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# Evaluation of the Macula in Diabetic Patients without Clinical Maculopathy by Optical Coherence Tomography Angiography

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## Abstract

**Background:** The prevalence of diabetes (DM) is increasing worldwide. Microvascular complications like diabetic retinopathy and neuropathy are very likely to occur in diabetic patients.

**Aim:** To assess capillary plexuses and the foveal avascular zone (FAZ) in diabetic cases without clinical maculopathy using OCTA.

**Patients and methods:** This observational study was conducted on ninety eye cases at an outpatient clinic in the Ophthalmology Department of Sayed Galal University Hospital from May 2022 to January 2023. cases were divided into two groups: thirty eyes in ordinary people and sixty eyes in patients with diabetes, who were divided into two subgroups: group (a) involved thirty eyes with DM cases without DR, and group (b) included 30 eyes with non-proliferative diabetic retinopathy.

**Results:** There was a significant variance among groups regarding BCVA. There was no significant variance regarding IOP and CMT ( $p > 0.01$ ). There was a high significant variance among groups regarding SCP% and DCP% ( $p < 0.001$ ). There was also a significant variation in FAZ in SCP and IN DCP ( $p = 0.01$ ). Significant correlations were among FAZ and cholesterol, TG, and HbA1c ( $p < 0.0001$ ). At the same time, FAZ and IOP had an insignificant association ( $p > 0.01$ ).

**Conclusion:** OCTA is a noninvasive method that can help diagnose and monitor eyes with DR. OCTA was used to identify enlargement of the FAZ and accurately delineate the edges of these zones in SCP & DCP in DM cases without clinical maculopathy.

**Keywords:** Macula; Diabetic patients; Optical coherence tomography angiography

## 1. Introduction

The prevalence of people with DM is rising all over the world.<sup>1</sup> even though treatments for diabetes have progressed a long way in the last 20 years, many people who have DM are still at high risk for microvascular consequences like DR and diabetic neuropathy. DR is the most severe complication that can happen to people with both type 1 and type 2 DM.<sup>2</sup>

Recently, OCTA, a new noninvasive depth-resolved retinal scan method, has made it easier to assess early changes in the macular and peripapillary capillary networks in people with diabetes.<sup>3</sup>

Microvascular changes seen by OCTA mainly include remodelling and enlargement of the FAZ, capillary nonperfusion, and lower vascular

density. More recently, it was found that cases of DM are more likely to have venous beading increased vascular tortuosity in the macular region.<sup>4,5</sup>

The study's goal was to assess capillary plexuses and the FAZ using OCTA in diabetic patients with no clinical maculopathy

## 2. Patients and methods

This observational study was performed on ninety eyes of cases going to an outpatient clinic in the Department of Ophthalmology of Sayed Galal University Hospital from May 2022 to January 2023.

Inclusion criteria: forty to sixty years old, history of type 2 DM for more than five years, and explicit ocular media.

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Exclusion criteria: proliferative DR, optical coherence tomography evidence of various types of diabetic macular oedema, refractive error of greater than +/- six diopters, opaque media, history of surgery on the eye (except for cataract extraction) that is greater than twelve months, history of therapy for DR or maculopathy (for example, laser or intravitreal injections), acquired or congenital retinal or optic nerve disorder that may affect interpretation of the results, uncooperative cases, & cases with poor fixation.

#### Ethical consideration

The ethical guidelines established by the ethical committees of the hospitals at Al-Azhar University were followed. After being informed about the study, every participant gave written permission.

#### Study Tools

The control group comprised thirty eyes from fifteen healthy people of similar age and gender. Each person's eyes were examined as recommended for correct statistical analysis. Group of study: Sixty eyes of DM cases were split into two groups: Group (a) has thirty eyes from people with diabetes who do not have DR, and Group (b) has thirty eyes from people with diabetes with non-proliferative diabetic retinopathy.

All subjects underwent evaluations by Careful history-taking.

A full ophthalmological assessment includes measuring the BCVA utilizing Snellen's chart and converting it to LogMAR notation, which is used in statistical analysis. The measurement of refraction was conducted using the Topcon auto-refractometer RM 800. The slit lamp biomicroscopy is performed to examine the anterior segment for the identification of any abnormalities such as corneal opacity, lens opacity, & anterior chamber activity. Assessment of IOP via the Goldmann application tonometer. The posterior segment inspection involves the use of a binocular indirect ophthalmoscope & indirect slit lamp biomicroscopy using a +90 volk lens. This allows for a good evaluation of the macula and optic nerve heads and any past surgery or retinal laser treatment. Measurement of HbA1c. Assessment of Lipid Profile, including cholesterol, HDL, triglycerides, VLDL, and LDL measurements. Utilizing Standard Structural Optical Coherence Tomography to examine the optic nerve head and macula (SWEPT source OCT, Topcon's DRI Optical Coherence Tomography Triton) (SWEPT source-OCT) scans (512 A-scans, 20°×20°) with the "OCT2 Module" can record up to 100,000 A-scans per second with a transverse section of eight micrometres and 2.6 micrometer digital resolution.

The following imaging protocol was applied:

**Macula scan:** The central scanning raster lines focused on the fovea. The central foveal thickness was automatically assessed by SWEPT source OCT, specifically as the thickness of the central one-millimetre sub-field in the Early Treatment DR Study configuration. A macula map was utilized to measure the overall thickness of the retina, the ganglion cell complex, and the outer retinal layer.

**Optic disc scan:** SWEPT source OCT provides RNFL thickness values and measurements of the cup/disc (C/D) ratio.

**Optical coherence tomography angiography:** for FAZ measurement of all eyes utilizing the same machine. Optical Coherence Tomography angiograms of the deep and superficial networks were captured. The deep and superficial capillary plexuses were distinctly assessed using automatic layers' segmentation. Performed by optical coherence tomography, the superficial capillary plexus was segmented from the internal limiting membrane to the inner nuclear layer, and the deep capillary plexus was segmented from the internal limiting membrane to the outer plexiform layer. The foveal avascular zone area was evaluated in both layers, utilizing the "Draw region" tool to outline the foveal avascular zone area (the inner border of the most visible central blood capillaries). Image J software estimated The vessel area density after changing the collected pictures into binary formats. Three separate researchers masked all other results to the retinal thickness and best correct visual acuity and performed this manual measurement. To get the most out of the study, we averaged their measurements. The protocol consisted of a sequence of two hundred and fifty-six sections covering a central 10° × 10° area recorded in high-resolution mode (512 A-scans) spaced by six micrometres among individual sections.

#### Statistical analysis

The information was entered into the computer and analyzed using version 20.0 of the IBM SPSS software program (Armonk, NY: IBM Corp.). In describing qualitative data, percentages and numbers were utilized. Utilizing the Kolmogorov-Smirnov test, the normality of the distribution was confirmed. The range (maximum and minimum values), standard deviation, mean, interquartile range (IQR), and median were employed to characterize the quantitative data. At the 5% significance level, the derived results were deemed significant. ANOVA and the chi-square test were both employed. 0.05 is considered significant, and 0.01 percent is considered highly significant.

### 3. Results

This table demonstrated that there wasn't significant variation among groups as regard demographic data (Age and Gender) p= (0.44, 0.88) respectively. (Table 1)

Table (1): Comparison among groups regarding demographic data

	GROUP (A)	GROUP (B)	CONTROL L	P
AGE(YEARS)				0.44
MEAN ± SD	45.93 ± 2.35y	44.33 ± 2.54y	43.6 ± 2.91y	
MEDIAN (MINIMUM - MAXIMUM)	45 (42-51)y	44 (40-49)y	44 (38-49)y	
GENDER				0.88
MALE	12	17	14	
FEMALE	18	13	16	

X2: Chi Square, ANOVA Test, p value >0.05: nonsignificant, p value <0.05 significant

This table demonstrated that there was high significant variation among groups regarding duration and hemoglobin A1C p <0.001. (Table 2)

Table 2. Comparison among groups as regard characters of DM.

	GROUP (A)	GROUP (B)	CONTROL	P VALUE
TYPE OF DM				
TYPE 2	30	30	-	1
DURATION(YEARS)				<0.001
MEAN ± SD	17.23 ± 0.82y	25.13 ± 2.33y	-	
MEDIAN (MINIMUM-MAXIMUM)	17 (16-19)y	25 (22-29)y	-	
HBA1C(%)				<0.001
MEAN ± SD	5.99 ± 0.37%	7.82 ± 0.8%	4.79 ± 0.23%	
MEDIAN (MINIMUM-MAXIMUM)	5.95 (5.4-6.6)%	7.7 (6.4-9.2)%	4.8 (4.5-5.2)%	

This table showed that there was a high significant distinction among groups regarding lipid profile (TG, HDL, LDL, and VLDL) p<0.001 in all parameters. (Table 3)

Table 3. Comparison between groups as regard lipid profile

	GROUP (A)	GROUP (B)	CONTROL	P VALUE
CHOLESTEROL				<0.001
MEAN ± SD	192.17 ± 10.86mg/dl	220.27 ± 20.39 mg/dl	138.93 ± 5.37 mg/dl	
MEDIAN (MINIMUM-MAXIMUM)	190 (176-214) mg/dl	219 (189-252) mg/dl	138 (131-151) mg/dl	
TG				<0.001
MEAN ± SD	171.57 ± 8.37 mg/dl	218.43 ± 23.29 mg/dl	131.17 ± 5.09 mg/dl	
MEDIAN (MINIMUM - MAXIMUM)	172 (158-184) mg/dl	214.5 (186-267) mg/dl	131.5 (122-140) mg/dl	
HDL				<0.001
MEAN ± SD	44.37 ± 2.59 mg/dl	42.23 ± 1.61 mg/dl	51.03 ± 4.27 mg/dl	
MEDIAN (MINIMUM - MAXIMUM)	44 (40-50) mg/dl	42 (40-45) mg/dl	51.5 (43-58) mg/dl	
LDL				<0.001

MEAN ± SD	91.13 ± 6.53 mg/dl	124.37 ± 13.12 mg/dl	79.37 ± 5.19 mg/dl	
MEDIAN (MINIMUM - MAXIMUM)	90.5 (79-105) mg/dl	126 (97-145) mg/dl	79.5 (71-89) mg/dl	
VLDL				<0.001
MEAN ± SD	34.83 ± 1.9 mg/dl	38.53 ± 3.14 mg/dl	30.13 ± 1.57 mg/dl	
MEDIAN (MINIMUM - MAXIMUM)	35 (32-39) mg/dl	38 (33-45) mg/dl	30 (28-33) mg/dl	

### ANOVA Test

This table showed that there was a high significant variance among groups with regard to BCVA and Fundus Exp <0.001. On the other hand, no significant variation was found regarding IOP and CMT p-values greater than 0.01. (Table 4)

Table 4. Comparison among groups as regard BCVA, IOP, Fundus Ex and CMT.

	GROUP (A)	GROUP (B)	CONTROL	P VALUE
BCVA(LOGMAR)				<0.001
MEAN ± SD	0.3 ± 0.13	0.47 ± 0.26	0.21 ± 0.09	
MEDIAN (MINIMUM - MAXIMUM)	0.3 (0.1-0.6)	0.45 (0.1-1)	0.2 (0.1-0.4)	
IOP(MMHG)				>0.01
MEAN ± SD	15.37 ± 2.09mmHg	16.1 ± 2.21 mmHg	15.7 ± 1.12 mmHg	
MEDIAN (MINIMUM - MAXIMUM)	16 (12-19) mmHg	17 (15-18) mmHg	16 (14-18) mmHg	
FUNDUS EX				
NORMAL	30	0	30	
MILD NPDR	0	30	0	
CMT				<0.01
MEAN ± SD	235.21 ± 2.03µm	238.51 ± 19.04 µm	223.3 ± 8.2 µm	
MEDIAN (MINIMUM-MAXIMUM)	236 (230-240) µm	239 (220-258) µm	224 (207-236) µm	

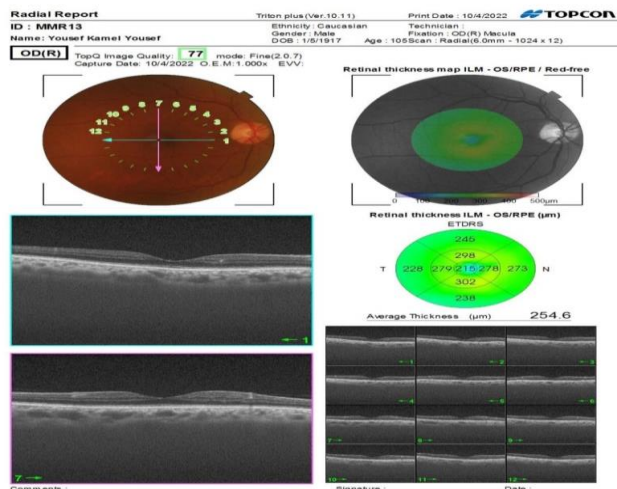
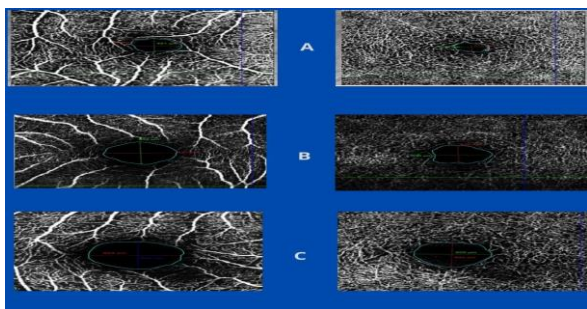


Figure 1. Macular Thickness using Topcon's DRI OCT Triton.

This table showed that there was high significant variation among groups regarding SCP% and DCP% p-values lower than 0.001, but there was significant variation with regard to FAZ IN SCP and IN DCP p = 0.01. (Table 5)

**Table 5. Comparison among groups regarding FAZ IN SCP, DCP, Macular perfusion in SCP% and DCP%**

	GROUP (A)	GROUP (B)	CONTROL	P
FAZ IN SCP				0.01
MEAN ± SD	0.35 ± 0.12mm <sup>2</sup>	0.41 ± 0.17 mm <sup>2</sup>	0.31 ± 0.11 mm <sup>2</sup>	
MINIMUM - MAXIMUM	0.2-0.55 mm <sup>2</sup>	0.2-0.68 mm <sup>2</sup>	0.18-0.63 mm <sup>2</sup>	
FAZ IN DCP				0.01
MEAN ± SD	0.27 ± 0.08 mm <sup>2</sup>	0.32 ± 0.11 mm <sup>2</sup>	0.22 ± 0.11 mm <sup>2</sup>	
MINIMUM - MAXIMUM	0.17 -0.50 mm <sup>2</sup>	0.12-0.50 mm <sup>2</sup>	0.08-0.50 mm <sup>2</sup>	
SCP%				<0.01
MEAN ± SD	47.62 ± 4.18%	45.1 ± 2.81%	50.97 ± 3.93%	
MEDIAN (MINIMUM - MAXIMUM)	47.81 (38-53) %	44.5 (41-50) %	51 (44-58) %	
DCP%				<0.01
MEAN ± SD	52.3 ± 2.17%	50.03 ± 0.76%	56 ± 2.17%	
MEDIAN (MINIMUM - MAXIMUM)	52 (49-56) %	50 (49-51) %	56 (52-61) %	



**Figure 3. DCP (right) & FAZ in SCP (left) of A. normal healthy individual B. no retinopathy cases C. NPDR cases demonstrate enlargement of FAZ in SCP & DCP In DR cases.**

This table demonstrated that there were strong significant correlations among foveal avascular zone & cholesterol, TG, and HbA1c (p<0.0001). While there was an insignificant correlation between FAZ and IOP (p-value > 0.01), (Table 6)

**Table 6. Correlations among Foveal avascular zone & risk factors**

CORRELATIONS		
CHOLESTEROL	r	0.494**
	P	<0.0001
TG	r	.428**
	P	<0.0001
HBA1C	r	.550**
	P	<0.0001
IOP	r	.231
	P	>0.01

P value< 0.05 is significant; P value< 0.01 is highly significant

**4. Discussion**

The main results of this study were the following: There was no significant variance between the two groups regarding sex and age. This was by Mazhar et al., who demonstrated no statistically significant variance in the occurrence of diabetic retinopathy among the two genders. The result has also been shown in other studies. 6, 7

A clinic-based retrospective longitudinal study of Japanese people with type 2 DM found that being women was an independent risk factor for the enhancement of diabetic retinopathy, with more cases of PDR in women at the start of the investigation.8 Also, DR gets worse during pregnancy, which suggests that sex hormones may play a role in retinal damage in diabetes.9

Our findings demonstrated significant variance between the two groups regarding duration and HbA1c.

This study found that DR risk increased when the duration of DM increased. Azeze et al. also discovered that having diabetes for a longer time is strongly correlated with the progression of diabetic retinopathy. This discovery supports their findings. One possible explanation for this correlation is that the retinal artery widens with increasing DM duration; this is a subclinical marker of endothelial function impairment, eventually leading to diabetic retinopathy. 10

Regarding HbA1c, Shiferaw et al. reported twenty-three articles with 18,099 study participants involved in their meta-analysis.11 When haemoglobin A1C was examined as a categorical variable, poor glycemic control (a haemoglobin A1C greater than seven percent) was correlated to an increased risk of DR in comparison to having reasonable glycemic control (odds ratio = 1.25; 95% confidence interval: 1.14, 1.38). Similar results about glycosylated haemoglobin were shown in the study of Keech et al.12

Our findings indicated a statistically significant difference in lipid profile among both groups. Ucgun et al. conducted a clinical study to evaluate the association between lipid lelipidsin the blood and exudative diabetes maculopathy in a group of fifty-four cases with NPDR. The study population consisted of twenty-seven cases with exudative diabetes macular oedema (group A) and similar cases without the disease (group B). The serum cholesterol concentrations (p-value = 0.038) and low-density lipoprotein cholesterol (p-value = 0.026) exhibited a statistically significant rise in group A. However, the two groups had no significant variances in the levels of very low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, or triglycerides. 13 In contrast, in the current study, Rashidi et al.

reported no significant variations among subjects with and without DR in total low-density lipoprotein cholesterol, triglycerides, or high-density lipoprotein.<sup>14</sup>

In this work, there was a high, significant variance between BCVA and Fundus Ex among both groups. However, no significant difference was found regarding IOP and CMT.

This was in line with AHMED et al.'s cross-sectional design in total. One hundred and two of fifty-one selected Egyptian DM subjects, twenty men and thirty-one women, were selected. Eyes enrolled in the investigation were split into three groups as follows: Group one: eyes with non-clinically detectable diabetic retinopathy; Group two: eyes with non-proliferative diabetic retinopathy; Group three: eyes with proliferative diabetic retinopathy. The findings demonstrated a statistically significant reduction in best-corrected visual acuity in eyes with proliferative diabetic retinopathy in comparison to eyes with non-proliferative diabetic retinopathy and eyes with no clinically detectable DR.<sup>15</sup>

On the other hand, Hanyuda et al. found that the intraocular pressure values were significantly greater in participants with DM than in those without DM ( $14.4 \pm 0.1$  versus  $13.9 \pm 0.1$  mm of mercury,  $P < 0.001$ ).<sup>16</sup>

Our results showed a high significant variance among groups regarding SCP% and DCP%; there was also significant variance about FAZ IN SCP IN DCP.

Takase et al. showed that Optical Coherence Tomography Angiography (RTVue XR Avanti) images of sixty-three eyes had been analyzed. The eyes were age-matched control eyes: twenty-four eyes with NDR, twenty eyes with nonproliferative diabetic retinopathy (three eyes with NPDR (moderate), and seventeen eyes with NPDR (mild). ImageJ software calculated the foveal avascular zone area in each eye's DCP and superficial capillary plexus. The images are binarily analyzed before measuring the FAZ area in millimetre squares. Compared to the control group ( $0.25 \pm 0.06$  mm<sup>2</sup>), the NDR and diabetic retinopathy groups showed a significantly higher mean foveal avascular zone area ( $0.37 \pm 0.07$  millimetres square) in the SCP ( $0.38 \pm 0.11$  millimetres square), with a p-value of less than 0.01. In the DCP, the control group also had an average foveal avascular zone area of  $0.38 \pm 0.11$  millimetres square. In comparison, the NDR and diabetic retinopathy groups had significantly larger average foveal avascular zone areas of  $0.54 \pm 0.13$  millimetres square and  $0.56 \pm 0.12$  millimetres square, respectively (P-value greater than 0.01). These results suggest that optical coherence tomography angiography may effectively find early microvascular changes before retinopathy is present during clinical

assessment.<sup>17</sup>

Laotaweerungsawat et al. reported their study: 329 eyes from 329 cases were involved in this study: ninety non-DM patients, 170 DM cases without retinopathy, fifty-seven cases of diabetes causing nonproliferative diabetic retinopathy ranging from mild to moderate, twelve people with diabetes with severe nonproliferative diabetic retinopathy to PDR. Patients underwent optical coherence tomography angiography imaging. They noted an enhancement in the FAZ area as the severity of illness enhanced; the control group demonstrated a statistically significant distinction compared to the NPDR/PDR group. The foveal avascular zone area is more significant in eyes with diabetic retinopathy compared to controls and cases without the disease, according to some investigators.<sup>18</sup>

Our study demonstrated solid and significant associations between the foveal avascular zone and cholesterol, TG, and HbA1c.

This agreed with Schreur et al., who demonstrate that mean haemoglobin A1C ( $p < 0.001$ , HR 1.023), haemoglobin A1C variability (p-value lower than 0.001, heart rate 1.054), age of onset of type one diabetes (p-value lower than 0.001, HR 1.024), high-density lipoprotein cholesterol ( $p = 0.002$ , HR 0.502), & total cholesterol ( $p = 0.029$ , HR 1.210) demonstrated an independent correlation with faster progress of any form of diabetic retinopathy. The mean haemoglobin A1C ( $p < 0.001$ , HR 1.023) was associated with the quick progression of DR.<sup>19</sup> Research has investigated the impact of elevated blood sugar levels on the advancement and progress of DR. An exponential enhancement in the risk of microvascular problems is likely to occur with increasing levels of haemoglobin A1C. Consequently, those who exhibit more significant variance in haemoglobin A1C are at a higher average risk. One further hypothesis that could be considered is that enhancing glycemic control may result in an early deterioration in retinopathy prior to a subsequent enhancement in the long term. This occurrence has been documented by the Complications Trial & Diabetes Control. The retina may not have sufficient time to recover from the harmful impacts of elevated haemoglobin A1C through low haemoglobin A1C times due to the rapid fluctuations in glycemic control.<sup>19</sup>

#### 4. Conclusion

OCTA is a useful technique in monitoring and diagnosing DR due to its noninvasive nature. Enlargement of FAZ in DCP and superficial capillary plexuses in DM cases without clinical maculopathy was detected utilizing optical coherence tomography angiography, which precisely delineated the edges of these zones. Despite the clinical fundus picture, DM duration affects macular perfusion.

## Disclosure

The authors have no financial interest to declare in relation to the content of this article.

## Authorship

All authors have a substantial contribution to the article

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