Egyptian Journal of Ophthalmology (MOC) 2024;4(2):*70-79*

Evaluation of Choroidal Changes in Diabetic Retinopathy

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Received: 13-12-2023, Accepted: 1-1-2024, Published online:16-6-2024

EJO(MOC) 2024;4(2):70-79.

Short title*:* Evaluation of Choroidal Changes in Diabetic Retinopathy

Abstract

PURPOSE. This research aimed to assess the choroidal alterations in a substantial cohort of diabetic patients, at various phases, using swept source optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA).

METHODS. Between February 2022 and February 2023, patients with type II diabetes who had not yet started ocular treatment were included in the study at Tanta University Hospitals. Fundus Fluorescein angiography (FFA) was used to grade the stage of diabetic retinopathy (DR). We used the swept source OCT to get high-definition scans of the retina and choroid. We also got thickness maps of the choroid (CT) and volume maps of the choroid (CV). We used OCTA to find the vascular density index (VDI) at the retinal and choroidal levels. We used multivariate linear regression models to investigate how severe DR was linked to Choroidal thickness and volume, as well as VDI.

RESULTS. The final analysis comprised 100 subjects, who were categorized into the following four groups: controls, diabetics without DR, non-proliferative DR, and proliferative DR (PDR). Patients with PDR had substantially thinner CT ($p < 0.001$), lower CV ($p < 0.001$), and lower VDI ($p < 0.001$) than the other groups, after adjusting for other variables. A significant correlation was observed between higher average CT and improved best corrected visual acuity(BCVA).This study also establishes a negative correlation between the retinal and choroidal vascular density index and the foveal avascular zone area. It also establishes a positive correlation between the duration of diabetes and severity of diabetic eye disease. Moreover, This study shows a positive correlation between the foveal avascular zone area and the Visual Acuity by LogMar. Visual acuity is also affected by the severity of diabetic eye disease; the more advanced the diabetic retinopathy , the worse the BCVA.

CONCLUSIONS. With DR progression , CT and CV decreased. Also , VDI decreased with DR progression . These results add to the increasing evidence that changes to the choroid contribute to the development of DR.

Keyword : Choroidal changes , Diabetic Retinopathy , Choroidal thickness , Choroidal Volume , Vascular density index , foveal avascular zone area .

INTRODUCTION

Diabetes mellitus (DM) is a very frequent chronic illness that is now undergoing significant worldwide expansion. By 2040, it is estimated that the worldwide number of people with diabetes will reach 642 million.(1) Diabetic retinopathy (DR) is a prevalent chronic consequence of diabetes. DR is now the primary cause of vision loss in the global working-age population, resulting in blindness.(2) Among those diagnosed with diabetes, 34.6% exhibit different levels of severity in DR, and as many as 10.2% have impaired vision.(3)

Presently, the study of the development and characteristics of DR predominantly centers on the harm inflicted on the retinal vascular system by DM. Histopathological investigations have shown that diabetes may induce choroidopathy, in addition to DR.(4)

Choroidal thickness (CT) is an important metric for determining the structure of the choroid[5]. Previously, only indocyanine green angiography, laser flowmetry, and ultrasonography could be used to check the status of the choroid. These approaches, however, do not offer a visual picture of the choroidal layers' three-dimensional structure[6]. With the introduction of OCT, it became possible to image ocular tissues in a non-invasive and high-resolution manner. EDI employing spectral-domain (SD) OCT scans has been proven to provide images with higher resolution and deeper penetration. This method allows for quantitative and cross-sectional imaging of the choroid[7].

Swept-source OCT (SS-OCT) has the potential to provide high-quality 3D choroidal imaging due to its longer wavelength (1050 nm) and faster scanning speed (100,000 A-scan/s).[8] OCTA may serve as a rapid and non-invasive imaging method for aiding in the observation of microvascular changes at the capillary level. [9]

Therefore, the aim of this research was to assess the alterations in the choroid of diabetic patients, both with and without DR, of different degrees of severity, using SS-OCT and OCTA imaging techniques.

PATIENTS AND METHODS

Participants

This research was conducted at Tanta University Hospitals in El-Gharbia, Egypt. It was a prospective, cross-sectional controlled study. Prior to their participation, all participants in this study provided an informed written consent. The inclusion criteria were: Treatment naïve patients with type II diabetes on oral hypoglycemic drugs (controlled with HBA1c < 7%) without known history of hypertension. They were classified as following; Group 1: Diabetic patients without DR (20 eyes), group 2: Diabetic patients with NPDR (30 eyes), Group 3: diabetic patients with PDR (30 eyes), and group 4 (the control group of age & sex matched individuals (20 eyes)).

Exclusion criteria include: (1) High myope patients with spherical equivalent more than – 6.0 diopters. (2) Any choroidal pathology, that may alter CT as Lupus, Behcet' disease, etc. (3) Any previous intra-ocular intervention including cataract surgery and laser treatment, and any previous intra-vitreal injections. (4) Media opacity interfering with adequate clinical evaluation and investigations as dense cataract, vitreous hemorrhage, etc. (5) Patients with poor fixation; as physical and mental handicap preventing OCT imaging, (6) Patients with other ocular pathology as optic atrophy, uncontrolled glaucoma, etc.

Ethics and Consent:

The research approval of the study was obtained from IRB of Faculty of Medicine at Tanta University before starting the study on February 2022 (code number 35248/2/22). All subjects provided written informed consent prior to study participation.

General Information

Standardized questionnaires were utilized for collecting general information such as age, gender, diabetes duration, medication adherence, presence of other chronic conditions, and lifestyle.

Ocular Examination

A thorough visual examination was performed for all individuals. The slit lamp biomicroscopy and ophthalmoscopy techniques were used to assess the anterior and posterior segments. The uncorrected and best corrected visual acuity (BCVA) were evaluated using Snellen's chart and transformed into LogMAR for statistical evaluation.

FFA Imaging

The Heidelberg fluorescein angiography device (Spectralis, Heidelberg, Germany) was used to obtain fluorescein angiography images, that were used to stage diabetic patients .

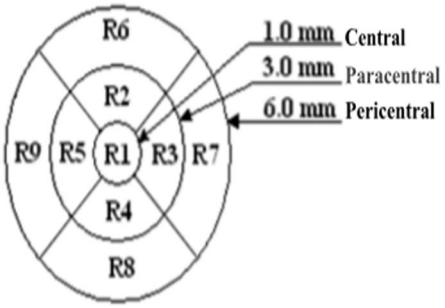
SS-OCT Imaging

Using SS-OCT (DRI-OCT Triton, Topcon, Japan) device, high-definition images of the choroid and retina were acquired. With an acquisition pace of 100,000 A scans per second, this instrument produces an in-vivo axial resolution of 8 μm.

The SS-OCT system's automated layer segmentation software was used to analyze the resulting images. In the nine subfields defined by the ETDRS, the CT and CV were computed and displayed automatically. The inner and outer regions of the macula are demarcated by the ETDRS grid at distances of 1 to 3

mm (paracentral) and 3 to 6 mm (pericentral), respectively (Fig. 1).

Furthermore, the average CT was computed for each of the nine grids. A single ophthalmologist with extensive experience conducted all OCT scans while remaining unaware of the study protocol. The study selected participants who possessed sufficient image quality. Using a caliber, the central subfoveal CT was also manually determined in microns. This was defined as the distance between the inner border of the sclera and the exterior border of the RPE/Bruch's membrane complex.



Region	Parameter
R1	Central subfield area
R2	Superior paracentral area
R3	Nasal paracentral area
R4	Inferior paracentral area
R5	Temporal paracentral area
R6	Superior pericentral area
R7	Nasal pericentral area
R8	Inferior pericentral area
R9	Temporal pericentral area

Figure 1: Diagram showing different areas in choroidal thickness/volume maps

OCT-A Imaging

The macula was imaged using the 3 x 3 mm and 6 x 6 mm scanning protocols. The macular region was evaluated at four levels: (1) Superficial retinal capillary plexus level (SCP), which spans from the internal limiting membrane to the outer border of the inner plexiform layer ,(2) the deep retinal capillary plexus level (DCP) extends from the outer boundary of the inner plexiform layer to the outer boundary of the outer plexiform layer, (3) the innermost layer of the retina, known as the deep retinal layer and (4) the choriocapillaris level extends from the level of Bruch's membrane to a point about 30 µm below it. The FAZ region was calculated automatically by quantifying the size of the FAZ.

Vascular Density map photos provide subjective data. The pictures were processed using the ImageJ program (IJ 1.46 r edition, U.S. National Institutes of Health, Bethesda, Maryland, USA) for this purpose. The procedure included collecting photographs with dimensions of 450 x 350 pixels and converting them into binary pictures to calculate the vascular density index (VDI) as a percentage, thereby yielding quantitative data.

Statistical Analyses

The data were organized and examined using the Statistical Package for the Social Sciences (SPSS). The current iteration is 29.00 and it is situated in Chicago, Illinois, United States of America. The qualitative data in this study were converted into quantitative form via the use of numerical values and percentages. The mean value was shown by the standard deviation (SD) for the quantitative data. Anova tests were used to compare quantitative data with more than two means. A p-value less than or equal to 0.05 was deemed statistically significant. The correlation coefficient measures the degree of the linear relationship between two variables.

RESULTS

Clinical and Demographic Features of the Participants

100 patients that were eligible were included in this research. The subjects were divided into four categories: controls, diabetics without DR, non-participants with DR, and patients with PDR. Table 1 displays the participants' basic demographic and clinical characteristics. With an average age of 54.100 ± 4.909 years old ,12 patients (60%) were female and 8(40%) were male in the control group of twenty.

The average age of the 20 diabetic patients without DR was 57.0 ± 4.507 years, while 9 (45%) of the patients were female and 11 (55%) were male. The average age of the 30 patients with NPDR was 54.133 ± 4.995 years, and 15 of those patients were male and 15 were female. With an average age of 55.533 ± 3.082 years, 15 (50%) of the 30 patients diagnosed with PDR were female and 15 (50%) were male.

The No DR group had an average duration of 4.55 ± 1.731 years of diabetes, the NPDR group had 10.6 ± 2.415 years, and the PDR group had 14.167 ± 3.119 years. In LogMAR, the average BCVA in the control group was 0.0, in no DR patients it was 0.122 ± 0.115, in NPDR patients it was 0.677 ± 0.216, and in PDR patients it was 0.803 ˆ 0.185.

Table (1): Demographic and Clinical Data of the subjects.

		Groups				
		Control	**No DR**	**NPDR**	**PDR**	**P-value**
Age	**Range**	44 - 59	50 - 62	45 - 64	50 - 60	0.095
(Years)	**Mean ± SD**	54.100 ± 4.909	57.000 ± 4.507	54.133 ± 4.995	55.533 ± 3.082	
Sex	**Male**	8 (40%)	11 (55%)	15 (50%)	15 (50%)	0.811
	Female	12 (60%)	9 (45%)	15 (50%)	15 (50%)	
Duration of	**Range**	-	2 – 8	6 - 15	7 – 20	**<0.001***
DM (Years)	**Mean ± SD**	-	4.550 ± 1.731	10.600 ± 2.415	14.167 ± 3.119	
Visual Acuity	**Range**	0	0 – 0.2	0.4 – 0.8	0.5 - 1	**<0.001***
LogMAR	**Mean ± SD**	0	0.122 ± 0.155	0.677 ± 0.216	0.803 ± 0.185	

TUKEY'S Test

P1	**P2**	**P3**	**P4**	**P5**	**P6**
0.743	<0.001*	<0.001*	<0.001*	<0.001*	0.027*

Distribution of CT in Macula

Table 2 represents the CT of participants. The mean central subfoveal CT measurement of 276.450 ± 26.165 μm for the control group, was 248.900 ± 38.729 μm for the no DR group, was 209.433 ± 54.283 μm for the NPDR group and was 172.500 ± 24.500 μm for the PDR group.

Table (2): Comparison between the stage of DR and the Choroidal thickness.

Choroidal		**Groups**				**ANOVA**	
thickness (micron)		**Control**	**No DR**	**NPDR**	**PDR**	**F**	**P-value**
Central	**Range**	240 - 300	150 - 280	130 - 270	124 - 226	29.193	**<0.001***
(Subfoveal)	**Mean ± SD**	276.450 ± 26.165	248.900 ± 38.729	209.433 ± 54.283	172.500 ± 24.500		
Superior	**Range**	275 - 300	182 - 280	113 - 270	128 - 240	43.063	**<0.001***
	Mean ± SD	290.350 ± 13.582	259.450 ± 32.926	213.600 ± 55.771	183.367 ± 27.727		
Inferior	**Range**	220 - 299	180 - 279	125 - 280	127- 255	27.908	**<0.001***
	Mean ± SD	280.500 ± 18.202	254.850 ± 38.101	215.400 ± 58.100	178.233 ± 27.140		
Nasal	**Range**	255 -297	174 - 286	126 -270	126 - 229	34.724	**<0.001***
	Mean ± SD	280.450 ± 19.952	249.450 ± 42.374	206.833 ± 67.416	173.700 ± 24.649		
Temporal	**Range**	275 - 300	175 - 298	118 - 271	128 - 228	43.236	**<0.001***
	Mean ± SD	286.150 ± 18.624	242.250 ± 38.745	210.767 ± 51.302	178.933 ± 26.342		
Average paracentral and pericentral areas		282.78 ± 19.305	250.98 ± 38.175	211.201±57.374	177.35±26.07	32.826	**<0.001***

Regarding the average paracentral and pericentral areas , CT was 282.78 ±19.305 μm for the control group. The mean CT measurement for patients who did not have DR was 250.98 ± 38.175 μm. The average CT for patients who had NPDR was 211.201 ± 57.374 μm . A mean CT measurement of 177.35 ± 26.07 μm was obtained for individuals who were diagnosed with proliferative diabetic retinopathy (PDR). There was a statistically significant difference in the mean CT between these groups, with a p-value of less than 0.001. In each of the nine subregions, the CT measurements demonstrated a trend toward lower values in the PDR group.

Distribution of Choroidal Volume in Macula

Table 3 represents the CV of participants. The mean central subfoveal CV was 0.245 ± 0.038 mm^3 for the control group, 0.219 ± 0.037 mm^3 for the no DR patients, 0.193 ± 0.02 mm^3 for the NPDR patients, and 0.149 ± 0.032 for the PDR patients. Regarding the average paracentral and pericentral areas, CV was 0.427 ± 0.071 mm3 for the control group, 0.364 ± 0.070 mm^3 for the no DR patients, 0.323 ± 0.029 mm^3 for the NPDR patients, 0.252 ± 0.072 mm^3 for the PDR patients. Among of measurements in the nine subregions, the CV showed a trend toward lower values in the PDR group.

Table (3): Comparison between the stage of DR and the CV.

Choroidal volume (mm^3)		**Groups**				**ANOVA**	
		Control	**No DR**	**NPDR**	**PDR**	**F**	**P-value**
Central (subfoveal)	**Range**	0.19 - 0.3	0.17 - 0.28	0.16 - 0.24	0.11 - 0.27	41.616	**<0.001***
	Mean ± SD	0.245 ± 0.038	0.219 ± 0.037	0.193 ± 0.020	0.149 ± 0.032		
Superior 3mm	**Range**	0.4 - 0.56	0.26 - 0.59	0.29 - 0.48	0.18 - 0.48	41.361	**<0.001***
	Mean ± SD	0.473 ± 0.056	0.415 ± 0.086	0.362 ± 0.045	0.281 ± 0.065		
Inferior 3mm	**Range**	0.31 - 0.63	0.22 - 0.56	0.3 - 0.39	0.11 - 0.49	26.979	**<0.001***
	Mean ± SD	0.469 ± 0.101	0.400 ± 0.085	0.338 ± 0.028	0.278 ± 0.087		
Nasal 3mm	**Range**	0.31 - 0.63	0.29 - 0.55	0.3 - 0.38	0.11 - 0.53	29.129	**<0.001***
	Mean ± SD	0.471 ± 0.095	0.398 ± 0.072	0.333 ± 0.029	0.271 ± 0.099		
Temporal 3mm	**Range**	0.38 - 0.59	0.25 - 0.52	0.3 - 0.37	0.15 - 0.49	45.750	**<0.001***
	Mean ± SD	0.479 ± 0.063	0.388 ± 0.069	0.323 ± 0.022	0.280 ± 0.080		
Average Paracentral area		0.427 ± 0.071	0.364 ± 0.070	0.32 ± 0.029	0.252 ± 0.072	34.950	**<0.001***

Distribution of vascular density indices:

Table 4 represents the VDI at SCP of the participants. The average VDI was 42.004 ± 1.662 %, 40.051 ± 1.142 %, 38.508 ± 1.177 %, and 36.601 ± 1.246 % for the control, no DR, NPDR, and PDR groups, respectively. The average VDI at DCP of the participants, was 42.195 ± 1.583 %, 40.755 ± 1.247 %, 37.519 ± 1.080 % and 36.500 ± 1.299 % for the control, no DR, NPDR, and PDR groups, respectively. The average VDI at CC of the participants was 52.276 ± 1.033 %, 49.877 ± 1.328 %, 48.634 ± 1.703 % and 46.719 ± 1.520 % for the control, no DR, NPDR, and PDR groups, respectively. The average VDI at CC of the participants was 52.276 ± 1.033 %, 49.877 ± 1.328 %, 48.634 ± 1.703 % and 46.719 ± 1.520 % for the control, no DR, NPDR, and PDR groups, respectively.

Table (4): Comparison of the Vascular Density Index at deep retinal capillary plexus, at superficial retinal capillary, and at choriocapillaris level distribution in all the studied groups.

VDI at SCP	**Groups**				**ANOVA**	
	Control	**No DR**	**NPDR**	**PDR**	**F**	**P-value**
Range	38.972 - 44.354	38.532 - 42.345	36.211 - 40.243	34.234 - 39.342	75.256	**<0.001***
Mean ±SD	42.004 ± 1.662	40.051 ± 1.142	38.508 ± 1.177	36.601 ± 1.246		
TUKEY'S Test						
P1	**P2**	**P3**	**P4**	**P5**	**P6**	
<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	
VDI at DCP	**Control**	**No DR**	**NPDR**	**PDR**	**F**	**P-value**
Range	39.748 - 44.365	38.765 - 42.882	35.465 - 39.654	32.983 - 38.212	134.805	**<0.001***
Mean ±SD	42.195 ± 1.583	40.755 ± 1.247	37.519 ± 1.080	35.500 ± 1.299		
TUKEY'S Test						
P1	**P2**	**P3**	**P4**	**P5**	**P6**	
0.004*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	
VDI at CC	**Control**	**No DR**	**NPDR**	**PDR**	**F**	**P-value**
Range	50.323 - 53.982	48.222 - 52.311	46.323 - 52.32	42.323 - 48.22	60.912	**<0.001***
Mean ±SD	52.276 ± 1.033	49.877 ± 1.328	48.634 ± 1.703	46.719 ± 1.520		
TUKEY'S Test						
P1	**P2**	**P3**	**P4**	**P5**	**P6**	
<0.001*	<0.001*	<0.001*	0.021*	<0.001*	<0.001*	

Distribution of FAZ area at superficial retinal plexus:

Table 5 represents the FAZ of the participants. The average FAZ was 0.283 ± 0.045 mm^2 for the control group, 0.391 ± 0.036 mm^2 for the no DR patients, 0.525 ± 0.142 mm^2 for the NPDR patients, and 0.620 ± 0.106 mm^2 for the PDR patients.

Table (5): Comparison of the Superficial FAZ area in all the studied groups.

Superficial FAZ area (mm^2)	**Groups**				**ANOVA**	
	Control	**No DR**	**NPDR**	**PDR**	**F**	**P-value**
Range	0.272 - 0.339	0.311 - 0.472	0.422 - 0.682	0.497 - 0.705	10.213	**<0.001***
Mean ±SD	0.283 ± 0.045	0.391 ± 0.036	0.525 ± 0.142	0.620 ± 0.106		
TUKEY'S Test						
P1	**P2**	**P3**	**P4**	**P5**	**P6**	
0.148	0.004*	<0.001*	0.650	0.015*	0.155	

Association between FAZ area and BCVA by LogMAR:

Figure 2 Illustrates the correlation between the size of the FAZ and the level of visual acuity (BCVA) evaluated using the logarithm of the minimum angle of resolution (LogMAR) scale. A substantial positive correlation was seen between them ($r=0.398$, $p < 0.001$).

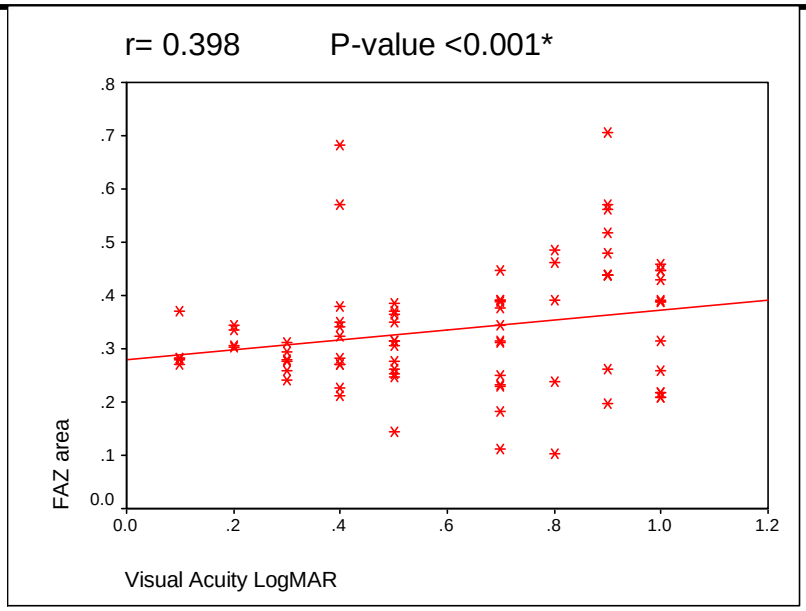


Figure 2: correlation between FAZ area and Visual acuity by LogMAR

Association between FAZ area and Vascular density indices:

The data shown in **Figure 3** illustrates the relationship between the area of the FAZ and the VDI . There was a statistically significant negative correlation between them. The correlation coefficient (r) was -0.204 (p = 0.049) for SCP, -0.292 (p = 0.009) for DCP, and -0.224 (p = 0.046) for CC.

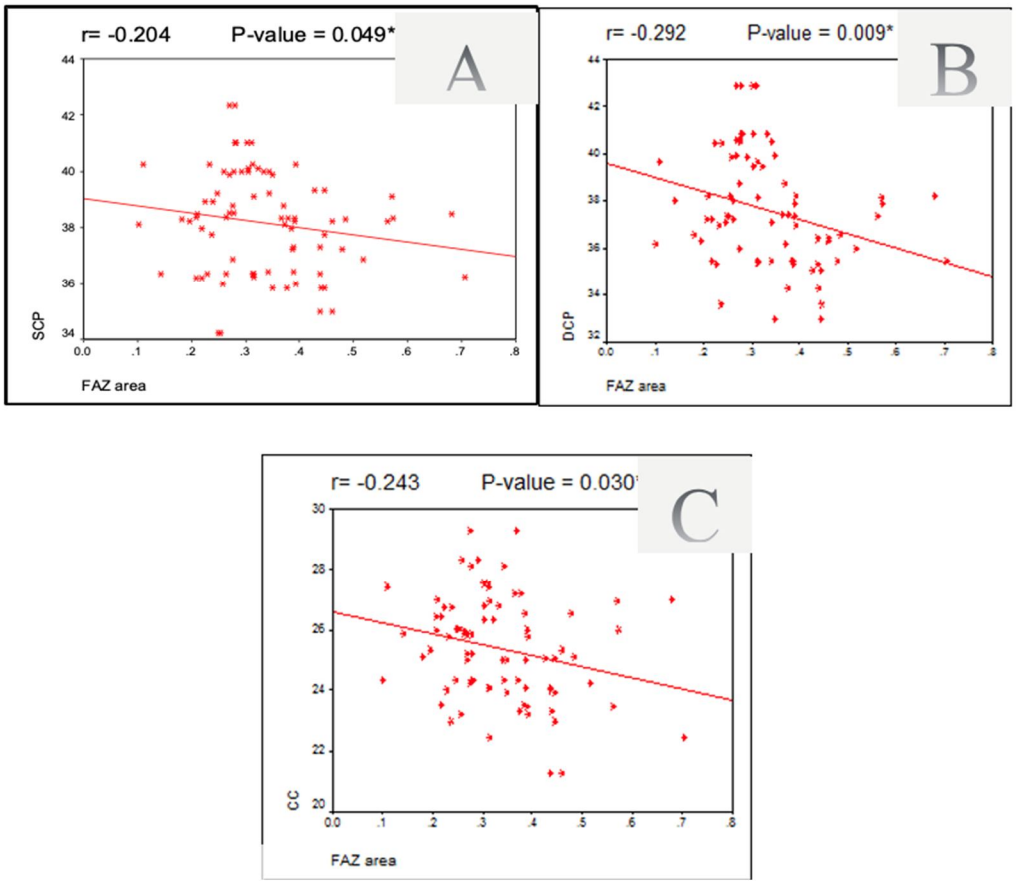


Figure 3: Correlation between FAZ area and Vascular density index at; (A) superficial capillary plexus, (B) deep capillary plexus, (C) choriocapillaris

DISCUSSION

The choroid serves as the main provider of oxygen and nutrients to the outer retina, and it is also the only source of blood flow to the avascular fovea. Choroid angiopathy seems to be involved in the underlying mechanisms and advancement of DR. Some researchers have suggested that diabetic choroidopathy may be responsible for unexplained visual acuity decline in diabetic individuals without retinal changes [10]

Regarding the age and gender of the participants in this research, there were no statistically significant differences observed among the various groups (P=0.095) (P=0.811).

In this study, the mean values of duration of diabetes varied among the different groups (p <0.001). The longer the duration of DM, the more severe the state of the retinopathy. The duration of diabetes seems to be a significant factor that raises the likelihood of DR advancing. Li et al.[11] found that the duration of diabetes is a separate risk factor for the development of various levels of DR, including no-retinopathy, in individuals with type 2 diabetes. In the current study, the distribution of the visual acuity by LogMar was found to be variable among the studied groups but concluding that the more advanced the state of DR the worse the BCVA.

This research used SS-OCT technology to examine the correlation between CT and CV with DR and diabetic-related factors in a substantial sample from the population. The findings indicated that the CT and CV had a tendency to diminish as DR advances. Additionally, it was shown that as the stage of DR progresses, the thickness of the choroid (CT) decreases, and the choroidal vascularity (CV) decreases as well. Additionally, it was shown that the PDR group had the most slender mean choroidal thickness and the lowest mean choroidal volume.

Prior research examining the correlation between CT and DR severity yielded contradictory findings. Several investigations have shown that the choroid in individuals with DR has a reduction in thickness. For example, Lains *et al.* [12] , Shen *et al.* [13] using (EDI-OCT) , Horvath *et al.* [14] using SS-OCT, Esmaeelpour *et al.* [15] using three dimensional 1060-nm (3D-1060nm-OCT), Vujosevic *et al.* [16] using SD- OCT, Querques *et al.* [17] Using EDI OCT, it was discovered that a decrease in CT was associated with the severity of DR. Nevertheless, other studies have shown an increase in CT thickness or no change in CT thickness when examining DR. For example, Rewbury *et al.*[18], Wang *et al.* [19], Kim *et al.* [20], all using EDI-OCT stated that CT increased significantly as the severity worsened from mild/moderate/NPDR to PDR.

This research found a significant difference in choroidal volume across the various groups in all tested locations (p < 0.001*). Additionally, it was discovered that the PDR group had the lowest CV. In agreement with that Gupta *et al.* [21], studied 462 participants and showed, in multiple regression analysis, that participants with diabetes have significantly thinner mean CT and smaller choroidal volume. On the other hand, Ghaseemi *et al*[22] who studied 176 eyes, and showed dissimilar results. The Choroidal Thickness (CT) and Choroidal Volume (CV) measurements were obtained and subjected to statistical analysis. It was observed that the volume of the choroid declines from the first phases of DR until NPDR stage, followed by a little increase in volume during the PDR stage.

This research found a substantial difference in the vascular density index at the SCP deep retinal capillary plexus, and choriocapillaris up to a depth of 30 microns below the basement membrane. The difference was seen among all the studied locations (p <0.001*). Additionally, it was evident that when the level of DR increased, the level of VDI decreased. The PDR group has the lowest VDI. Concurring with this TSAI *et al.* [23], Alsheikh *et al.* [24], Wang *et al.* [25], confirmed that the VDI decreases as DR progressed.

This research used OCTA to produce automated FAZ measurements, which revealed a good association between LogMar Visual acuity and automated FAZ. In agreement with this, Samara *et al.* [26] It was observed that the average size of the FAZ was larger in eyes of individuals with diabetes compared to eyes of those without diabetes.

This study also showed a negative correlation between the automated FAZ area and vascular density index measured at various regions. In agreement with that, Khadamy *et al.* [27] conducted a study which concluded that lower vascular density

and increased FAZ size were associated with more severe DR clinical scale.

CONCLUSIONS

As DR progressed, CT and CV declined. VDI declined as DR advanced. As the disease worsened, the FAZ area enlarged. These results add to the increasing evidence that changes to the choroid plexus contribute to the development of DR.

ACKNOWLEDGEMENT: None

Data Availability: The authors declare that all data supporting the findings of this study are available within the article and its supplementary information file.

Competing interests: The authors declare no competing interests.

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Ethics declarations: All procedures performed in the study followed the 1964 Helsinki declaration and its later amendments, University Ethics Committee approved the project.

Conflict of interest

Mohamed S. Morsy, Hamdy A. El-Koumy, Tamer E. Wasfy, Sharif Y. El Emam. All authors have no conflicts of interest that are directly relevant to the content of this review.

Funding: No sources of funding were used to conduct this review.

Reviewer disclosures: No relevant financial or other relationships to disclose.

Declaration of interest: No financial affiliations or financial involvement with any organization or entity with a financial competing with the subject matter or materials discussed in the review.

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