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Original article

Correlation between Macular Non-Perfusion and Patterns of Corresponding Retinal Layers in Diabetic Patients

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ABSTRACT

Background: Diabetic retinopathy is a common deficiency of diabetes mellitus. Diabetic macular ischemia [DMI] is a permanent form of diabetic maculopathy, and its presence reduces the potential benefits of diabetic retinopathy management. Optical coherence tomography [OCT] is used to precisely and reliably measure the macular thickness and outline the retinal layers. Optical coherence tomography angiography [OCTA] can be utilized as a reliable tool to classify the superficial capillary plexus [SCP], the deep capillary plexus [DCP] and the capillary non-perfusion [NP].

Aim of the work: The current research aimed to investigate the correlation between macular non-perfusion that diagnosed by OCTA and patterns of macular layers that diagnosed by OCT scans through the same parts, in a trial to help in the evaluation of both structural and vascular integrity.

Patients and Methods: The study included 250 eyes of 125 diabetic patients. All study participants were scanned by OCTA. OCT angiograms were re-sampled with OCT scans from the same region, permitting synchronous evaluation of structure and blood flow.

Results: 250 of 125 diabetic patients were categorized into two groups according to capillary NP, ischemic [G1] and non-ischemic [G2]. In current study the incidence of DMI was 40%. The incidence of DCPNP was 100% in eyes with DMI while the incidence of SCPNP was 71%. The incidence of foveal avascular zone [FAZ] irregularity, disorganization of the retinal inner layers [DRIL], inner/outer segment IS/OS and external limiting membrane ELM disruptions were 100%, 83%, 95%, 71% respectively among eyes with DMI. DCPNP was more found in all eyes with FAZ irregularity, DRIL, IS/OS and ELM disruption than SCP NP which makes it as the central cause of structural changes in the retina during ischemia. There was a strong positive correlation between the appearance of FAZ irregularity, DRIL, IS/OS and ELM disruption with each of the duration and severity of DR.

Conclusion: FAZ irregularity, DRIL, IS/OS and ELM disruption are considered reliable OCT/OCTA findings that reflect an underling DMI and their existence can influence the visual prognosis.

Keywords: Diabetic Macular Ischemia; Optical Ccoherence Tomography Angiography; Disorganization; Retina; Deep Capillary Plexus.

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* Main subject and any subcategories have been classified according to the research topic.

INTRODUCTION

Diabetic retinopathy [DR] is a well-known complication of diabetes mellitus [DM] and is considered a dominating cause affecting vision worldwide [1]. Its prevalence is 34.6% worldwide [2]. It may induce numerous drawbacks including diabetic macular edema [DME] and diabetic macular ischemia [DMI] [3]. DMI is an alarming sign of DM. We are still inadequately understanding the pathogenesis, progress, complications, and management options for this disease [4]. DMI is typically associated with retinal dysfunction. DR progression is expected by its diagnosis [5]. DMI is defined as enlargement and disturbance of the foveal avascular zone [FAZ] and also retinal capillary NP in other non-contiguous macula parts [6].

In patients with retinal microcirculation [deep capillary plexus, blood flow is classified predominantly into superficial capillary plexus [SCP] and deep capillary plexus [DCP]. The choroidal circulation, including photoreceptor internal section [IS] band, which is the most valuable oxygen user, tends to be the most essential vascular supply to the central macula [7]. The DCP is likely to be responsible for up to 15% of the photoreceptors' blood supply [8].

Optical coherence tomography angiography [OCTA] has been applied for three dimensional mapping at microcirculation level. It enables the recognition of retinal and choroidal configurations via motion contrast imaging and scanning at high speed, which discriminates blood flow by evaluating signal de-correlations between scans. Both inner and outer retinal capillary plexus are imaged in contra-distinction in traditional angiography, which does not efficiently image the outer plexus [9]. OCTA is advantageous being a non-invasive, dyeless method that undoubtedly outlines abnormal retinal vessels and non-perfusion areas [10].

Recent publications have shown that OCTA specifically indicates non-perfusion in DR [11], presenting an objective, automatic analysis of macular capillary NP as a possible indication of central ischemia [12]. The disturbance of photoreceptors [13], the disruption of the external limiting membrane [ELM] and the disorganisation of the retinal inner layers [DRIL] in OCT in diabetic patients could seem to be credible indicators of underlying non-perfusion [14]. Recently, there has been an attention to determine the prognostic value of changes on OCT such as the integrity of retinal layers [15].

AIM OF THE WORK

The goal of this analysis was, therefore, to define the association between macular non-perfusion and macular layer patterns from the same region, enabling both structural and vascular integrity to be assessed.

PATIENTS AND METHODS

Study population & design: The study included 250 patients with diabetes with or without clinical manifestations of DR. Their age was varied from 18 to 50 years old. Patients with former intraocular surgery or other retinal pathology [retinal artery occlusion, retinal vein occlusion vitreo-macular traction, glaucoma, high myopia… etc.] were ***excluded*** from the study. Moreover, patients with a history of macular laser photocoagulation, those who have significant media opacity that prevents adequate image, patients with poor image quality on OCTA [e.g. poor signal strength <5, poor fixation leading to motion or doubling artifacts] were also ***excluded*** from the study.

Examination protocol & measurements: Each participant had a thorough ophthalmologic examination, that included refraction, best corrected visual acuity [BCVA], intra ocular pressure [IOP] measured by Goldmann applanation tonometry, slit-lamp biomicroscopic examination of the anterior segment and dilated fundus examination [with the aid of +90 diopter non-contact lens]. DR severity was defined and graded on the basis of the modified [early treatment diabetic retinopathy study [ETDRS] criteria**.**

Image acquisition protocol: All images were gained using OCTA system [Optovue RTVue XR Avanti; Inc., Fremont, CA, USA]. This scheme uses the algorithm of split-spectrum amplitude de-correlation angiography [version 2017.100.0.35] and runs to obtain OCTA volumes consisting of 304 x 304 A-scans at 70,000 A-scans per second. Using an advanced software algorithm, OCTA images of the superficial and deep capillary networks were generated separately. The boundaries of SCP ranged from 3μm below the inner restricting membrane to 15μm below the IPL on the basis of these default settings [inner plexiform layer], DCP extended from 15 to 70 um below IPL, OCT angiograms are resampled

with OCT scans from the same region, permitting structures and blood flow to be measured simultaneously. In 6 mm x 6 mm parts based on the fovea, the scan field was captured. Structural images were used to discern whether regions of hypo-reflectivity or hyper-reflectivity were not actual [e.g., due to intraretinal fluid or hard exudates]. DMI was identified as FAZ and its perifoveal capillary arcade disturbance and retinal capillary loss [non-perfusion] in other non-contiguous areas of the macula.

The superficial and deep capillary plexus are tested in other noncontiguous areas of the macula for foveal avascular zone disturbance or retinal capillary failure [capillary non perfusion].

Retinal layers were examined by OCT scans in the same areas of capillary non perfusion for the absence or presence of disruption at the inner segment /outer segment [IS/OS], external limiting membrane [ELM] and DRIL. IS/OS disruption was defined as discontinuity in the IS/OS layer. ELM disruption was defined as any discontinuity in the ELM.

DRIL is the failure to recognize the borders between the complex of the ganglion cell-inner plexiform layer and was assessed as a single layer complex because of the difficulties of separating between these two layers in scans without pathology of normal retinas.

Statistical analysis: data were analyzed by the statistical package for social sciences, version 20.0 [IBM, SPSS Inc., Chicago, Illinois, USA]. Quantitative [numerical] data were represented as mean± standard deviation [SD]. Qualitative data were introduced in the form of their frequencies and percentages. One sample *t*-test was used to compare between two means and Chi-square [x^2] was used to calculate the association between qualitative parameters. The p-value < 0.05 was then found to be statistically significant.

RESULTS

250 eyes of 125 diabetic patients [40 female patients and 85 males] were enrolled in this study. Their mean age was 37.52±8.32 years. They were classified into two groups according to the existence of non-perfusion [NP] on OCTA into: Group 1 [G1] ischemic group with 100 eyes [40%] & Group 2 [G2] non-ischemic group with 150 eyes [60%].There was a statistically significant difference between both groups regarding duration of DM, with a significant increase in G1 than G2 [15.05±4.58 vs. 9.49±4.37 years, respectively]. Besides, there was a statistically significant difference between both groups regarding mean BCVA, which was lower in G1 than G2 [0.11±0.08 vs 0.82±0.17]. The incidence of ischemia among diabetic patients was 40%. All eyes [100%] in G1 had FAZ irregularity, [71%] of them had both SCP and DCPNP while [29%] had DCPNP alone without SCPNP. So, DCPNP alone was responsible for 29% of the incidence of FAZ irregularity and this incidence increases to 71% when both capillary plexus are affected [Table 1].

IS/OS disruption: There was a highly statistically significant difference between both groups. Among 100 eyes with NP, there were 95 eyes with IS/OS disruption in G1 compared to zero in G2. 71 eyes had both SCP and DCPNP and 24 eyes had DCPNP alone without SCPNP. So, DCPNP was responsible for 25.2% of the incidence of IS/OS disruption and this incidence increase to 74.7% when there is both capillary plexus affection [Table 2 & 3].

DRIL: There was a highly statistically significant difference between both groups. Among 100 eyes of G1, the DRIL was recognized among 83% compared to none in G2. Of eyes with DRIL, 71 [85.5%] had both SCP and DCP NP and 12 [14.4%] had DCP NP alone without SCP NP. So, DCP NP was responsible for 14.4% of the incidence of DRIL and this incidence increases to 85.5% when there was both capillary plexus affection [Tables 2 & 3].

ELM disruption: There was a highly statistically significant difference between groups. In G1, it was reported among [71%] while no patients developed it in G2. All eyes with ELM disruption had both SCP and DCPNP; no eyes had DCPNP alone. It seems that ELM disruption was more prevalent when both capillary plexus are affected together [Tables 2 & 3].

Relationship between OCT findings and duration of diabetes, BCVA and DR Grade:

IS/OS Disruption: Among 95 eyes with IS/OS disruption, there were 31 [32.6%] eyes of DM duration less than 10 years and 64 [64.3%] eyes with a duration of more than 10 years. Also there were 31 [32.6%] eyes with moderate NPDR and 64 [67.4%] with higher grades of retinopathy [severe NPDR &

PDR]. Additionally, there were 56 [58.9%], 16 [16.8%], 8 [8.4 %], 15 [15.7%] had BCVA of 0.05, 0.1, 0.166, and 0.25 respectively [Table 4].

DRIL: Among 83 eyes with DRIL, there were 31 [37.7%] of DM duration <10 years and 52 [62.3%] with a duration of > 10 years. Also there were 31 [37.7%] with moderate NPDR and 52 [62.3%] with higher grades of retinopathy [severe NPDR & PDR]. Besides, there was 25 [67.4%], 16 [19.2%], 8 [9.6%], 3 [3.6%] had BCVA of 0.05, 0.1, 0.166, 0.25 respectively [Table 4].

ELM disruption: Among 71 eye with ELM disruption, there were 22 [30.9%] eyes of DM duration < 10 years and 49[69.1%] eyes with a duration of > 10 years. Besisdes, there were 22 [30.9%] with moderate NPDR and 49[69.1%] with higher grades of retinopathy [severe NPDR & PDR]. Additionally, 56 [78.8%], 15 [21.1%] eyes had BCVA of 0.05 and 0.1 respectively [Table 4].

FAZ irregularity: Among 100 eyes with irregular FAZ, there were 36 [36%] of DM duration < 10 years and 64 [64%] with a duration of > 10 years. Also there were 36 [36%] eyes with moderate [non proliferative diabetic retinopathy] NPDR and 64 [64%] eyes with higher grades of retinopathy [severe NPDR & PDR]. Furthermore, BCVA 56 [56%], 16 [16%], 8 [8%] eyes, 15 [15%], 5 [5%] had BCVA of 0.05, 0.1, 0.166, 0.25, 0.3 respectively **[Table 4].**

Table [1]: Comparison between the ischemic group and non-ischemic groups according to non-perfusion [SCP & DCP].

		Ischemic Group [n=100]	Non Ischemic Group [n=150]	Total [n=250]	x^2	p-value
Non perfusion [SCP]	Non perfusion	71 [71.0%]	0 [0.0%]	71 [28.4%]	148.743	<0.001**
	Normal	29 [29.0%]	150 [100.0%]	179 [71.6%]		
Non Perfusion [DCP]	Non perfusion	100 [100.0%]	0 [0.0%]	100 [40.0%]	250.000	<0.001**
	Normal	0 [0.0%]	150 [100.0%]	150 [60.0%]		

x^2: Chi-square test; **p-value <0.001 [highly significant]

Table [2]: Comparison between the ischemic group and non-ischemic groups according to OCT features.

OCT		Ischemic Group [n=100]	Non Ischemic Group [n=150]	Total [n=250]	t/x2	p-value
FAZ	Irregular	100 [100.0%]	0 [0.0%]	100 [40.0%]	250.000	<0.001**
	Normal	0 [0.0%]	150 [100.0%]	150 [60.0%]		
IS/OS	Disrupted	95 [95.0%]	0 [0.0%]	95 [38.0%]	229.839	<0.001**
	Normal	5 [5.0%]	150 [100.0%]	155 [62.0%]		
ELM	Disrupted	71 [71.0%]	0 [0.0%]	71 [28.4%]	148.743	<0.001**
	Normal	29 [29.0%]	150 [100.0%]	179 [71.6%]		
DRIL	No	17 [17.0%]	150 [100.0%]	167 [66.8%]	186.377	<0.001**
	Present	83 [83.0%]	0 [0.0%]	83 [33.2%]		

Table [3]: The correlation between the OCT finding and the level of capillary NP.

	Total number in ischemic group [100]	Eyes with both SCP and DCP NP	Eyes with isolated DCP NP [without SCP NP]	*r*
IS/OS disruption	95	71[74.7%]	24[25.2%]	-0.7806
DRIL	83	71[85.5%]	12[14.4%]	-0.8378
ELM disruption	71	71[100%]	0%	-0.7991
FAZ irregularity	100	71[71%]	29[29%]	-0.7442

Table [4]: The relationship between OCT finding and duration , BCVA and DR Grade in the G1 group.

	Time		BCVA					DR severity	
	10 years	>10 years	0.05	0.1	0.166	0.25	0.3	moderate NPDR	Severe NPDR & PDR
FAZ irregularity	36 [36%]	64[64%]	56[56%]	16[16%]	8[8%]	15[15%]	5[5%]	36[36%]	64[64%]
IS/OS disruption	31[32.6]	64[67.4%]	56[58.9%]	16[16.8%]	8[8.4%]	15[15.7%]	0[0.0%]	31[32.6%]	64[67.4%]
DRIL	31[37.7%	52[62.3%]	56[67.4%]	16[19.2%]	8[9.6%]	3[3.6%]	0[0.0%]	31[37.7%]	52[62.3%]
ELM	22[30.9%]	49[69.1%]	56[78.8%]	15[21.2%]	0[0.0%]	0[0.0%]	0[0.0%]	22[30.9%]	49[69.1%]

DISCUSSION

DMI is a significant clinical aspect of DR. The specific depletion of pericytes and basement memberane thickening of retinal capillaries. It is postulated to be due to sensitivity for a long period of time to elevated blood glucose. DMI is clinically characterised by an enlargement of the FAZ and of the capillary NP paramacular regions. OCTA is a promising alternative or supplement to both OCT and fluorescein angiography [FA] in the management of DR. There have been numerous advances using OCTA imaging in diabetic eyes, with an earlier detection of diabetic changes, adequate grading of DR, and more durable quantitative measurements. Morphological and qualitative estimation of vascular changes adds to our knowledge of the patho-physiology of DR [16].

In the current study, the incidence of DMI was 40% and that approve with Sim *et al.* who have illustrated that [approximately 41%] of patients with DR have macular ischemia [17].

In the current work, there was a statistically significant difference between both groups in the incidence of ischemia. FAZ irregularity could be a sign of DMI. 71% of them have both SCP and DCP NP, and only 29% of them had DCP NP alone. This comes in agreement with the results of Khadamy *et al.* [16], Mihailovic *et al.* [18] Choi *et al*.[19], and De Carlo *et al*.[20]; as they found that long before retinopathy progresses, the FAZ region is swollen in the SCP and DCP in diabetic eyes relative to healthy individuals.

There was a matter of debate among studies regarding the level of ischemia. In the current study, FAZ irregularities were found to be more at DCP than controls.This was consistent with Freiberg *et al*.[21] and Minnella *et al*.[22]. However, the studies performed by Ishibazawa *et al*.[3] found that capillary non-perfusion areas are larger in the SCP than in the DCP in DR.

We also have found a strong association between FAZ irregularity and decreased BCVA, long duration of DM, severity of DR. This also was proved by Lee *et al*.[23] and Gozlan *et al*[24], who found that irregularities in the structure or perfusion of FAZ profoundly affect vision. FAZ is enlarged in diabetic eyes as a result of loss of integrity of blood vessels, the shape of FAZ is non-symmetrical due to gaps, holes, or notches of the capillary plexus and the degree of FAZ disruption is correlated with increased DR severity and decreased BCVA, which agrees with our results.

In the present research, a statistically significant relation was found between the presence of interruption of outer retinal layers and each of SCP and DCP NP. This was in line with Lee *et al.* [23] who found a significant correlation between outer retinal abnormalities, especially photoreceptor disruption and the presence of DMI. Also, we found that 14.4 % of cases with outer retinal disruption was at DCP alone which was consistent with Scarinci *et al*.[25] who observed that photoreceptor disruption on OCT in eyes with DMI corresponds to areas of capillary non-flow at the level of DCP using OCTA.

We also found a strong correlation between IS/ OS disruption and decreased BCVA, long duration of DM and severity of DR. There was nearly an approval among studies about that. Nesper *et al.* [26], Hareedy *et al.* [27] and Abd Elhamid [28]. Who claimed that there is a strong relation between the integrity of photo-receptor layer& BCVA.This was approved with our results.

In the current study there was a statistically significant difference between both groups in the incidence of DRIL.Also there was a statistically significant correlation between the presence of DRIL and both SCP&DCP non perfusion. This agrees with the study conducted by Joltikov *et al*.[29] and Moein *et al*.[30] who found that In patients with DRIL, OCT can display retinal ischemia and indicate that retinal ischemia and usual vasculature loss contribute to DRIL. Also, Onishi *et al.* [31] noticed that ischemia can occur at multiple levels in relation to the presence of disorganization of the retinal inner layers which agrees with our results.

We also have found a strong association between DRIL and decreased BCVA, long duration of DM, severity of DR. Das R *et al*.[32] found that the likelihood of having DRIL were greater in eyes with disrupted ELM, disrupted IS/OS and found also the occurrence of DRIL was more likely in eyes with PDR. They concluded that there is an association between both DRIL and IS/OS disruption and increasing DR severity which agree with our results.

Conclusion: OCTA has a significant role in the detection of DMI and identification of its level.The

statistically significant correlation between OCT finding, regarding outer and inner retinal layers and DMI had led us to use OCT as an accurate tool to predict the presence of DMI.

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