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Assessment of Retinal Microvascular Changes in Diabetic Patients Using Optical Coherence Tomography Angiography

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ABSTRACT

Background: A predominant and various microvascular outcome of diabetes mellitus (DM) is diabetic retinopathy (DR), which leads to loss of vision gradually and blindness if not treated early. **Aim:** Detecting retinal microvascular changes in diabetic cases can help detect early diabetic changes and manage them effectively, ultimately improving the quality of life for these patients. **Patients and methods:** This observational, analytical, cross-sectional research has been performed on ninety eyes, separated into three groups: Group I (DM no. DR): 30 eyes of diabetic cases that had no diabetic retinopathy; Group II (NPDR): 30 eyes of DM cases who had non-proliferative DR; and Group III (PDR): 30 eyes of diabetic cases that had proliferative diabetic retinopathy in the Outpatient Clinic in the Ophthalmology Department at Suez Canal University in Ismailia City. **Results:** The mean BCVA was significantly lesser among the more severe diabetic group, with statistically significant distinctions ($p<0.001$). The average thickness of retina was significantly greater among the more severe diabetic group, with statistically significant differences. The measurement of vessel density demonstrated the most accurate ability to detect and categorize DR, with the best level of sensitivity for the two diagnosis and categorization and the greatest level of specificity in categorization of retinopathy. **Conclusion:** The optical coherence tomography-angiography information may be employed to evaluate the DR extent and to give early indications prior to fundus lesions happening within diabetic cases. The DR was worsened by the decline in vessel density in DCP and SCP.

Keywords: Diabetic retinopathy, BCVA, OCTA

INTRODUCTION

A predominant and various microvascular outcome of DM is diabetic retinopathy (DR), which leads to loss of vision gradually and blindness if not treated early. According to reports, DR affects 30% to 45% of people with diabetes mellitus (DM), and one diabetic patient out of every ten also has DR that threatens their vision **(1)**.

A rising range of imaging techniques can be applied to the detection, assessment, diagnosis, and managing of DR. Fluorescein angiography with dye is presently the benchmark to determine the arterial leakage amount and the presence of ischemia. Depending on how DR manifests, imaging modalities like B-scan ultrasound, fluorescein angiography and optical coherence tomography (OCT), can be used with exam procedures **(2)**.

Sodium fluorescein angiography is presently the "benchmark" in assessing the blood vessels in diabetic retinopathy. This technique uses a fluorescent mineral dye to analyze the condition of the arteries and detect any leakage. Fluorescein angiography is a diagnostic technique that may detect abnormal blood vessels, involving retinal neovascularization or intraretinal microvascular abnormalities, as well as microaneurysms (which appear as small areas of intense fluorescence), areas of reduced blood flow (which appear as sparse areas of reduced fluorescence enclosed by large retinal vessels), and other medical conditions **(3)**. In the various stages of DR, new noninvasive imaging procedures like OCTA may be able to reveal important details regarding microvascular changes, the retina's state of perfusion, and the risk that retinopathy may progress. Using OCTA, the retinal and choroidal vasculatures can be seen in volumetric, dye-free, and at micron-scale resolutions thanks to the motion contrast supplied by flowing erythrocytes [(4)].

Erythrocyte movement in capillaries is detected using this technology's split-spectrum amplitude-decorrelation angiography (SSADA) technique [(5)]. It is possible to distinguish between the deep and superficial capillary plexuses (SCP and DCP) of the retina as well as the choriocapillaris (CC) using depth-resolved retinal vascular structure pictures provided by OCTA [(6)].

The foveal avascular zone area (FAZA), which is surrounded by a ring of foveal capillaries, is the region of the retina's macula that is typically devoid of capillaries. The foveal capillaries' perfusion changes have significant effects on the case's eyesight [(7)].

This study aimed to detect retinal microvascular changes in diabetic patients. This will allow us to discover early diabetic changes on the retina and manage them well before they get worse, aiming to increase the quality of life for diabetic patients.

PATIENTS AND METHODS

This observational analytical cross-sectional research has been performed on ninety eyes separated into three groups: Group I (DM no. DR): 30 eyes of diabetic cases with no diabetic retinopathy; Group II (NPDR): 30 eyes of diabetic cases who had non-proliferative diabetic retinopathy; and Group III (PDR): 30 eyes of DM cases that had proliferative DR in the Outpatient Clinic in the Ophthalmology Department at Suez Canal University in Ismailia City from July 2023 and lasted for 6 months.

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Inclusion criteria: Both sexes, age between 30 and 70 years' old**,** diabetic patients, duration of diabetic mellitus of 10 years or more [(8)] and intraocular pressure less than 20.
Exclusion criteria: A great deal of media opacity that prevents high-quality imaging; motion and blinking artefacts on the photographs; and the images of low quality. Intravitreal anti-VEGF after prior focused or general retinal laser photocoagulation, taking retinal or neurotoxic medications, severe myopia (nearsightedness of at least -6 diopters), previous macular and ocular conditions, any eye surgery or trauma from the past, any autoimmune or systemic disease, prior procedures other than a straightforward phacoemulsification (greater than three months ago), any inflammatory conditions or recent or ongoing infections (systemic and/or ocular and pregnancy, uncontrolled hypertension, or biologic medicines that depress the immune system).

Methods: All enrolled patients were evaluated by detailed ophthalmic examination, history taking and OCT-ANGIO

Procedure: The method of capturing OCT-angiography: An OCT angiography scan measuring six millimeters × six millimeters was conducted on the macular area. The signal was transmitted from the inner limiting membrane (ILM) to the retinal pigment epithelium (RPE), leading to the creation of en face retinal angiograms. Only the pictures of patients with a signal strength index of forty or above and no remaining motion artifacts were retained and utilized for further investigation. Nidek Advanced Vision Information System Additional software has been utilized for quantifying and outline the FAZA. A circular region with an outward diameter of three millimeters and an inner diameter of one millimeter was utilized to define the area surrounding the fovea during further examination. Additionally, a circular region with an outer diameter of five millimeters and an inner diameter of three millimeters has been utilized to define the area surrounding the perifovea. The OCTA system provided the vessel density for each of these locations in an automated manner. The retinal thickness was evaluated using the retina map mode, which encompasses a six millimeters x six millimeters area centered at the fovea. This measurement was performed concurrently with the evaluation of the retinal vasculature utilizing the OCT equipment. The measurement included the entire retinal thickness, among the ILM and the center of the RPE-Bruch membrane complex. The outer retina refers to the section of the retina that is among the middle of the RPE-Bruch membrane complex and the outer margin of the IPL. The inner retina refers to the region of the retina that is among the ILM and the outer boundary of the IPL. Retinal thickness denotes the average thickness of a particular region. The fovea refers to the central area of a one-millimeter ring, whereas the perifovea and parafovea are detected in a comparable way as in the OCT angiography. The OCT system automatically generated the average measurements of the complete, inner, and outer retinal thicknesses for the three specified regions.

Ethical considerations: All the procedures of the research were accepted by the Radiology Department and the Investigation Ethics Committee of Faculty of Medicine, Suez Canal University. Administrative consents required were taken. The purpose of this study was to perform research on humans in compliance with the Declaration of Helsinki, the code of ethics of the World Medical Association.

Data management: A statistical analysis was conducted by entering pre-coded data into the computer utilizing the statistical package of social science software program, version 26 (SPSS). Data has been gathered utilizing the mean, standard deviation, median, and IQR for quantitative variables and the ANOVA test of independent samples for qualitative variables, as well as the number, frequency, and percentage. The chi square and Fisher exact tests have been utilized for comparing qualitative variables, while the independent test has been utilized for comparing quantitative variables between both groups that were normally distributed. Nonparametric Kruskal-Wallis and Mann-Whitney tests have been utilized for comparing quantitative variables that weren't normally distributed. Sensitivity and specificity as determined by ROC analysis. When applicable, additional statistical tests were implemented. Statistical significance has been detected as a P value is < 0.05.

RESULTS

Table 1 demonstrates that age, gender and period of DM disease were comparable among the research groups.

Table 1: Basic data of the studied group (N=90).

		DM no DR group (n=thirty)	NPDR group (n=thirty)	PDR group (n=thirty)	P-value
Age	(Years)	55.6 ± 7.15	52.4±7.9	53.1±7.5	0.224[1]
Gender n, (%)	Male	15(50%)	18(60%)	17(56.7%)	0.73[2]
	Female	15(50%)	12(40%)	13(43.3%)	
Type of DM	T1DM	2(6.6%)	1(3.3%)	1(3.3%)	
	T2DM	28(93.4%)	29(96.7%)	29(96.7%)	0.847[3]
Duration of DM	(Years)	14.3±3.2	14.9± 2.5	15.1 ± 1.9	0.463[1]

1.ANOVA test used. 2. Chi square test used. 3. Fisher exact test used. DM: Diabetes mellitus, T1DM: type 1 Diabetes mellitus, T2DM: type 2 Diabetes mellitus.

Table 2 shows that the mean BCVA was significantly lower among more severe diabetic group with statistically significant distinctions. Post hoc test outcomes showed variation among DM with no DR group with other DR groups.

Table 2: Comparison of best corrected visual acuity among the studied group (N=90).

BCVA (LogMAR)	DM no DR group (n= thirty)	Non-proliferative diabetic retinopathy group (n=thirty)	Proliferative diabetic retinopathy group (n= thirty)	P-value
OD	0.78 ± 0.14	0.5±0.15$^{\$}$	0.44±0.21$^{\$}$	**<0.001*²** p1=<0.001 p2=<0.001 p3=0.27
OS	0.76± 0.11	0.51±0.16$^{\$}$	0.41±0.20$^{\$}$	**<0.001*²** p1=<0.001 p2=<0.001 p3=0.82

BCVA; best corrected visual acuity, OD; right eye, OS; left eye, $: Significant difference compared to DM no DR group, 1. ANOVA test used. 2. Kruskal-Wallis Test used, *: Statistically significant difference. p1: Group 1 vs Group 2, p2: Group 1 vs Group 3, p3: Group 2 vs Group 3.

Table 3 shows that the mean vessel density in SCP was significantly lower among more severe diabetic group with statistically significant distinctions. Post hoc test outcomes showed difference among DM with no DR group with other DR groups.

Table 3: Comparison of vessel density in SCP among the studied group (N=90).

SCP (mm)		DM no DR group (n= thirty)	NPDR group (n= thirty)	PDR group (n= thirty)	P-value
OD	Whole	6.77 ± 1.22$^{¥£}$	3.8±1.13	3.6±1.4	**<0.001*²** p1=<0.001 p2=<0.001 p3=0.81
	Inner	6.67± 1.18$^{¥£}$	4.4±1.13	3.6±1.5	**<0.001*²** p1=<0.001 p2=<0.001 p3=0.03
	Outer	7.01 ± 1.4$^{¥£}$	4.9±2.3	3.7±1.2	**<0.001*²** p1=<0.001 p2=<0.001 p3=0.02
OS	Whole	8.4 ±1.7$^{¥£}$	4.0±1.1	3.6±1.3	**<0.001*²** p1=<0.001 p2=<0.001 p3=0.051
	Inner	8.7± 1.28$^{¥£}$	3.9±0.9	3.8±1.2	**<0.001*²** p1=<0.001 p2=<0.001 p3=0.19
	Outer	7.9± 1.19$^{¥£}$	3.9±1.16	3.7±0.9	**<0.001*²** p1=<0.001 p2=<0.001 p3=0.053

SCP; superficial capillary plexus, OD; right eye, OS; left eye, ¥: Significant difference compared to NPDR group, £: Significant difference compared to PDR, 1. ANOVA test used. 2. Kruskal-Wallis Test used, *: Statistically significant difference. p1: Group 1 vs Group 2, p2: Group 1 vs Group 3, p3: Group 2 vs Group 3.

Table 4 shows that the mean vessel density in DCP was lower among more severe diabetic group with statistically significant distinctions. Post hoc test outcomes showed distinction among DM with no DR group with other DR groups.

Table 4: Comparison of vessel density in deep capillary plexus among the studied group (N=90).

DCP (mm)		DM no DR group (n= thirty)	Non-proliferative diabetic retinopathy group (n= thirty)	Proliferative diabetic retinopathy group (n= thirty)	P-value
OD	Whole	4.33 ± 1.08¥£	2.3±0.89	1.5±0.43	**<0.001*²** p1=<0.001 p2=<0.001 p3=<0.001
	Inner	4.6± 0.92¥£	2.7±0.65	2.06±0.5	**<0.001*¹** p1=<0.001 p2=<0.001 p3=0.01
	Outer	4.32± 1.1¥£	2.8±0.17	2.08±0.29	**<0.001*²** p1=<0.001 p2=<0.001 p3=<0.001
OS	Whole	4.9 ± 1.2¥£	2.1±1.01	1.4±1.1	**<0.001*²** p1=<0.001 p2=<0.001 p3=0.25
	Inner	4.52 ± 0.98¥£	2.0±0.72	1.2±0.78	**<0.001*²** p1=<0.001 p2=<0.001 p3=<0.001
	Outer	4.36± 1.11¥£	2.9±0.33	1.3±0.33	**<0.001*²** p1=<0.001 p2=<0.001 p3=<0.001

Abbreviations: DCP; deep capillary plexus, OS; left eye, $: Significant difference compared to DM no DR group, ¥: Significant difference compared to NPDR group, 1. ANOVA test used. 2. Kruskal-Wallis Test used, *: Statistically significant difference. p1:Group 1 vs Group 2, p2:Group 1 vs Group 3, p3:Group 2 vs Group 3.

Table 5 illustrates that the mean FAZ was significantly higher in area and perimeter and lower in circulatory among more severe diabetic group with statistically significant distinctions. Post hoc test results displayed variations among DM with no DR group with other DR groups and between NPDR group and PDR group.

Table 5: Comparison of fovea avascular zone parameters among the studied group (N=90).

FAZ (mm)		DM no DR group (n=thirty)	Non-proliferative diabetic retinopathy group (n= thirty)	Proliferative diabetic retinopathy group (n= thirty)	P-value
OD	Area	0.37 ± 0.12	0.54±0.13	1.21±0.40¥$	**<0.001*2** p1=<0.001 p2=<0.001 p3=<0.001
	Perimeter	4.2± 0.61	4.9±0.11$	7.2±0.9¥$	**<0.001*1** p1=<0.001 p2=<0.001 p3=<0.001
	Circulatory	0.77± 0.04	0.50±0.03$	0.37±0.09¥$	**<0.001*2** p1=<0.001 p2=<0.001 p3=<0.001
OS	Area	0.51 ± 0.12	0.58±10.14	1.28±0.35¥$	**<0.001*2** p1=<0.001 p2=<0.001 p3=<0.001
	Perimeter	4.1± 0.47	5.0±0.23$	6.84±0.87¥$	**<0.001*2** p1=<0.001 p2=<0.001 p3=<0.001
	Circulatory	0.83± 0.05	0.52±0.03$	0.38±0.08¥$	**<0.001*2** p1=<0.001 p2=<0.001 p3=<0.001

FAZ; fovea avascular zone, $: Significant difference compared to DM no DR group, ¥: Significant difference compared to NPDR group, 1. ANOVA test used. 2. Kruskal-Wallis Test used, *: Statistically significant difference. p1: Group 1 vs Group 2, p2: Group 1 vs Group 3, p3: Group 2 vs Group 3

Table 6 shows that the mean retinal thickness was significantly higher among more severe diabetic group with statistically significant distinctions. Post hoc test outcomes showed significant difference among DM with no DR group with other DR groups and between NPDR group and PDR group.

Table 6: Comparison of retinal thickness among the studied group (N=90).

	DM no DR group (n=thirty)	Non-proliferative diabetic retinopathy group (n=thirty)	Proliferative diabetic retinopathy group (n=thirty)	P-value
OD	254.9 ± 11.3	321.5±21.6$	634.7±21.1¥$	**<0.001*1** p1=<0.001 p2=<0.001 p3=<0.001
OS	235.29± 10.1	325.3±22.7$	660.9±19.8¥$	**<0.001*1** p1=<0.001 p2=<0.001 p3=<0.001

OD; right eye, OS; left eye, $: Significant difference compared to DM no DR group, ¥: Significant difference compared to NPDR group, 1. ANOVA test used. 2. Kruskal-Wallis Test used, *: Statistically significant difference. p1: Group 1 vs Group 2, p2:Group 1 vs Group 3, p3:Group 2 vs Group 3

Table 7 indicates that vessel density had the best level of sensitivity for both diagnosing and classifying diabetic retinopathy, and the maximum level of specificity for categorizing retinopathy.

Table 7: Assessing the reliability of OCT angiography parameters in diagnosing and categoring DR.

Parameter	DR vs	NDR	PDR vs	NPDR
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
FAZ	85%	89%	71%	88%
SCP	83%	90%	89%	80%
DCP	89%	88%	83%	86%

DISCUSSION

The research found that there were insignificant variations in gender, age, and length of diabetes illness among the research groups ($p > 0.05$). The average best-corrected visual acuity was significantly smaller in the more severe diabetes group, with statistically significant distinctions ($p<0.001$). The post hoc test outcomes showed a significant distinction among the group of cases with diabetes mellitus but no DR and the other groups with DR. OCTA can be used to measure the morphological and density characteristics of retinal blood vessels, which helps in evaluating the extent of DR.

Samara *et al.* [9] observed an insignificant distinction in the FAZA among eyes with NPDR and eyes with PDR. In contrast, **Nesper *et al.*** [10] showed a significantly greater FAZA in proliferative diabetic retinopathy eyes comparing with non-proliferative diabetic retinopathy eyes.

Our investigation revealed that the FAZA in eyes with PDR and NPDR was significantly greater comparing with eyes with the control (diabetic cases who had no diabetic retinopathy) group. Furthermore, the enhance in foveal avascular zone area was particularly pronounced in PDR eyes. Similarly, in the research conducted by **Onishi *et al.*,** [11] VD significantly decreased in each plexus within cases with diabetic retinopathy compared to individuals without the condition. **Dimitrova *et al.*** [12] proved a significant reduction in both deep and superficial retinal vascular densities in DM cases when compared to healthy individuals.

Lei *et al.* [13] performed research to determine if the reduced blood flow in the retina of cases with DR affects larger blood vessels or smaller capillaries. They examined the flow of blood in large vessels and superficial capillaries separately, and they found that the flow of blood within these two types of vessels didn't show any changes in diabetic retinopathy. They discovered that the reduced retinal blood flow is primarily seen in the capillary layer.

Research has also examined alterations in the retinal blood vessels diameter within eyes affected by diabetic retinopathy. **Tang *et al.*** [14] discovered that the retinal blood vessels diameter rises when diabetic retinopathy worsens. This indicates that the eyes affected by DR have telangiectasia and hyper-perfusion. The parameter used to measure these blood vessels diameter is referred to as the retinal diameter index.

According to **Lei *et al.*** [13], the researchers discovered that as diabetic retinopathy developed, the size of the blood vessels in the retina had progressive dilation. This development could be attributed to the widening of small retinal venules or a rise in flow of blood within the retina throughout DR. **Onishi *et al.*** [11] discovered that the adjusted flow index (AFI), a measure that estimates blood flow, was higher within cases having DM and NDR in comparison to individuals with normal eyes. However, as diabetic retinopathy advances, the deep and superficial capillary plexuses, in addition to MCP adjusted flow index exhibit a declining pattern, with the MCP and deep capillary plexuses adjusted flow index showing a more obvious pattern.

One potential description is that there could be an automatic regulation of blood flow in the SCP (superficial capillary plexus) during the early stage of DR. This regulation may result in stable blood flow in the superficial retinal stage, although the blood flow in the deep retinal layer might see a significant drop. The enhancement of retinal blood circulation during the initial phases of diabetic retinopathy corresponds to the findings of the research conducted by **Grunwald *et al.*** [15]. Nevertheless, most of the mainstream research maintains the belief that during the initial phase of diabetic retinopathy, there are significant modifications in the parameters of the SCP when compared to the individuals' eyes without the condition. Furthermore, as the severity of diabetic retinopathy progresses, the alterations in the deep plexus become more obvious [12].

A separate investigation conducted by **Kim *et al.*** [16] examined additional OCTA parameters, particularly those derived from binary processing of OCTA images. These parameters include skeletonized vessel density (SVD), perfusion density (PD), VLD, VDI, fractal dimensions (FD), and AFI. The authors revealed that cases with NPDR exhibited significantly lower values of SVD, VD, FD, and VDI compared to the healthy control group.

The measurement of vessel density demonstrated the greatest sensitivity in both diagnosing and classifying diabetic retinopathy and the highest specificity in classifying retinopathy.

Lei *et al.* [13] suggested that capillary vascular length density (VLD) could be an accurate metric for assessing diabetic retinopathy, as it has a great level of specificity and sensitivity in identifying various stages of

diabetic retinopathy. Vascular length density is a notion that bears similarities to SVD.

In their study, **Durbin *et al*. [(17)]** found that they could differentiate among healthy eyes and eyes with diabetic retinopathy using two measures: vascular density and perfusion density in the superficial retinal layer. They obtained an AUC of 0.893 for VD and 0.794 for PD, showing that the diagnostic accuracy of VD is higher than that of perfusion density in the superficial retinal layer. Contrary to other researchers' beliefs, DCP parameters were considered more significant.

CONCLUSION

The optical coherence tomography angiography data may be utilized to measure the extent of DR and provide early signals prior to the development of fundus lesions in diabetic cases. The declining density of blood vessels in the SCP and DCP has been correlated with the deterioration of diabetic retinopathy.

DECLARATIONS

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- **Conflicts of interest:** No conflicts of interest.
- **Competing interests:** None

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