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Assessment of the impact of low-density lipoprotein cholesterol on retinal vessels using optical coherence tomography angiography

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Abstract

Background Low-density lipoprotein cholesterol (LDL-C) is acknowledged as an independent risk factor (IRF) for atherosclerotic cardiovascular disease. Nevertheless, studies on the impact of LDL-C on microvasculature are still scarce. The retina, abundant in microvasculature, can now be examined for microvascular alterations through the novel, non-invasive, and quantitative optical coherence tomography angiography (OCTA) technique.

Methods In this cross-sectional study, 243 patients from the geriatric department were recruited (between December 2022 and December 2023). Individuals were classified into four groups based on their LDL-C levels: Group 1 (≤ 1.8 mmol/L), Group 2 (> 1.8 mmol/L to ≤ 2.6 mmol/L), Group 3 (> 2.6 mmol/L to ≤ 3.4 mmol/L), and Group 4 (> 3.4 mmol/L). The OCTA results including retinal vessel density (VD), foveal avascular zone (FAZ) area, macula thickness, and retinal nerve fiber layer (RNFL) thickness were contrasted across these groups. T-tests, analysis of variance, Welch's tests, or rank-sum tests were employed for statistical comparisons. In cases where significant differences between groups were found, post-hoc multiple comparisons or rank-sum tests were performed for pairwise group comparisons. Spearman's correlation coefficient was employed to perform bivariate correlation analysis to evaluate the relationship between LDL-C levels and various OCTA measurements. Multivariable regression analysis was used to evaluate the association between LDL-C levels and various OCTA measurements. Linear regression analysis or mixed-effects linear models were applied.

Results It was discovered that individuals with LDL-C levels exceeding 2.6 mmol/L (Groups 3 and 4) exhibited reduced VD in the retina, encompassing both the optic disc and macular regions, compared to those with LDL-C levels at or below 2.6 mmol/L (Groups 1 and 2). A negative correlation among LDL-C levels and retinal VD was identified, with r values spanning from −0.228 to -0.385. Further regression analysis presented β values between −0.954 and −2.378. Additionally, no notable disparities were detected among the groups regarding FAZ area, macular thickness, and RNFL thickness.

Conclusions The outcomes of this study suggest that elevated LDL-C levels constitute an IRF for decreased VD across the entire retina.

Trial registration NCT05644548, December 1, 2022.

Keywords Dyslipidemia, LDL-C, Microvasculature, Retinal vessels, OCTA

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Background

Dyslipidemia is recognized globally as a prevalent chronic disease [1–3]. Blood lipids consist of various components, with the clinically significant ones being low-density lipoprotein cholesterol (LDL-C), triglycerides, and lipoprotein(a), etc. Among these, LDL-C is extensively acknowledged as an independent risk factor (IRF) for atherosclerotic cardiovascular disease (ASCVD), encompassing coronary heart disease, stroke, and peripheral arterial disease [1, 2, 4]. Furthermore, numerous guidelines delineate specific targets for LDL-C management in patients across various ASCVD risk stratifications [1, 2, 4] Nevertheless, studies on the impact of LDL-C on microvasculature are still scarce.

The retina is characterized by its rich microvasculature. Retinal vessels are essential for maintaining normal vision and represent the only microvascular network that can be directly observed in vivo [5]. Optical coherence tomography (OCT), a high-resolution and instantaneous optical imaging method, has become instrumental in this field. The advancement of optical coherence tomography angiography (OCTA), a cutting-edge, non-invasive imaging technology, facilitates rapid and quantitative analysis of retinal vessels, thereby offering valuable insights into retinal vessel changes [6]. Due to its straightforward application and user-friendliness, OCTA is also suitable for follow-up examinations and dynamic monitoring of microvascular alterations [6]. Consequently, assessing retinal vessels via OCTA provides an optimal window for comprehending microvascular changes.

Previous studies have applied OCTA to explore the effects of systemic diseases such as hypertension and diabetes mellitus on the retinal vasculature. The results showed significant changes in retinal vasculature in patients with hypertension or diabetes compared to controls [7, 8]. In these studies, dyslipidemia was considered only as a comorbidity and different lipid components were also not differentiated, lacking studies addressing the effects of LDL-C on the retinal vasculature. Consequently, this study focused on LDL-C to investigate its impact on retinal vessels using OCTA.

Methods

Research methodology and participants

A cross-sectional study encompassed individuals hospitalized in the Department of Geriatrics at Beijing Tongren Hospital from December 2022 to December 2023. Participants were included based on the criteria of being aged 18 years or older and consenting to undergo OCTA examination. Exclusion criteria involved acute infection phase, presence of malignant tumors, autoimmune disorders, recent myocardial infarction, glaucoma, inability to cooperate with OCTA examination, and severe cataracts or fundus hemorrhage impacting OCTA results. Based on targets for LDL-C management recommended by widely recognized guidelines, individuals were classified into four groups based on their LDL-C levels [1, 2, 4]: Group 1 (LDL-C $\leq$ 1.8 mmol/L), Group 2 (LDL-C > 1.8 mmol/L to $\leq$ 2.6 mmol/L), Group 3 (LDL-C > 2.6 mmol/L to $\leq$ 3.4 mmol/L), and Group 4 (LDL-C > 3.4 mmol/L).

The study obeyed to the standards stipulated in the Declaration of Helsinki. The research methodology was sanctioned by the designated local ethics board (Ethics Committee of Beijing Tongren Hospital Affiliated to Capital Medical University) (approval No. TREC2022-KY068). Participants or their authorized representatives offered written informed consent. The trial registration number is NCT05644548.

Data collection

Patient data were procured from the hospital's medical record system. For this study, the gathered information included: demographic details (sex, age, smoking history, height, weight), medical history (hypertension, diabetes mellitus, hyperuricemia, obstructive sleep apnea hypopnea syndrome (OSAHS), chronic obstructive pulmonary disease (COPD), family history of early onset cardiovascular disease), medication usage (statins, antiplatelet drugs), laboratory analyses (LDL-C, serum creatinine, cystatin C, glycated hemoglobin (HbA1c), hemoglobin), and 24-hour ambulatory blood pressure (ABP) measurement outcomes (mean systolic blood pressure (MSBP), mean diastolic blood pressure (MDBP)).

OCTA examination

The study utilized 6×6 mm angiograms obtained with the RTVue XR device and Avanti 2017.1.0.155 software (Optovue, Inc., Fremont, CA, USA). The system parameters of the OCT scanner used in this study are as follows: OCT Image Acquisition Rate: 70,000 A-scans/second; Axial Resolution (in tissue): Depth: 5 μm; Scan Range: Depth 2 to 3 mm, Transverse 2 mm to 12 mm; Scan Beam Wavelength $\lambda = 840 \pm 10$ nm. Scanning range is from internal limiting membrane to retinal pigment epithelium. The examinations were conducted by technicians within the ophthalmology examination room. Mydriasis was induced 30 min before the examination. Data were gathered from each participant's right eye [9]. Moreover, 3 participants had only functional left eye. Data from those participants' left eye were included.

The primary anatomical components of the retina include the optic disc and the macula [5]. The optic disc, also called the optic papilla, is a circular, disc-like structure where the central retinal artery arises, the retinal vein returns and the optic nerve head traverses the retina to constitute the optic nerve. The macula, which contains

a high concentration of photoreceptor cells, is responsible for the highest visual acuity. The central retinal artery and associated capillaries linked to venous branches supply blood to the retina. The central retinal artery penetrates the retina at the optic disc and progressively branches into capillaries. Within the macular region, capillary density diminishes, and terminal capillaries converge to form a ring. The region enclosed by this ring, lacking blood vessels, is identified as the foveal avascular zone (FAZ).

OCTA is capable of quantifying retinal vessels and providing data on vessel density (VD), FAZ area, FAZ perimeter, macula thickness, and retinal nerve fiber layer (RNFL) thickness (Fig. 1). Retinal vessels are arranged radially in the optic disc region, known as radial peripapillary capillaries (RPC). The average VD is measured from the entire image, encompassing the inside disc and peripapillary capillaries. The RNFL thickness measurement is averaged from the peripapillary capillary region. In the macular area, retinal vessels are categorized into

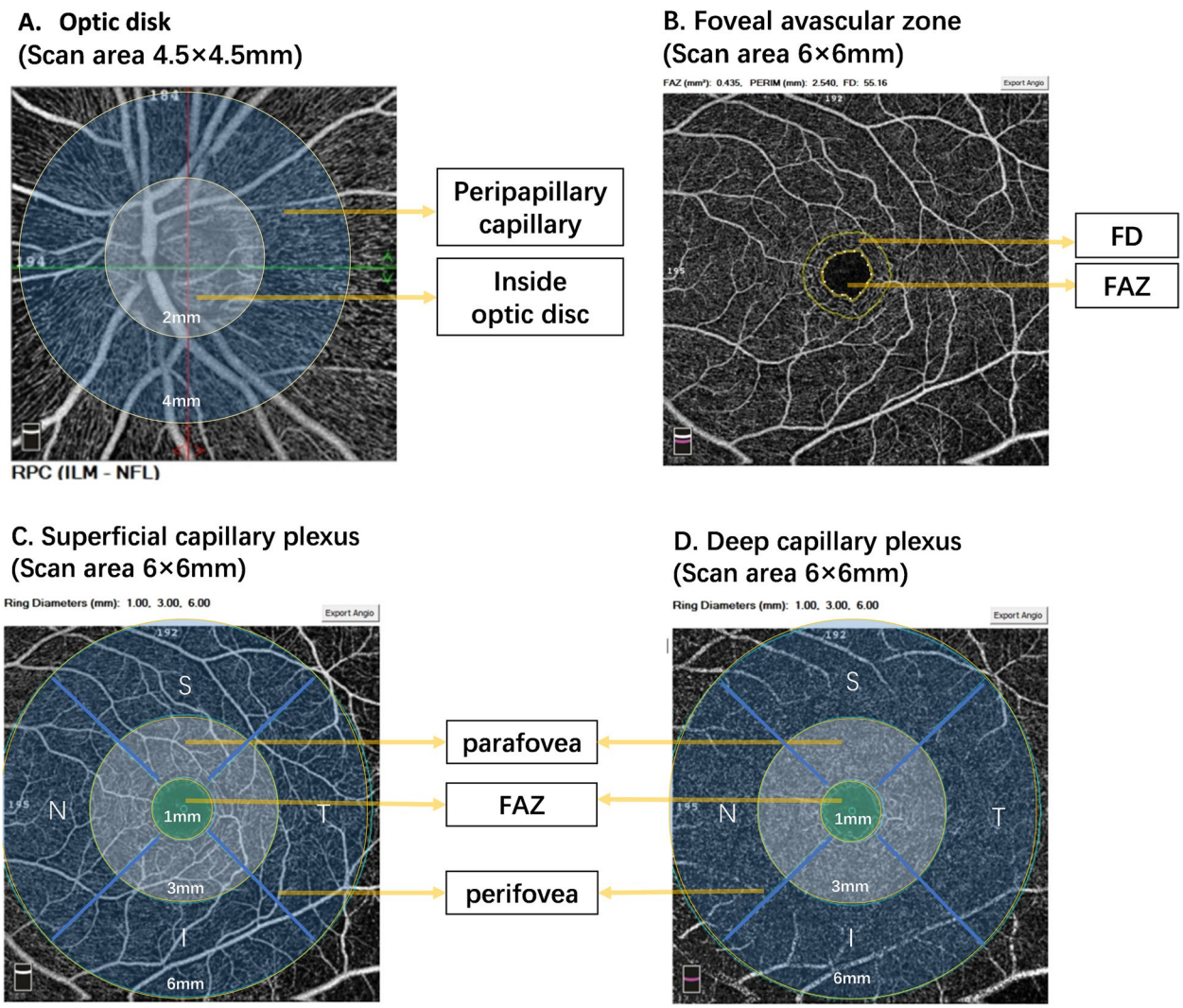

Fig. 1 Measurement zones and parameters of OCTA. Panel A: Within the optic disc area, the RPC is displayed. The gray region (a circular region 2 mm in diameter) signifies the optic disc, whereas the blue region (an annular area with a diameter of 2 – 4 mm) represents the peripapillary capillary. The RPC VD is calculated as the average value of the entire image, and the RNFL thickness is averaged from the blue region. Panel B: Depicts the FAZ in the macular region. The central avascular circular area indicates the FAZ, surrounded by an annular area representing the VD within a 300 μm wide ring around the FAZ, termed FD. Panel C: Illustrates the SCP in the macular region. The green region (a circular region 1 mm in diameter) signifies the FAZ, the gray region (an annular area with a diameter of 1 – 3 mm) represents the parafovea, and the blue region (an annular area with a diameter of 3 – 6 mm) indicates the perifovea. The SCP is segmented into four quadrants: superior (S), inferior (I), temporal (T), and nasal (N). The VD is computed as the average value of these four quadrants. Additionally, the FAZ thickness can be measured. Panel D: Displays the DCP, which is denser than the SCP. The green, gray, and blue regions, along with the quadrant divisions, are identical to those in the SCP

the superficial capillary plexus (SCP) and the deep capillary plexus (DCP). The SCP displays uniform blood flow signals and regular arrangement, while the DCP, though finer, also maintains regular morphology and arrangement. Macular retinal vessels are segmented into two concentric zones: the inner ring called parafovea (1–3 mm diameter), and the outer ring called perifovea (3–6 mm diameter). VD in both rings is averaged across four quadrants (superior (S), inferior (I), temporal (T), and nasal (N)). Moreover, OCTA can quantify VD within a 300 μm wide ring surrounding the FAZ, termed FD. VD is expressed as a percentage, representing the ratio of

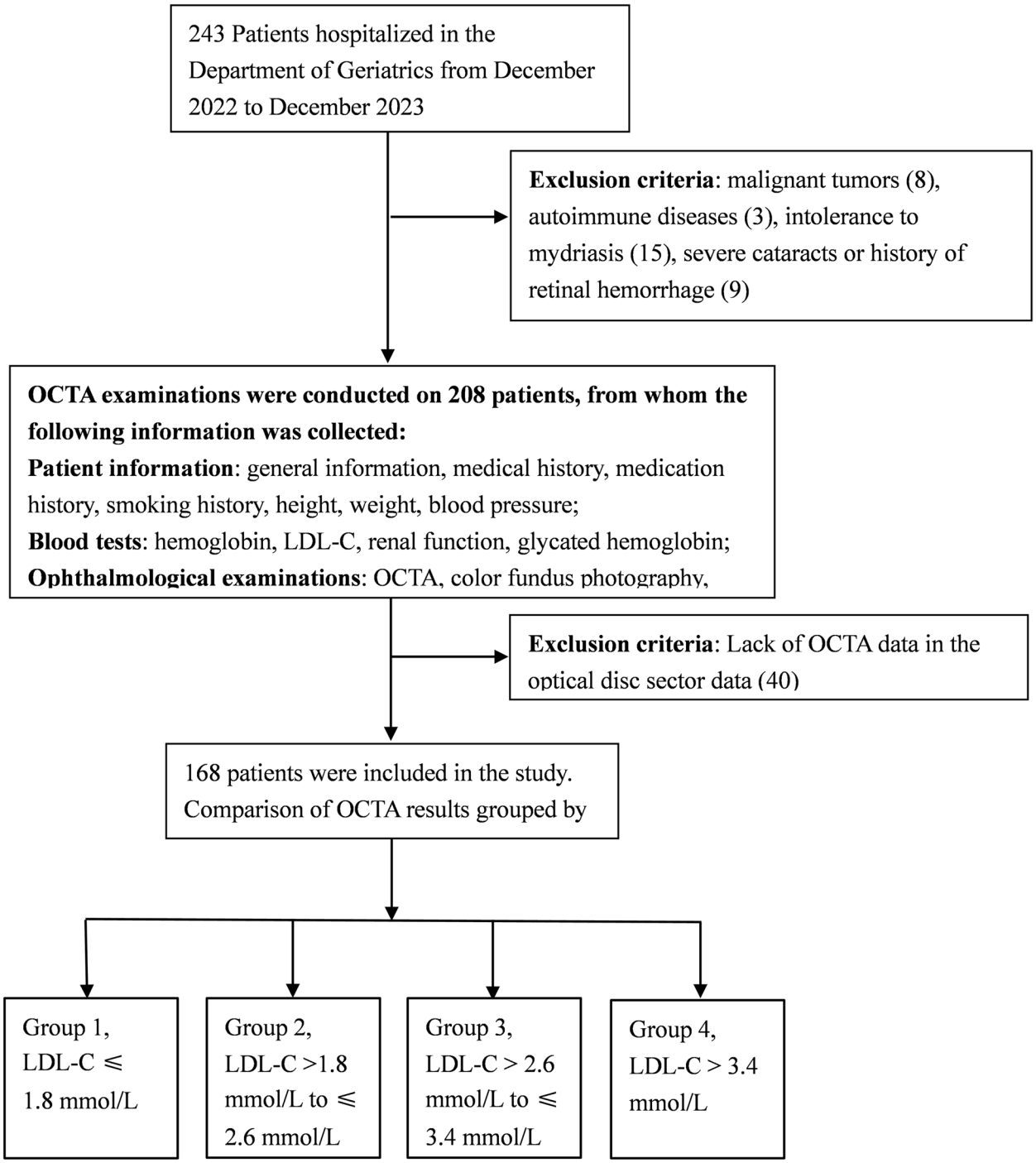

Fig. 2 Flow chart. LDL-C: low-density lipoprotein cholesterol. OCTA: optical coherence tomography angiography

the area filled by vessels, without differentiating between arteries and veins. In healthy individuals, retinal VD correlates solely with age [10]. A decrease in VD, indicating vessel sparsity, suggests vascular narrowing or occlusion. The RNFL thickness norm is approximately 100 μm [8]; values above this indicate RNFL edema, while lower values imply RNFL atrophy. Normal macular thickness ranges from 200 to 300 μm [11]; increased thickness signifies macular edema, a significant cause of vision loss. The FAZ area among individuals with normal vision varies from 0.071 mm^2 to 0.527 mm^2 [12]. An enlarged FAZ area indicates sparse vessels around the FAZ, possibly signifying vessel narrowing or occlusion.

Every participant received both color fundus photography and OCTA examinations. Ophthalmologists analyzed the results and communicated the findings to the patients. Color fundus photography, the most commonly employed fundus examination in clinical settings, detects retinal exudates, hemorrhages, and neovascularization but does not facilitate quantitative analysis.

Statistical analysis

Quantitative data were denoted as mean ± standard deviation (normally distributed variables) or median and interquartile range (non-normally distributed variables), while qualitative data were denoted as counts (percentages). Qualitative data were examined utilizing chi-square tests. Normality tests were conducted on all quantitative data. For data exhibiting normal distribution, statistical comparisons were conducted utilizing t-tests, analysis of variance, or Welch's tests. For data not following a normal distribution, rank-sum tests were employed. In cases where significant differences between groups were found, post-hoc multiple comparisons (for normally distributed data) or rank-sum tests (for non-normally distributed data) were performed for pairwise group comparisons. Spearman's correlation coefficient was employed to perform bivariate correlation analysis to evaluate the relationship between LDL-C levels and various OCTA measurements. Multivariable regression analysis was used to evaluate the association between LDL-C

Table 1 Comparison of clinical features among groups grouped by LDL-C levels

	Group 1 (n=39) ≤1.8mmol/L	**Group 2 (n=43) > 1.8mmol/L to ≤2.6mmol/L**	**Group 3 (n=49) > 2.6mmol/L to ≤3.4mmol/L**	**Group 4 (n=37) > 3.4mmol/L**	***P* value**
Age (years), mean± SD	64.18±9.54	64.95±6.90	62.47±11.94	61.14±11.00	0.271
Sex (Male), n (%)	33(84.6)	30(69.8)	32(65.3)	27(73.0)	0.229
Comorbidity					
Hypertension, n (%)	26(66.7)	30(69.8)	32(65.3)	30(81.1)	0.408
Diabetes mellitus, n (%)	29(74.4)	23(53.5)	32(65.3)	27(73.0)	0.17
Hyperuricemia, n (%)	7(17.9)	8(18.6)	9(18.4)	6(16.2)	0.993
OSAHS, n (%)	6(15.4)	4(9.3)	4(8.2)	4(10.8)	0.741
COPD, n (%)	2(5.1)	1(2.3)	0(0.0)	1(2.7)	0.348
Statin, n (%)	27(69.2)	30(69.8)	16(32.7)	12(32.4)	< 0.001
Antiplatelet, n (%)	15(38.5)	16(37.2)	11(22.4)	11(29.7)	0.329
Smoking and ex-smoking, n (%)	20(51.3)	19(44.2)	21(42.9)	21(56.8)	0.558
Family history of early onset CVD, n (%)	1(2.6)	2(4.7)	0(0.0)	0(0.0)	0.177
BMI (kg/m^2), mean± SD	24.72±3.20	25.10±3.31	24.56±2.74	24.98±3.40	0.849
Mean systolic blood pressure (mmHg), median [Q1; Q3]	125.00 [117.00;134.00]	120 [114.00;134.00]	126.00 [115.50;137.50]	129.00 [120.50;141.00]	0.115
Mean diastolic blood pressure (mmHg), mean± SD	72.97±8.38	71.58±6.72	73.67±9.05	75.89±9.33	0.15
Laboratory test					
LDL-C (mmol/L), median [Q1; Q3]	1.54[1.17;1.71]	2.16[2.02;2.37]	2.94[2.76;3.16]	3.79[3.53;4.16]	< 0.001
HBAIC (%), median [Q1; Q3]	6.60[5.90;7.90]	6.20[5.90;6.80]	6.20[5.70;8.10]	6.80[6.10;7.70]	0.156
Hemoglobin (g/L), mean± SD	134.28±14.34	136.09±14.79	137.31±15.16	140.51±16.53	0.337
eGFR (ml/min), median [Q1; Q3]	89.10 [75.93;109.22]	92.56 [81.30;103.37]	94.59 [77.21;108.54]	93.40 [72.27;106.96]	0.983

levels and various OCTA measurements. Linear regression analysis (for normally distributed data with homogeneity of variance) or mixed-effects linear models (for non-normally distributed data) were applied. Confounders were selected based on lipid management guidelines and previous studies [1, 2, 7, 8], including age, sex, hypertension, diabetes mellitus, statins, antiplatelet drugs, smoking history, body mass index (BMI), blood pressure, HbA1C, Hemoglobin and eGFR. All examinations were bidirectional, and significance was established at $P<0.05$. The entirety of the data analysis was executed utilizing SPSS 22.0 software (SPSS, Inc., Chicago, IL, USA).

Results

Two hundred and forty-three individuals were assessed for eligibility in this study. Eight patients were diagnosed with malignant tumors, three with active autoimmune diseases, fifteen were unable to tolerate mydriasis, and nine had severe cataracts or a history of fundus hemorrhage; all of these patients were excluded. OCTA examinations were conducted on 208 patients. However, 40 patients were excluded due to the absence of OCTA data in the optical disc sector. Consequently, 168 patients were included in the final analysis (Fig. 2).

Individuals were categorized into four groups on the basis of their LDL-C levels. Group 1 ($n=39$) had LDL-C ≤ 1.8 mmol/L, Group 2 ($n=43$) had LDL-C > 1.8 mmol/L to ≤ 2.6 mmol/L, Group 3 ($n=49$) had LDL-C > 2.6 mmol/L to ≤ 3.4 mmol/L, and Group 4 ($n=37$) had LDL-C > 3.4 mmol/L. The groups exhibited no notable disparities in terms of general characteristics (age, sex), comorbidities (hypertension, diabetes mellitus, hyperuricemia, OSAHS, COPD), antiplatelet drugs, smoking history (including current smokers and ex-smokers with ≥ 1-year history), family history of early onset CVD, BMI, blood pressure (MSBP, MDBP), and laboratory test results (HbA1c, hemoglobin, eGFR, computed utilizing the CKD-EPI Cystatin and Creatinine 2012 Equation) (Table 1). Statistically significant differences were observed in statin medication usage rates among the groups. Groups 1 and 2 exhibited higher statin usage rates, consistent with the lower LDL-C levels in these groups.

In the optic disk area, significant variations in RPC VD were detected among the groups (Table 2). Further comparisons between groups indicated that individuals with LDL-C levels exceeding 2.6 mmol/L (Groups 3 and 4) exhibited reduced RPC VD in contrast to those whose LDL-C levels were at or below 2.6 mmol/L (Groups 1 and 2) (Fig. 3). However, no notable disparities in RPC VD were noted between Groups 1 and 2 or between Groups 3 and 4. Additionally, no notable disparities were detected among the groups regarding RNFL thickness.

Table 2 Comparison of OCTA results among groups grouped by LDL-C levels

	Group 1 (n=39) ≤1.8mmol/L	Group 2 (n=43) > 1.8mmol/L to ≤2.6mmol/L	Group 3 (n=49) > 2.6mmol/L to ≤3.4mmol/L	Group 4 (n=37) > 3.4mmol/L	*P* value
Optic disk					
RNFL thickness (μm), median [Q1; Q3]	108.51 [102.00; 116.00]	112.30 [103.00; 121.00]	105.60 [93.00; 118.00]	104.90 [102.00; 113.00]	0.123
RPC VD (%), median [Q1; Q3]	54.99 [54.20; 56.30]	56.43 [55.10; 58.00]	52.24 [49.80; 54.75]	52.40 [52.13; 54.55]	< 0.001
Macula					
SCP parafovea VD (%), median [Q1; Q3]	48.80 [45.70; 51.30]	50.10 [45.60; 51.90]	45.80 [43.30; 49.00]	46.50 [43.05; 49.05]	0.001
SCP perifovea VD (%), mean± SD	47.47±3.96	47.39±3.44	44.64±4.12	44.42±4.58	< 0.001
DCP parafovea VD (%), median [Q1; Q3]	51.90 [48.80; 54.80]	52.30 [49.80; 55.20]	49.30 [47.30; 52.25]	48.90 [47.10; 51.30]	< 0.001
DCP perifovea VD (%), mean± SD	47.07±5.42	46.73±4.44	42.87±5.15	42.50±5.82	< 0.001
Thickness (μm), median [Q1; Q3]	255.00 [237.00; 266.00]	256.00 [237.00; 268.00]	252.00 [235.00; 266.50]	252.00 [243.25; 261.75]	0.732
FAZ					
Area (mm^2), mean± SD	0.30±0.10	0.27±0.10	0.32±0.12	0.31±.08	0.079
Perimeter (mm), mean± SD	2.13±.38	2.04±.34	2.27±.37	2.19±.45	0.042
FD (%), median [Q1; Q3]	49.20 [45.23; 51.93]	49.01 [46.76; 52.93]	50.01 [44.85; 53.63]	49.25 [45.61; 51.49]	0.742

OCTA Optical coherence tomography angiography, *LDL-C* Low-density lipoprotein cholesterol, *RNFL* Retinal nerve fiber layer, *Q1* Lower quartile, *Q3* Upper quartile, *RPC* Radial peripapillary capillary, *VD* Vessel density, *SCP* Superficial capillary plexus, *SD* Standard deviation, *DCP* Deep capillary plexus, *FAZ* Foveal avascular zone, *FD* VD within 300μm width ring surrounding the FAZ

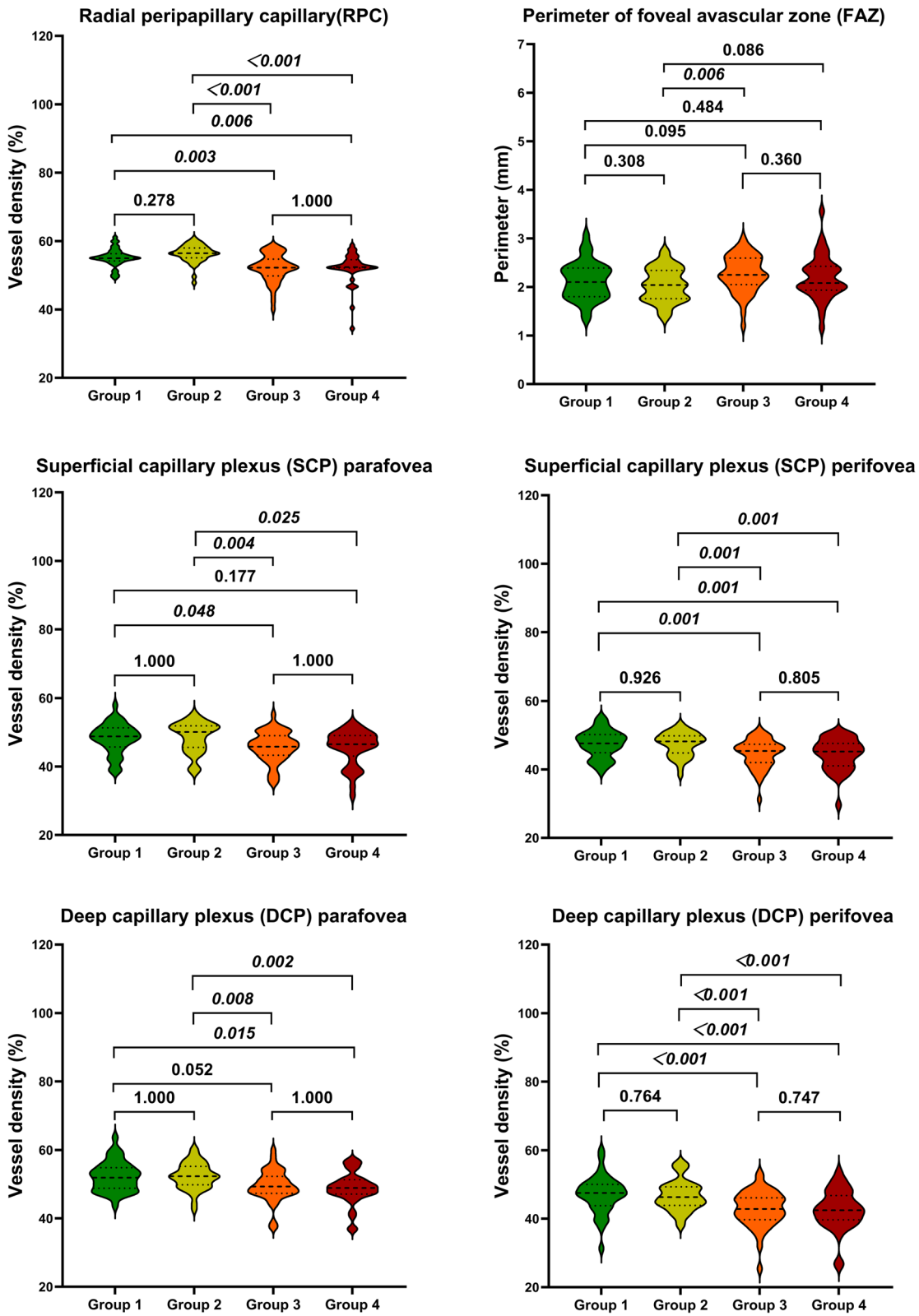

Fig. 3 Comparison of retinal VD and FAZ perimeter among groups grouped by LDL-C levels. Group 1: LDL-C ≤ 1.8 mmol/L; Group 2: LDL-C ＞ 1.8 mmol/L to ≤ 2.6 mmol/L; Group 3: LDL-C ＞ 2.6 mmol/L to ≤ 3.4 mmol/L; Group 4: LDL-C > 3.4 mmol/L

In the macular region, substantial variations in SCP VD (including parafovea and perifovea) were observed across all groups (Table 2). Subsequent inter-group analyses demonstrated that individuals with LDL-C levels above 2.6 mmol/L (Groups 3 and 4) had decreased VD in both parafovea and perifovea compared to those with LDL-C levels at or below 2.6 mmol/L (Groups 1 and 2) (Fig. 3). Similarly, significant differences in DCP VD (including parafovea and perifovea) were observed among all groups (Table 2). Further inter-group comparisons revealed that individuals with LDL-C levels exceeding 2.6 mmol/L (Groups 3 and 4) exhibited lower VD in both parafovea and perifovea compared to those with LDL-C levels at or below 2.6 mmol/L (Groups 1 and 2) (Fig. 3). Moreover, in both SCP and DCP, perifoveal VD differences were more pronounced among the groups (Fig. 3). Nevertheless, no significant differences in SCP and DCP VD (including parafovea and perifovea) were detected between Groups 1 and 2 or between Groups 3 and 4 (Fig. 3). Individuals with LDL-C levels exceeding 2.6 mmol/L displayed lower retinal VD. Reducing LDL-C levels beneath 1.8 mmol/L failed to yield further improvements in retinal VD. Additionally, no notable disparities were detected among the groups regarding FAZ area, FD, and macular thickness. A substantial variation in FAZ perimeter was discerned between Group 2 and 3. Nevertheless, no meaningful distinctions were evident among the remaining groups.

In this study, the connection between LDL-C levels and various OCTA parameters was further examined. The analysis indicated negative correlations between LDL-C levels and RPC VD, SCP VD (including parafovea and perifovea), and DCP VD (including parafovea and perifovea), with correlation coefficients (r) spanned from −0.228 to -0.385 (Table 3). Additionally, multivariable regression analysis revealed negative association between LDL-C and retinal vessel density (encompassing both optic disc and macular regions, from superficial to deep layers), with β values ranging from −0.954 to -2.378 (Table 3). The results of multivariable regression analysis, including other baseline clinical features and retinal vessel density, are presented in Table 4.

In summary, LDL-C impacts all retinal vessels, extending from the optic disk area to the macular region and spanning from the superficial to the deep layers. As LDL-C levels rise, retinal VD diminishes. LDL-C is recognized as an IRF for decreased retinal VD. The outcomes of this study suggest that LDL-C levels have no substantial impact on RNFL thickness, macular thickness, or FAZ area.

Discussion

The retina, positioned on the inner posterior surface of the eyeball, is abundant in microvessels [5]. The central retinal artery penetrates the retina at the optic disc, gradually, branching progressively into capillaries that culminate in the FAZ surrounding the central fovea. These capillaries gradually merge into retinal veins, which exit through the optic disc region. Due to these features, retinal vessels in the optic disc area encompass the central retinal artery, retinal veins, and adjacent vascular branches. Conversely, the macular region is mainly composed of capillaries and terminal capillaries. OCTA facilitates the detection of retinal VD in both the optic disc and macular regions, offering clinicians a good view of microvascular changes. Some OCTA instruments could also automatically analyze retinal vasculature diameter and length [13], while the OCTA instrument applied in this study could not. There are still some limitations of OCTA technology. Currently, OCTA cannot image the entire retina [14]. A study has demonstrated that OCTA, when used in conjunction with ultra-wide-angle color fundus photography, matches the effectiveness of fundus fluorescein angiography (gold standard) in detecting changes in fundus vasculature [15].

Table 3 Correlation and regression analysis between LDL-C levels and retinal OCTA results

	r	*P* value	β	95% CI	*P* value
RNFL thickness	-0.114	0.140			
RPC VD	-0.365	0.000	-1.283	(-1.884, -0.682)	< 0.001
SCP parafovea VD	-0.228	0.003	-0.954	(-1.689, -0.219)	0.011
SCP perifovea VD	-0.282	0.000	-1.197	(-1.793, -0.602)	0.001
DCP parafovea VD	-0.342	0.000	-1.656	(-2.337, -0.975)	< 0.001
DCP perifovea VD	-0.385	0.000	-2.378	(-3.208, -1.549)	< 0.001
Area of FAZ	0.12	0.12			
Perimeter of FAZ	0.126	0.103			
FD	0.003	0.973			
Macula thickness	-0.064	0.409			

RNFL Retinal nerve fiber layer, *RPC* Radial peripapillary capillary, *VD* Vessel density, *SCP* Superficial capillary plexus, *DCP* Deep capillary plexus, *FAZ* Foveal avascular zone, *FD* VD within 300 μm width ring surrounding the FAZ

Table 4 Multivariable regression analysis of retinal OCTA results

	RPC VD			SCP parafovea VD			SCP perifovea VD			DCP parafovea VD			DCP perifovea VD		
	β	95% CI	*P value*	β	95% CI	*P value*	β	95% CI	*P value*	β	95% CI	*P value*	β	95% CI	*P value*
Age	-0.077	(-0.136, -0.018)	0.011	-0.165	(-0.232, -0.098)	<0.001	-0.094	(-0.179, -0.010)	0.028	-0.019	(-0.088, 0.050)	0.587	-0.082	(-0.200, 0.035)	0.168
Sex (Male)	-0.751	(-2.110, 0.607)	0.277	-1.068	(-2.676, 0.541)	0.192	-1.476	(-3.225, 0.272)	0.097	-0.717	(-2.280, 0.847)	0.367	-3	(-5.239, -0.761)	0.009
Hypertension	-1.301	(-2.616, 0.015)	0.053	-1.882	(-3.432, -0.332)	0.018	-1.8	(-3.285, -0.315)	0.018	-0.357	(-1.884, 1.171)	0.645	-0.835	(-2.737, 1.067)	0.387
Diabetes mellitus	-0.311	(-1.595, 0.972)	0.633	0.465	(-1.056, 1.986)	0.547	-0.221	(-1.606, 1.164)	0.753	-0.936	(-2.405, 0.532)	0.21	-0.507	(-2.281, 1.266)	0.573
Statin	1.451	(0.255, 2.647)	0.018	0.016	(-1.425, 1.458)	0.982	1.033	(-0.446, 2.513)	0.17	1.401	(0.020, 2.782)	0.047	3.133	(1.238, 5.029)	0.001
Antiplatelet	1.496	(0.207, 2.784)	0.023	0.291	(-1.260, 1.841)	0.712	0.414	(-1.195, 2.024)	0.612	-0.253	(-1.756, 1.250)	0.74	-1.42	(-3.481, 0.641)	0.176
Smoking and ex-smoking	0.724	(-0.488, 1.936)	0.24	0.417	(-1.024, 1.858)	0.569	-1.152	(-2.733, 0.429)	0.152	0.272	(-1.126, 1.670)	0.701	-0.673	(-2.698, 1.352)	0.513
BMI	0.045	(-0.150, 0.240)	0.652	0.186	(-0.044, 0.415)	0.112	0.256	(0.063, 0.449)	0.01	0.022	(-0.202, 0.246)	0.847	0.121	(-0.148, 0.390)	0.377
Mean systolic blood pressure	-0.061	(-0.105, -0.016)	0.008	-0.073	(-0.126, -0.020)	0.007	-0.1	(-0.168, -0.033)	0.004	-0.049	(-0.101, 0.002)	0.061	-0.028	(-0.123, 0.066)	0.553
Mean diastolic blood pressure	-0.03	(-0.102, 0.042)	0.414	0.052	(-0.033, 0.137)	0.226	0.137	(0.027, 0.247)	0.015	-0.046	(-0.128, 0.037)	0.275	-0.002	(-0.155, 0.151)	0.979
LDL-C	-1.283	(-1.884, -0.682)	<0.001	-0.954	(-1.689, -0.219)	0.011	-1.197	(-1.793, -0.602)	<0.001	-1.656	(-2.337, -0.975)	<0.001	-2.378	(-3.208, -1.549)	<0.001
HBAIC	-0.314	(-0.715, 0.087)	0.124	-0.362	(-0.838, 0.113)	0.134	-0.34	(-0.733, 0.054)	0.09	-0.56	(-1.016, -0.104)	0.016	-0.467	(-1.015, 0.081)	0.094
Hemoglobin	-0.003	(-0.043, 0.037)	0.895	0.045	(-0.002, 0.092)	0.058	-0.031	(-0.074, 0.012)	0.158	-0.026	(-0.072, 0.020)	0.271	0.024	(-0.036, 0.084)	0.437
eGFR	0.012	(-0.017, 0.041)	0.403	0.06	(0.028, 0.093)	<0.001	0.018	(-0.016, 0.052)	0.299	0.013	(-0.020, 0.046)	0.425	-0.004	(-0.051, 0.043)	0.881

BMI Body mass index, *LDL-C* Low-density lipoprotein cholesterol, *HbA1c* Glycated hemoglobin, *eGFR* Estimated glomerular filtration rate, *RPC* Radial peripapillary capillary, *VD* Vessel density, *SCP* Superficial capillary plexus, *DCP* Deep capillary plexus

LDL-C is a well-documented contributor to ASCVD risk, with elevated levels contributing to atherosclerotic changes in large vessels. This study's findings indicate that LDL-C impacts microvessels (i.e., retinal vessels). Higher LDL-C levels were found to be associated with reduced retinal VD, suggesting vascular stenosis or occlusion. This effect was evident along the entire course of retinal vessels, from the central retinal artery at the optic disc to the terminal capillaries in the macular region. Additionally, an LDL-C level of 2.6 mmol/L emerged as a threshold, with patients having LDL-C > 2.6 mmol/L showing lower retinal VD. Lowering LDL-C to levels beneath 1.8 mmol/L seemed to provide no additional advantages. Previous research has identified dyslipidemia as an independent risk factor for reduced retinal vessel density in diabetic patients [16], consistent with the results of this study. However, in that study, dyslipidemia was diagnosed based on medical history, without differentiating between the effects of LDL-C and triglycerides. Additionally, the two groups with LDL-C levels ≤ 2.6 mmol/L (Groups 1 and 2) exhibited higher statin usage rates, consistent with the lower LDL-C levels in these groups. These two variables were correlated. In future, the sample size could be expanded to explore the effects and mechanisms of statin on retinal vessels.

In this study, no correlation was identified between LDL-C levels and RNFL thickness. Previous studies have indicated that diabetic patients with elevated serum apolipoprotein B exhibit thinner RNFL compared to those with diabetes alone [17]. However, this difference was confined to the superior region RNFL, with no significant differences observed in other regions (including nasal, temporal, and inferior) or in the average RNFL thickness across the entire area between the two groups. In prior studies, serum apo B concentration has been positively correlated with LDL-C levels [17]. The present study measured the average RNFL thickness, revealing no statistically significant difference in RNFL thickness between groups with varying LDL-C levels, which is consistent with previous research findings.

In this study, no correlation was identified between LDL-C levels and FAZ area in this study. Prior research has demonstrated that in diabetic patients, LDL-C levels are positively correlated with FAZ area [18]. However, the FAZ area among individuals with normal vision varies widely, from 0.071 mm^2 to 0.527 mm^2. Therefore, even if differences occur between groups, they may not exceed the normal range and may lack clinical significance. The correlation between LDL-C levels and FAZ area and FD warrants further investigation with a larger sample size.

Strengths and Limitation.

While previous studies have focused on the effects of LDL-C on the macrovasculature, this study focused on the effects of LDL-C on the microvasculature. Retina is a microvessel-rich tissue; therefore, we applied Optical Coherence Tomography Angiography (OCTA), a cutting-edge imaging technology, that allows for rapid, non-invasive, and quantitative analysis of changes in retinal vasculature. However, this study is subject to several constraints. The number of participants is limited. Additionally, some participants' optic disc area data were not acquired due to the improper operation of the OCT software, an issue that can be mitigated in future studies. Regarding the causal relationship between LDL-C and retinal vasculopathy, future cohort studies could be conducted for further clarification.

Conclusions

Dyslipidemia is a prevalent chronic condition, and LDL-C is a lipid component closely associated with clinical outcomes. The retina, characterized by its abundance of microvessels, can be assessed using OCTA, a non-invasive and quantitative method, to elucidate the effects of LDL-C on microvasculature. This study's findings suggest that elevated LDL-C levels constitute an IRF for decreased VD across the entire retina (encompassing both optic disk and macular regions).

Abbreviations

ABP	Ambulatory blood pressure
ASCVD	Atherosclerotic cardiovascular disease
COPD	Chronic obstructive pulmonary disease
DCP	Deep capillary plexus
FAZ	Foveal avascular zone
HbA1c	Glycated hemoglobin
I	Inferior
IRF	Independent risk factor
LDL-C	Low-density lipoprotein cholesterol
MDBP	Mean diastolic blood pressure
MSBP	Mean systolic blood pressure
N	Nasal
OCT	Optical coherence tomography
OCTA	Optical coherence tomography angiography
OSAHS	Sleep apnea hypopnea syndrome
RNFL	Retinal nerve fiber layer
RPC	Radial peripapillary capillaries
S	Superior
SCP	Superficial capillary plexus
T	Temporal
VD	Vessel density

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Authors' contributions

CG and YH designed the study. XJ, YZ and ZZ performed the OCTA examinations and interpreted the results. YH and JM collected data. YH, KC and MQ analyzed and interpreted the data. YH was a major contributor in writing the manuscript. CG, XJ, KC, GW, QL, and QL revised the manuscript. All authors have approved the submitted version. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Informed consent was obtained from all subjects and/or their legal guardian(s). The current research was reviewed and approved by the Ethics Committee of Beijing Tongren Hospital Affiliated to Capital Medical University (approval No. TREC2022-KY068). All methods were performed in accordance with relevant guidelines and regulations.

Consent for publication
The OCTA images of one patient were contained in this manuscript. This patient gave written consent form for his OCTA images to be published in this study.

Competing interests
The authors declare no competing interests.

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References

1. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111–88.
2. Li JJ, Zhao SP, Zhao D, et al. 2023 China guidelines for lipid management. J Geriatr Cardiol. 2023;20(9):621–63.
3. Li Z, Zhu G, Chen G, et al. Distribution of lipid levels and prevalence of hyperlipidemia: data from the NHANES 2007–2018. Lipids Health Dis. 2022;21(1):111.
4. Grundy SM, Stone NJ, Bailey AL. NLA/PCNA guideline on the management of blood cholesterol. Executive summary: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. J Am Coll Cardiol. 2019;73(24):3168–209 /ABC/ACPM/ADA/AGS/APhA/ASPC/. 2018 AHA/ACC/AACVPR/AAPA.
5. Susan S. Gray's anatomy: the anatomical basis of clinical practice. 41st ed. Elsevier; 2015.
6. Kalra G, Zarranz-Ventura J, Chahal R, et al. Optical coherence tomography (OCT) angiolytics: a review of OCT angiography quantitative biomarkers. Surv Ophthalmol. 2022;67(4):1118–34.
7. Sun C, Ladores C, Hong J, et al. Systemic hypertension associated retinal microvascular changes can be detected with optical coherence tomography angiography. Sci Rep. 2020;10(1):9580.
8. Tombolini B, Borrelli E, Sacconi R, Bandello F, Querques G. Diabetic macular ischemia. Acta Diabetol. 2022;59(6):751–9.
9. Al-Sheikh M, Tepelus TC, Nazikyan T, Sadda SR. Repeatability of automated vessel density measurements using optical coherence tomography angiography. Br J Ophthalmol. 2017;101(4):449–52.
10. Takayama K, Kaneko H, Ito Y, et al. Novel classification of early-stage systemic hypertensive changes in human retina based on OCTA measurement of choriocapillaris. Sci Rep. 2018;8(1):15163.
11. Wen-bin W. Atlas of optical coherence tomography angiography. 1st ed. People's Medical Publishing House; 2016. (In Chinese).
12. Sun Z, Yang D, Tang Z, Ng DS, Cheung CY. Optical coherence tomography angiography in diabetic retinopathy: an updated review. Eye (Lond). 2021;35(1):149–61.
13. Yang J, Chang S, Chen IA, et al. Volumetric characterization of microvasculature in ex vivo human brain samples by serial sectioning optical coherence tomography. IEEE Trans Biomed Eng. 2022;69(12):3645–56.
14. Borrelli E, Viggiano P, Evangelista F, Toto L, Mastropasqua R. Eyelashes artifact in ultra-widefield optical coherence tomography angiography. Ophthalmic Surg Lasers Imaging Retina. 2019;50(11):740–3.
15. Cui Y, Zhu Y, Wang JC, et al. Comparison of widefield swept-source optical coherence tomography angiography with ultra-widefield colour fundus photography and fluorescein angiography for detection of lesions in diabetic retinopathy. Br J Ophthalmol. 2021;105(4):577–81.
16. Sun MT, Huang S, Chan W, et al. Impact of cardiometabolic factors on retinal vasculature: a 3×3, 6×6 and 8×8-mm ocular coherence tomography angiography study. Clin Exp Ophthalmol. 2021;49(3):260–9.
17. Shi R, Lu Y, Liu D, Guo Z. Association of serum apolipoprotein B with retinal neurovascular structural alterations in patients with type 2 diabetes: an optical coherence tomography angiography study. Acta Diabetol. 2021;58(12):1673–81.
18. Lee DH, Yi HC, Bae SH, et al. Risk factors for retinal microvascular impairment in type 2 diabetic patients without diabetic retinopathy. PLoS One. 2018;13(8): e0202103.

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