

The Association Between Lipid Profile and Subfoveal Choroidal Thickness in Chinese Patients with Proliferative Diabetic Retinopathy Secondary to Type 2 Diabetes

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Introduction: Extensive studies have studied the factors associated with subfoveal choroidal thickness (SFCT). However, studies of the association between lipid profile and SFCT in patients with proliferative diabetic retinopathy (PDR) in type 2 diabetes remain limited. Thus, we aimed to investigate the relationship between lipid profile and SFCT in patients with PDR.

Materials and Methods: This was a retrospective cross-sectional study. The included participants were inpatients who underwent vitrectomy for PDR with type 2 diabetes and contralateral eyes of PDR patients meeting the criteria. Multivariate linear regression analysis was used to determine the independent association between lipid profile and SFCT.

Results: A total of 131 participants with PDR were enrolled in the final analysis. The average age of the participants was 55.76 ± 9.88 years, and the average SFCT was 276.10 ± 92.92 μm . Multivariate linear regression model results showed that in the fully adjusted model, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) had a negative association with SFCT ($\beta = -16.51$, 95% CI: $-29.57, -3.46$; $P = 0.0148$; $\beta = -42.65$, 95% CI: $-82.60, -2.70$; $P = 0.0390$; $\beta = -17.89$, 95% CI: $-33.24, -2.54$; $P = 0.0245$, respectively), while triglyceride was not significantly associated with SFCT ($\beta = 5.23$, 95% CI: $-18.57, 29.02$; $P = 0.6678$). Furthermore, the results of stratified analysis showed that except for triglyceride, the trends of total cholesterol, HDL-C, LDL-C, and SFCT were consistent among different stratifications in participants.

Conclusion: The cholesterol profile had a significant negative association with SFCT in Chinese PDR patients, but triglyceride was not significantly associated with SFCT. This suggests that these systemic imbalances contribute to choroidal changes, and often coexist in diabetic patients.

Keywords: cholesterol, subfoveal choroidal thickness, proliferative diabetic retinopathy, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol

Introduction

The choroid plays a crucial role in the visual process, accounting for more than 85% of the blood supply of the ophthalmic artery and the nutrient supply for both the retinal pigment epithelium (RPE) and photoreceptors.¹ A considerable decrease in choroidal blood flow may lead to the destruction of photoreceptors and affect visual function.² Recent advances in the development of spectral-domain optical coherence tomography (SD-OCT) and enhanced depth imaging (EDI)-OCT have facilitated the quantitative measurement of choroidal thickness.³

Diabetic retinopathy (DR) is the main cause of visual impairment and blindness in working age population.⁴⁻⁶ Modifiable (ie, hyperglycaemia, hypertension, hyperlipidaemia and obesity) and non-modifiable factors (ie, duration of

diabetes and genetic susceptibility) are involved in the development of DR.^{7–9} In addition to the factors mentioned above, previous studies^{10–17} have proved that renal function impairment, especially low estimated glomerular filtration rate (eGFR), is involved in the development of DR. In addition to retinal changes, choroid abnormalities are also common in diabetes patients.

Extensive studies have shown that subfoveal choroidal thickness (SFCT) decreases substantially with age^{18–20} and ocular axial length.^{18,21,22} Moreover, SFCT is associated with various systemic diseases including hypertension,²³ coronary artery disease,²⁴ diabetes,^{25–27} carotid stenosis,^{28,29} heart failure,³⁰ and hyperlipidemia.³¹ As such, SFCT is a useful biomarker for predicting cardiovascular risk.

More recently, studies have focussed on the relationship between cholesterol and SFCT.^{32–34} Wong et al found an association between hypercholesterolemia and increased SFCT in the healthy population.³² The authors speculate that lipid accumulation on the choroid and hypertrophy of vascular smooth muscle cells are responsible for this phenomenon. Aydin et al³⁴ found that low-density lipoprotein cholesterol (LDL-C) levels were inversely correlated with SFCT in both eyes of patients with cardiovascular risk factors. However, they failed to find the correlation between cholesterol levels and SFCT. Abnormal cholesterol metabolism is closely associated with various ocular diseases, such as age-related macular degeneration (AMD),³⁵ hypertensive retinopathy,³⁶ DR,^{37–39} and diabetic macular edema (DME).⁴⁰ Choroid is an important vascular tissue in the eye, which is also affected by diabetes and can cause visual impairment in diabetes patients.⁴¹ Yazgan et al found that macular choroidal thickness may be the earliest determiner to detect the onset of DR in patients with prediabetes.⁴² What's more, a recent study has shown a positive correlation between normal cholesterol levels including LDL-C and high-density lipoprotein cholesterol (HDL-C), and SFCT in adolescent children with type 1 diabetes.³³ This suggests lipid metabolism may play a role in SFCT in patients with DR. However, the relationship between lipid profile and SFCT in patients with proliferative diabetic retinopathy (PDR) secondary to type 2 diabetes remains underexplored. Here we conducted a cross-sectional study to explore the association between lipid profile and SFCT in PDR patients.

Materials and Methods

Study Population

This was a retrospective cross-sectional study. This study was performed in line with the principles of the Declaration of Helsinki and ethical approval was obtained from the West China Hospital of Sichuan University (2020–834). Data used were anonymized and the requirement for informed consent was therefore waived. The study participants were inpatients with type 2 diabetes who had definite indications for vitrectomy, no absolute contraindications, and underwent vitrectomy for PDR at the Ophthalmology Department of West China Hospital of Sichuan University from May 2020 to February 2022. And the contralateral eye in these PDR patients meeting the following criteria were included as subjects in the study. Firstly, the contralateral eyes of PDR patients were graded as PDR with clear refractive media, and no history of vitrectomy. Secondly, included patients had a fasting blood glucose lower than 8 mmol/L, blood glucose < 11 mmol/L 2 hours after 3 meals, and consistent blood glucose levels for at least 7 days. Finally, included participants had no missing serum lipid variables. Patients meeting any of the following criteria were excluded from the study. Firstly, refractive error exceeding ± 6.00 diopters, or an ocular axial length of more than 26.50 mm. Secondly, acquired immune deficiency syndrome, syphilis, or leukemia. Thirdly, type 1 diabetes. Iris neovascularization or neovascular glaucoma, uveitis, retinal vein occlusion, retinal artery occlusion, paracentral acute middle maculopathy, AMD, ocular trauma, endophthalmitis, and other eye conditions. Finally, poor quality EDI-OCT images with no discernable choriocapillary boundaries.

Laboratory Variables

All relevant laboratory tests were completed on admission. Fasting laboratory values included serum lipid profile, fasting blood glucose, preoperative glycosylated hemoglobin A1c (HbA1c), serum creatinine, and eGFR. Some studies have defined chronic kidney disease as an eGFR of < 60 mL/min/1.73 m² and/or urine albumin-creatinine ratio ≥ 30 mg/g.⁴³ Therefore, eGFR was used as a stratification factor of renal function, which was divided into two groups (eGFR ≥ 60 (mL/min \times 1.73 m²) group and eGFR < 60 (mL/min \times 1.73 m²) group). In our study, the serum fasting lipid profile included triglyceride, total

cholesterol, LDL-C, and HDL-C. According to the Chinese Adult Dyslipidemia Prevention Guide (2007 edition), hypercholesterolemia was defined as fasting serum total cholesterol concentrations greater than 6.22 mmol/L (240 mg/dL).⁴⁴

EDI-OCT Imaging

All participants underwent comprehensive ocular examinations, including visual acuity, intraocular pressure (IOP), ocular axial length, slit-lamp examination, and EDI-OCT. The EDI-OCT examination was conducted after pupil dilation with compound tropicamide eye drops (Mydrin-P; Santen, Osaka, Japan). The standardized EDI-OCT scans were obtained using SD-OCT (Heidelberg Engineering; Heidelberg, Germany) and carried out by experienced technicians in the afternoon, avoiding diurnal variations. The EDI-OCT measurements of central macular thickness (CMT) and SFCT centered on the fovea were taken by horizontal/vertical scans. CMT was measured automatically, while SFCT was measured manually using digital calipers provided by the Heidelberg Eye Explorer software. CMT was defined as the perpendicular distance in the macula from the inner limiting membrane to the RPE. SFCT was defined as the distance in the macula from the outer border of the hyper-reflective line corresponding to the RPE perpendicular to the choriocleral interface. EDI-OCT images of poor quality where it was difficult to distinguish choriocleral boundaries were excluded. Two experienced physicians who were blinded to the patients clinical data performed measurements independently, and the average of all measurements was used for the final statistical analysis.

Other Variables

Relevant baseline characteristics important for the management of hospitalized patients with PDR were retrieved from the electronic medical record system. Demographic information included age, sex and education level. Education level was grouped into junior high school or below, senior high school, and college or above. Hypertension history was defined as a physician diagnosis or the use of antihypertensive medication. Diabetes mellitus was defined as physician diagnosis or the use of insulin/ oral glucose-lowering drugs. Relevant medical history included diabetes duration, hypertension history, chronic kidney disease history, stroke history, and heart disease history. The degree of panretinal photocoagulation (PRP) in the contralateral eyes of PDR patients and the history of anti-vascular endothelial growth factor (VEGF) therapy were collected. The degree of PRP was grouped into 3 categories, none, partial, and whole, according to the scope of the laser. The above data were all obtained from the self-reported medical conditions by participants. Systemic medication history including oral glucose-lowering drugs, insulin treatment, and oral antihypertensive drugs (eg calcium antagonist) was extracted. Physical characteristics at initial presentation including height, weight, and systolic and diastolic blood pressure (DBP) were extracted. The body mass index (BMI) was calculated as the weight (kilogram) divided by the height (meter) squared.

Statistical Analysis

Demographic characteristics and study outcomes were summarized using descriptive statistics. Continuous variables were summarized with means \pm standard deviation, and the categorical variables with frequencies and percentages. The variation was described and evaluated using the χ^2 -test or Kruskal–Wallis test. Multivariate linear regression analysis was used to detect the independent association between lipid profile and SFCT, and smooth curve fitting was used to present the tendency. Candidate confounders were selected based on their associations with the outcomes of interest, or a change in effect estimate of more than 10%.^{45,46} Stratified analysis, using the multivariate linear regression model with smooth curve fitting, showed a nonlinear (after adjusting for all covariates) correlation between age and SFCT in patients with PDR. The inflection point was the age of 53 years (data not shown) using the two-piecewise multivariate linear regression model. Statistical analyses were performed using Empower Stats (<http://www.empowerstats.com>; X&Y Solutions Inc., Boston, MA) and R software, version 3.4.3 (<http://www.R-project.org/>, The R Foundation). A two-sided $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristics of Participants

A total of 131 participants with PDR were enrolled in the final analysis. The average age of the participants was 55.76 ± 9.88 years old, and 63.36% of them were men. The average SFCT was 276.10 ± 92.92 μm and the average ocular axial length was 23.22 ± 1.02 mm. The participants were divided into 2 groups according to total cholesterol level.⁴⁴ Except

for triglyceride, total cholesterol, HDL-C, LDL-C, hypertension, and application of calcium antagonists, there was no statistically significant difference in other variables between the two groups. Baseline characteristics are listed in Table 1.

Univariate Analysis

The results of univariate analysis revealed a significant negative association between SFCT and both total cholesterol and HDL-C in participants ($\beta = -16.08$, 95% CI: $-29.25, -2.91$; $P = 0.0181$; $\beta = -42.66$, 95% CI: $-81.44, -3.89$; $P = 0.0329$,

Table 1 Baseline Characteristics of Participants with Proliferative Diabetic Retinopathy

	Mean \pm SD/n (%)	Total Cholesterol (mmol/L)		P-value
		<6.22	≥ 6.22	
N	131	119	12	
Age (year)	55.76 \pm 9.88	55.55 \pm 9.81	57.83 \pm 10.79	0.449
Male sex	83 (63.36%)	77 (64.71%)	6 (50.00%)	0.314
SBP (mmHg)	139.60 \pm 20.31	138.88 \pm 20.26	145.92 \pm 20.53	0.257
DBP (mmHg)	85.08 \pm 10.82	85.34 \pm 11.05	82.75 \pm 8.56	0.434
BMI (kg/m ²)	24.24 \pm 3.00	24.25 \pm 3.03	24.19 \pm 2.81	0.953
Duration of diabetes (year)	12.57 \pm 6.99	12.47 \pm 6.93	13.50 \pm 7.75	0.629
Visual acuity (logMAR)	0.75 \pm 0.54	0.72 \pm 0.54	1.03 \pm 0.45	0.056
IOP (mmHg)	16.27 \pm 4.08	16.29 \pm 4.14	16.04 \pm 3.57	0.847
Ocular axial length (mm)	23.22 \pm 1.02	23.25 \pm 1.02	22.87 \pm 0.97	0.347
CMT (μ m)	289.83 \pm 128.46	288.38 \pm 128.51	304.19 \pm 132.73	0.686
SFCT (μ m)	276.10 \pm 92.92	278.67 \pm 86.68	250.57 \pm 143.76	0.320
Education level				0.665
Junior high school or below	75 (57.25%)	69 (57.98%)	6 (50.00%)	
Senior high school	26 (19.85%)	24 (20.17%)	2 (16.67%)	
College or above	30 (22.90%)	26 (21.85%)	4 (33.33%)	
Systemic diseases				
Hypertension	67 (51.15%)	57 (47.90%)	10 (83.33%)	0.019
Chronic kidney disease history	35 (26.72%)	31 (26.05%)	4 (33.33%)	0.587
Stroke history	8 (6.11%)	8 (6.72%)	0 (0.00%)	0.354
Heart disease history	6 (4.58%)	6 (5.04%)	0 (0.00%)	0.426
Systemic medication history				
Insulin treatment	80 (61.07%)	71 (59.66%)	9 (75.00%)	0.299
Oral glucose-lowering drugs	98 (74.81%)	90 (75.63%)	8 (66.67%)	0.495
Calcium antagonists	41 (31.30%)	34 (28.57%)	7 (58.33%)	0.034
Ophthalmological treatment history				
Anti-VEGF therapy	40 (30.53%)	37 (31.09%)	3 (25.00%)	0.662
PRP				0.333
None	57 (43.51%)	54 (45.38%)	3 (25.00%)	
Partial	27 (20.61%)	23 (19.33%)	4 (33.33%)	
Whole	47 (35.88%)	42 (35.29%)	5 (41.67%)	
Laboratory data				
Fasting blood glucose (mmol/L)	7.22 \pm 2.69	7.15 \pm 2.76	7.93 \pm 1.78	0.341
HbA1c (%)	7.66 \pm 1.71	7.75 \pm 1.77	6.86 \pm 0.66	0.140
Total cholesterol (mmol/L)	4.60 \pm 1.19	4.34 \pm 0.89	7.14 \pm 0.79	<0.001
HDL-C (mmol/L)	1.31 \pm 0.41	1.28 \pm 0.34	1.60 \pm 0.78	0.009
LDL-C (mmol/L)	2.68 \pm 1.02	2.47 \pm 0.76	4.77 \pm 0.98	<0.001
Triglyceride (mmol/L)	1.50 \pm 0.75	1.44 \pm 0.70	2.08 \pm 1.02	0.004
Serum creatinine (μ mol/L)	152.02 \pm 189.46	147.48 \pm 182.98	197.00 \pm 250.25	0.390
eGFR (mL/min \times 1.73m ²)	65.79 \pm 30.04	67.38 \pm 30.16	50.07 \pm 24.71	0.057

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; HbA1c, hemoglobin A1c; logMAR, logarithmic minimum resolution angle; IOP, intraocular pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; CMT, central macular thickness; SFCT, subfoveal choroidal thickness; VEGF, vascular endothelial growth factor; PRP, panretinal photocoagulation.

respectively), while LDL and triglyceride were not significantly associated with SFCT ($\beta = -15.27$, 95% CI: -30.72 , 0.17 ; $P = 0.0548$; $\beta = -3.01$, 95% CI: -24.36 , 18.34 ; $P = 0.7828$, respectively). Compared to women, men were more likely to have higher SFCT ($\beta = 38.91$, 95% CI: 6.44 , 71.38 ; $P = 0.0203$). There was a statistically significant difference in SFCT by age, DBP, chronic kidney disease history, oral glucose-lowering drugs, and calcium antagonists. We found that other factors were not statistically associated with SFCT. The results of univariate analysis are shown in Table 2.

Table 2 Univariate Linear Regression Analysis of SFCT in Participants with Proliferative Diabetic Retinopathy

	β , 95% CI	P-value
Age, per 1 year increase	-2.68 (-4.24, -1.13)	0.0009
Male vs female	38.91 (6.44, 71.38)	0.0203
SBP, per 1 mmHg increase	0.57 (-0.26, 1.41)	0.1815
DBP, per 1 mmHg increase	1.85 (0.30, 3.40)	0.0213
BMI, per 1 kg/m ² increase	2.72 (-2.90, 8.34)	0.3451
Duration of diabetes, per 1 year increase	-0.51 (-2.84, 1.82)	0.6663
Visual acuity, per 1 logMAR increase	1.40 (-28.46, 31.27)	0.9268
IOP, per 1 mmHg increase	1.04 (-2.91, 4.99)	0.6073
Ocular axial length, per 1 mm increase	-0.47 (-1.89, 0.94)	0.5134
CMT, per 1 μ m increase	0.02 (-0.10, 0.14)	0.7524
Education level		
Junior high school or below	Reference	
Senior high school	-9.96 (-51.66, 31.74)	0.6403
College or above	6.78 (-32.80, 46.36)	0.7376
Systemic diseases		
Hypertension vs absent	-3.80 (-35.75, 28.15)	0.8161
Chronic kidney disease history vs absent	38.58 (3.10, 74.07)	0.0350
Stroke history vs absent	-1.30 (-68.01, 65.41)	0.9695
Heart disease vs absent	5.49 (-70.92, 81.89)	0.8883
Systemic medication history		
Insulin vs absent	22.16 (-10.38, 54.70)	0.1842
Oral glucose-lowering drugs vs absent	-43.36 (-79.39, -7.33)	0.0198
Calcium antagonists vs absent	37.18 (3.33, 71.03)	0.0332
Ophthalmological treatment history		
Anti-VEGF therapy vs absent	32.04 (-2.20, 66.28)	0.0690
PRP		
None	Reference	
Partial	5.83 (-36.43, 48.09)	0.7874
Whole	34.28 (-1.36, 69.92)	0.0617
Laboratory data		
Fasting blood glucose, per 1 mmol/L increase	-2.10 (-8.04, 3.85)	0.4902
HbA1c, per 1% increase	0.50 (-3.64, 4.64)	0.8144
Total cholesterol, per 1 mmol/L increase	-16.08 (-29.25, -2.91)	0.0181
HDL-C, per 1 mmol/L increase	-42.66 (-81.44, -3.89)	0.0329
LDL-C, per 1 mmol/L increase	-15.27 (-30.72, 0.17)	0.0548
Triglyceride, per 1 mmol/L increase	-3.01 (-24.36, 18.34)	0.7828
Serum creatinine, per 1 μ mol/L increase	0.08 (-0.00, 0.16)	0.0648
eGFR, per 1 mL/min \times 1.73m ² increase	-0.12 (-0.66, 0.41)	0.6470

Abbreviations: CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; HbA1c, hemoglobin A1c; logMAR, logarithmic minimum resolution angle; IOP, intraocular pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; CMT, central macular thickness; SFCT, subfoveal choroidal thickness; VEGF, vascular endothelial growth factor; PRP, panretinal photocoagulation.

The Relationship Between Lipid Profile and SFCT in Patients with PDR

We used a multivariate linear regression model to evaluate the associations between SFCT and total cholesterol, HDL-C, LDL-C and triglyceride (Table 3). Three adjusted models are shown in Table 3. In adjusted model I (adjusted age, sex), SFCT was not significantly associated with total cholesterol, HDL-C, LDL-C and triglyceride ($\beta = -13.48$, 95% CI: $-26.87, -0.09$; $P = 0.0506$; $\beta = -33.94$, 95% CI: $-73.31, 5.43$; $P = 0.0936$; $\beta = -12.90$, 95% CI: $-28.60, 2.80$; $P = 0.1098$; $\beta = -1.71$, 95% CI: $-22.95, 19.52$; $P = 0.8747$, respectively). In adjusted model II (adjusted age, sex, ocular axial length), the results revealed a significantly negative association between SFCT and both total cholesterol and HDL-C ($\beta = -14.71$, 95% CI: $-27.42, -2.00$; $P = 0.0251$; $\beta = -42.38$, 95% CI: $-80.27, -5.40$; $P = 0.0267$), while there was no relationship between SFCT and LDL-C or triglyceride ($\beta = -14.98$, 95% CI: $-29.91, -0.06$; $P = 0.0513$; $\beta = 3.60$, 95% CI: $-17.10, 24.29$; $P = 0.7340$, respectively). Furthermore, in adjusted model III (adjusted age, gender, ocular axial length, PRP, duration of diabetes, serum creatinine, DBP, HbA1c, anti-VEGF therapy, oral glucose-lowering drugs, and oral calcium antagonists), SFCT had a significantly negative association with total cholesterol, HDL-C, and LDL-C ($\beta = -16.51$, 95% CI: $-29.57, -3.46$; $P = 0.0148$; $\beta = -42.65$, 95% CI: $-82.60, -2.70$; $P = 0.0390$; $\beta = -17.89$, 95% CI: $-33.24, -2.54$; $P = 0.0245$, respectively), while the result of triglyceride was consistent ($\beta = 5.23$, 95% CI: $-18.57, 29.02$; $P = 0.6678$). We divided participants by total cholesterol into 2 groups according to the Chinese Adult Dyslipidemia Prevention Guide (2007 edition).⁴⁴ Compared to the group with total cholesterol < 6.22 mmol/L, the hypercholesterolemia group had lower SFCT in these different adjusted models. However, these trends did not show statistical differences.

Smooth Curve Fitting Between Lipid Profile and SFCT in PDR Patients

Smooth curve fitting showed that SFCT decreased with increasing concentration of total cholesterol, HDL-C, and LDL-C but not triglyceride, in patients with PDR (Figure 1).

The Results of Stratified Analyses Between Lipid Profile and SFCT in PDR Patients

Each stratification was adjusted for all factors (age, gender, ocular axial length, PRP, duration of diabetes, serum creatinine, DBP, HbA1c, anti-VEGF therapy, oral glucose-lowering drugs, and oral calcium antagonists), except the stratification factor itself. All the results of the stratified analysis were shown in Table 4. Except for triglyceride, the trends of total cholesterol, HDL-C, LDL-C, and SFCT were consistent among different stratifications in patients with PDR.

Discussion

Study results demonstrate a relationship between lipid profile and SFCT in patients with PDR. These results show a negative association between the concentration of cholesterol profile and SFCT in PDR patients, indicating that cholesterol may play an important role in choroidal thickness. However, triglyceride was not statistically associated

Table 3 Relationship Between Lipid Profile and SFCT in Participants with Proliferative Diabetic Retinopathy

Exposure	Model I		Model II		Model III	
	β , 95% CI	P-value	β , 95% CI	P-value	β , 95% CI	P-value
Total cholesterol (mmol/L)	-13.48 (-26.87, -0.09)	0.0506	-14.71 (-27.42, -2.00)	0.0251	-16.51 (-29.57, -3.46)	0.0148
HDL-C (mmol/L)	-33.94 (-73.31, 5.43)	0.0936	-42.38 (-80.27, -5.40)	0.0267	-42.65 (-82.60, -2.70)	0.0390
LDL-C (mmol/L)	-12.90 (-28.60, 2.80)	0.1098	-14.98 (-29.91, -0.06)	0.0513	-17.89 (-33.24, -2.54)	0.0245
Total cholesterol (mmol/L) group						
<6.22	Reference		Reference		Reference	
≥6.22	-20.91 (-75.85, 34.03)	0.4571	-27.03 (-79.37, 25.31)	0.3130	-42.07 (-97.70, 13.55)	0.1414
Triglyceride (mmol/L)	-1.71 (-22.95, 19.52)	0.8747	3.60 (-17.10, 24.29)	0.7340	5.23 (-18.57, 29.02)	0.6678

Notes: Model I adjusted for: age and sex. Model II adjusted for age, sex, and ocular axial length. Model III adjusted for age, gender, ocular axial length, PRP, duration of diabetes, serum creatinine, DBP, HbA1c, anti-VEGF therapy, oral glucose-lowering drugs, and oral calcium antagonists.

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SFCT, subfoveal choroidal thickness; VEGF, vascular endothelial growth factor; PRP, panretinal photocoagulation.

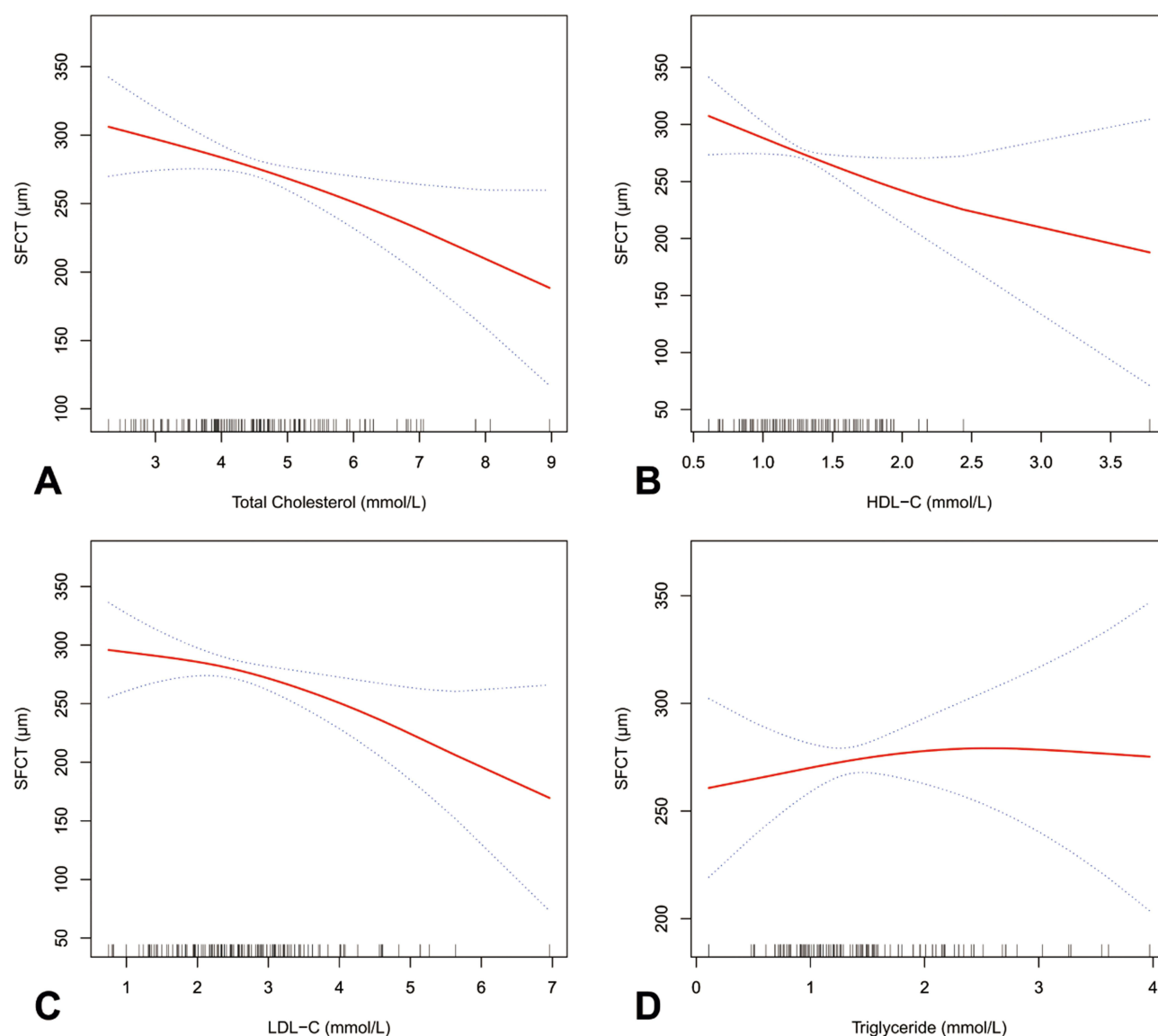


Figure 1 Smooth curve fitting between lipid profile and SFCT in patients with proliferative diabetic retinopathy. (A–D) present the tendency between total cholesterol, HDL-C, LDL-C, triglyceride, and SFCT, respectively.

with SFCT. To the best of our knowledge, this is the first study targeting at evaluating the association between lipid profile and SFCT in patients with PDR.

Recently, attention has been increasingly drawn to the relationship between abnormal lipid metabolism and ocular microvascular complications in diabetes. The association between abnormal cholesterol metabolism and DR^{39,47} was well-reviewed. The metabolically active retina obtains essential lipids by endogenous biosynthesis,^{48,49} and from systemic circulation.^{50,51} The cholesterol metabolism of retina and brain is different from that of other peripheral organs and is separated from the system circulation.⁵² In the healthy retina, most exogenous cholesterol is transmitted through the RPE layer and gradually spread throughout the entire retina. However, in the diabetic retina, the hyperglycemia-induced damage of the internal and external blood-retinal barriers makes the absorption of cholesterol in the retina abnormally increase. The choroid is one of the most complex vascular networks in the human body and choroidal circulation is essential for maintaining retinal homeostasis.⁵³ Such findings illustrated that most exogenous cholesterol passes through the choroidal circulatory system, suggesting the choroidal circulatory system is susceptible to lipid metabolism.

Table 4 The Results of Stratified Analysis in Participants with Proliferative Diabetic Retinopathy

Y= SFCT, μm	N	Total Cholesterol (mmol/L)		HDL-C (mmol/L)		LDL-C (mmol/L)		Triglyceride (mmol/L)	
		β , 95% CI	P-value	β , 95% CI	P-value	β , 95% CI	P-value	β , 95% CI	P-value
Gender									
Female	48	-19.80 (-38.61, -0.99)	0.0492	-98.49 (-163.85, -33.14)	0.0066	-23.98 (-46.19, -1.77)	0.0441	24.47 (-7.69, 56.63)	0.1479
Male	83	-12.18 (-30.17, 5.81)	0.1896	-31.20 (-82.95, 20.54)	0.2420	-11.63 (-32.92, 9.65)	0.2884	-1.72 (-35.40, 31.97)	0.9208
Age (year)									
<53	45	-30.22 (-59.36, -1.08)	0.0538	-51.53 (-128.77, 25.71)	0.2039	-29.00 (-64.82, 6.82)	0.1262	-0.71 (-36.39, 34.97)	0.9692
≥ 53	86	-14.29 (-31.00, 2.41)	0.0985	-42.64 (-92.30, 7.03)	0.0975	-15.59 (-34.82, 3.63)	0.1169	11.14 (-21.88, 44.16)	0.5110
PRP									
None	57	-13.47 (-32.77, 5.84)	0.1793	-95.84 (-161.33, -30.35)	0.0066	-12.65 (-35.52, 10.21)	0.2848	34.69 (-9.48, 78.86)	0.1318
Partial	27	-9.92 (-44.14, 24.31)	0.5879	-12.18 (-102.96, 78.60)	0.8002	-14.04 (-58.44, 30.36)	0.5550	-14.62 (-72.10, 42.86)	0.6334
Whole	47	1.88 (-28.89, 32.64)	0.9058	-45.95 (-133.77, 41.86)	0.3141	-3.94 (-34.69, 26.81)	0.8036	36.86 (-6.00, 79.73)	0.1034
Oral glucose-lowering drugs									
No	33	-14.93 (-60.04, 30.18)	0.5263	-72.23 (-211.16, 66.69)	0.3243	-20.03 (-84.82, 44.76)	0.5536	14.98 (-53.27, 83.23)	0.6732
Yes	98	-17.33 (-30.51, -4.14)	0.0121	-35.07 (-75.34, 5.20)	0.0923	-17.48 (-32.68, -2.28)	0.0273	-3.19 (-30.69, 24.31)	0.8207
Calcium antagonist									
No	90	-19.31 (-34.06, -4.56)	0.0127	-33.21 (-73.40, 6.97)	0.1102	-19.47 (-36.97, -1.97)	0.0330	-0.68 (-28.68, 27.32)	0.9621
Yes	41	-19.30 (-58.12, 19.52)	0.3403	-57.26 (-199.69, 85.16)	0.4391	-20.59 (-60.76, 19.58)	0.3260	11.40 (-47.28, 70.08)	0.7070
Anti-VEGF therapy									
No	91	-16.38 (-31.59, -1.17)	0.0386	-53.00 (-96.93, -9.07)	0.0210	-16.84 (-34.77, 1.09)	0.0703	10.08 (-16.99, 37.15)	0.4681
Yes	40	-24.29 (-50.84, 2.26)	0.0881	-33.63 (-137.75, 70.50)	0.5339	-25.21 (-57.15, 6.74)	0.1377	-30.42 (-78.58, 17.75)	0.2301
eGFR ($\text{mL}/\text{min} \times 1.73\text{m}^2$)									
<60	55	-19.87 (-42.49, 2.76)	0.0952	14.42 (-95.03, 123.88)	0.7979	-23.18 (-48.02, 1.66)	0.0771	-25.61 (-68.01, 16.80)	0.2456
≥ 60	76	-18.26 (-35.43, -1.08)	0.0421	-51.84 (-95.40, -8.29)	0.0236	-17.90 (-38.59, 2.79)	0.0960	24.39 (-9.94, 58.72)	0.1697
Hypertension history									
No	64	-15.95 (-34.62, 2.71)	0.1016	-54.18 (-114.53, 6.18)	0.0860	-13.82 (-33.67, 6.03)	0.1799	18.59 (-17.86, 55.04)	0.3234
Yes	67	-20.32 (-45.64, 5.01)	0.1230	-33.20 (-96.86, 30.45)	0.3122	-22.99 (-52.89, 6.92)	0.1391	-4.63 (-43.84, 34.57)	0.8179
Chronic kidney disease history									
No	96	-14.57 (-28.57, -0.56)	0.0453	-39.69 (-76.36, -3.02)	0.0374	-12.86 (-29.24, 3.51)	0.1280	7.64 (-17.68, 32.97)	0.5560
Yes	35	8.25 (-43.39, 59.88)	0.7597	18.59 (-191.86, 229.04)	0.8654	7.30 (-58.29, 72.89)	0.8309	13.03 (-50.67, 76.73)	0.6955

Notes: Each stratification was adjusted for all factors (age, gender, ocular axial length, PRP, duration of diabetes, serum creatinine, DBP, HbA1c, anti-VEGF therapy, oral glucose-lowering drugs, and oral calcium antagonists), except the stratification factor itself.

Abbreviations: CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; SFCT, subfoveal choroidal thickness; VEGF, vascular endothelial growth factor; PRP, panretinal photocoagulation.

Many studies have demonstrated the relationship between cholesterol profile and SFCT. In animal studies, choroidal atherosclerotic changes can occur in the presence of hypercholesterolemia.^{54–56} Salazar et al⁵⁴ found that in rabbits, the choroid thickened with hypercholesterolemia. After normalization of serum cholesterol level, choroidal changes were not completely reversible. In addition to increased thickness, lipid accumulation on the choroid and hypertrophy of endothelial and vascular smooth muscle cells were seen. In addition to previous animal studies,^{54–56} Wong et al examined 6147 adults aged 45–84 years old from the MESA cohort and found the mean SFCT was thicker in healthy participants with hypercholesterolemia.³² Recently, Marta et al³³ found the physiological cholesterol concentration was positively correlated with SFCT in children with type 1 diabetes during puberty. In contrast, in the present study, we found a negative correlation between cholesterol levels including total cholesterol, LDL-C and HDL-C, and SFCT in PDR patients. We speculate our results on the relationship between cholesterol concentration and SFCT differed from previous studies due to the different study populations. Our research population was middle-aged and elderly patients with PDR. Ageing is an established risk factor for a wide range of chorioretinal diseases. Studies^{53,57} have found an age-related accumulation of various cellular and blood-derived products in the RPE/choroid complex, such as lipids, and advanced glycation end-products. This indicates abnormalities in cholesterol homeostasis sharing phenotypic features with atherosclerosis. In addition to ageing, hyperglycemia can also cause choroidal vascular damage, such as arteriosclerotic changes.¹ Bhutto et al confirmed microvascular changes, such as vascular tortuosity, vascular diameter changes, and arterial stenosis in the diabetic rat model.⁵⁸ Several clinical trials^{59,60} have shown that choriocapillaris dropout in DR, especially in PDR eyes. Biswas et al⁶¹ found that translocator protein (TSPO), a cholesterol-binding protein involved in mitochondrial cholesterol transport, is expressed in choroidal endothelial cells (CECs). Furthermore, TSPO ligands promote cholesterol efflux and suppress oxidative stress and inflammation in CECs. In addition to increased exogenous cholesterol caused by age and hyperglycemia; abnormal cholesterol efflux caused by decreased TSPO arising from a decrease in CECs resulting from choriocapillaris dropout is another reason for choroidal atherosclerotic changes in PDR patients. Besides, as a common contributor to atherosclerosis, the existence of diabetes with or without hypertension and hypercholesterolemia can also cause choroidal vascular changes like those of atherosclerosis.⁶² The choroid may be prone to arteriosclerotic processes to the same degree as other organs, specifically, considering the choroid an extremely vascular terminal organ associated with the largest flow per mm³ in the body.⁶³ Here, we speculate that these choroidal vascular changes induced by age and cholesterol profile in patients with PDR can cause tissue ischemia. In the early stage, ischemia can be compensated for by the continuous expansion of choroidal vessels, leading to choroidal thickening. In the late stage, ischemia can no longer be compensated for and leads to choroid blood vessel obstruction, resulting in choroidal thinning. Atherosclerosis-related diseases are associated with decreased SFCT.^{34,64–66} This supports our hypothesis, indicating prominent reductions of SFCT could provide a useful biomarker for predicting cardiovascular risk in patients of advanced age.

Interestingly, we found that the trend between SFCT and HDL-C was consistent with that between SFCT and both total cholesterol and LDL-C in PDR patients. In contrast to the atherogenic properties of total cholesterol and LDL-C, HDL-C is considered to have independent atheroprotective properties. HDL-C has both antioxidant and anti-inflammatory properties and plays a central role in reverse cholesterol transport and endothelial homeostasis.⁶⁷ However, the anti-atherosclerotic effect of very high HDL-C in cardiovascular disease is currently controversial.^{68–70} In ophthalmology, several studies have shown that AMD is positively associated with HDL-C,^{71,72} although conflicting results have been found. A meta-analysis by Wang et al⁷² showed a significantly positive association between HDL-C and AMD, suggesting people with high HDL-C levels may be at an increased risk for AMD. In addition to AMD, HDL-C is also significantly associated with hypertensive retinopathy,³⁶ suggesting extremely high HDL reflects a specific atherosclerotic condition. A plausible explanation for this discrepancy is that HDL-C can be modified via myeloperoxidase-associated mechanisms under certain conditions, thus losing its protective effect and becoming atherogenic.^{67,68,73} Myeloperoxidase-associated modification of HDL may be one of the mechanisms.⁷³ Findings from NO BLIND study⁷⁴ confirmed that high HDL cholesterol is a risk factor for DR. Therefore, we speculated that the negative correlation between HDL-C and SFCT may be due to modification of HDL-C causing HDL-C to become atherogenic in diabetes.

Conversely, the present study failed to find an association between triglyceride concentrations and SFCT in patients with PDR. Currently, to our knowledge, no studies targeted at the relationship between triglycerides and SFCT. Gupta et al found that lower triglyceride level was associated with peripapillary choroidal thickening.⁷⁵ However, the study only proved

a correlation between triglyceride level and peripapillary choroidal thickness, not a quantitative analysis. Hence, the mechanism remains unclear.

In the present study, we found that the use of specific drugs may also be one of the reasons for affecting SFCT. This was the case specifically for oral glucose-lowering drugs and calcium antagonists; thus, we took these factors into statistical analyses. According to the Chinese Adult Dyslipidemia Prevention Guide (2007 edition),⁴⁴ the proportion of hypercholesterolemia in patients with PDR was not enough to determine a relationship between hypercholesterolemia and SFCT. Nevertheless, in this study, we observed a negative trend between them. Although the clinical significance of SFCT in PDR patients is not fully understood, cholesterol concentrations are a modifiable variable, which could be reduced by the cholesterol-lowering drugs, increasing SFCT in PDR patients. The findings of this study warrant further investigation through clinical, large-scale, and long-term prospective studies.

There are some limitations to our study. Firstly, our results were obtained in a homogeneous population of Chinese patients with PDR. Therefore, findings cannot be extrapolated to other populations. Secondly, we were unable to obtain the history related to cholesterol-lowering drugs. Cholesterol levels can be adjusted with cholesterol-lowering drugs. However, the use of cholesterol-lowering drugs is likely to be a confounding factor, due to being a contributing factor to the thickening of the SFCT in patients with PDR. It is however noteworthy that the lack of information on exposure as a result of such errors could bias results, thus resulting in an underestimation of the association between cholesterol profile and SFCT. Thirdly, in this study, the EDI-OCT measurements of SFCT centered on the fovea were taken by horizontal/vertical scans. However, the choroidal thickness varies at different locations in each person. Therefore, our results cannot be extrapolated to choroidal thickness in other locations. Furthermore, manually measured SFCT may have measurement errors. Considering this, future further study using automated quantification of SFCT would be beneficial.

Conclusions

In conclusion, our results showed a significant negative association between cholesterol profile and SFCT in Chinese patients with PDR. Cholesterol imbalances contribute to choroidal thickness changes and often coexist in diabetic patients. This would enable a full evaluation of the exact role of cholesterol profile in the SFCT in PDR patients. As such, further additional research in experimental models should also be undertaken.

Abbreviations

SD-OCT, spectral-domain optical coherence tomography; EDI, enhanced depth imaging; SFCT, subfoveal choroidal thickness; LDL-C, low-density lipoprotein cholesterol; AMD, age-related macular degeneration; DR, diabetic retinopathy; DME, diabetic macular edema; HDL-C, high-density lipoprotein cholesterol; PDR, proliferative diabetic retinopathy; HbA1c, glycosylated hemoglobin A1c; eGFR, estimated glomerular filtration rate; BCVA, best-corrected visual acuity; IOP, intraocular pressure; CMT, central macular thickness; RPE, retinal pigment epithelium; PRP, panretinal photocoagulation; VEGF, vascular endothelial growth factor; DBP, diastolic blood pressure; TSPO, translocator protein; CECs, choroidal endothelial cells.

Data Sharing Statement

The primary data for this study is available from the corresponding author (Meixia Zhang) on reasonable request.

Ethical Approval and Consent to Participate

The trial has received ethical approval from the West China Hospital of Sichuan University. The data were anonymous and informed consent was waived by the approving Institutional Review Board because of the retrospective nature of the study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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