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ORIGINAL RESEARCH

Association Between Increased Lipid Profiles and Risk of Diabetic Retinopathy in a Population-Based Case-Control Study

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Purpose: We aimed to investigate the association between lipid profiles and diabetic retinopathy (DR).

Patients and Methods: This case-control study, which was conducted between November 2019 and August 2021, comprised 309 patients with DR, 186 patients with diabetes mellitus, and 172 healthy controls. Serum cholesterol (CHOL), triglyceride (TRIG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), small dense LDL-C (SDLDL-C), apolipoprotein A (APOA), APOB, APOE and lipoprotein (a)(LPA) levels were assessed. Patients were divided into two groups according to median age and glycated hemoglobin (HbA1c) level. Linear and logistic regression analyses were performed to assess the association between lipid levels and DR.

Results: CHOL, TRIG, HDL-C, APOB, APOE, and SDLDL-C levels were significantly higher in the DR group than in the healthy control group, and TRIG levels were lower in the DR group than in the DM group ($P < 0.05$), especially in the ≤57-year-old and the HbA1c ≤7.2% subgroups. Linear regression analyses showed that CHOL, TRIG, APOA, APOB, APOE, and SDLDL-C levels were associated with HbA1c levels. Multivariable logistic regression analyses indicated that CHOL (odds ratio [OR] = 1.32, 95% confidence interval [CI] = 1.112–1.566), TRIG (OR = 1.269, 95% CI = 1.030–1.563), HDL-C (OR = 43.744, 95% CI = 17.12–111.769), APOB (OR = 7.037, 95% CI = 3.370–14.695), APOE (OR = 1.057, 95% CI = 1.038–1.077), and SDLDL-C (OR = 14.719, 95% CI = 8.304–26.088) levels were risk factors for DR ($P < 0.05$).

Conclusion: Increased lipid levels were risk factors for DR, and lipid level control should be strengthened, especially in younger adults or in patients with HbA1c ≤7.2%.

Keywords: lipids, dyslipidemia, diabetes mellitus, diabetic retinopathy, younger population, HbA1c

Introduction

Diabetic retinopathy (DR), a major complication of diabetes mellitus (DM), is a retinal microvascular disease that can result in blindness in working-age adults.[1–3] Worldwide, approximately 93 million people older than 40 years have been estimated to have DR (estimated prevalence, 34.6%; estimated prevalence rate for vision-threatening DR, 10.2% [n = 28 million people]). China has the highest number of people with DM aged between 20 and 79 years, and the prevalence of DR in China has been reported to range from 24.7% to 37.5%.[2,4] The diagnosis rates for DM and DR appear to be increasing annually, and DR is a global health burden that consequently increases the socioeconomic burden.

In the Diabetes Control and Complications trial and in the Epidemiology of Diabetes Interventions and Complications trials, intensive glycemic control was found to have reduced the risk of onset and the progression of DR.[5,6] Several epidemiological studies and clinical trials have reported DM duration, hyperglycemia, and hypertension as the main risk factors for DR.[7–9] Some studies have shown that, despite early blood-glucose control in patients with type 2 DM, the risk of DM-related complications remains.[10] Along with abnormal blood-glucose metabolism, other factors such as obesity,

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dyslipidemia, inflammation, and insulin resistance have been reported to play a role in the onset and development of DM-related complications.[11] However, considerable controversy remains concerning the role of lipids in the pathogenesis of DR. Some studies have shown that serum lipids are associated with DR.[12–14] High-density lipoprotein cholesterol (HDL-C) and apolipoprotein A (APOA) levels were inversely associated with DR, whereas APOB levels were positively associated with DR.[12] However, in a recent large epidemiology study, lipid levels including those of low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC) were associated with a lower risk of DR in people of Malay, Indian, and Chinese ethnicities.[9] Moreover, other studies have found no significant differences between lipid levels and DR risk.[15]

Therefore, reports concerning the correlation between serum lipid levels and DR have been inconsistent and unclear. This study aimed to compare differences in abnormal lipid metabolism among healthy controls, patients with DM, and those with DR and assess the associations between serum lipid levels and DR.

Materials and Methods

This case-control study was approved by the Ethics Committee of the Eye and Eye and Ear Nose Throat (ENT) Hospital of Fudan University, Shanghai, China, and was conducted in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all patients to use their clinical data in this study. Patients with DR were recruited from the Department of Ophthalmology and Visual Sciences at the Eye and ENT Hospital of Fudan University between November 2019 and August 2021. Sex- and age-matched patients with DM and healthy controls were consecutively recruited among individuals who participated in annual health screenings during the study period.

Inclusion and Exclusion Criteria

Patients with DR

Ophthalmologists diagnosed DR in accordance with the American Academy of Ophthalmology guidelines,[4] and diagnoses were verified through reviewing patient histories and medical records at the time of recruitment.

Inclusion criteria for patients with DR comprised the following. Patients who meet the above diagnostic criteria, with clear diagnosis of DR (presence of retinal hemorrhages, microaneurysms, cotton wool spots, and/or panretinal photocoagulation laser scars found on colored fundus photographs and/or dilated slit lamp examination by an ophthalmologist),[16,17] who had complete clinical data, who had not recently used lipid-lowering medications recently (within 3 months), and who were aged >18 years.

We excluded patients with other retinal diseases, such as macular degeneration, retinal vein occlusion, and pathologic myopia; those with any other eye diseases, such as glaucoma, ocular trauma, inflammation, and tumors; those with any systemic diseases, such as acute infectious diseases, autoimmune disease, or cancer. Patients with blood-borne infectious diseases, mental illness, abnormal blood coagulation, severe liver and kidney dysfunction, malnutrition and pregnancy were also excluded.

Patients with DM

Inclusion criteria for patients with DM comprised the following. Patients aged >18 years previously diagnosed with type I or type II DM, according to the American Diabetes Association guidelines.[18]

We excluded patients who had eye diseases that could potentially affect visual acuity; those who had undergone any intraocular surgery within the previous 2 months; those with diabetic ketoacidosis; those with DM-related complications, mental illness, or any systemic diseases, such as acute infectious diseases, autoimmune diseases, or cancer. Patients with blood-borne infectious diseases, abnormal blood coagulation, severe liver and kidney dysfunction, malnutrition, and pregnancy were also excluded.

Healthy Controls

We included age- and sex-matched healthy controls.

Exclusion criteria comprised patients with DM with any eye diseases that could potentially affect visual acuity; those who had undergone intraocular surgery within the previous two months; and those with systemic diseases, such as acute infectious diseases, autoimmune disease, or cancer. Others with blood-borne infectious diseases, mental illness, abnormal blood coagulation, severe liver and kidney dysfunction, malnutrition, pregnancy were all excluded.

In total, 366 patients with DR, 284 patients with DM, and 396 healthy controls were excluded. Finally, 667 patients were included in our study, comprising 309 patients with DR (6 patients with type 1 and 303 patients with type 2), 186 patients with DM (4 patients with type 1 and 182 patients with type 2), and 172 healthy controls. Figure 1 shows the flow chart of the cross-sectional studies.

Patient Examinations

Visual acuity assessment, intraocular pressure measurement using applanation tonometry, slit-lamp biomicroscopy, fundus examination using indirect ophthalmoscopy, fundus photography, B-scan ultrasonography, optical coherence

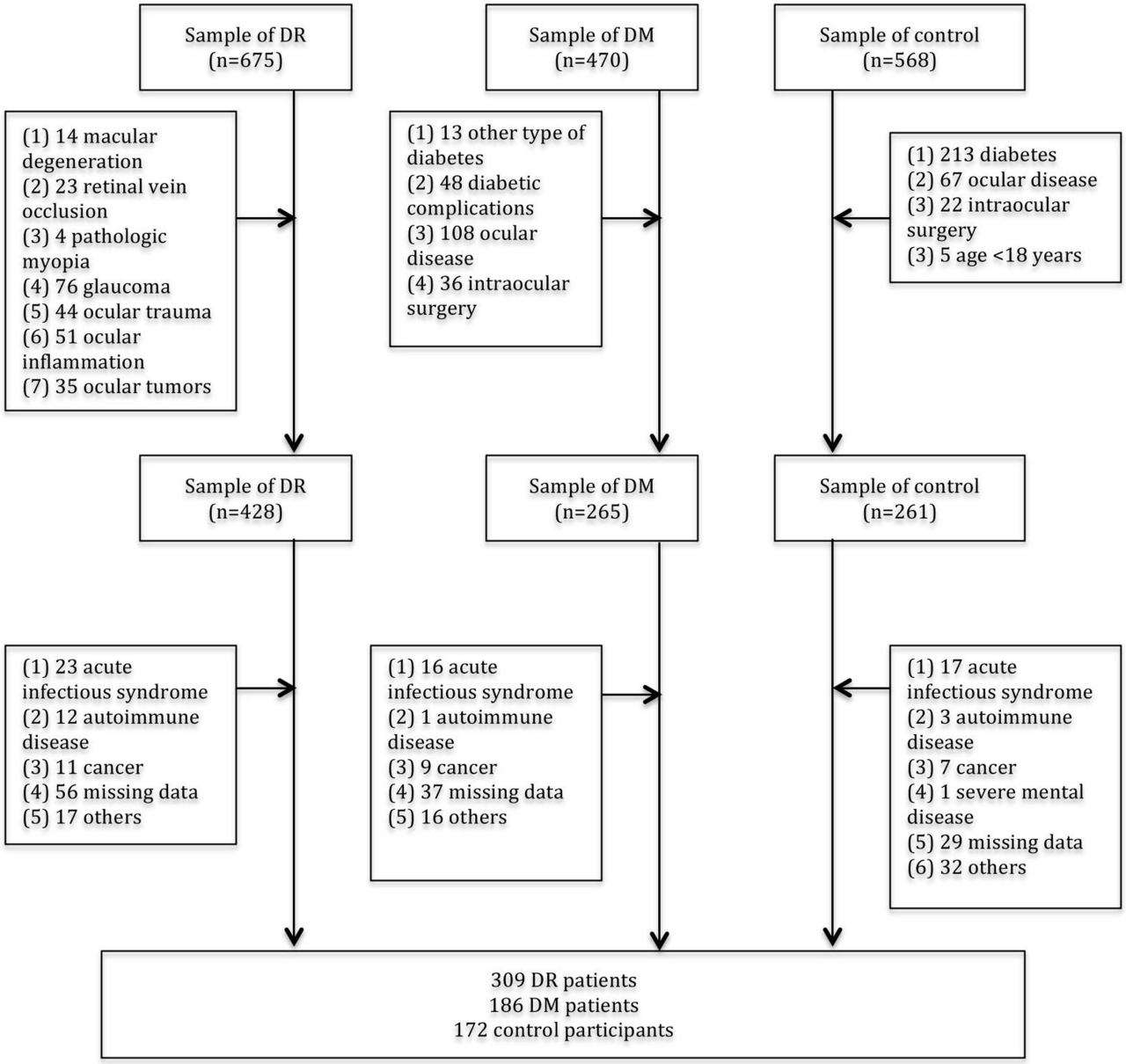

Figure 1 The study population flow chart.
Abbreviations: DR, diabetic retinopathy; DM, diabetes mellitus.

tomography, and fluorescein angiography were performed for every patient with DR. Patients with DM and healthy controls underwent an initial ophthalmologic examination, including visual acuity assessment, slit-lamp biomicroscopy, fundus examination via indirect ophthalmoscopy, and fundus photography.

Body mass index (BMI, body weight in kg/height^2 in m^2) was also assessed. According to the standardized protocol, brachial artery blood pressure was measured following a 5-min rest period. Hypertension was defined as a systolic blood pressure ≥140 mmHg and a diastolic blood pressure ≥90 mmHg. The duration of DM was calculated as the difference between the self-reported time of diagnosis and the time of examination.

The status of patients who have taken antihypertensive and hypoglycemic medications in the past month or are taking these medications was recorded. Moreover, patients who have not taken lipid-lowering medications recently (in the past 3 months) but have taken lipid-lowering medications in the past (3 months previously) were recorded. Laboratory testing of fasting (>8 h) blood samples was performed at the Department of Clinical Laboratory, Eye, and ENT Hospital of Fudan University. Samples were centrifuged at 3500 rpm for 10 min and measured within 2 h of collection. Glycated hemoglobin (HbA1c) was measured by high-performance liquid chromatography. (Glycated Hemoglobin Analyzer MQ6000, Shanghai, China), and blood urea nitrogen (BUN), creatinine (CREA) and uric acid (UA) were measured by enzymatic colorimetry (Roche Cobas 8000C702, Mannheim, Germany). Serum cholesterol (CHOL), triglyceride (TRIG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and small dense LDL-C (SDLDL-C) levels were also measured by enzymatic colorimetry (Roche Cobas 8000C702, Mannheim, Germany). Serum apolipoprotein A (APOA), apolipoprotein B (APOB), apolipoprotein E (APOE), and lipoprotein (a) (LPA) levels were measured by immunoturbidimetry (Roche Cobas 8000C702, Mannheim, Germany). To ensure the credibility of the test results, a daily quality control analysis was performed. The intra-assay and inter-assay coefficients of variation ranged from 2.1% to 3.8% and 3.1% to 4.5%, respectively.

Statistical Analyses

Data analysis was performed using SPSS (version 23.0; IBM Corp., Armonk, NY). Normality was assessed using the Kolmogorov–Smirnov test. Data for non-normally distributed variables were analyzed using non-parametric tests. All numerical variable data are presented as mean ± standard deviation. Differences among groups were analyzed using Student's *t*-test, analysis of variance, and the Mann–Whitney *U*-test, as appropriate. Categorical variables were analyzed using Fisher's exact and chi-squared tests, as appropriate.

Patients were divided into two groups according to median age and HbA1c level. Correlations between lipid and HbA1c levels were analyzed using multivariable linear regression analyses, adjusted for age, sex, BMI, hypertension, HbA1c level, duration of diabetes, insulin injection, oral hypoglycemic agents, eye laser or surgery, smoking status, drinking status, oral antihypertensive agents, oral lipid-lowering agents, family history, and cardiovascular, kidney, and cerebrovascular diseases. Logistic regression analyses were performed to assess the presence of an independent association between lipid levels and the risk of DR. The odds ratio (OR) and their corresponding 95% confidence intervals (CIs) were determined using logistic regression models, adjusted for age, sex, BMI and hypertension. A two-sided P value < 0.05 was considered statistically significant.

Results

Patient Characteristics

Based on the inclusion criteria, 667 patients were included in this study, comprising 309 patients with DR (male, n = 165; female, n = 144), 186 patients with DM (male, n = 94; female, n = 92), and 172 healthy controls (male, n = 79; female, n = 93). In the three groups, sex (P = 0.291) and age (P = 0.303) were highly matched. Compared with healthy controls and patients with DM, patients with DR had a higher rate of hypertension, higher HbA1c level, longer duration of DM, higher number of insulin injections, and higher rates of kidney and cerebrovascular diseases (P < 0.05). Table 1 shows the patient demographic data and clinical characteristics.

Table 1 Clinical Characteristics and Lipid Profiles of the DR, DM and Control Groups

	Control Group	DM Group	DR Group	F/t	P
N	172	186	309		
Gender (Male/Female)	79/93	94/92	165/144	2.467	0.291
Age (years)	55.51±9.45	57.29±10.63	56.57±11.83	1.196	0.303
BMI (Kg/m^2)	23.85±3.10	24.41±3.43	24.46±3.70	1.869	0.155
Hypertension N(%)	44 (25.58%)	68 (36.56%)	148 (47.90%)	6.068	<0.001[abc]
CHOL (mmol/L)	4.39±1.14	4.80±1.00	4.69±1.28	5.84	0.003[ab]
TRIG (mmol/L)	1.49±0.97	2.24±2.01	1.80 ±1.26	12.387	<0.001[abc]
HDL-C (mmol/L)	1.01±0.22	1.40±2.13	1.25±0.34	5.097	0.006[ab]
LDL-C (mmol/L)	2.77±0.95	3.00±0.88	2.85±1.11	2.516	0.082[a]
APOA (mmol/L)	1.26±0.27	1.34±0.41	1.29±0.29	2.78	0.063[a]
APOB (mmol/L)	0.86±0.24	1.02±0.26	1.01±0.34	16.167	<0.001[ab]
APOE (mmol/L)	35.61±10.81	47.36±24.96	45.74±20.80	50.642	<0.001[ab]
LPA (mmol/L)	154.47±184.30	141.64±183.54	179.12±256.68	3.773	0.152
SDLDL (mmol/L)	0.66±0.42	1.44±0.92	1.36±0.68	139.229	<0.001[ab]
HbA1c (%)	–	7.10±1.29	7.70±1.53	−4.633	<0.001
BUN (mmol/L)	–	5.78±1.65	7.31±2.76	−7.214	<0.001
CREA (umol/L)	–	68.60±17.34	80.36±54.98	2.999	0.083
UA (mmol/L)	–	0.34±0.10	0.34±0.09	0.054	0.957
DM duration (Years)	–	5.24±6.12	12.85±8.16	112.873	<0.001
Insulin N(%)	–	22 (11.83%)	184 (59.55%)	108.816	<0.001
Hypoglycemic agents N(%)	–	91 (48.92%)	173 (55.99%)	2.327	0.127
Eye lasers or surgery N(%)	–	40 (21.51%)	83 (26.86%)	1.783	0.182
Smoking N(%)	–	27 (14.52%)	48 (15.53%)	0.094	0.76
Drinking N(%)	–	21 (11.29%)	40 (12.94%)	0.294	0.588
Antihypertensive agents N(%)	–	54 (29.03%)	87 (28.16%)	0.044	0.834
Lipid-lowering agents N(%)	–	9 (4.84%)	20 (6.47%)	0.562	0.453
DM Family history N(%)	–	24 (12.90%)	134 (43.37%)	49.582	<0.001
Cardiovascular disease N(%)	–	14 (7.53%)	21 (6.80%)	0.094	0.759
Kidney disease N(%)	–	2 (1.08%)	44 (14.24%)	23.871	<0.001
Cerebrovascular disease N(%)	–	1 (0.54%)	23 (7.44%)	12.002	0.001

Notes: Differences between two groups were analysed using Student's *t*-test. Differences among three groups were analysed using one-way ANOVA; [a]p <0.05 for the difference between control and DM groups (LSD post hoc test); [b]p <0.05 for the difference between DR and control groups (LSD post hoc test); [c]p <0.05 for the difference between DR and DM groups (LSD post hoc test).

Abbreviations: DM, diabetic mellitus; DR, diabetic retinopathy; N, number; BMI, body mass index; CHOL, cholesterol; TRIG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; APOA, apolipoprotein A; APOB, apolipoprotein B; APOE, apolipoprotein E; LPA, lipoprotein a; SDLDL-C, small dense low-density lipoprotein cholesterol; HbA1c, hemoglobin A1c; BUN, blood urea nitrogen; CREA, serum creatine; UA, uric acid.

Among patients with DR, BMI (P = 0.165) and age (P = 0.112) were highly matched between the male and female groups. However, women were more likely to have longer diabetes duration and higher levels of lipids (CHOL, HDL-C, APOA, APOB, and APOE) but less likely to be smokers and drinkers (P < 0.05) than men (Supplementary Table 1).

Comparison of Lipid Profiles Among the Three Groups and Among the Age-Based Subgroups

Compared with the control group, the mean serum CHOL, TRIG, HDL-C, APOB, APOE, and SDLDL-C levels in the DR group were significantly higher (P < 0.05), signifying that the lipid profiles in patients with DR were generally higher than those in the healthy population. However, compared with patients with DM, patients with DR had a lower TRIG level (P < 0.05) (Table 1).

To further compare the differences in the lipid profiles among the three groups, we further divided the patients into two subgroups according to median age (≤57 years and >57 years). Similar to the previous results, in the ≤57-year-old subgroup (Table 2), patients with DR had significantly higher levels of lipid profiles (CHOL, TRIG, HDL-C, LDL-C,

Table 2 Comparison of Lipid Profiles in the Age ≤ 57 Years Subgroup of DR, DM and Control Groups

	Control Group	DM Group	DR Group	F	P
N	88	96	154		
Gender (Male/Female)	57/31	55/41	87/67	1.724	0.422
Age (years)	47.95±5.86	48.83±7.41	47.10±8.43	1.573	0.209
BMI (Kg/m^2)	24.42±2.66	24.99±3.73	24.59±3.91	0.641	0.527
CHOL (mmol/L)	4.07±0.85	5.03±0.92	4.76±1.35	18.195	<0.001[ab]
TRIG (mmol/L)	1.24±0.65	2.63±2.44	1.80±1.26	18.201	<0.001[abc]
HDL-C (mmol/L)	1.00±0.24	1.24±0.30	1.23±0.35	18.43	<0.001[ab]
LDL-C (mmol/L)	2.44±0.69	3.10±0.79	2.96±1.17	12.28	<0.001[ab]
APOA (mmol/L)	1.29±0.30	1.34±0.27	1.30±0.30	0.826	0.439
APOB (mmol/L)	0.81±0.19	1.09±0.25	1.05±0.36	24.558	<0.001[ab]
APOE (mmol/L)	33.03±9.57	51.78±26.18	47.05±24.10	64.524	<0.001[ab]
LPA (mmol/L)	158.28±218.09	99.09±142.19	194.90±306.34	8.505	0.014[c]
SDLDL (mmol/L)	0.51±0.25	1.96±0.90	1.44±0.69	20.92	<0.001[abc]

Notes: Differences among three groups were analysed using one-way ANOVA; [a]p <0.05 for the difference between control and DM groups (LSD post hoc test); [b]p <0.05 for the difference between DR and control groups (LSD post hoc test); [c]p <0.05 for the difference between DR and DM groups (LSD post hoc test).
Abbreviations: DM, diabetic mellitus; DR, diabetic retinopathy; N, number; BMI, body mass index; CHOL, cholesterol; TRIG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; APOA, apolipoprotein A; APOB, apolipoprotein B; APOE, apolipoprotein E; LPA, lipoprotein a; SDLDL-C, small dense low-density lipoprotein cholesterol.

APOB, APOE, LPA, and SDLDL-C) compared to the healthy controls, and patients with DR had lower TRIG and SDLDL-C levels than patients with DM (P < 0.05) (Figure 2). However, this difference in lipid profiles was not evident in patients in the >57-year-old subgroups, where we found that only the APOE and SDLDL-C levels were higher in patients with DR than in healthy controls and patients with DM (P < 0.05)(Supplementary Table 2).

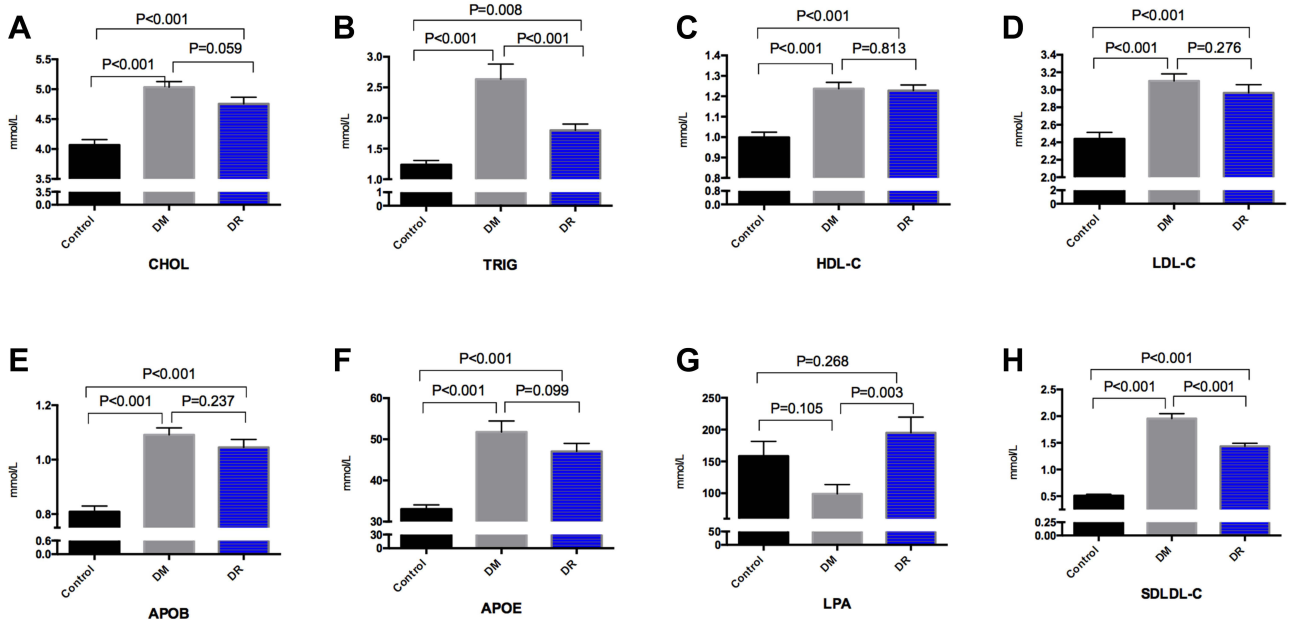

Figure 2 The differences in lipid levels (CHOL (**A**) TRIG (**B**) HDL-C (**C**) LDL-C (**D**) APOB (**E**) APOE (**F**) LPA (**G**) SDLDL-C (**H**)) among healthy controls, patients with DM and patients with DR in the ≤57-year-old subgroup.
Abbreviations: DR, diabetic retinopathy; DM, diabetes mellitus; CHOL, cholesterol; TRIG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; APOB, apolipoprotein B; APOE, apolipoprotein E; LPA, lipoprotein a; SDLDL-C, small dense low-density lipoprotein cholesterol.

Comparison of Lipid Profiles Between Patients with DR and Those with DM in the Treatment and Non-Treatment Subgroups

We divided patients with DR and DM into the treatment and non-treatment subgroups according to whether they had received hypoglycemic treatment (including insulin injections or oral hypoglycemic agents). In the non-treatment subgroup, our results showed that the serum LPA levels in the DR group were significantly higher than those in the DM group, and that the serum SDLDL-C levels in the DR group were significantly lower than those in the DM group. However, in the subgroup with hypoglycemic treatment, the serum SDLDL-C levels in the DR group were significantly higher than those in the DM group ($P < 0.05$) (Supplementary Table 3).

Comparison of Lipid Profiles Between Patients with DR and Those with DM in Terms of HbA1c Levels

To determine whether blood-glucose control levels affect lipid levels, we divided patients with DR and those with DM into two subgroups according to the median HbA1c level. In the subgroup with HbA1c ≤7.2%, the levels of CHOL, TRIG, LDL-C, and APOA levels in patients with DR were lower than in those with DM ($P < 0.05$) (Figure 3). However, in the subgroup with poor glycemic control (HbA1c >7.2%), no significant difference in serum lipid levels was found between patients with DR and those with DM ($P > 0.05$) (Supplementary Table 4).

Association Between Serum Lipid Levels and HbA1c Levels in Patients with DR

Multivariable linear regression analyses showed that CHOL (B = 0.170; 95% CI, 0.059–0.344; P = 0.006), TRIG (B = 0.172; 95% CI, 0.072–0.350; P = 0.003), APOA (B = 0.133; 95% CI, 0.077–1.301; P = 0.027), APOB (B = 0.147; 95%

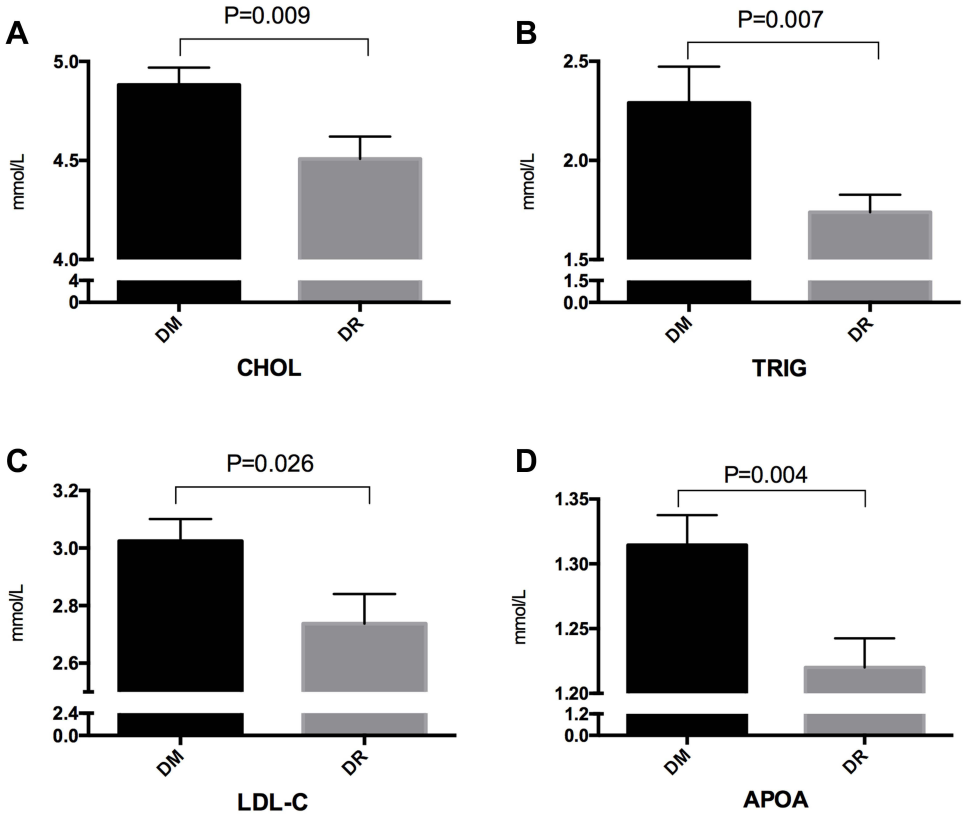

Figure 3 The differences in lipid levels (CHOL (**A**) TRIG (**B**) LDL-C (**C**) APOA (**D**)) between patients with DR and those with DM in the HbA1c ≤7.2% subgroup.
Abbreviations: DR, diabetic retinopathy; DM, diabetes mellitus; CHOL, cholesterol; TRIG, triglyceride; LDL-C, low-density lipoprotein cholesterol; APOA, apolipoprotein A.

CI, 0.105–1.195; P = 0.020), APOE (B = 0.152; 95% CI, 0.003–0.020; P = 0.001), and SDLDL-C (B = 0.197; 95% CI, 0.171–0.715; P = 0.001) levels were positively associated with HbA1c in patients with DR (Table 3).

Logistic Regression Analyses of the Association Between Lipid Profiles and Patients with DR

In a multivariable logistic regression analysis adjusted for confounding factors, CHOL (B 0.278, OR 1.32, 95% CI 1.112–1.566, P = 0.001), TRIG (B 0.238, OR 1.269, 95% CI 1.030–1.563, P = 0.026), HDL-C (B 3.778, OR 43.744, 95% CI 17.12–111.769, P < 0.001), APOB (B 1.951, OR 7.037, 95% CI 3.370–14.695, P < 0.001), APOE (B 0.056, OR 1.057, 95% CI 1.038–1.077, P < 0.001), and SDLDL-C (B 2.689, OR 14.719, 95% CI 8.304–26.088, P < 0.001) were risk factors for DR (Table 4).

Table 3 Association Between Lipid Profiles and HbA1c Levels in Patients with DR

	Pearson Correlations Analysis		Multivariable Linear Regression Analyses		
	r	P	B	P	95% CI
CHOL (mmol/L)	0.165	0.004	0.170	0.006	0.059 to 0.344
TRIG (mmol/L)	0.011	0.851	0.172	0.003	0.072 to 0.350
HDL-C (mmol/L)	0.088	0.122	0.075	0.214	−0.192 to 0.854
LDL-C (mmol/L)	0.148	0.009	0.094	0.133	−0.040 to 0.298
APOA (mmol/L)	0.165	0.004	0.133	0.027	0.077 to 1.301
APOB (mmol/L)	0.128	0.024	0.147	0.020	0.105 to 1.195
APOE (mmol/L)	0.112	0.049	0.152	0.010	0.003 to 0.020
LPA (mmol/L)	−0.055	0.336	−0.033	0.581	−0.001 to 0
SDLDL-C (mmol/L)	0.187	0.001	0.197	0.001	0.171 to 0.715

Note: Analysis adjusted for gender, age, body mass index, hypertension, HbA1c, duration of diabetes, insulin injection, oral hypoglycemic agents, eye lasers or surgery, smoking, drinking, oral antihypertensive agents, oral lipid-lowering agents, DM family history, cardiovascular disease, kidney disease and cerebrovascular disease.

Abbreviations: DR, diabetic retinopathy; HbA1c, hemoglobin A1c; CHOL, cholesterol; TRIG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; APOA, apolipoprotein A; APOB, apolipoprotein B; APOE, apolipoprotein E; LPA, lipoprotein a; SDLDL-C, small dense low-density lipoprotein cholesterol.

Table 4 Logistic Regression Analyses of the Association Between Lipid Profiles in Patients with DR and Healthy Controls

	B	P	OR	95% CI
CHOL (mmol/L)	0.278	0.001	1.32	1.112 to 1.566
TRIG (mmol/L)	0.238	0.026	1.269	1.030 to 1.563
HDL-C (mmol/L)	3.778	<0.001	43.744	17.12 to 111.769
LDL-C (mmol/L)	0.182	0.064	1.2	0.989 to 1.455
APOA (mmol/L)	0.646	0.074	1.908	0.939 to 3.875
APOB (mmol/L)	1.951	<0.001	7.037	3.370 to 14.695
APOE (mmol/L)	0.056	<0.001	1.057	1.038 to 1.077
LPA (mmol/L)	0.001	0.267	1.001	1.000 to 1.001
SDLDL-C (mmol/L)	2.689	<0.001	14.719	8.304 to 26.088

Note: Analysis adjusted for gender, age, body mass index and hypertension.

Abbreviations: DR, diabetic retinopathy; CHOL, cholesterol; TRIG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; APOA, apolipoprotein A; APOB, apolipoprotein B; APOE, apolipoprotein E; LPA, lipoprotein a; SDLDL-C, small dense low-density lipoprotein cholesterol; OR, odds ratio; CI, confidence interval.

Discussion

The effects of dyslipidemia on DR have been reported; however, the results were controversial. Moreover, there are few studies on the association between lipid profiles and DR at different ages, between sexes, and at different levels of blood glucose control. Our study showed that increased lipid levels were risk factors for DR, especially in younger populations and/or in patients with HbA1c ≤7.2%, suggesting that control of lipid levels should be strengthened in those patients. Furthermore, we found that lipid levels were positively associated with HbA1c levels, and that patients with intensive glycemic control had lower lipid levels than those with non- intensive glycemic control, indicating that dyslipidemia might play a vital role in the onset and development of DR, and that intensive diabetes treatment is necessary in older adults or in those with sub-optimal blood-glucose control.

Several clinical and laboratory studies have investigated the association between lipid levels and DR but with inconsistent results. A cross-sectional study of 224 patients with DM showed that the HDL-C and APOA levels were inversely associated with DR, whereas APOB levels were positively associated with DR.[12] Van leiden et al conducted a population-based cross-sectional study comprising 626 individuals and reported that elevated plasma CHOL, TRIG, and LDL-C levels were associated with DR.[19] The FinnDiane Study showed that patients with proliferative DR had higher CHOL, LDL-C, TRIG, and APOB levels compared with patients with non-proliferative DR.[20] We also found that CHOL, TRIG, HDL-C, and APOB levels were risk factors for DR. However, Chatziralli et al reported that TRIG, TC, LDL-C, and HDL-C levels were not associated with DR.[21] One possible reason for the inconsistency between their results and our results is that their study used regression analysis that did not exclude the influence of other confounding factors, whereas our study excluded confounding factors, such as age, sex, BMI, underlying diseases, medication, DM-related macrovascular complications, and other eye diseases that may affect vision, to the extent possible.

Moreover, we also found that APOE and SDLDL-C levels were risk factors for DR. APOE and SDLDL-C are plasma proteins involved in lipoprotein metabolism.[22,23] Some studies have shown that SDLDL-C plays an important role in cardio- and cerebrovascular diseases, such as coronary heart disease and ischemic stroke.[24–26] However, few studies have investigated the role of SDLDL-C in eye disease, especially in DR. To the best of our knowledge, only one clinical study has reported a strong positive correlation between SDLDL-C and APOB levels, reporting that SDLDL-C was a sensitive marker in predicting the need for laser treatment in patients with DR.[27] Few studies have reported an association between serum APOE levels and the risk of DR. Ukkola et al suggested that the role of the APOE phenotype was associated with the risk of DM-related complications (including macro- and microvascular diseases).[28] One possible explanation for this finding is that APOE gene polymorphisms affect serum CHOL levels; however, further large-scale studies are required to confirm this.

Our study findings prompt three further considerations.

First, it remains unclear why dyslipidemia is a risk factor for DR. The possible explanations for this are as follows. Oxidative stress, energy metabolism, and inflammation may be involved in the pathogenesis and disease progression of DR.[29–31] Some studies have shown that DR is a chronic inflammatory disease, suggesting that lipid metabolism is associated with the inflammatory state of DR.[32,33] Tikhonenko et al found an association between decreased lipid levels and the proinflammatory state of DR, which was related to increased gene expression of inflammatory markers, such as vascular endothelial growth factor, intercellular adhesion molecule-1, tumor necrosis factor-α, and interleukin-6.[34] Rezzola et al showed that inflammation mediates angiogenic vitreous activity in DR.[31] Furthermore, several studies have found a positive association between inflammation and lipid metabolism and DM-related complications.[35–37] Additionally, lipid oxidation may mediate oxidative stress in patients with DM, which leads to the occurrence and development of DR.[38,39] Mitochondria are the main source of intracellular reactive oxygen and the target of oxidative damage. Mitochondrial oxidative stress and decreased adenosine triphosphate concentration required for energy metabolism are believed to play an important role in the development of DR.[40,41] Lipids not only affect mitochondrial function but also directly affect phospholipids, causing changes in the lipid structure of cell membranes participating in the pathogenesis of DR.[42,43] Therefore, dyslipidemia is a risk factor for DR.

Second, our study showed that patients with DR had significantly higher lipid profile levels compared to healthy controls, especially in the ≤57-year-old subgroup. Some studies have also reported significantly high lipid levels in

middle-aged or younger individuals.[44,45] Therefore, it remains to be determined why the lipid levels were higher in younger patients than in older ones. The reasons may be as follows: (a) long-term unhealthy working conditions and lifestyles among young working-age adults can easily induce hyperlipidemia. Studies have shown that frequently staying up late,[46] a sedentary lifestyle,[47,48] long-term mental stress,[49] and work pressure[50,51] are common causes of abnormal lipid metabolism in younger individuals. (b) Dietary habits in younger adults may not always be well-balanced, with an excessive intake of saturated fatty acids and an insufficient intake of vitamins compared with the dietary habits of older adults.[52,53] (c) Younger individuals are more likely to have unhealthy lifestyle habits, such as smoking and excessive alcohol intake, than old ones, and these cumulative risk factors can lead to the development of hyperlipidemia.[54] Unhealthy lifestyle and dietary among middle-aged or younger adults can result in premature tissue and organ aging and abnormal body metabolism. Therefore, compared with older adults, the lifestyles of younger adults may lead to dyslipidemia, which has been found to be increasingly common in middle-aged and young adults. However, few studies have investigated the differences in lipid levels in patients with DR at different ages. Therefore, the clinical value of lipid levels in younger populations needs to be further elucidated through large-scale studies.

Third, it remains unclear why lipid levels in patients with DR are lower than in those with DM in the HbA1c ≤7.2% subgroup. Generally, the severity of hyperglycemia is a major risk factor for developing retinopathy. As shown in Table 1, patients with DR had higher HbA1c levels compared with those with DM (sex and age were highly matched), which is in line with the feature that DR is a microvascular complication of diabetes. Current guidelines recommend a target HbA1c level of 7.0% or less for most patients with diabetes, especially in patients with diabetic complications.[55] Therefore, for patients with DR, they need to be more compliant in order to obtain a satisfactory level of glycemic control; that is, they should receive a stricter diabetes diet and intensive DM treatment. In the HbA1c ≤7.2% subgroup, we found that the proportion of patients with low carbohydrate intake and intensive glycemic control in the DR group was higher than that in the DM group. Therefore, we hypothesized that the lower lipid levels in patients with DR than that in patients with DM in the HbA1c ≤7.2% subgroup may be attributed to the fact that patients with DR in this subgroup were more compliant than patients with DM, which means low carbohydrate intake and intensive glycemic control could be the explanations for this finding. One explanation may be the effect of intensive glucose control (INT). INT has an important role in the treatment of microvascular complications of type 2 diabetes and the use of oral hypoglycemic agents and insulin was increased to a greater degree in the intensive control group than in the standard control group.[5] We reviewed the clinical data and found that almost all patients with DR received intensive diabetes treatment, which was not the case for patients with DM in the HbA1c ≤7.2% subgroup. Studies have shown that hyperglycemic medication can affect lipid metabolism while controlling blood glucose and play an important role in lowering lipid levels.[56–58] Meanwhile, Azad et al investigated the association between INT and lipid parameters on the progression of DR and demonstrated that the patients who were assigned to the INT group with reduced CHOL, TRIG, or LDL-C levels had a lower risk of DR progression at the end of the study, which was similar to our results.[59] Therefore, we believed that this was attributed to the INT of patients with DR. However, there are few studies on the association between intensive diabetes treatment and lipids, and more studies are expected to confirm our viewpoint.

Another explanation is low-carbohydrate diet. The main source of energy for the Asian population is carbohydrates. Increased carbohydrate intake increased the synthesis of lipids.[60] High carbohydrate diet was positively associated with elevated TG and LDL-C levels in Korean adults. Carbohydrate intake from starchy foods was positively associated with the risk of dyslipidemia in the Chinese population. The low-carbohydrate diet plays a role in lowering blood glucose, improving glucose tolerance, and increasing insulin sensitivity. Moreover, low-carbohydrate diet is effective in improving lipid metabolism.[61] Therefore, low-carbohydrate intake can effectively reduce lipid synthesis while controlling blood glucose, resulting in lower blood lipid levels in the DR group than in the DM group in the subgroup with better blood glucose control (HbA1c ≤7.2%). This also explains why SDLDL is lower in patients with DR compared to those with DM in the non-treatment subgroup, where the patients had not been taking hypoglycemic treatments. We reviewed the clinical data of patients with DM who are not taking hypoglycemic treatments and found that most of them were newly diagnosed and had never received hypoglycemic therapy before. These people did not follow a strict diabetic diet and had a higher carbohydrate intake compared to patients with a long duration of DM or those who already had DR. Therefore, SDLDL levels in patients with DM are higher than those in patients with DR due to

differences in dietary structure. In addition, this was further confirmed by the results grouped by age. In the elderly population (aged >57 years old) with a healthy diet, the SDLDL level of DR patients is higher than that of DM patients (Supplementary Table 2), while in the younger population (aged ≤57 years old) who had more carbohydrates intake, the SDLDL level of patients with DR is lower than that of patients with DM (Figure 2). We aimed to conducted more studies to confirm our results.

Hypertension and longer diabetes duration were risk factors for developing DR,[62,63] which was consistent with the results of our study. The proportion of patients with DR significantly increased with the diabetes duration.[7] Strict blood pressure control in patients with hypertension and diabetes can lead to clinically important reduction in complications related to diabetes, progression of DR, and deterioration of visual acuity.[64] In addition, the role of other factors in DR, such as age and kidney, cerebrovascular, and coronary artery diseases remains unclear.[65,66] To exclude the influence of these factors, which may be associated with DR and lipid profiles, regression analysis was performed in this study, adjusting for confounders (age, hypertension, longer duration of diabetes, etc.). The results revealed that the lipid profiles remained associated with DR.

This study has some limitations. First, this was a single-center study, and our results may not be applicable to individuals of other ethnicities or those residing in other regions. Second, this was a case-control study, and the exact mechanism of lipid metabolism in DR was unclear; therefore, further clinical and laboratory studies are required. Moreover, we did not investigate the role of lipids in DR of differing severities. A multicenter, large-sample study is required to confirm our study results. Third, this study only detected the total APOE concentration, and we did not detect the concentrations of APOE4 and other APOE subtypes. Finally, although this study considered confounding factors such as age, sex, BMI, underlying diseases, medication, DM-related macrovascular complications, and other eye diseases that may affect vision to the extent possible, we did not conduct detailed investigations on patients' eating habits and lifestyles, which may have influenced our results.

Conclusion

In conclusion, increased lipid levels, especially of CHOL, TRIG, HDL-C, APOB, APOE and SDLDL-C were significant risk factors for DR, especially in younger population and/or in patients with HbA1c ≤7.2%, which suggests that dyslipidemia may play a vital role in the onset and development of DR. Therefore, in these populations, the lipid levels are of great importance in DR and should be actively controlled. In older adults or in those with sub-optimal blood glucose control, active control of blood glucose should be a main priority, and control of lipid level control should be strengthened after blood glucose control is achieved.

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Disclosure

All authors have no conflicts of interest in relation to this work.

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