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ORIGINAL ARTICLE

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Non-linear relationship between age and subfoveal choroidal thickness in Chinese patients with proliferative diabetic retinopathy

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Abstract

BACKGROUND

No study has investigated the change regularity between age and subfoveal choroidal thickness (SFCT) in proliferative diabetic retinopathy (PDR).

AIM

To investigate the relationship between the SFCT and age in Chinese patients with PDR.

METHODS

This was a cross-sectional retrospective study. The participants were hospitalized individuals with type 2 diabetes who underwent vitrectomy for PDR. Contralateral eyes that met the criteria were included in the study. All necessary laboratory tests were performed at the time of admission. Central macular thickness (CMT) and SFCT were two quantitative assessments made using enhanced depth imaging optical coherence tomography. CMT was measured automatically and SFCT was measured manually with digital calipers provided by the Heidelberg Eye Explorer software.

RESULTS

The final analysis included a total of 234 individuals with PDR. The average age was 55.60 years old ± 10.03 years old, and 57.69% of the population was male. Univariate analysis revealed a significant negative connection between age and

SFCT in patients with PDR [β = -2.44, 95% confidence interval (95%CI): -3.46 to -1.42; $P < 0.0001$]. In the fully adjusted model, the correlation between SFCT and age remained steady (β = -1.68, 95%CI: -2.97 to -0.39; $P = 0.0117$). Spline smoothing showed that the relationship between SFCT and age in patients with PDR was non-linear, with an inflection point at 54 years of age.

CONCLUSION

Our findings suggest that age is a key determinant of choroidal thickness. The non-linear link between SFCT and age in PDR patients should be taken into account.

Key Words: Age; Subfoveal choroidal thickness; Proliferative diabetic retinopathy; Optical coherence tomography; Central macular thickness

Core Tip: In the present study, the average subfoveal choroidal thickness (SFCT) of patients with proliferative diabetic retinopathy (PDR) was inversely correlated with age, and a reduction of 1.68 μm in SFCT per year was observed. Additionally, there was a progressively increasing trend in SFCT of 2.00 μm per year before the age of 54 years and a negative correlation of 4.89 μm per year after the age of 54 years; therefore, age around 54 years might be an important turning point. This is the first study to reveal a relationship between age and SFCT in patients with PDR.

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INTRODUCTION

The choroid is a highly vascularized tissue in the eye that is affected by various systemic abnormalities affecting the blood vessels and is crucial to the physiology and pathogenesis of various ocular diseases[1]. As the only source of metabolic exchange in the avascular fovea, the choroid has the highest blood flow per unit weight of any human tissue[2]. The maintenance of retinal function requires structurally and functionally normal choroidal vessels. Impaired choroidal function may lead to photoreceptor dysfunction and death, eventually leading to vision loss[3].

Optical coherence tomography (OCT) provides high-resolution images of retinal microstructures in a non-invasive and rapid manner, which greatly improves the ability to diagnose and follow up fundus diseases, such as diabetic macular edema and diabetic retinopathy (DR)[4]. Moreover, OCT enables choroidal thickness quantification. Compared with traditional OCT, improved enhanced depth imaging OCT (EDI-OCT) can provide more reliable measurements of choroidal thickness by providing better resolution and depth of field[5]. The thickest component of the choroid in healthy humans is located in the macular avascular zone. Although there are considerable differences between individuals, the subfoveal choroidal thickness (SFCT) is approximately 350 μm[6,7]. The choroidal thickness in the periphery is approximately 264 μm[7].

Several studies have reported an association between the SFCT and age, sex, and ocular axial length. Studies at home and abroad have shown that the average loss rate of SFCT in healthy participants is 1.4-4.8 μm per year[8-15]. However, conflicting results have been reported in healthy participants. According to a study by Ding *et al*[16], in patients under the age of 60 years, SFCT showed no relationship with age. In participants beyond the age of 60 years, SFCT dramatically decreases by 5.40 m for every year of life and has a negative correlation with age. Recently, Huo *et al*[8] discovered that SFCT decreases linearly with age, with a more pronounced decline after reaching 50 years of age, which is associated with aging and a higher spherical equivalent in myopia but is not related to sex, foveal thickness, or intraocular pressure within the normal range. However, another study[17] showed that the mean SFCT demonstrated a significant positive correlation with refractive error but a significant negative correlation with age. This correlation was observed in patients under 60 years of age with respect to age, refractive error, and ocular axial length, but not in subjects aged > 60 years. These contradictory results indicate that although it is generally recognized that SFCT decreases with age in a healthy population, the change regularity of different ages and ethnic groups may differ.

Currently, there are no studies on the change regularity between age and SFCT in patients with proliferative DR (PDR), and the relationship between the both is often used only as a secondary supplement. Therefore, we used EDI-OCT to measure SFCT in Chinese patients with PDR and explored the change regularity between age and SFCT.

MATERIALS AND METHODS

Study population

A description of the study population can be found in the literature[18,19]. This was a retrospective and cross-sectional study. West China Hospital of Sichuan University provided ethical permission for the trial. The study was retrospective in nature and the obtained data were anonymized, thus the Institutional Review Board decided that informed consent was not necessary [No. 2020 (834)]. Patients who underwent vitrectomy for PDR with type 2 diabetes between May 2020 and February 2022 and were hospitalized to the West China Hospital of Sichuan University's Ophthalmology Department served as the study's participants. Patients with PDR and contralateral eyes that met the following criteria were included.

Inclusion criteria: (1) The contralateral eyes of patients with PDR were included, which were also graded as PDR with clear refractive media and no vitrectomy had been performed previously; and (2) Fasting blood glucose was < 8 mmol/L and blood glucose level was < 11 mmol/L two hours after three meals. In addition, blood glucose levels persisted for at least 7 days.

Exclusion criteria: (1) Ocular axial length more than 26.50 mm or refractive error exceeding ± 6.00 diopters; (2) Syphilis, leukemia, acquired immune deficiency syndrome, *etc*.; (3) Type 1 diabetes; (4) Retinal artery occlusion, retinal vein occlusion, neovascular glaucoma or iris neovascularization, paracentral acute middle maculopathy, uveitis, ocular trauma, endophthalmitis, age-related macular degeneration, and other ocular diseases; and (5) Poor-quality EDI-OCT images with no discernible chorioscleral interfaces.

Variables

Upon admission, all required laboratory testing was completed. Fasting laboratory values included glycosylated hemoglobin A1c (HbA1c), serum lipid profile, renal profile [*e.g*., serum cystatin C, estimated glomerular filtration rate (eGFR), serum creatinine, serum blood urea nitrogen, and uric acid], hepatic function, and serum lipid profile. The electronic medical record system provides pertinent baseline characteristics that are essential for managing hospitalized patients with PDR. The demographic data encompassed age, gender, ethnicity, and educational attainment. The three categories for educational attainment were junior high school or below, senior high school, or college or above. Relevant medical histories included hypertension, diabetes duration, diabetic nephropathy, stroke, anemia, and heart disease. A history of hypertension was defined as the use of antihypertensive medications or a physician's diagnosis. Diabetes mellitus was defined as the use of insulin/oral hypoglycemic agents or a physician's diagnosis. The history of anti-vascular endothelial growth factor (VEGF) therapy and the degree of pan-retinal photocoagulation (PRP) in the target eyes of patients with PDR were documented. The degree of PRP was classified into three categories based on the scope of the laser: None, partial, or whole. Systemic medication history included insulin treatment, oral glucose-lowering drugs, and oral antihypertensive drugs (calcium antagonists). Height, weight, diastolic blood pressure (DBP), and systolic blood pressure (SBP) were taken at the time of initial presentation. Weight in kilograms divided by height in meters squared (kg/m^2) yielded the body mass index.

eGFR was used as a stratification factor of renal function, which was divided into four groups [eGFR < 30, 30 ≤ eGFR < 60, 60 ≤ eGFR < 90, eGFR ≥ 90 (mL/minutes × 1.73 m^2)]. Hypercholesterolemia was defined as fasting serum with a total cholesterol concentration greater than 6.22 mmol/L (240 mg/dL)[20], according to the Chinese Adult Dyslipidemia Prevention Guide (2007 edition).

EDI-OCT imaging

Every individual had a thorough ocular examination, including intraocular pressure, visual acuity, ocular axial length, slit-lamp examination, and EDI-OCT. The description of EDI-OCT imaging can be found in our previous literature[18,19]. After mydriasis, compound tropicamide eye drops (Mydrin-P; Santen, Osaka, Japan) were used for EDI-OCT. Standardized EDI-OCT images were obtained in the afternoon by technicians using spectral-domain OCT (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany) to avoid diurnal variations. The quantitative measurements, such as central macular thickness (CMT) and SFCT, were acquired using EDI-OCT with the horizontal/vertical scans intersecting the fovea center (ART 100 frames, High Speed). CMT was measured automatically. Using digital calipers that the Heidelberg Eye Explorer software supplied, the SFCT was measured manually. CMT was defined as the vertical distance from the inner limiting membrane to the retinal pigment epithelium (RPE) at the fovea. The SFCT was defined as the vertical distance from the outer surface of the RPE to the chorioscleral interface in the macula. Measurements were carried out separately by two skilled doctors who were blind to the patient's clinical information, achieving 85% uniformity within a tolerance of ± 15 μm. Consequently, all measurements were averaged for the final statistical analysis.

Statistical analysis

Descriptive statistics were used to summarize demographic characteristics and study outcomes. Continuous variables were presented as mean ± SD, while the categorical variables were shown as frequencies and percentages. The χ^2 test or Kruskal-Wallis test was employed to assess variation. To address the nonlinearity between age and SFCT, a multivariate linear regression model with spline smoothing (penalized spline method) was utilized[21,22]. The inflection point was calculated using a recursive algorithm if nonlinearity was detected, and a two-piecewise multivariate linear regression model was developed[23]. The selection of confounders was based on their association with outcomes or changes in effect estimates > 10%[24,25]. Statistical analyses were performed using R software, version 3.4.3 (http://www.R-project.org/, The R Foundation) and Empower Stats (http://www.empowerstats.com; X&Y Solutions Inc., Boston, MA, United States). Statistical significance was defined as a two-sided *P* value of < 0.05.

RESULTS

Baseline characteristics of participants

The final analysis included a total of 234 patients with PDR. The characteristics of the participants with PDR are summarized in Table 1. With 57.69% of the population being male, the mean age was 55.60 years old ± 10.03 years old. The SFCT was 264.70 μm ± 83.28 μm, and the average ocular axial length was 23.17 mm ± 0.99 mm.

Univariate analysis in patients with PDR

In patients with PDR, age and SFCT showed a significant negative connection [β = -2.44, 95% confidence interval (95%CI): -3.46 to -1.42; $P < 0.0001$] according to the results of univariate analysis. Compared with women, men exhibited a positive association with SFCT (β = 31.08, 95%CI: 9.81-52.36; $P = 0.0046$). There were significant differences in DBP, height, weight, history of diabetic nephropathy, anti-VEGF therapy, calcium antagonists, insulin treatment, oral glucose-lowering drugs, serum creatinine, HDL-C, total cholesterol, and SFCT. Compared to non-PRP, the whole PRP was associated with SFCT. These results revealed that other factors were not significantly correlated with SFCT. The results of the univariate analysis are presented in Table 2.

Relationship between age and SFCT in patients with PDR

As indicated in Table 3, we evaluated the relationship between age and the SFCT score using a multivariate linear regression model. We also present three adjusted models. In Model I (adjusted for sex and ocular axial length), the results revealed a significant negative relationship between age and SFCT (β = -2.23, 95%CI: -3.29 to -1.18; $P < 0.0001$). In Model II (adjusted for sex, ocular axial length, anti-VEGF therapy, PRP, calcium antagonists, insulin treatment, and oral glucose-lowering drugs), the relationship between age and SFCT was consistent (β = -1.96, 95%CI: -3.03 to -0.90; $P = 0.0004$). Furthermore, in Model III (adjusted for sex, ocular axial length, anti-VEGF therapy, PRP, calcium antagonists, insulin, oral glucose-lowering drugs, serum creatinine, duration of diabetes, HbA1c, DBP, and total cholesterol), the correlation between SFCT and age remained steady (β = -1.68, 95%CI: -2.97 to -0.39; $P = 0.0117$). Overall, age was negatively correlated with the average SFCT.

Spline smoothing between age and SFCT in patients with PDR

In patients with PDR, we found a non-linear connection between age and SFCT using a multivariate linear regression model with spline smoothing. The adjustment strategy was the same as that used in Model III, as shown in Figure 1. By employing the two-piecewise multivariate linear regression model, we determined that the inflection point was the age of 54 years, which showed a progressive increase trend in SFCT at a rate of 2.00 μm per year before the age of 54 years and a negative correlation with a decrease of 4.89 μm per year after the age of 54 years. These findings are summarized in Table 4.

Results of stratified analysis between age and SFCT in patients with PDR

The adjustment strategy for each stratification was identical to that of Model III except for the stratification factor. Table 5 displays all the findings from the stratified analysis. In patients with PDR, the downward trends in age and SFCT remained consistent across various stratifications, except for patients with a history of anemia.

DISCUSSION

In the present study, age was inversely correlated with PDR patients' average SFCT and a 1.68 μm annual decrease in SFCT. This study also showed a progressive increase trend in SFCT with 2.00 μm per year before the age of 54 years and a negative correlation with 4.89 μm per year after the age of 54 years, age around 54 years might be an important turning point. This is the first study to reveal a relationship between age and SFCT in patients with PDR.

In the present study, a yearly reduction of 1.68 μm in SFCT in PDR patients was found to be similar to the average rate of loss of 1.40-4.80 μm per year[8-15] in healthy participants, indicating that age plays a critical role in evaluating choroidal thickness. However, not all studies have reached the aforementioned conclusions. A study[26] that involved 140 healthy Saudi Arabian women aged 18-29 years found no significant association between SFCT and age. Additionally, Ding *et al*[16] found that SFCT was negatively correlated with age in healthy Chinese subjects over 60 years old, with an average annual loss of 5.40 μm per year, whereas no significant relationship was found in subjects aged < 60 years. Conversely, another study[17] showed that age was significantly correlated with the SFCT in participants aged < 60 years, whereas this correlation was not observed in participants aged > 60 years. Recently, Huo *et al*[8] found that the SFCT showed an age-related linear decrease with a steep decline after 50 years of age in healthy Chinese participants. Regarding the contradictory research results, we postulated that although it is generally recognized that SFCT decreases with age in a healthy population, the change regularity of different ages and ethnic groups may differ. In this present study, we found that around age 54 years might be an important turning point in patients with PDR and a progressive increase trend in SFCT with 2.00 μm per year before the age of 54 years; whereas after this age, a negative correlation with a loss of 4.89 μm per year was observed, which may also explain, to some extent, the conflicting results in different age groups in healthy subjects.

Hyperglycemia, in addition to age, can result in damage to the choroidal blood vessels[27]. The concept of diabetic choroidopathy (DC) was introduced by Saracco *et al*[28]. Subsequent investigations into the histopathological changes

Table 1 Baseline characteristics of participants

Item	mean ± SD/*n* (%)
Age (year)	55.60 ± 10.03
SBP (mmHg)	136.98 ± 20.75
DBP (mmHg)	82.92 ± 10.90
Height (cm)	161.72 ± 8.16
Weight (kg)	62.91 ± 10.83
BMI (kg/m^2)	23.99 ± 3.07
Duration of diabetes (year)	12.27 ± 6.80
Visual acuity (logMAR)	0.73 ± 0.53
IOP (mmHg)	16.28 ± 4.16
Fasting blood glucose (mmol/L)	7.40 ± 2.87
Serum urea nitrogen (mmol/L)	8.47 ± 4.39
Serum creatinine, μmol/L	145.98 ± 182.39
eGFR (mL/minutes × 1.73 m^2)	66.95 ± 30.47
Uric acid (mmol/L)	377.59 ± 87.59
Triglyceride (mmol/L)	1.50 ± 0.75
Total cholesterol (mmol/L)	4.60 ± 1.19
HDL-C (mmol/L)	1.31 ± 0.41
LDL-C (mmol/L)	2.68 ± 1.02
HbA1c (%)	7.73 ± 1.74
Ocular axial length (mm)	23.17 ± 0.99
CMT (μm)	283.76 ± 122.66
SFCT (μm)	264.70 ± 83.28
Gender	
Female	99 (42.31)
Male	135 (57.69)
Education level	
Junior high school or below	147 (63.64)
Senior high school	40 (17.32)
College or above	44 (19.05)
Hypertension history	
No	126 (53.85)
Yes	108 (46.15)
Diabetic nephropathy history	
No	188 (80.34)
Yes	46 (19.66)
Stroke history	
No	222 (94.87)
Yes	12 (5.13)
Anemia history	
No	162 (69.23)
Yes	72 (30.77)

Heart disease history	
No	222 (94.87)
Yes	12 (5.13)
PRP	
None	111 (47.44)
Partial	43 (18.38)
Whole	80 (34.19)
Anti-VEGF therapy	
No	175 (74.79)
Yes	59 (25.21)
Insulin treatment	
No	113 (48.29)
Yes	121 (51.71)
Oral glucose-lowering drugs	
No	59 (25.21)
Yes	175 (74.79)
Calcium antagonists	
No	183 (78.54)
Yes	50 (21.46)

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: Pan-retinal photocoagulation.

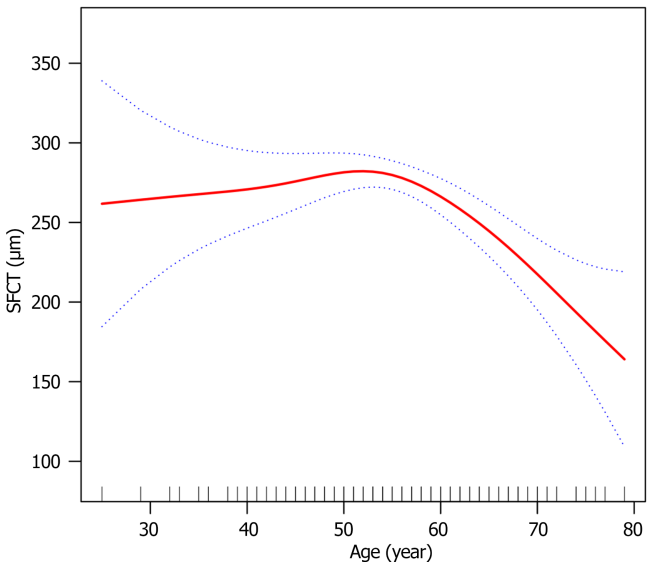

Figure 1 The multivariate linear regression model with spline smoothing showed that the relationship between age and subfoveal choroidal thickness in patients with proliferative diabetic retinopathy was non-linear. SFCT: Subfoveal choroidal thickness.

associated with DC revealed similarities with DR, such as the atrophy and loss of choroidal capillary endothelium, capillary stenosis and shedding, layered deposition, curved and beaded vessels, and choroidal neovascularization[29,30]. Further research by Bhutto *et al*[31] confirmed microvascular changes in the choroid including vascular tortuosity, changes in vascular diameter, and arterial stenosis in diabetic rat models. Histopathological findings align with en-face OCT imaging, which provides a clear view of vascular remodeling in DC. Ferrara *et al*[32] conducted a cross-sectional study involving 76 diabetic patients and found evidence of choroidal vascular remodeling, characterized by irregular,

Table 2 Univariate linear regression analysis of subfoveal choroidal thickness measurements by enhanced depth imaging-optical coherence tomography

	β, 95%CI	*P* value
Male *vs* female	31.08 (9.81 to 52.36)	0.0046
Age, per 1-year increase	-2.44 (-3.46 to -1.42)	< 0.0001
Education level		
Junior high school or below	Reference	
Senior high school	-19.95 (-48.87 to 8.97)	0.1778
College or above	2.39 (-25.48 to 30.26)	0.8666
SBP, per 1 mmHg increase	0.42 (-0.11 to 0.95)	0.1222
DBP, per 1 mmHg increase	1.27 (0.26 to 2.27)	0.0141
Height, per 1 cm increase	1.74 (0.41 to 3.08)	0.0111
Weight, per 1 cm increase	1.17 (0.17 to 2.17)	0.0234
BMI, per 1 kg/m^2 increase	1.96 (-1.63 to 5.55)	0.2865
Duration of diabetes, per 1-year increase	-0.40 (-1.99 to 1.20)	0.6269
Hypertension *vs* absent	-2.97 (-24.42 to 18.48)	0.7862
Diabetic nephropathy history *vs* absent	40.23 (13.83 to 66.64)	0.0031
Stroke history *vs* absent	2.07 (-46.41 to 50.55)	0.9333
Anemia *vs* absent	12.80 (-10.31 to 35.91)	0.2788
Heart disease *vs* absent	-19.42 (-67.84 to 28.99)	0.4325
PRP		
None	Reference	
Partial	4.02 (-24.99 to 33.03)	0.7861
Whole	31.00 (7.32 to 54.69)	0.0109
Anti-VEGF therapy *vs* absent	30.55 (6.24 to 54.86)	0.0145
Insulin *vs* absent	23.81 (2.63 to 44.99)	0.0286
Oral glucose-lowering drugs *vs* absent	-28.96 (-53.31 to -4.62)	0.0205
Calcium antagonists *vs* absent	40.49 (14.86 to 66.13)	0.0022
Visual acuity, per 1 LogMAR increase	-12.24 (-32.49 to 8.01)	0.2374
IOP, per 1 mmHg increase	2.27 (-0.32 to 4.86)	0.0876
Fasting blood glucose, per 1 mmol/L increase	-2.34 (-6.06 to 1.39)	0.2201
Serum urea nitrogen, per 1 mmol/L increase	1.63 (-0.81 to 4.06)	0.1910
Serum creatinine, per 1 μmol/L increase	0.08 (0.02 to 0.14)	0.0092
eGFR, per 1 mL/minutes × 1.73m^2 increase	-0.15 (-0.50 to 0.20)	0.3938
Uric acid, per 1 mmol/L	-0.01 (-0.14 to 0.11)	0.8322
Triglyceride, per 1 mmol/L increase	-3.01 (-24.36 to 18.34)	0.7828
Total cholesterol, per 1 mmol/L increase	-16.08 (-29.25 to -2.91)	0.0181
HDL-C, per 1 mmol/L increase	-42.66 (-81.44 to -3.89)	0.0329
LDL-C, per 1 mmol/L increase	-15.27 (-30.72 to 0.17)	0.0548
HbA1c, per 1 % increase	-5.36 (-16.77 to 6.04)	0.3590
CMT, per 1 μm increase	0.02 (-0.06 to 0.11)	0.5839
Ocular axial length, per 1 mm increase	-18.57 (-34.96 to -2.18)	0.0282

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: Pan-retinal photocoagulation.

Table 3 Relationship between age and subfoveal choroidal thickness in different models

Exposure	Model I		Model II		Model III	
	β (95%CI)	*P* value	β (95%CI)	*P* value	β (95%CI)	*P* value
Age (year)	-2.23 (-3.29 to -1.18)	< 0.0001	-1.96 (-3.03 to -0.90)	0.0004	-1.68 (-2.97 to -0.39)	0.0117

Model I adjusted for sex and ocular axial length; Model II adjusted for sex, ocular axial length, anti-vascular endothelial growth factor (VEGF) therapy, pan-retinal photocoagulation (PRP), insulin treatment, oral glucose-lowering drugs, and calcium antagonists; Model III adjusted for sex, ocular axial length, anti-VEGF therapy, PRP, insulin treatment, oral glucose-lowering drugs, calcium antagonists, diastolic blood pressure, hemoglobin A1c, duration of diabetes, serum creatinine, and total cholesterol. CI: Confidence interval; DBP: Diastolic blood pressure; HbA1c: Hemoglobin A1c; SFCT: Subfoveal choroidal thickness; VEGF: Vascular endothelial growth factor; PRP: Pan-retinal photocoagulation.

Table 4 Non-linearity addressed by a two-piecewise linear regression model

For exposure: Age	SFCT (μm)		
Outcome, Model	β	95%CI	*P* value
Fitting model by standardized linear regression	-1.68	-2.97 to -0.39	0.0117
Fitting model by two-piecewise linear regression			
Inflection point of age	54.00		
≤ 54	2.00	-0.16 to 4.17	0.0712
> 54	-4.89	-6.87 to -2.90	< 0.0001
Log likelihood ratio test			< 0.0010

The adjustment strategy was the same as the adjusted Model III.

curved, beaded vessels, local dilatation, and stenosis in all patients at different stages of DR. Although OCT studies have attempted to determine the changing trend of choroidal thickness in diabetic patients, no consistent conclusion has been reached[33,34]. Several authors have found that decreased choroidal thickness is associated with diabetes[35-41], and studies[38,42,43] have found that choroidal thickness is significantly decreased in diabetic patients without clinical evidence of retinopathy indicating that reduced choroidal blood flow may be the initial event, which is consistent with the results of studies on choroidal vessels[44]. A recent study involving a large sample (1347 patients) of type 2 diabetic patients without any history of ocular treatment found that choroidal thickness initially increased in the early stages of DR and subsequently decreased as DR progressed[45]. However, in studies comparing the pathological changes in the retina and choroid of spontaneously diabetic torii (SDT) rats and normal Sprague-Dawley (SD) rats, the average thickness of the retina and choroid was significantly increased in SDT rats compared to normal SD rats, indicating choroidal edema in SDT rats[46]. Additionally, evidence suggests that the choroid may become thicker in patients with DR, rather than thinner[33,39,40,47-50]. Kim *et al*[47] found significant thickening of the choroid in the eyes of patients with DR, which increased with progression from severe non-PDR to untreated PDR severity. Another recent study by Zhang *et al*[48] identified a significant increase in choroidal thickness in the temporal (750 μm) and upper (1500 μm and 2250 μm) quadrants in diabetic subjects compared with healthy controls. Some studies have shown that choroidal thickness decreases in the early stages of DR and increases in the late stages[51,52].

The possible reasons for these different observations are as follows: First, the normal physiological fluctuation in choroidal thickness, which can be as high as 67 μm throughout the day regardless of the presence of diabetes, must be considered[53]. Other factors such as age and ocular axial length can also contribute to variations in choroidal thickness [54]. Additionally, different OCT systems and measurement parameters used in these studies may have affected our results[33,55]. Furthermore, the focus of the current studies on the measurement of SFCT may not fully capture the choroidal changes that occur throughout the central region and the mid-periphery in patients with diabetes. Moreover, studies on the effects of diabetes on choroidal vasculature often examine different stages of DR, leading to the inclusion of patients who have received previous DR treatments, such as anti-VEGF therapy or PRP. These treatments may affect choroidal thickness independently of diabetes-induced changes[32-34]. Manual measurement of choroidal thickness using EDI-OCT may result in a measurement error. Therefore, it is unclear whether diabetes directly affects choroidal

Table 5 Results of stratified analysis between age and subfoveal choroidal thickness in patients with proliferative diabetic retinopathy

Y = SFCT, μm	*n*	β, 95%CI	*P* value
Gender			
Female	99	-0.38 (-2.39 to 1.64)	0.7157
Male	135	-2.63 (-4.51 to -0.74)	0.0074
Hypertension history			
No	126	-1.19 (-2.65 to 0.27)	0.1137
Yes	108	-3.27 (-5.42 to -1.12)	0.0037
Education level			
Junior high school or below	147	-2.13 (-3.90 to -0.36)	0.0198
Senior high school	40	-0.72 (-4.44 to 3.00)	0.7086
College or above	44	-2.09 (-5.23 to 1.06)	0.2054
Diabetic nephropathy history			
No	188	-1.76 (-3.06 to -0.46)	0.0089
Yes	46	-1.29 (-6.51 to 3.94)	0.6341
Stroke history			
No	222	-1.48 (-2.80 to -0.16)	0.0294
Yes	12	Not applicable	
Heart disease history			
No	222	-1.61 (-2.90 to -0.32)	0.0153
Yes	12	Not applicable	
Anemia history			
No	162	-2.62 (-4.15 to -1.08)	0.0011
Yes	72	1.16 (-1.62 to 3.93)	0.4176
PRP			
None	111	0.05 (-1.78 to 1.87)	0.9602
Partial	43	-3.64 (-6.62 to -0.66)	0.0257
Whole	80	-4.56 (-7.00 to -2.11)	0.0006
Anti-VEGF therapy			
No	175	-1.03 (-2.56 to 0.50)	0.1891
Yes	59	-3.95 (-6.57 to -1.32)	0.0055
Insulin treatment			
No	113	-1.16 (-2.82 to 0.49)	0.1711
Yes	121	-2.34 (-4.42 to -0.25)	0.0304
Oral glucose-lowering drugs			
No	59	-2.85 (-5.15 to -0.56)	0.0180
Yes	175	-2.13 (-3.27 to -0.99)	0.0003
Calcium antagonists			
No	183	-1.27 (-2.56 to 0.02)	0.0550
Yes	50	-3.00 (-7.47 to 1.48)	0.1993
Total cholesterol group (mmol/L)			
< 6.22	119	-1.78 (-3.74 to 0.18)	0.0788
≥ 6.22	12	Not applicable	

eGFR group (mL/minutes × 1.73 m^2)			
< 30	30	-3.83 (-8.33 to 0.68)	0.1198
≥ 30, < 60	61	-3.45 (-7.12 to 0.22)	0.0719
≥ 60, < 90	81	-1.47 (-4.21 to 1.27)	0.2976
≥ 90	62	0.11 (-1.87 to 2.08)	0.9161

Not applicable means that the model failed because of the small sample size. The adjustment strategy for each stratification was identical to that of Model III except for the stratification factor. CI: Confidence interval; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate; SFCT: Subfoveal choroidal thickness; VEGF: Vascular endothelial growth factor; PRP: Pan-retinal photocoagulation.

thickness. To shed light on this matter, studies focusing on diabetic patients without any diabetes treatment or known ocular comorbidities may provide valuable insights[56].

Our study has several strengths. First, it represents a significant improvement in researching the nonlinearity of addressing compared with previous studies. We were able to identify the turning point between age and SFCT in PDR patients, which increased the statistical power and greatly enhanced the clinical significance. Second, although this was an observational study and, therefore, susceptible to potential confounding factors, we employed strict statistical adjustment to minimize any residual confounders. Finally, we ensure the reliability of the results by conducting a stratified analysis to test the robustness of our findings. Despite these intriguing results, this study has several limitations. First, the participants in this study consisted solely of Chinese PDR patients. Therefore, when interpreting our findings, it is essential to exercise caution owing to ethnic limitations and disease types. Second, the study population consisted of patients with PDR who underwent either anti-VEGF or PRP treatment, which could potentially affect choroidal thickness [57,58], as opposed to treatment-naïve patients. Although we considered these factors as confounding variables, our results may have been biased. Finally, similar to all observational studies, there is the possibility of uncontrolled confounders despite efforts to control for known potential confounding factors.

CONCLUSION

We found, in summary, that the average SFCT of individuals with PDR decreased by 1.68 μm year with age, and that age 54 may represent a significant turning point. Our findings imply that age has a significant role in choroidal thickness and that, when examining the relationship between SFCT and age in PDR patients, we should take the non-linear association into account.

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FOOTNOTES

Author contributions: Lei CY and Zhang MX designed the research study; Lei CY and Xie JY performed the research; Ran QB contributed analytic tools; Lei CY and Xie JY analyzed the data and wrote the manuscript; and all authors have read and approved the final manuscript.

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