7.7)	163 (8.6)	81 (6.7)	291 (7.9)	0.0†	0.69
Statin use	1326 (52)	1053 (56)	571 (48)	1880 (51)	0.01†	0.23
Anti-DM use	2385 (94)	1782 (94)	1146 (95)	3301 (90)	…	…
Clinical condition, n (%)						
Nephropathy	1891 (75)	1891 (100)	566 (47)	0	…	…
Retinopathy	1218 (48)	574 (30)	1202 (100)	0	…	…
Hypertension	2076 (82)	1588 (84)	981 (82)	2427 (66)	0.15†	<0.01

A total of 2535 case subjects were reported and were matched, within sites and within strata defined by sex, to 3683 control subjects. A total of 574 case subjects had both kidney and eye disease. For the secondary analysis of kidney disease or retinopathy, separately, sites were included that reported ≥10 case subjects. The kidney disease analysis included all 24 sites and 1891 case subjects, whereas the retinopathy analysis included 21 sites and 1202 case subjects. Difference (Δ) denotes the meta-analytic estimate of the mean difference between case and control subjects on general parameters of the study, allowing random intercepts for matched strata. DM indicates diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol.

*Denotes Δ estimated after log transformation.

†Denotes Δ as the meta-analytic odds ratio for the dichotomous characteristic.

versus 0.7 mmol/L) was 2.24 (95% CI, 1.78–2.83; Figure 3). The OR for a kidney disease complication corresponding to a 1-quintile difference in HDL-C was 0.86 (95% CI, 0.82–0.91; Figure 2); the OR was <1.0 in 23 of the 24 sites. Using categorical factors for HDL-C, the OR comparing fifth to first quintiles was 0.58 (95% CI, 0.47–0.73; Figure 3). In models that mutually adjusted for triglycerides and HDL-C, the OR for kidney disease was 1.20 (95% CI, 1.13–1.28) for a quintile increase in triglycerides and 0.92 (95% CI, 0.87–0.97) for a quintile increase in HDL-C (Figure 4). Kidney disease case subjects could qualify on the basis of albuminuria or low glomerular filtration rate; their characteristics are shown in Tables II and III in the online-only Data Supplement, respectively. The kidney disease ORs for triglycerides and HDL-C, individually and in mutual adjustment, were significant for low glomerular filtration rate (n=522 case subjects) and for albuminuria (n=1517 case subjects; Figure 5; Figures I to VI in the online-only Data Supplement).

The analysis of retinopathy included 21 sites that submitted ≥10 retinopathy case subjects, and the total number of case subjects was 1202. The OR for a retinopathy complication was 1.09 (95% CI, 1.02–1.16) per quintile of triglycerides and 0.93 (95% CI, 0.86–1.0) per quintile of HDL-C using models that controlled for the matching factors only. However, additional control for hypertension and HbA_{1c} weakened these associations, and they did not remain significant. For triglycerides, the OR was 1.04 (95% CI, 0.98–1.11), and for HDL-C it was 0.97 (95% CI, 0.90–1.05; Figure 6). The ratio of triglycerides to HDL-C also did not have a significant association with retinopathy (OR, 1.04 [95% CI, 0.98–1.11] per quintile).

The ORs (95% CIs) for retinopathy per quintile of plasma triglycerides or HDL-C, not mutually adjusted, were determined according to the 4 definitions or conditions: (1) Maculopathy (n=169 case subjects): triglycerides 1.09 (0.95–1.26); high-density lipoprotein (HDL-C) 0.97 (0.78–1.19); (2) laser surgery: triglycerides 1.03 (0.93–1.14), HDL-C 0.93 (0.82–1.06); (3) fundus photography EDTRS: triglycerides 1.04 (0.92–1.16), HDL-C 0.98 (0.82–1.17); and (4) dilated ophthalmoscopy Diabetic Retinopathy Disease Severity score: triglycerides 1.00 (0.92–1.08), HDL-C 1.01 (0.94–1.10). Therefore, the results were similar and not significant across these retinopathy outcomes.

We evaluated the possible influence of coexisting kidney disease status on ORs associated with retinopathy for triglycerides and HDL-C. There were 630 retinopathy case subjects who did not have kidney disease, which constituted 52% of the total retinopathy case subjects. The OR (95% CI) for retinopathy for triglyceride was 0.97 (0.89–1.04) for the subset compared with 1.04 (0.98–1.11) for the total group; for HDL-C

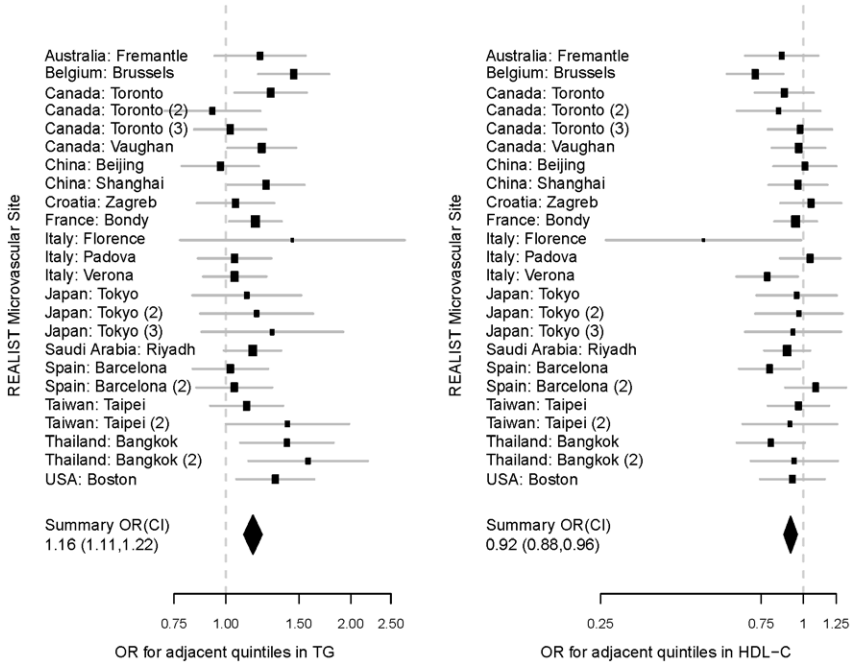

Figure 1. Odds ratio (OR) for diabetic kidney disease or retinopathy associated with a quintile increase in blood triglycerides (TG; 0.5 mmol/L) or high-density lipoprotein cholesterol (HDL-C; 0.2 mmol/L). Controlled by matching for age, sex, duration of diabetes mellitus, and low-density lipoprotein cholesterol level and by inclusion of hypertension and hemoglobin A_{1c} in the multiple variable model. Size of symbols is proportional to number of case subjects. Test for heterogeneity among sites: TG, P=0.22; HDL-C, P=0.42. CI indicates confidence interval; and REALIST, Residual Risk Lipids and Standard Therapies study.

levels, it was 1.03 (0.93–1.14) for the subset compared with 0.97 (0.90–1.05) for the total group.

Because HbA_{1c} level was strongly associated with case status, the ORs for microvascular diseases, kidney or eye, were determined for those with HbA_{1c} above or below the median, 7.4%. ORs for those with HbA_{1c} above the median (mean HbA_{1c} 9.0% for 1554 case subjects, 8.9% for 1659 control subjects) were 1.14 (1.07–1.22) for triglycerides and 0.96 (0.91–1.03) for HDL; for those below the median (mean HbA_{1c} 6.6% for 901 case subjects and 2007 control subjects), they were 1.15 (1.07–1.24) for triglycerides and 0.87 (0.81–0.93) for HDL. These models were not adjusted for HbA_{1c}. Heterogeneity tests for these analyses were not significant.

There were 564 case subjects who had both kidney disease and retinopathy. The OR for case status of both kidney disease and retinopathy compared with 3318 control subjects was 1.16 (95% CI, 1.07–1.25) for a 1-SD increase in triglyceride and 0.88 (95% CI, 0.80–0.96) for a 1-SD increase in HDL-C, similar to those in the full group.

Adjustment for prevalent cardiovascular disease in the matched conditional logistic regression meta-analysis had little impact on key inferences. The OR (95% CI) for increasing adjacent quintiles of triglyceride was 1.23 (1.15–1.31), and for HDL-C, it was 0.87 (0.82–0.92).

Additional sensitivity analyses evaluating those whose blood sample was taken in the fasting state (n=1306 case

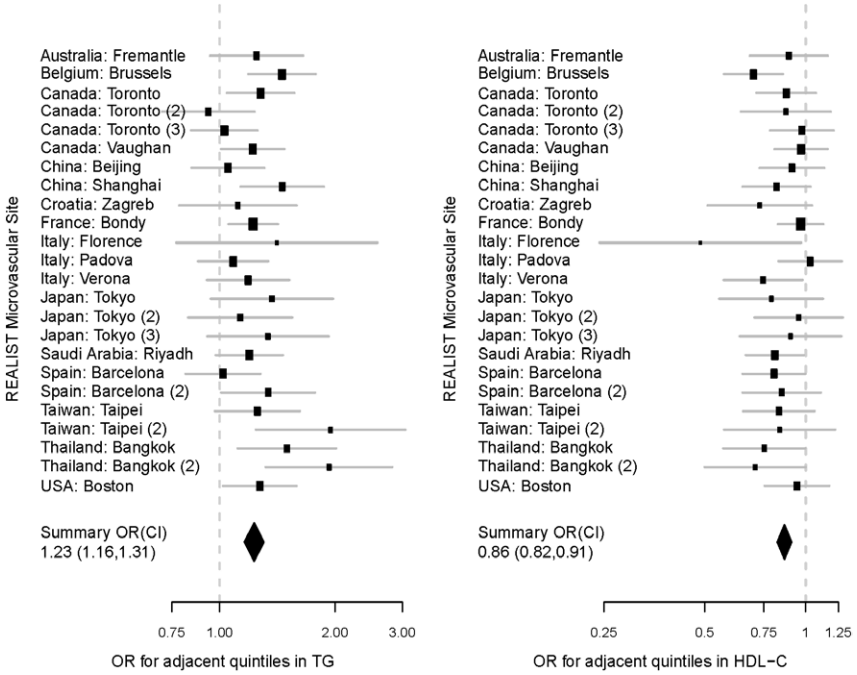

Figure 2. Odds ratios (OR) for kidney disease for triglycerides (TG; **left**) and high-density lipoprotein cholesterol (HDL-C; **right**), not mutually adjusted. Matching variables, covariates, and symbols are described in the legend to Figure 1. The analysis included all 24 sites and 1891 case subjects. Test for heterogeneity among sites: TG, P=0.14; HDL-C, P=0.58. CI indicates confidence interval; and REALIST, Residual Risk Lipids and Standard Therapies study.

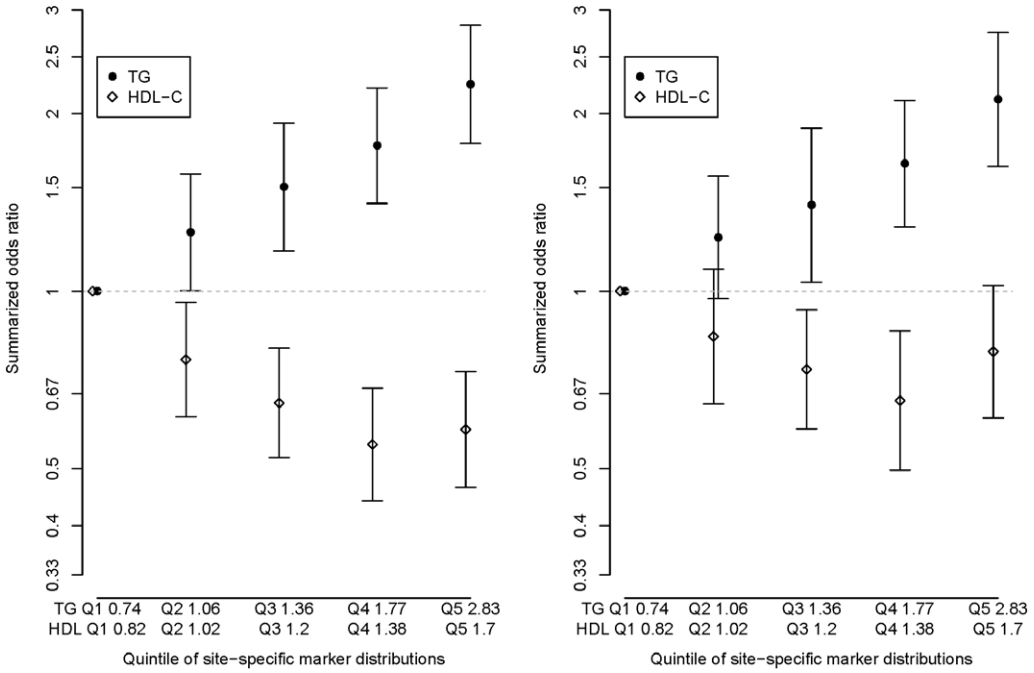

Figure 3. Quintile-specific odds ratios for diabetic kidney disease associated with levels of blood triglycerides (TG) or high-density lipoprotein cholesterol (HDL-C). Matching variables and covariates are described in the legend to Figure 1. **Left**, TG and HDL-C not mutually adjusted; **right**, mutually adjusted. The medians for the quintiles (Q1–Q5) are on the horizontal axis.

subjects for kidney, 803 for eye) showed an OR (95% CI) for a microvascular complication associated with triglycerides of 1.16 (1.09–1.24) compared with 1.16 (1.11–1.22) for the total group. For a microvascular complication associated with HDL-C, the OR was 0.91 (0.86–0.96) compared with 0.92 (0.88–0.96) for the total group.

Similarly, subgroup analysis of those who were not taking statins or fibrates returned ORs that were the same (or approximately the same) as for the full sample. For kidney disease in the no lipid-treatment group, the OR for a 1-SD change in triglycerides was 1.24 (1.14–1.34), and for HDL-C, it was 0.83 (0.77–0.90; n=704 case subjects and 1570 control subjects). For retinopathy in the no lipid-treatment group, the OR for triglycerides was 0.99 (0.90–1.10), and for HDL-C, it was 0.99 (0.87–1.12; n=549 case subjects and 1318 control subjects).

The associations of triglycerides and HDL-C with kidney disease or retinopathy were similar among the geographic regions and ethnicities. Eight European sites were preponderantly (74%) white, and 9 Asian sites were preponderantly

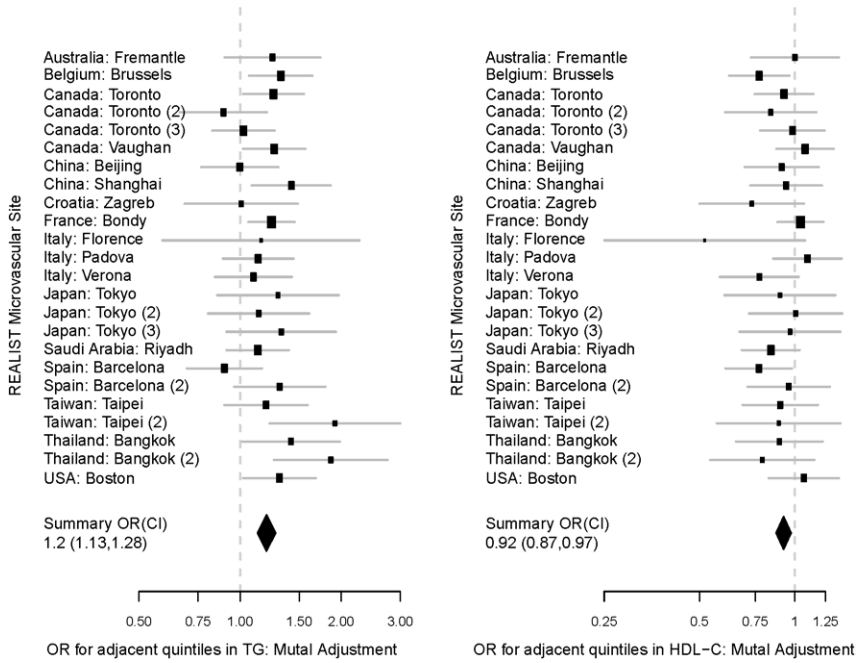

Figure 4. Odds ratio (OR) for kidney disease for triglycerides and high-density lipoprotein cholesterol (HDL-C), mutually adjusted. Matching variables, covariates, and symbols are described in the legends to Figures 1 and 2. Test for heterogeneity among sites: TG, *P*=0.19; HDL-C, *P*=0.64. CI indicates confidence interval; and REALIST, Residual Risk Lipids and Standard Therapies study.

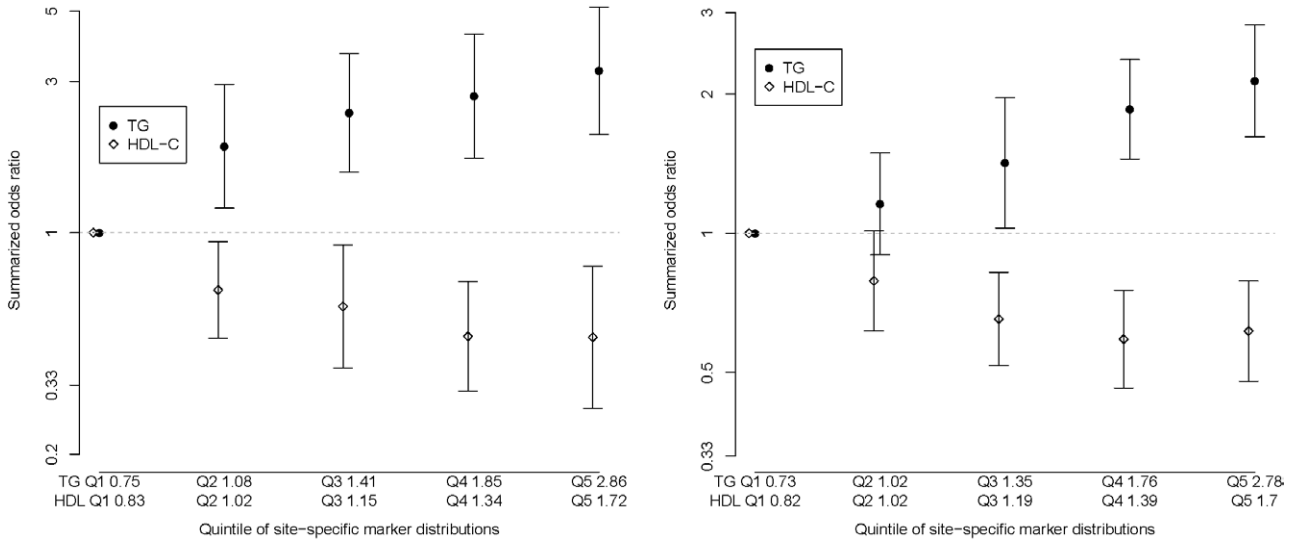

Figure 5. Odds ratio for kidney disease defined by either low estimated glomerular filtration rate (n=522 case subjects) or albuminuria (n=1517 case subjects) according to triglycerides (TG) or high-density lipoprotein cholesterol (HDL-C), not mutually adjusted. Matching variables, covariates, and symbols are described in the legend to Figure 1. Test for heterogeneity among sites (linear trend) for low estimated glomerular filtration rate: TG, *P*=0.24; HDL-C, *P*=0.03. Test for heterogeneity among sites (linear trend) for albuminuria: TG, *P*=0.04; HDL-C, *P*=0.65. Q1 through Q5 indicate quintiles 1 through 5.

(89%) nonwhite. The ORs for adjacent quintiles of triglyceride were 1.13 (95% CI, 1.03–1.23) for Europe and 1.21 (95% CI, 1.10–1.34) for Asia; for adjacent quintiles of HDL-C, the ORs were 0.89 (95% CI, 0.78–1.01) for Europe and 0.94 (95% CI, 0.86–1.02) for Asia.

Discussion

Diabetes mellitus is the major cause of renal failure and vision loss in adults.[1–4] Current treatments are effective in reducing the risk of development and progression; however, the residual risk for these complications remains high.[6,41,42] Because the prevalence of type 2 diabetes mellitus continues to increase worldwide, it is expected that its major complications, kidney disease and retinopathy, will increase in parallel. New targets and treatments are urgently needed.

In the present study, triglycerides and HDL-C were significantly and independently associated with diabetic microvascular disease and specifically with kidney disease. The associations with retinopathy were not robust after adjustment for hypertension and HbA_{1c}. These associations were similar in magnitude among the sites and among geographic regions.

The strengths of the present study include its global scope of inclusion of sites and consistency of findings, demonstrated by lack of heterogeneity in nearly all of the meta-analyses, which supports wide generalizability across regions and ethnicities. The matching procedure that equalized age, sex, duration of

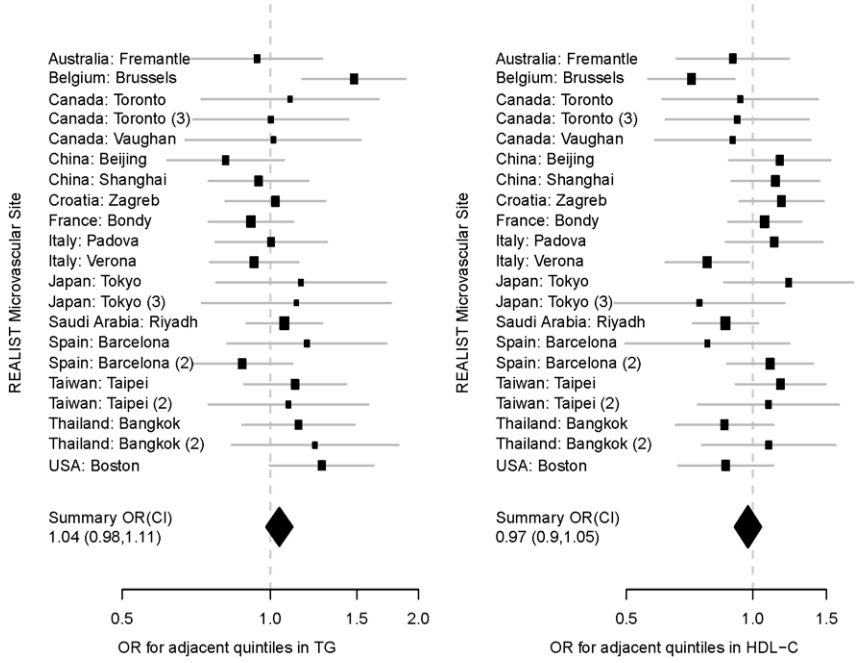

Figure 6. Odds ratio (OR) for retinopathy associated with a quintile increase in blood triglycerides (TG; **left**) or high-density lipoprotein cholesterol (HDL-C; **right**). Matching variables, covariates, and symbols are described in Figure 1. TG and HDL-C not mutually adjusted. Sites were included that reported ≥10 case subjects. The retinopathy analysis included 21 sites and 1202 case subjects. Test for heterogeneity among sites: TG, *P*=0.30; HDL-C, *P*=0.08. CI indicates confidence interval; and REALIST, Residual Risk Lipids and Standard Therapies study.

diabetes mellitus, and LDL-C concentration reduced the probability of confounding and reverse causation. The findings for total microvascular events and for kidney disease were robust after adjustment for hypertension and HbA_{1c}, 2 major influences on the occurrence of diabetic microvascular disease. The present study had a large number of case subjects with diabetic microvascular disease; this reduced the chance of a false-negative, which might have occurred in previous studies on HDL-C and microvascular disease.

Limitations of the present study are its cross-sectional design and the potential for reverse causation; however, a typical example of reverse causation, more aggressive treatment of lipid levels in case subjects, would bias the results to the null, because treatment would decrease triglycerides and raise HDL-C in the case subjects, the opposite of the actual results. It appears likely that matching case and control subjects on LDL-C equalized lipid treatment. The finding that lipid treatments were similar in the 2 groups supports this interpretation. The lipid laboratories at each site were not standardized or calibrated, although the laboratory survey that we conducted did not find serious differences in accuracy among the sites that participated, and the precision measurements were excellent. In any case, it would be unlikely that measurement error could occur differentially between case and control subjects. Although the blood samples were not required to be fasting, most were fasting, the same in case and control subjects, and the results for a fasting subgroup were similar to those for the total group.

Most previous studies reported that high plasma triglycerides were associated with diabetic kidney disease,[8,10,12–14,17,19–21,43] although several did not find an association.[7,9,16] With regard to HDL-C, the published literature is less consistent, with some studies showing a significant association,[8,16,17,19–21,43] and others not.[7,9–12,14,18] Certainly, type 2 errors could account for negative studies. In combination with previous studies, we consider the findings of the present study regarding both high triglycerides and low HDL-C, considered alone or together in multiple variable models with consistent direction of ORs among nearly all the sites and mostly nonsignificant tests of heterogeneity, as compelling evidence that triglycerides and HDL-C are indeed strongly associated with diabetic kidney disease.

The associations for retinopathy of triglycerides and HDL-C were weaker than for kidney disease and less robust after adjustment for known risk factors. The retinopathy literature is mixed with regard to triglycerides, with some studies showing a significant association[4,24,29,32] and others not[18,23,27,31,33,44] or showing mixed findings.[30] For HDL-C, none of the studies found a significant association with diabetic retinopathy,[4,18,23,24,26–28,30–33,44] with 1 exception.[29] The large number of case subjects (1202) in the present study provided sensitivity to identify even a relatively weak association between retinopathy and triglycerides and HDL-C if one existed. Measurement error for retinopathy determined by ophthalmoscope or even fundus photography that requires grading has the potential to reduce the strength of associations with triglycerides and HDL-C. However, the results for the association between triglycerides and HDL-C and retinopathy were similar regardless of the specific diagnostic criterion, including laser surgery. The results suggest that associations of triglycerides and HDL-C with retinopathy may be dependent on confounding by other risk factors for microvascular disease, specifically hypertension and HbA_{1c}, as we found.

The integrity of the blood-retinal barrier protects the retina against potentially harmful effects of extravasation of plasma lipoproteins. Apolipoprotein B lipoproteins may damage retinal capillaries, leading to extravasation, and they are present in retinas of diabetic people in proportion to the severity of retinopathy.[45] These mechanistic findings and the present results support the concept that mechanisms involved in regulation or dysregulation of intraretinal lipid transport might be potentially more important than plasma lipid levels in the pathogenesis of diabetic retinopathy.[46] This may differ from the effects of lipoproteins on kidney disease, in which extravasation of lipoproteins may more readily occur than in the retina.

Finally, the present study is restricted to information in clinic and hospital records that contain only standard lipid measurements needed for clinical management. It is possible that specific lipoprotein subfractions could be involved in retinopathy, such as apolipoprotein C-III–containing low-density lipoproteins and HDL that are strongly associated with coronary events[47,48] and adversely affect endothelial cells[49] or oxidized lipoproteins.[45]

In conclusion, this global study of lipid risk factors for diabetic microvascular disease provides strong evidence for independent associations for high triglycerides and low HDL-C. These associations apply to kidney disease. It is possible that retinopathy may also be affected by triglyceride or HDL-C levels, but the association appears weak. Nevertheless, larger populations and meta-analyses could be helpful to further investigate the relationship between retinopathy and dyslipidemia. Current guidelines for lipid treatment give more emphasis than before to the use of triglycerides and HDL-C for treatment thresholds and targets for macrovascular disease.[50] In view of the large and growing health burden of renal failure in diabetes mellitus, these findings have considerable importance in support of the establishment of additional lipid targets other than LDL-C to benefit the diabetic population at high residual risk for microvascular disease despite current standards of care.

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CLINICAL PERSPECTIVE

Diabetes mellitus is the major cause of renal failure and vision loss in adults. Current treatments are effective in reducing the risk of development and progression; however, the residual risk for these complications remains high. In this global case–control study of lipid risk factors for diabetic microvascular disease in 13 countries, triglycerides and high-density lipoprotein cholesterol were significantly and independently associated with diabetic microvascular disease and specifically with kidney disease. Case and control subjects were matched for low-density lipoprotein cholesterol, which averaged 2.3 mmol/L (89 mg/dL). The odds ratio for kidney disease increased by 23% for every 0.5 mmol/L (44 mg/dL) increase in triglycerides and decreased by 14% for every 0.2 mmol/L (8 mg/dL) increase in high-density lipoprotein cholesterol. The associations with retinopathy were not robust after adjustment for hypertension and hemoglobin A_{1c}. These associations were consistent and similar in magnitude among the sites and among geographic regions (Europe, Asia, Middle East, and North America). In view of the large and growing health burden of renal failure in diabetes mellitus, these findings have considerable importance in support of additional lipid targets other than low-density lipoprotein cholesterol to benefit the diabetic population at high residual risk for microvascular disease despite current standards of care.