Scientific Research Publishing

Open Journal of Ophthalmology, 2024, 14, 369-384
https://www.scirp.org/journal/ojoph
ISSN Online: 2165-7416
ISSN Print: 2165-7408

Detecting Pre and Early Retinal Changes in Patients with Type 2 Diabetes Mellitus Using Optical Coherence Tomography Angiography

Paul Mwale, Hanyu Zheng, Yan Zheng, Bin Jiang, Ying Li, Yujing Wang, Fang Li, Xiaomin Chen, Min Ke*

Department of Ophthalmology, Zhongnan Hospital of Wuhan University, Wuhan, China
Email: paulmwale557@gmail.com, *keminyk@163.com

How to cite this paper: Mwale, P., Zheng, H.Y., Zheng, Y., Jiang, B., Li, Y., Wang, Y.J., Li, F., Chen, X.M. and Ke, M. (2024) Detecting Pre and Early Retinal Changes in Patients with Type 2 Diabetes Mellitus Using Optical Coherence Tomography Angiography. *Open Journal of Ophthalmology*, **14**, 369-384.
https://doi.org/10.4236/ojoph.2024.144034

Received: August 31, 2024
Accepted: September 23, 2024
Published: September 26, 2024

Abstract

Background: Studies conducted previously indicated that gradual vascular changes in diabetic retinopathy (DR) include reduction in retinal vascular density and choroidal thickness. One device that can be used to detect these early changes is optical coherence tomographic angiography (OCTA). **Objective:** To detect the pre and early diabetic retinal and choroidal microvascular changes in patients with type 2 diabetes mellitus using OCTA. **Methods:** A total of 188 eyes were included in the study that was conducted at Zhongnan Hospital of Wuhan University Ophthalmology Department. Participants were divided into three groups: controls (90 eyes), pre-DR (70 eyes) and early-DR (28 eyes). We evaluated the changes in vascular density of deep capillary plexus (DCP), intermediate capillary plexus (ICP), superficial vascular complex (SVP), choroidal thickness (CT) and choroidal vascular index (CVI). **Results:** Vessel density (VD) of deep capillary plexus (DCP) and intermediate capillary plexus (ICP) at 3 × 3 mm was not significant. However, superficial vascular plexus (SVP), was significant in superior quadrant, $p = 0.033$. In DCP layer at 6 × 6 mm, significant difference was noted superiorly, $p = 0.023$ and ANOVA $p = 0.033$. However, ICP layer showed significant changes temporaly and inferiorly in 1 - 3 mm and 1 - 6 mm retinal rings, $p < 0.05$. The SVP layer showed a similar result to ICP with significant difference in temporal region, $p < 0.005$. Choroidal thickness (CT) and choroidal vascular index (CVI) at 15 × 12 mm, showed significant difference peripherally in the superior, temporal and inferior regions, $p < 0.005$. **Conclusion:** Our results reveal that although there were no clinical manifestations in the control group and the pre-DR group,

*Corresponding author.

changes in retinal and choroidal blood flow density had already occurred in the pre-DR group through OCTA detection, suggesting that early detection of the lesions provides an objective basis to prevent further retinal microvascular damage. Using OCTA parameters at 3 × 3 mm, 6 × 6 mm and 15 × 12 mm scan radius at different layers of the retina and choroid, we are able to detect early retinal microvascular and choroidal changes in patients with pre-DR and early-DR thereby saving the costs of dealing with advanced diabetic eye disease. OCTA therefore becomes a fundamental tool for the non-invasive diagnosis and prognosis of DR.

Keywords

OCTA, Pre-DR, Early-DR, Vessel Density

1. Introduction

Diabetes mellitus, particularly type 2 diabetes mellitus (T2DM) is a chronic condition that poses significant public health challenges globally [1]. One of the most severe complications associated with T2DM is diabetic retinopathy (DR), a microvascular complication that can lead to severe visual impairment and eventually blindness if left untreated. Early retinal and choroidal changes associated with DR may precede its clinical presentation [2]. What is most unfortunate is that these subtle changes in DR are often not detectable using traditional screening methods such as fundus photography or clinical examination such that by the time DR is visible through these methods, significant damage to the retinal and choroidal microvasculature may have already occurred, leading to more aggressive and expensive treatment approaches and an increased risk of irreversible visual impairment. This underscores the need for more advanced diagnostic techniques capable of detecting early preclinical retinal and choroidal changes in diabetic patients, potentially altering the disease course through early intervention [3].

Optical coherence tomography angiography (OCTA) is a relatively invention and non-invasive imaging modality that has the potential to revolutionize the early detection of retinal changes in T2DM patients [4]. OCTA enables detailed visualization of the retinal and choroidal microvasculature without the need for contrast agents, unlike traditional fluorescein angiography. It provides high-resolution, cross-sectional images of the retina by detecting changes in blood flow, making it highly sensitive to subtle vascular abnormalities that may be missed by other imaging techniques. Additionally, OCTA allows for quantitative analysis of key retinal features such as capillary density, perfusion and foveal avascular zone (FAZ) size, offering valuable insights into the microvascular health of the retina and choroid [5].

Several studies have demonstrated that OCTA can detect preclinical changes in the retinal microvasculature of diabetic patients, even in the absence of visible DR. For example, OCTA can identify early reductions in capillary density and alterations in retinal blood flow which are early indicators of diabetic retinal damage [6]. This

makes OCTA an ideal tool for monitoring disease progression and identifying patients at higher risk of developing DR, long before the onset of clinical symptoms. The ability to detect these early changes is crucial, as early intervention has been shown to significantly slow the progression of DR and reduce the risk of severe vision loss [7]. While OCTA provides valuable qualitative and quantitative information, standardizing its use in the detection of early retinal changes in diabetic patients will require consensus on which parameters are most predictive of DR development and progression. Additionally, the cost and availability of OCTA technology may present barriers to its widespread adoption, particularly in under-resourced settings where the burden of diabetes is often highest [8].

In this study, we aim to explore the utilization of OCTA in detecting preclinical and early retinal as well as choroidal changes in patients with T2DM. Specifically, we seek to identify which retinal layers and quadrants are most affected in preclinical and early stages of DR as we evaluate the potential of OCTA for integration into diabetic eye care protocols. Our investigation is particularly relevant in light of the increasing prevalence of diabetes and its complications in working-age adults. Early detection and timely intervention are key to reducing the global burden of diabetes-related vision loss. The use of OCTA to detect preclinical changes offers a promising solution to this challenge, and potentially transforms the way diabetic retinopathy is diagnosed and managed.

2. Methods

The study was approved by the institutional review board of Zhongnan Hospital of Wuhan University Ophthalmology Department (Wuhan, China; approval no. 20240985) in accordance with Helsinki Declaration. It included 188 eyes. Among them, 90 health control eyes without history of diabetes, 70 pre-DR eyes and 28 early-DR eyes. The following diagnostic criteria were used. Pre-DR: patients with type 2 diabetes mellitus but do not have fundus clinical signs of diabetic retinopathy; Early-DR: patients with type 2 diabetes mellitus and have atleast one microaneurysm seen on fundus examination, without diabetic proliferation and visual acuity is well preserved. The technical road map for the study selection processs is illustrated in **Figure 1**.

2.1. Inclusion and Exclusion Criteria for Participants

The inclusion criteria were as follows: 1) Subjects with a definitive diagnosis of Type 2 DM; 2) Subjects aged over 18; 3) SS-OCTA imaging quality index ≥ 8. The exclusion criteria were: 1) Ocular media opacity; 2) Subjects with serious systemic diseases (tumor, stroke, dementia, etc.); 3) History of ocular trauma and other vitreo-retinal surgery; 4) Use of medications that may have an impact on the retinal microvasculature; 5) Unable to cooperate with the examination due to nystagmus or other reasons; 6) Subjects with serious NPDR, PDR and DME; 7) Subjects with glaucoma, high myopia (spherical equivalent ≥ −6.00D), and other ocular conditions that may affect the retinal capillaries.

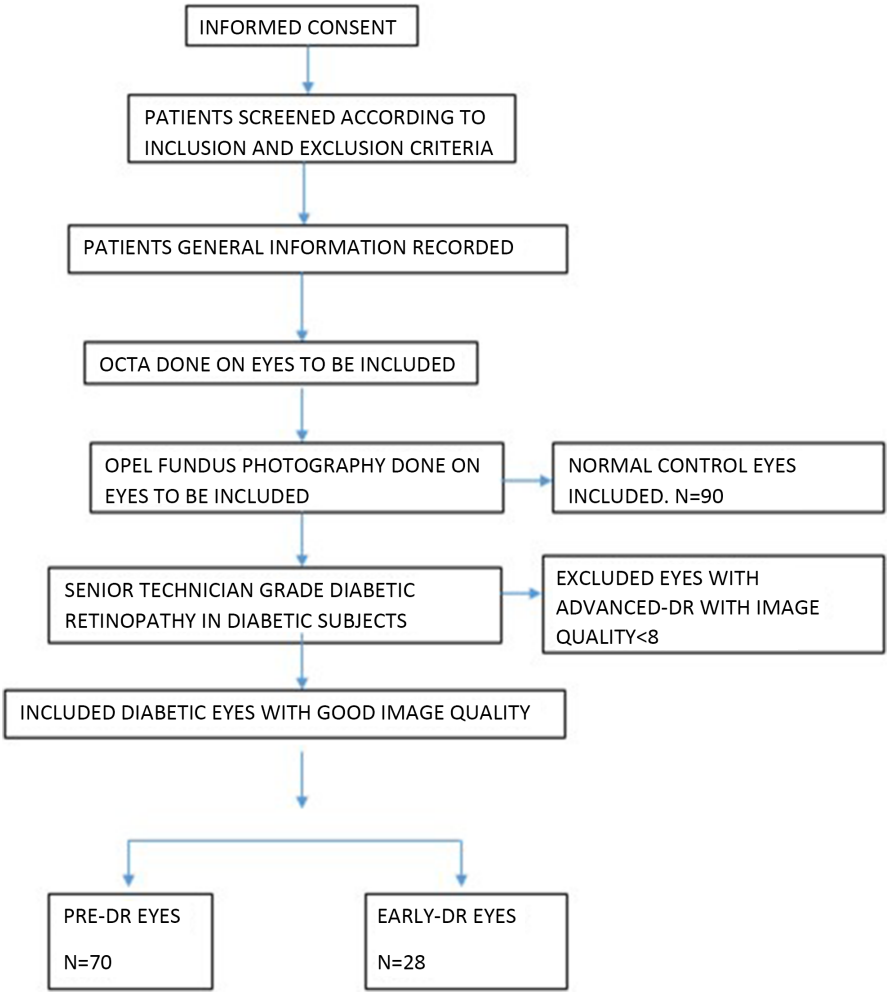

Figure 1. The study selection process.

2.2. Routine Baseline Parameters

We investigated patients and collected data for routine baseline parameters such as random blood glucose level, glycated haemoglobin, cholesterol level for low density lipoprotein, renal function tests, high blood pressure, body mass index and duration of diabetes mellitus. Participants received a comprehensive ophthalmic routine examination including best corrected visual acuity (BCVA), intra-ocular pressure, macular/optic nerve OCT and Opel fundus photography.

2.3. Instruments and Scanning Conditions

Vascular imaging was performed using Shiwei (VG200; Shiwei Imaging, Henan, China) Swept-source optical coherence tomography angiography (SS-OCTA). The system is equipped with a scan source which has a wavelength of approximately 1050 nm and a scan rate of 200,000 scans per second laser generated. The resolution is 5um in the axial direction, 15 um in the lateral direction, the scanning depth is 3 mm and each scan centered on the fovea of the eye. The scan radius from the central fovea in the OCTA machine were set at 15 × 12 mm, 6 × 6 mm and 3 × 3 mm

in measuring retinal vessel density (VD), choroidal thickness and choroidal vascular index (Figure 2). The system includes an integrated confocal scanning laser detection, and an eye-tracking tool that removes eye movement artifacts.

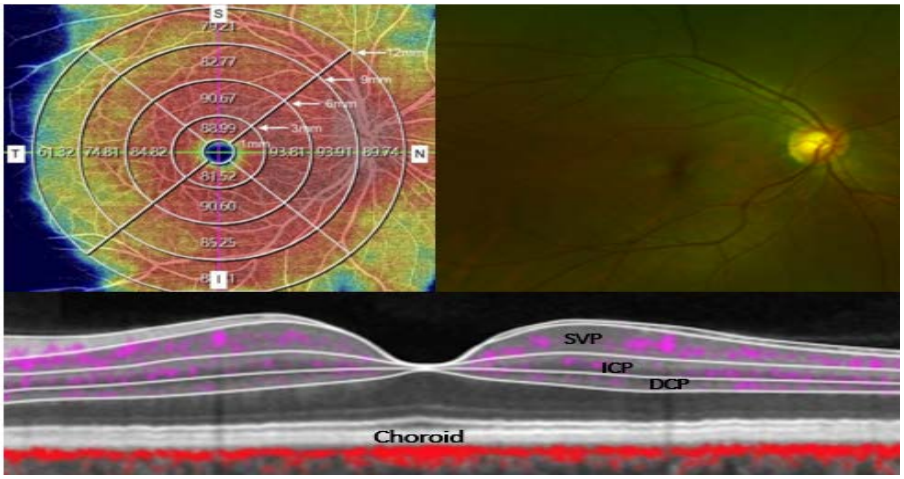

Figure 2. Measurements of retinal and choroidal blood flow zones in different layers and quadrants.

2.4. Statistical Analysis

The data obtained were statistically analyzed by SPSS version 26.0 software. Our data included the basic demographic information of the subjects, and the vascular complex of the superficial, intermediate and deep retina in the 3 × 3 mm, 6 × 6 mm and 15 × 12 mm radii. The choroidal vascular index (CVI) and choroidal thickness (CT) was also analysed at 15 × 12 mm radius. We used the independent samples t-test and one-way ANOVA to analyse the data. The analysed data was expressed as mean ± standard deviation. Results with $p < 0.05$ were considered a statistically significant difference.

3. Results

3.1. Characteristics of Participants

In this study, we analyzed 188 patients' eyes which included 90 control, 70 pre-DR and 28 early-stage DR. There was no significance difference in gender with $p = 0.991$. Also, there was no significant difference across the groups with age range mean ± standard deviation (control = 18 - 45 years, 44.84 ± 13.87, pre-DR = 25 - 58 years, 56.13 ± 10.39, early-DR = 26 - 65 years, 61.94 ± 8.78, $p = 0.056$). The BCVA of health control group was 0.89 ± 0.12 logMAR. The BCVA of pre-DR group was 0.87 ± 0.07 and the BCVA of early-DR group was 0.89 ± 0.11. There was no significant difference in BCVA across the groups with $p = 0.06$. There was no significant difference in intraocular pressure (IOP) between control, pre-DR and early-DR with mean ± standard deviation 15.58 ± 2.01, 15.423 ± 1.89 and 15.21 ± 1.62 respectively, $p = 0.373$. There was no significant difference in the HbA1c level and random blood sugar (RBS) between the pre-DR and early-DR

groups with p = 0.891 and p = 0.982 respectively. There was a higher percentage of patients with underlying comorbidities such as hypertension and high cholesterol level in the early-DR group compared to the pre-DR group with 56% hypertension and 70% high cholesterol level respectively (Table 1). There was no significant difference in the body mass index (BMI) across all groups p = 0.793.

3.2. Retinal Vascular Complexes

We compared the mean vessel density (VD) of vascular complexes in different quadrants of the retinal layers. The deep capillary plexus (DCP) layer at 3 ± 3 mm did not show any significant change in all the four quadrants (Table 2, Figure 3). Just like the DCP layer quadrants, the intermediate capillary plexus (ICP) did not show any significant change in all four quadrants. In the superficial vascular plexus (SVP), there was a significant difference that was noted in the superior quadrant between pre-DR and early-DR groups, p = 0.033. The data in this vascular complex also suggests that most vascular damage in type 2 diabetes mellitus begins superficially in the upper retina especially when examined using a smaller scan radius like 3 ± 3. This could be because Diabetic retinopathy progresses from mild to severe over time. As the disease progresses, these alterations can spread to the central retina. The higher metabolic activity renders the upper retina less tolerant to ischemia than other retinal quadrants. As a result, vascular injury may first appear in the upper retina before reaching other parts.

Table 1. Clinical characteristics of participants.

Characteristics	Controls	Pre-DR	Early-DR	p-Value
	n = 90	n = 70	n = 28	
Age, years, (Mean ± SD)	44.84 ± 13.87	56.13 ± 10.39	61.94 ± 8.78	0.056
Male/Female (n)	38/52	40/30	17/11	0.991
Eyes, Right/Left (n)	47/43	45/25	15/13	0.827
Intra-Ocular Pressure, mmHg (Mean ± SD)	15.58 ± 2.01	15.423 ± 1.89	15.21 ± 1.62	0.373
Best-Corrected Visual Acuity, logMAR (Mean ± SD)	0.89 ± 0.12	0.87 ± 0.07	0.89 ± 0.11	0.06
Duration of Diabetes, Years (Mean ± SD)	N/A	6.90 ± 6.35	19.34 ± 7.65	0.000
Diabettes Treatment:				
No Drug Therapy, n (%)	N/A	8 (11%)	3 (11%)	
Oral Hypoglycemic Agents, n (%)	N/A	38 (54%)	7 (26%)	
Insulin, n (%)	N/A	10 (14%)	11 (37%)	
Insulin and Oral Hypoglycemic Agents, n (%)	N/A	14 (21%)	7 (26%)	
Random Blood Sugar, mmol/L (Mean ± SD)	N/A	6.75 ± 1.74	6.76 ± 2.01	0.982
HbA1c (Mean ± SD)	N/A	7.42 ± 1.24	7.44 ± 1.35	0.891
Renal Disease	NIL	NIL	NIL	N/A
Hypertension, YES/NO (%)	39 (43%)/51 (57%)	13 (12%)/57 (88%)	16 (56%)/12 (44%)	N/A
High-Low Density Lipoprotein, YES/NO (%)	27 (30%)/63 (70%)	23 (27%)/47 (73%)	20 (70%)/8 (30%)	N/A
Body Mass Index (BMI), Kg/m^2 (Mean + SD)	23.91 ± 3.35	23.83 ± 3.43	24.24 ± 2.95	0.793

Table 2. SS-OCTA evaluated quadrants vessel density indices at 3 × 3 mm radius.

Deep capillary plexus (DCP)								
Variable	Radii	Controls	Pre-DR	Early-DR	Controls vs Pre-DR	Controls vs Early-DR	Pre-DR vs Early-DR	ANOVA
		n = 90	n = 70	n = 28	p-Value	p-Value	p-Value	p-Value
SUPERIOR	1 - 3 mm	13.89 ± 5.98	15.37 ± 6.76	15.51 ± 7.89	0.145	0.252	0.932	0.245
TEMPORAL	1 - 3 mm	14.32 ± 6.306	15.56 ± 6.31	16.57 ± 8.28	0.22	0.194	0.514	0.385
INFERIOR	1 - 3 mm	13.30 ± 6.51	14.37 ± 6.83	15.26 ± 8.57	0.315	0.2	0.588	0.38
NASAL	1 - 3 mm	12.56 ± 6.56	13.76 ± 6.37	13.53 ± 7.20	0.248	0.506	0.877	0.291
Intermediate Capillary Plexus (ICP)								
Variable	Radii	Controls	Pre-DR	Early-DR	Controls vs Pre-DR	Controls vs Early-DR	Pre-DR vs Early-DR	ANOVA
		n = 90	n = 70	n = 28	p-Value	p-Value	p-Value	p-Value
SUPERIOR	1 - 3 mm	32.69 ± 5.55	32.86 ± 6.34	31.33 ± 6.52	0.855	0.283	0.289	0.401
TEMPORAL	1 - 3 mm	30.98 ± 6.20	32.29 ± 6.14	30.57 ± 6.95	0.186	0.769	0.232	0.373
INFERIOR	1 - 3 mm	31.25 ± 5.84	32.51 ± 6.98	31.80 ± 7.52	0.215	0.684	0.658	0.212
NASAL	1 - 3 mm	31.01 ± 5.46	32.49 ± 6.02	31.05 ± 7.11	0.106	0.977	0.313	0.164
Superficial Vascular Plexus (SVP)								
Variable	Radii	Controls	Pre-DR	Early-DR	Controls vs Pre-DR	Controls vs Early-DR	Pre-DR vs Early-DR	ANOVA
		n = 90	n = 70	n = 28	p-Value	p-Value	p-Value	p-Value
SUPERIOR	1 - 3 mm	48.53 ± 5.32	48.91 ± 5.96	45.72 ± 7.95	0.672	0.089	0.033	0.562
TEMPORAL	1 - 3 mm	38.84 ± 5.17	40.29 ± 5.96	38.72 ± 6.72	0.103	0.921	0.26	0.194
INFERIOR	1 - 3 mm	48.75 ± 4.96	48.77 ± 7.38	47.45 ± 7.92	0.982	0.417	0.433	0.921
NASAL	1 - 3 mm	42.01 ± 5.32	43.16 ± 6.05	41.14 ± 9.60	0.203	0.652	0.309	0.515

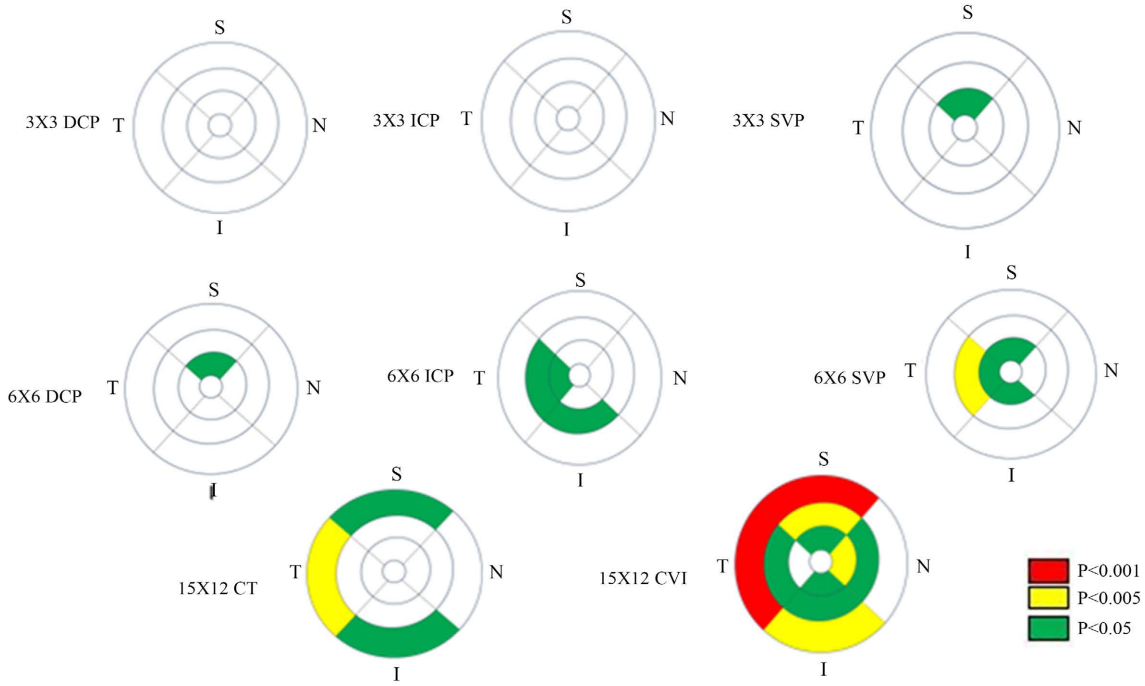

Figure 3. Swept source-optical coherence tomography angiography of retina and choroid at different scan radii.

In the DCP layer quadrants at 6 ± 6 mm scan radius, significant difference was noted in the superior quadrant with p = 0.023 and ANOVA p = 0.033. Other quadrants did not show any remarkable differences (Table 3, Figure 3). In the ICP layer quadrants at 6 ± 6, significant change was seen in temporal and inferior quadrants between pre-DR and early-DR subjects in 1 - 3 mm and 1 - 6 mm retinal

Table 3. SS-OCTA evaluated quadrants vessel density indices at 6 × 6 mm radius.

Deep capillary plexus (DCP)								
Variable	Radii	Controls	Pre-DR	Early-DR	Controls vs Pre-DR	Controls vs Early-DR	Pre-DR vs Early-DR	ANOVA
		n = 90	n = 70	n = 28	p-Value	p-Value	p-Value	p-Value
SUPERIOR	1 - 3 mm	6.72 ± 5.31	8.70 ± 5.500	8.42 ± 5.62	0.023	0.148	0.819	0.033
	1 - 6 mm	13.66 ± 6.11	14.15 ± 5.300	12.81 ± 4.74	0.593	0.502	0.247	0.67
	3 - 6 mm	15.72 ± 6.80	15.77 ± 5.65	14.12 ± 5.44	0.955	0.261	0.191	0.483
TEMPORAL	1 - 3 mm	8.721 ± 5.71	9.80 ± 5.98	9.66 ± 6.59	0.244	0.464	0.916	0.501
	1 - 6 mm	18.27 ± 7.12	19.02 ± 6.49	17.62 ± 7.48	0.496	0.676	0.36	0.503
	3 - 6 mm	21.13 ± 8.19	21.79 ± 7.14	20.01 ± 8.32	0.592	0.532	0.291	0.426
INFERIOR	1 - 3 mm	6.90 ± 5.28	7.70 ± 6.19	7.34 ± 6.64	0.38	0.722	0.797	0.671
	1 - 6 mm	11.96 ± 5.91	13.42 ± 5.78	11.55 ± 6.17	0.121	0.748	0.159	0.325
	3 - 6 mm	13.50 ± 6.65	15.15 ± 6.26	12.83 ± 7.08	0.111	0.648	0.114	0.245
NASAL	1 - 3 mm	6.88 ± 5.49	8.41 ± 5.89	8.75 ± 6.48	0.094	0.135	0.8	0.11
	1 - 6 mm	8.94 ± 6.15	10.23 ± 6.28	10.12 ± 6.13	0.197	0.38	0.937	0.31
	3 - 6 mm	9.56 ± 6.82	10.77 ± 6.71	10.52 ± 6.81	0.266	0.518	0.869	0.401
Intermediate capillary plexus (ICP)								
Variable	Radii	Controls	Pre-DR	Early-DR	Controls vs Pre-DR	Controls vs Early-DR	Pre-DR vs Early-DR	ANOVA
		n = 90	n = 70	n = 28	p-Value	p-Value	p-Value	p-Value
SUPERIOR	1 - 3 mm	31.84 ± 7.22	32.70 ± 6.88	30.56 ± 6.27	0.45	0.402	0.159	0.28
	1 - 6 mm	28.26 ± 6.60	29.33 ± 4.48	27.72 ± 5.08	0.225	0.694	0.126	0.348
	3 - 6 mm	27.19 ± 6.96	28.33 ± 4.44	26.87 ± 5.39	0.212	0.823	0.172	0.423
TEMPORAL	1 - 3 mm	33.32 ± 5.46	34.26 ± 6.31	30.49 ± 6.95	0.314	0.027	0.011	0.022
	1 - 6 mm	32.28 ± 6.10	33.74 ± 5.65	31.02 ± 7.30	0.123	0.365	0.051	0.127
	3 - 6 mm	31.97 ± 6.91	33.58 ± 5.98	31.19 ± 7.79	0.123	0.614	0.106	0.243
INFERIOR	1 - 3 mm	31.24 ± 7.15	31.50 ± 6.93	29.12 ± 6.94	0.815	0.172	0.128	0.229
	1 - 6 mm	25.64 ± 7.40	27.00 ± 5.73	24.41 ± 5.16	0.205	0.415	0.04	0.071
	3 - 6 mm	23.94 ± 8.15	25.64 ± 5.85	22.97 ± 5.56	0.127	0.559	0.042	0.083
NASAL	1 - 3 mm	32.72 ± 6.57	33.13 ± 6.43	30.43 ± 8.39	0.697	0.135	0.09	0.338
	1 - 6 mm	27.79 ± 7.64	28.20 ± 6.84	26.41 ± 7.04	0.724	0.397	0.248	0.456
	3 - 6 mm	26.32 ± 8.53	26.73 ± 7.61	25.21 ± 7.53	0.752	0.537	0.372	0.533

Continued

Superficial vascular plexus (SVP)								
Variable	Radii	Controls	Pre-DR	Early-DR	Controls vs Pre-DR	Controls vs Early-DR	Pre-DR vs Early-DR	ANOVA
		n = 90	n = 70	n = 28	p-Value	p-Value	p-Value	p-Value
SUPERIOR	1 - 3 mm	50.55 ± 5.42	51.09 ± 6.87	47.81 ± 7.78	0.581	0.039	0.043	0.237
	1 - 6 mm	45.62 ± 5.41	47.12 ± 4.87	46.23 ± 5.82	0.072	0.61	0.443	0.232
	3 - 6 mm	44.15 ± 6.22	45.94 ± 5.28	45.75 ± 5.98	0.056	0.233	0.876	0.097
TEMPORAL	1 - 3 mm	42.30 ± 4.65	44.22 ± 6.06	41.03 ± 6.26	0.03	0.25	0.022	0.017
	1 - 6 mm	36.63 ± 4.92	38.96 ± 5.35	36.79 ± 5.06	0.005	0.877	0.07	0.012
	3 - 6 mm	34.93 ± 5.53	37.37 ± 5.65	35.52 ± 5.44	0.007	0.62	0.144	0.028
INFERIOR	1 - 3 mm	5.65 ± 6.41	51.30 ± 6.96	47.14 ± 8.38	0.579	0.019	0.025	0.103
	1 - 6 mm	42.50 ± 6.524	43.46 ± 4.85	41.03 ± 5.40	0.304	0.281	0.033	0.255
	3 - 6 mm	40.00 ± 7.23	41.08 ± 5.09	39.17 ± 5.31	0.289	0.574	0.1	0.497
NASAL	1 - 3 mm	46.05 ± 5.20	46.74 ± 6.80	43.89 ± 8.99	0.481	0.235	0.092	0.497
	1 - 6 mm	48.86 ± 5.06	48.94 ± 4.78	48.02 ± 5.59	0.913	0.458	0.414	0.758
	3 - 6 mm	49.70 ± 5.56	49.60 ± 4.85	49.26 ± 5.32	0.913	0.715	0.758	0.906

rings, $p < 0.05$. A difference was also seen between controls vs early-DR with $p = 0.027$ and ANOVA $p = 0.022$. Vascular damage in the temporal quadrant of the intermediate capillary plexus layer of the retina in situations such as diabetic retinopathy is probably affected by a mixture of structural, hemodynamic, metabolic, and mechanical elements.

Just like the ICP layer, the SVP quadrants showed more significant differences in the temporal region, $p < 0.005$. But also, differences were seen in the 1 - 3 mm retinal rings of the superior and inferior quadrants, $p = 0.039$ and $p = 0.019$ respectively. The diabetic changes are more prominent around the central retina. The reason is that the central retina, including the macula, has a higher metabolic demand as a result of its central visual function. The higher metabolic activity renders the central retina less tolerant to ischemia than the peripheral retina.

3.3. Choroidal Thickness

In the choroidal thickness quadrants at 15 × 12 scan radius, significant differences were seen more peripherally (6 - 9 mm retinal rings) in the superior, temporal and inferior regions with $p < 0.05$ (Table 4, Figure 3). The inferior quadrant did not show any significant difference between the groups.

3.4. Choroidal Vascular Index

In the choroidal vascular index quadrants at 15 × 12 mm scan radius, significant differences were noted in all the regions and retinal rings with $p < 0.005$ (Table 5, Figure 3). The exception was the controls and pre-DR group which did not show

any differences. This is because prolonged hyperglycemia and the resultant microvascular anomalies cause diminished blood flow and ischemia in the choroid. This ischemia insult affects the choroidal arteries, reducing their ability to provide oxygen and nutrients to the outer retina.

Table 4. SS-OCTA evaluated choroidal thickness quadrants at 15 × 12 mm.

Variable	Radii	Controls	Pre-DR	Early-DR	Controls vs Pre-DR	Controls vs Early-DR	Pre-DR vs Early-DR	ANOVA
		n = 90	n = 70	n = 28	p-Value	p-Value	p-Value	p-Value
SUPERIOR	1 - 3 mm	349.98 ± 116.67	339.66 ± 104.92	331.10 ± 109.59	0.563	0.450	0.719	0.864
	3 - 6 mm	349.38 ± 102.43	326.36 ± 87.69	319.95 ± 95.55	0.135	0.180	0.751	0.284
	6 - 9 mm	342.31 ± 94.93	312.49 ± 76.47	304.55 ± 81.62	0.034	0.060	0.650	0.049
TEMPORAL	1 - 3 mm	360.42 ± 120.95	341.16 ± 104.36	343.13 ± 107.75	0.291	0.500	0.933	0.635
	3 - 6 mm	351.19 ± 110.31	319.80 ± 94.70	333.87 ± 105.11	0.060	0.465	0.521	0.200
	6 - 9 mm	328.99 ± 93.02	289.03 ± 80.72	307.85 ± 90.74	0.005	0.293	0.317	0.015
INFERIOR	1 - 3 mm	345.91 ± 121.01	335.17 ± 105.23	347.33 ± 120.06	0.557	0.957	0.621	0.786
	3 - 6 mm	329.22 ± 109.23	307.27 ± 85.72	316.49 ± 110.67	0.156	0.592	0.660	0.528
	6 - 9 mm	294.06 ± 94.36	266.18 ± 64.09	266.86 ± 80.85	0.028	0.172	0.965	0.296
NASAL	1 - 3 mm	333.14 ± 120.46	327.29 ± 109.39	323.82 ± 113.96	0.751	0.718	0.889	0.955
	3 - 6 mm	285.43 ± 111.26	277.97 ± 97.89	275.32 ± 101.95	0.658	0.670	0.905	0.966
	6 - 9 mm	222.08 ± 105.71	202.64 ± 70.31	202.20 ± 68.49	0.187	0.352	0.978	0.617

Table 5. SS-OCTA evaluated choroidal vascular index (CVI) quadrants at 15 × 12 mm.

Variable	Radii	Controls	Pre-DR	Early-DR	Controls vs Pre-DR	Controls vs Early-DR	Pre-DR vs Early-DR	ANOVA
		n = 90	n = 70	n = 28	p-Value	p-Value	p-Value	p-Value
SUPERIOR	1 - 3 mm	0.38 ± 0.04	0.39 ± 0.04	0.35 ± .05	0.348	0.010	0.002	0.019
	3 - 6 mm	0.36 ± 0.03	0.36 ± 0.03	0.33 ± 0.04	0.722	0.000	0.000	0.001
	6 - 9 mm	0.35 ± 0.02	0.35 ± 0.03	0.32 ± 0.04	0.598	0.002	0.000	0.003
TEMPORAL	1 - 3 mm	0.35 ± 0.03	0.35 ± 0.04	0.33 ± 0.04	0.963	0.041	0.099	0.101
	3 - 6 mm	0.34 ± 0.03	0.33 ± 0.03	0.31 ± 0.03	0.028	0.000	0.035	0.000
	6 - 9 mm	0.34 ± 0.03	0.33 ± 0.03	0.31 ± 0.04	0.131	0.000	0.015	0.009
INFERIOR	1 - 3 mm	0.38 ± 0.05	0.39 ± 0.04	0.36 ± 0.04	0.484	0.020	0.002	0.029
	3 - 6 mm	0.36 ± 0.03	0.36 ± 0.03	0.33 ± 0.04	0.852	0.002	0.002	0.032
	6 - 9 mm	0.36 ± 0.02	0.36 ± 0.03	0.33 ± 0.04	0.923	0.005	0.003	0.019
NASAL	1 - 3 mm	0.37 ± 0.04	0.38 ± 0.05	0.34 ± 0.04	0.288	0.003	0.001	0.004
	3 - 6 mm	0.36 ± 0.05	0.36 ± 0.04	0.33 ± 0.06	0.313	0.014	0.002	0.013
	6 - 9 mm	0.30 ± 0.04	0.30 ± 0.04	0.29 ± 0.04	0.447	0.073	0.232	0.188

4. Discussion

In this study, we performed a cross-sectional analysis of OCTA-derived parameters in two groups of patients with T2DM (pre-DR and early-DR) and one group of control participants.

We compared the mean vessel density (VD) of vascular complexes in different quadrants of the retinal layers. It was found that the deep capillary plexus (DCP) and intermediate capillary plexus (ICP) layer at 3 × 3 mm did not show any significant change in all four quadrants. However, in the superficial vascular plexus (SVP), there was a significant difference that was noted in the superior quadrant between pre-DR and early-DR groups with $p = 0.033$ (**Table 2**, **Figure 3**). These findings mean that when detecting for diabetic retinopathy at this scan radius, eye experts need to focus more on the superficial layer and specifically in the superior quadrant because that is where some significant change is most likely to be noted. A study conducted by Wang *et al.* (2022) [9] on detecting diabetic retinopathy using OCTA reported a significant difference in retinal microvasculature which was noted at 3mm scan radius. However, their study did not analyse the different quadrants of the three retinal layers. Our study is peculiar in a way that we analysed different retinal quadrants which is able to guide us clinically with regard to the retinal quadrants that get affected first at this scan radius. This is helpful and time saving to eye health practitioners as they will know which quadrant to concentrate on when looking for diabetic retinopathy pathologies. The data in this vascular complex suggests that most vascular damage in type 2 diabetes mellitus begins superficially in the upper retina. This is also in line with Xu *et al.*'s study (2022) [10], where they compared the retinal findings in pre and early-DR patients with the control participants and found that there was a decrease in vascular density of diabetic patients in superficial layer of the retina. However, in their study, it was not specified which quadrants revealed significant change as compared to our study which pointed out the superior quadrant to have a significant change. Furthermore, the higher metabolic activity renders the upper retina less tolerant to ischemia than other quadrants. As a result, vascular injury may first appear in the upper retina before spreading to other parts [11] [12].

In the DCP layer quadrants at 6 × 6 mm scan radius, significant difference was noted in the superior quadrant with $p = 0.023$ and ANOVA $p = 0.033$. However, ICP layer quadrant showed a rather different picture where significant change was seen in temporal and inferior quadrants between pre-DR and early-DR subjects in 1 - 3 mm retinal ring, $p < 0.05$ (**Table 3**, **Figure 3**). In a similar manner, Liu *et al.* (2022) [13] in their study which involved 103 participants reported a significant difference that was observed between control and diabetic groups in the DCP and ICP layer. The difference is that their study included a PDR group as well, and they did not analyse each quadrant like the case of our study. Nevertheless, the results showed similar findings in the DCP and ICP at 6 mm radius. Our study went further to analyse each quadrant in the three layers (DCP, SCP, SVP) which gives a more comprehensive understanding of which layer and quadrant is mostly

affected to give a precise guidance in clinical management of early diabetic retinopathy. What makes our study different further is that we did not include patients with proliferative diabetic retinopathy because our aim was to look for the very early retinal changes in diabetic patients. This is very important because the findings will help us come up with a well-tailored clinical management of patients with pre-diabetic retinopathy thereby preventing progression to advanced diabetic eye disease. Vascular damage in the temporal quadrant of the intermediate capillary plexus layer of the retina in situations such as diabetic retinopathy is probably affected by a mixture of structural, hemodynamic, metabolic, and mechanical elements [14]. The SVP layer quadrant showed almost a similar result like the ICP with significant change in the temporal region. Anatomical distinctions between different layers of the retina may make the ICP more susceptible to ischemia according to some researchers [15]-[17]. This is because ICP descends into the superficial venules via vertical anastomoses, and therefore, both ICP and SVP reveal a significant difference in our results. Previous studies, for example Qian *et al.* (2022) [18] found that there was a decrease in the Retinal vessel density (VD) of diabetic patients compared to normal individuals at 6mm scan radius and the rate of decrease is dependent on a number of factors such as the duration of diabetes, whether patient on medication or not and other retinal vascular comorbidities. However, their study did not specify which retinal rings where mostly affected in the early stages of diabetic retinopathy which is different from our findings which reveal that the vessels in the inner retinal ring are mostly affected than the ones in outer ring at 6 mm radius.

Zeng *et al.* (2023) [19] also in the same vein noted that vessel density changes in diabetic retinopathy are more prominent to retinal rings around the central retina due to the reason that the central retina, including the macula, has a higher metabolic demand as a result of its central visual function. The higher metabolic activity renders the central retina less tolerant to ischemia than the peripheral retina. This is evidenced in our results which show that most VD changes are concertrated around the retinal rings near the macular area as they spread out to further retinal rings in different quadrants. Research using optical coherence tomography angiography (OCTA) has demonstrated that in comparison to the nasal quadrant, the temporal quadrant of the macula typically has a greater capillary density. For this reason, the temporal quadrant is more vulnerable to the microvascular alterations linked to diabetic retinopathy [20]-[22]. This is because retinal acidosis in the early stages of diabetic retinopathy happens in this region. And in addition, most small vessels are very distant from large arterioles in this same region as well [23]-[25]. Our study revealed that at 6 mm scan radius, there is more involvement of temporal quadrant retinal vessels in both ICP and SVP layers than other quadrants.

In the choroidal thickness at 15 × 12 mm scan radius, our results showed a significant difference more peripherally (6 - 9 mm retinal rings) in the superior, temporal and inferior regions with $p < 0.05$. Our findings in the choroid provide

clues to suggest that choroid alterations play a role in the pathogenesis of DR. Similarly, a study conducted by Wang *et al.* (2020) [26] also reported a decrease in choroidal thickness in patients with diabetic retinopathy as the disease progressed. However, different from our study, theirs also included patients with proliferative diabetic retinopathy. The choroid is one of the most metabolically active tissues in the human body and abnormal choroidal thickness has been implicated in many retinal diseases, but results for DR have been controversial in different previous studies conducted. Our results reveal that there was a decrease in the choroidal thickness of DR patients compared to control subjects and we can presume that it would decrease further as the disease progresses. Our study also reveals that the choroid becomes thinner from the peripheral aspects of the retina going towards the central part as the diabetic retinopathy progresses from early to severe form of the disease (**Table 4**, **Figure 3**). Examination of the choroidal vascular index (CVI) revealed significant differences in all the regions and retinal rings with $p < 0.005$ (**Table 5**, **Figure 3**). This result indicates that CVI is a sensitive biomarker in OCTA choroidal changes for patients with diabetic retinopathy, and therefore, it can be relied upon to check for progression of diabetic retinopathy and patient monitoring as well as follow-ups during treatment. Sidorczuk *et al.* (2021) [27] defined CVI as the ratio of the luminal area (LA) to the total choroidal area (TCA). Compared with choroidal thickness, this parameter appears to be less dependent on various confounding factors. CVI has proven to be useful in the early diagnosis of various retinal and choroidal diseases including diabetic retinopathy induced choroidal pathologies. Although Sidorczuk *et al.*'s study focused on comparing FAZ and choroidal vessel findings between controls and diabetic patient's only, they noted that there was a significant decrease in the CVI of diabetic group compared to control group which agrees with our study. Different from previous published literature, the sample size was bigger in this current study and only included patients with pre-DR and early-DR so that the findings could help us prevent progression of the disease to proliferative diabetic retinopathy by detecting the changes early enough. This sensitivity of CVI to diabetic retinopathy is due to the fact that the choroidal vessels are fenestrated and therefore allow for the exchange of nutrients and waste products. This makes them more susceptible to changes in blood sugar levels and inflammation which are common in diabetes [28]-[30].

There were a few limitations to our study. First, this was a cross-sectional observational study. A longitudinal study should be performed to explain the relationship between the retinal and choroidal microvascular changes and disease progression in pre-DR and early-DR stages. Secondly, precise fundus examinations such as fluorescence fundus angiography were not used in pre-DR and early-DR patients to compare the findings with OCTA. Lastly, OCTA image artifacts can interfere with accurate assessment of the actual status of the retinal microvasculature; for example, projection artifacts might interrupt visualization of the deep layer.

5. Conclusion

Our results reveal that although there were no clinical manifestations in the control group and the pre-DR group, changes in retinal and choroidal blood flow density had already occurred in the pre-DR group through OCTA detection, suggesting that early detection of the lesions provides an objective basis to prevent further retinal microvascular damage. By analysing at an early stage, the retinal vessel density and choroidal thickness as well as vascular index of diabetic patients in different layers of the retina and in different quadrants at different scan radius of OCTA, we can easily identify which layer and quadrant of the retina is affected early in diabetic retinopathy and to what extent depends on the retinal rings involved. This quantitative evaluation of retinal and choroidal plexuses using OCTA impacts more on early intervention of diabetic retinopathy thereby preventing it from progressing to advanced diabetic eye disease. OCTA therefore becomes a fundamental tool for the non-invasive diagnosis and prognosis of DR.

Patient Consent

Consent was obtained from all the patients before being recruited into the study.

Authorship

Authors attest that they meet the current ICMJE criteria for authorship.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Kim, K., Kim, E.S. and Yu, S. (2017) Optical Coherence Tomography Angiography Analysis of Foveal Microvascular Changes and Inner Retinal Layer Thinning in Patients with Diabetes. *British Journal of Ophthalmology*, **102**, 1226-1231. https://doi.org/10.1136/bjophthalmol-2017-311149

[2] Li, H., Yu, X., Zheng, B., Ding, S., Mu, Z. and Guo, L. (2021) Early Neurovascular Changes in the Retina in Preclinical Diabetic Retinopathy and Its Relation with Blood Glucose. *BMC Ophthalmology*, **21**, Article No. 220. https://doi.org/10.1186/s12886-021-01975-7

[3] Garg, I., Uwakwe, C., Le, R., Lu, E.S., Cui, Y., Wai, K.M., *et al.* (2022) Nonperfusion Area and Other Vascular Metrics by Wider Field Swept-Source OCT Angiography as Biomarkers of Diabetic Retinopathy Severity. *Ophthalmology Science*, **2**, Article 100144. https://doi.org/10.1016/j.xops.2022.100144

[4] Li, J., Wei, D., Mao, M., Li, M., Liu, S., Li, F., *et al.* (2022) Ultra-Widefield Color Fundus Photography Combined with High-Speed Ultra-Widefield Swept-Source Optical Coherence Tomography Angiography for Non-Invasive Detection of Lesions in Diabetic Retinopathy. *Frontiers in Public Health*, **10**, Article 1047608. https://doi.org/10.3389/fpubh.2022.1047608

[5] Oh, K., Kang, H.M., Leem, D., Lee, H., Seo, K.Y. and Yoon, S. (2021) Early Detection of Diabetic Retinopathy Based on Deep Learning and Ultra-Wide-Field Fundus Images. *Scientific Reports*, **11**, Article No. 1897.

https://doi.org/10.1038/s41598-021-81539-3

[6] Becker, K., Klein, H., Simon, E., Viollet, C., Haslinger, C., Leparc, G., *et al.* (2021) In-Depth Transcriptomic Analysis of Human Retina Reveals Molecular Mechanisms Underlying Diabetic Retinopathy. *Scientific Reports*, **11**, Article No. 10494. https://doi.org/10.1038/s41598-021-88698-3

[7] Sun, Z., Yang, D., Tang, Z., Ng, D.S. and Cheung, C.Y. (2020) Optical Coherence Tomography Angiography in Diabetic Retinopathy: An Updated Review. *Eye*, **35**, 149-161. https://doi.org/10.1038/s41433-020-01233-y

[8] Boned-Murillo, A., Albertos-Arranz, H., Diaz-Barreda, M.D., Orduna-Hospital, E., Sánchez-Cano, A., Ferreras, A., *et al.* (2021) Optical Coherence Tomography Angiography in Diabetic Patients: A Systematic Review. *Biomedicines*, **10**, Article 88. https://doi.org/10.3390/biomedicines10010088

[9] Wang, W., Liu, S., Qiu, Z., He, M., Wang, L., Li, Y., *et al.* (2020) Choroidal Thickness in Diabetes and Diabetic Retinopathy: A Swept Source OCT Study. *Investigative Opthalmology & Visual Science*, **61**, Article 29. https://doi.org/10.1167/iovs.61.4.29

[10] Xu, F., Li, Z., Gao, Y., Yang, X., Huang, Z., Li, Z., *et al.* (2022) Retinal Microvascular Signs in Pre- and Early-Stage Diabetic Retinopathy Detected Using Wide-Field Swept-Source Optical Coherence Tomographic Angiography. *Journal of Clinical Medicine*, **11**, Article 4332. https://doi.org/10.3390/jcm11154332

[11] Markan, A., Agarwal, A., Arora, A., Bazgain, K., Rana, V. and Gupta, V. (2020) Novel Imaging Biomarkers in Diabetic Retinopathy and Diabetic Macular Edema. *Therapeutic Advances in Ophthalmology*, **12**. https://doi.org/10.1177/2515841420950513

[12] La Mantia, A., Kurt, R.A., Mejor, S., Egan, C.A., Tufail, A., Keane, P.A., *et al.* (2019) Comparing Fundus Fluorescein Angiography and Swept-Source Optical Coherence Tomography Angiography in the Evaluation of Diabetic Macular Perfusion. *Retina*, **39**, 926-937. https://doi.org/10.1097/iae.0000000000002045

[13] Liu, T., Lin, W., Shi, G., Wang, W., Feng, M., Xie, X., *et al.* (2022) Retinal and Choroidal Vascular Perfusion and Thickness Measurement in Diabetic Retinopathy Patients by the Swept-Source Optical Coherence Tomography Angiography. *Frontiers in Medicine*, **9**, Article 786708. https://doi.org/10.3389/fmed.2022.786708

[14] Park, Y.G., Kim, M. and Roh, Y.J. (2020) Evaluation of Foveal and Parafoveal Microvascular Changes Using Optical Coherence Tomography Angiography in Type 2 Diabetes Patients without Clinical Diabetic Retinopathy in South Korea. *Journal of Diabetes Research*, **2020**, Article 6210865. https://doi.org/10.1155/2020/6210865

[15] Fogel-Levin, M., Sadda, S.R., Rosenfeld, P.J., Waheed, N., Querques, G., Freund, B.K., *et al.* (2022) Advanced Retinal Imaging and Applications for Clinical Practice: A Consensus Review. *Survey of Ophthalmology*, **67**, 1373-1390. https://doi.org/10.1016/j.survophthal.2022.02.004

[16] Koutsiaris, A.G., Batis, V., Liakopoulou, G., Tachmitzi, S.V., Detorakis, E.T. and Tsironi, E.E. (2023) Optical Coherence Tomography Angiography (OCTA) of the Eye: A Review on Basic Principles, Advantages, Disadvantages and Device Specifications. *Clinical Hemorheology and Microcirculation*, **83**, 247-271. https://doi.org/10.3233/ch-221634

[17] Du, K., Huang, X., Chen, C., Kong, W., Xie, L. and Wei, W. (2021) Macular Structure and Microvasculature Changes in Aids-Related Cytomegalovirus Retinitis Using Optical Coherence Tomography Angiography. *Frontiers in Medicine*, **8**, Article 696447. https://doi.org/10.3389/fmed.2021.696447

[18] Qian, J., Haq, Z., Yang, D., Jin, J.Q. and Stewart, J.M. (2022) Duration of Diabetes as a Risk Factor for Retinal Microvasculature Alterations Detected with Optical Coherence

Tomography Angiography in Patients without Clinical Retinopathy. *Diagnostics*, **12**, Article 3020. https://doi.org/10.3390/diagnostics12123020

[19] Zeng, Y., Liu, M., Li, M., Wei, D., Mao, M., Liu, X., *et al.* (2023) Early Changes to Retinal Structure in Patients with Diabetic Retinopathy as Determined by Ultrawide Swept-Source Optical Coherence Tomography-Angiography. *Frontiers in Endocrinology*, **14**, Article 1143535. https://doi.org/10.3389/fendo.2023.1143535

[20] Nguyen, T.-T.P., Ni, S., Khan, S., Wei, X., Ostmo, S., Chiang, M.F., *et al.* (2022) Advantages of Widefield Optical Coherence Tomography in the Diagnosis of Retinopathy of Prematurity. *Frontiers in Pediatrics*, **9**, Article 797684. https://pubmed.ncbi.nlm.nih.gov/35118032/ https://doi.org/10.3389/fped.2021.797684

[21] Ong, C., Wong, M., Cheong, K., Zhao, J., Teo, K. and Tan, T. (2023) Optical Coherence Tomography Angiography in Retinal Vascular Disorders. *Diagnostics*, **13**, Article 1620. https://doi.org/10.3390/diagnostics13091620

[22] Dingerkus, V.L.S., Munk, M.R., Brinkmann, M.P., Freiberg, F.J., Heussen, F.M.A., Kinzl, S., *et al.* (2019) Optical Coherence Tomography Angiography (OCTA) as a New Diagnostic Tool in Uveitis. *Journal of Ophthalmic Inflammation and Infection*, **9**, Article No. 10. https://doi.org/10.1186/s12348-019-0176-9

[23] Goh, J.K.H., Cheung, C.Y., Sim, S.S., Tan, P.C., Tan, G.S.W. and Wong, T.Y. (2016) Retinal Imaging Techniques for Diabetic Retinopathy Screening. *Journal of Diabetes Science and Technology*, **10**, 282-294. https://doi.org/10.1177/1932296816629491

[24] Bowditch, E., Chang, A. and Mehta, H. (2021) Developments in Non-Invasive Imaging to Guide Diagnosis and Treatment of Proliferative Diabetic Retinopathy: A Systematic Review. *International Journal of Translational Medicine*, **1**, 332-352. https://doi.org/10.3390/ijtm1030020

[25] Hogg, R.E., Wright, D.M., Dolz-Marco, R., Gray, C., Waheed, N., Teussink, M.M., *et al.* (2021) Quantitative Parameters from OCT Angiography in Patients with Diabetic Retinopathy and in Those with Only Peripheral Retinopathy Compared with Control Participants. *Ophthalmology Science*, **1**, Article 100030. https://doi.org/10.1016/j.xops.2021.100030

[26] Ferreira, L.B., Williams, K.A., Best, G., Haydinger, C.D. and Smith, J.R. (2023) Inflammatory Cytokines as Mediators of Retinal Endothelial Barrier Dysfunction in Non-infectious Uveitis. *Clinical & Translational Immunology*, **12**, e1479. https://doi.org/10.1002/cti2.1479

[27] Mohite, A.A., Perais, J.A., McCullough, P. and Lois, N. (2023) Retinal Ischaemia in Diabetic Retinopathy: Understanding and Overcoming a Therapeutic Challenge. *Journal of Clinical Medicine*, **12**, Article 2406. https://doi.org/10.3390/jcm12062406

[28] Park, J.J., Soetikno, B.T. and Fawzi, A.A. (2016) Characterization of the Middle Capillary Plexus Using Optical Coherence Tomography Angiography in Healthy and Diabetic Eyes. *Retina*, **36**, 2039-2050. https://doi.org/10.1097/iae.0000000000001077

[29] Wang, X., Cai, X., Li, S., Li, T., Long, D. and Wu, Q. (2022) Wide-Field Swept-Source OCTA in the Assessment of Retinal Microvasculature in Early-Stage Diabetic Retinopathy. *BMC Ophthalmology*, **22**, Article No. 473. https://doi.org/10.1186/s12886-022-02724-0

[30] Simonett, J.M., Scarinci, F., Picconi, F., Giorno, P., De Geronimo, D., Di Renzo, A., *et al.* (2017) Early Microvascular Retinal Changes in Optical Coherence Tomography Angiography in Patients with Type 1 Diabetes Mellitus. *Acta Ophthalmologica*, **95**, e751-e755. https://doi.org/10.1111/aos.13404