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Association of Deep Retinal Capillary Plexus ischemia with Inner Segment/Outer Segment Disruption in Diabetic Macular Ischemia

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ABSTRACT

Background: Diabetic macular ischemia (DMI) is an important cause of visual impairment in patients with diabetic retinopathy. In some patients, it may lead to irreversible visual loss.

Purpose: The aim of the work was to assess the presence of outer retinal structural changes at the level of inner segment /outer segment (IS/OS) in relation to macular capillary non-perfusion at the level of deep capillary plexus (DCP) in diabetic retinopathy (DR).

Patients and Methods: A prospective observational study was carried on 250 eyes of 125 patients. They underwent scanning using Optical coherence tomography/ Optical coherence tomography angiography (OCT/OCTA) simultaneously.

Results: 250 of 125 diabetic patients were classified according to presence of capillary non perfusion (NP), into two groups (ischemic- non ischemic). The incidence of DCP NP was 100% in eyes with DMI while the incidence of superficial capillary plexus (SCP) NP was 71% . The incidence of foveal avascular zone (FAZ) irregularity, inner segment /outer segment (IS/OS) disruption was 100% and 95% respectively among eyes with DMI. DCP NP was more than SCP NP in eyes with FAZ irregularity, which make it the possible main cause of the structural changes in the retina during ischemia. There was a strong association between the presence of IS/OS disruption with duration, severity of DR and BCVA.

Conclusion: It could be concluded that IS/OS disruption is associated with ischemia at DCP. It could be considered a reliable OCT findings that indicate an underling DMI and their presence can affect visual prognosis.

Keywords: Diabetic macular ischemia, Optical coherence tomography angiography, Inner segment /outer segment disruption

INTRODUCTION

Diabetic macular ischemia (DMI) is an important category of diabetic retinopathy (DR) characterized by enlargement and disruption of the foveal avascular zone (FAZ) [(1)]. There is occlusion and atrophy of retinal capillaries in the macula, with narrowing or obliteration of precapillary arterioles [(2)]. The resulting tissue hypoxia leads to up regulation of growth factors, e.g. vascular endothelial growth factor [(3.4)]. In some cases, however, more extensive ischemia develops, and becomes the predominate feature of the maculopathy, in such cases, profound and irreversible visual loss may occur [(5)].

The human macular vascular supply is a complex system comprised of three interconnected capillary plexuses; the superficial capillary plexus (SCP), which lies in the retinal nerve fiber layer, while the middle (MCP) and deep capillary plexus (DCP) are located at the inner and outer borders of the inner nuclear layer, respectively [(6,7)]. This complex vascular arrangement leaves the fovea and the outer retina avascular, with their oxygen demand primarily dependent on diffusion from the choroidal circulation [(8)]. Choroidal circulation appears to be the most important blood supply to the central macula, including photoreceptor inner segment (IS), which is most likely the most important consumer of oxygen[(9)]. It is likely that the DCP is responsible for up to 15% of the blood supply to the photoreceptors especially during dark adaptation [(10)].

Optical coherence tomography angiography (OCTA) has been used for three dimensional mapping at microcirculation level. It allows detection of retinal and choroidal structures via motion contrast imaging and high speed scanning, which detect blood flow by analyzing signal decorrelations between the scans. Both inner and outer retinal capillary plexuses are imaged in contradistinction in conventional angiography, which does not effectively image the outer plexus [(11)].

Many publications have shown that OCTA clearly detects non-perfusion in DR [(12)]. It provides an objective automated study of macular capillary non perfusion (NP) as a potential sign of central ischemia [(13)]. It appears that in diabetic patients, the disruption of photoreceptors [(14)], the external limiting membrane (ELM) disruption and disorganization of the retinal inner layers (DRIL) in optical coherence tomography (OCT) can be manifestation of underlying non-perfusion [(15)].

The aim of the work was to assess the presence of outer retinal structural changes at the level of inner segment /outer segment (IS/OS) in relation to macular capillary non-perfusion at the level of deep capillary plexus (DCP) and photoreceptor abnormalities in diabetic retinopathy (DR).

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PATIENTS AND METHODS

This prospective, cross sectional study included a total of 250 eyes of 125 diabetic patients aged from 18 to 50 years, attending at Al-Zahraa University Hospital. This study was conducted between August 2018 to December 2019. An informed written consent was obtained from each participant for participation in the study and for publication of data, after receiving a full explanation about the study.

***Ethical Consideration*:**

Approval was obtained from the Ethics Board of Al-Azhar University committee. All procedures were conducted in accordance with the Helsinki Declaration guidelines.

Inclusion criteria included diabetic patients with clinical signs of DR.

Exclusion criteria included patients under treatment of medical vascular diseases, history of macular laser photocoagulation, other retinal pathology (retinal artery occlusion, retinal vein occlusion, ARMD, High myopia, macular scar… etc.), patients with poor image quality on OCT angiography (poor signal strength signal <50, poor fixation leading to motion or doubling artifacts).

All patients were subjected to detailed history taking, full ophthalmological examination, including visual acuity, best-corrected visual acuity (BCVA) using an autorefractometer and Landolt's broken ring chart with visual acuity expressed in in decimal units, slit-lamp biomicroscopy, intraocular pressure measurement, fundus examination was done to grade DR according to ETDRS study**.** Visual impairment was graded as mild, moderate and severe. The mild visual impairment was when the visual acuity was worse than 0.5to 0.3. The moderate visual impairment was when the visual acuity was worse than 0.3 to 0.1. The severe visual impairment was when the visual acuity was worse than 0.1.

Image acquisition protocol:

All OCT angiography images were acquired by an OCTA system (Optovue RTVueXR Avanti; Inc., Fremont, CA, USA). This system uses split-spectrum amplitude decorrelation angiography algorithm (version 2017.100.0.35) and operates at 70,000 A-scans per second to acquire OCTA volumes consisting of 304x304 A- scans. OCTA images of the superficial and deep capillary networks were generated separately using the automated software algorithm. Based on these default settings, the boundaries of SCP extended from 3 um below the internal limiting membrane to 15 um below the IPL, The DCP extended from 15 to 70 um below the IPL, OCT angiograms were resampled with OCT scans from the same area simultaneously.

DMI was defined as a disruption of the FAZ and its perifoveal capillary arcade, and by retinal capillary loss (areas of non-perfusion or void of flow) in other noncontiguous areas of the macula. Superficial and deep capillary plexus were examined for the presence of disruption of the foveal avascular zone or presence of retinal capillary loss in other noncontiguous areas of the macula (capillary non perfusion).

Retinal layers were examined by OCT scans in the same areas of capillary non perfusion for the absence or presences of inner segment /outer segment (IS/ OS) of photoreceptors disruption which was defined as any discontinuity in the IS/OS layer.

Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as a mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done: Independent-samples t-test of significance was used when comparing between two means, One sample t-test, Chi-square (x^2) test of significance was used in order to compare proportions between qualitative parameters, The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following: Probability(P-value): P-value$\leq$0.05 was considered significant-value $\leq$0.001 was considered as highly significant-value >0.05 was considered insignificant.

RESULTS

250 eyes of 125 diabetic patients. They were classified into two groups according to the presence of capillary NP *on* OCTA into: Group (1) ischemic group with 100 eyes which comprises (40%) & group (2) Non ischemic group with 150 eyes which comprises (60%). Group (1) included 22 female patients (33%) and 28 male patients (67%) while group (2) included 26 female patients (33%) and 49 male patients (67%). Their mean age was 43.42 years ± 5.04 SD (Range 35-50) and it was 33.58 years ± 8.32 SD (Range 22-50 years) in group 2**.**

There was a highly statistically significant difference between both groups as regard mean duration of diabetes (p-value<0.001). The mean DM duration was 15.05 years± 4.58 SD (range 10-25years) in group (1) and it was 9.49 yeas ±4.37 SD ranges (8-20 years) in group (2). The incidence of ischemia among diabetic patients was 40%.All eyes 100 (100%) in group (1) had FAZ irregularity, 71(71%) eyes of them had SCP NP while 100(100%)eyes had DCP NP (Table 1).

Table (1): Comparison between ischemic group and non-ischemic group according to non-perfusion level (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****
Non-Perfusion (DCP)					
Non-Perfusion	**100 (100.0%)**	**0 (0.0%)**	**100 (40.0%)**	**250.000**	**<0.001****

x^2: Chi-square test; **p-value <0.001 HS,SCP(superficial capillary plexus),DCP(Deep capillary plexus).

There was a highly statistically significant difference between both groups as regard IS/OS disruption, where among 100 eyes with NP, there were 95 eyes with IS/OS disruption in group (1) compared to zero% with no cases in group (2), 71 (74.7%) eyes of them had both SCP and DCP NP (Figure 1) and 24 (25.2%) eyes had DCP NP alone (Figure2) without SCP NP (Table 2 & 3).

Table (2): Comparison between ischemic group and non-ischemic group according to OCT/OCTA features.

OCT	Ischemic Group (n=100)	Non-Ischemic Group (n=150)	Total (n=250)	t/x2#	P-value
Irregular FAZ	**100 (100.0%)**	**0 (0.0%)**	**100 (40.0%)**	**250.000**	**<0.001****
IS/OS Disruption	**95 (95.0%)**	**0 (0.0%)**	**95 (38.0%)**	**229.839**	**<0.001****

FAZ, foveal avascular zone.IS/OS , inner segment/outer segment

Table (3): Correlation between the OCT finding and the level of capillary NP.

	Total number in ischemic group (100)	Eyes with SCP & DCP NP	Eyes with DCP NP	X^2	P-value
S/OS Disruption	**95**	**71(74.7%)**	**24(25.2%)**	**12.888**	**<0.001****

Among 95 eyes with IS/OS disruption, there were 31(32.6%) eyes had duration of diabetes less than 10 years and 64 (67.3%) eyes with duration of more than 10 years with p value(<0,0001). Regarding BCVA, there was 2 0 (21.05%)eyes,24(25.2%)eyes, 55 (57.8 %) eyes ,had mild ,moderate and severe visual impairment respectively with p value(<0,0001). Also the grades of diabetic retinopathy varied among eyes with IS/OS disruption ,where we found 31 eyes showed moderate non proliferative diabetic retinopathy(NPDR) ,32 eyes showed severe NPDR and also 32 eyes showed proliferative diabetic retinopathy(PDR) .This was statistically insignificant (Table4).

Table (4): Correlation between OCT finding and duration, BCVA and DR Grade.

	IS/OS disruption		X^2	P-value
	No	%		
Duration of DM				
<10 Years	31	32.6	22.9263	< 0.0001
>10 Years	64	67.3		
BCVA				
Mild impairment	20	21.05		
Moderate impairment	24	25.2	34.0811.	< 0.00001
Severe impairment	55	57.8		
Severity of DR				
Moderate	31	32.6	0.0316	< .05
Severe	32	33.6		
PDR	32	33.6		

DM, diabetes mellitus. IS/OS, inner segment/outer segment .BCVA, best-corrected visual acuity. DR, diabetic retinopathy.

DISCUSSION

Diabetic macular ischemia (DMI) is a troublesome complication of diabetes mellitus. The pathogenesis, progression, consequences, and treatment options for this disease are still poorly understood [16]. DMI is defined by an enlargement of the FAZ and presence of capillary NP at the paramacular areas [17].

Optical coherence tomography angiography (OCTA) is a new device that provides the ophthalmologists with the capability to explore both the superficial capillary plexus (SCP) and deep capillary plexus (DCP) of the retina. Several studies [18, 19], using either spectral domain optical coherence tomography (OCT) or OCTA reported on the relationship between vascular abnormalities and the outer retinal structure in diabetic retinopathy at the level of both SCP and DCP [20].

Specifically, changes at the level of the DCP on OCTA seem to be associated with photoreceptors loss [21]. However, since there is not an evidence whether these retinal findings should be considered only anatomical retinal changes or associated with a functional impairment, more studies are needed to assess any potential pathological correlation between the DCP impairment and functional alteration into the macular area in patients with diabetic macular ischemia.

Several studies tried to illustrates the relationship between IS/OS disruption and macular ischemia. **Lee *et al.*** [21] studied the relationship between foveal ischemia and spectral-domain optical coherence tomography findings in ischemic diabetic macular edema and found a significant correlation between outer retinal abnormalities, especially photoreceptor disruption and the presence of DMI. This was consistent with our results where we found statistically significant correlation between the presence of an interruption of IS/OS junction and ischemia at both SCP and DCP.

In addition, **Lee *et al.*** [21]**,** work based on fundus fluorescein angiography in detecting DMI. More studies tried to detect the level of ischemia utilizing the segmentation function of OCTA. **Scarinci *et al.*** [20] observed that photoreceptors disruption on OCT in eyes with DMI corresponds to areas of capillary non-flow at the level of DCP using OCTA. This was in excellent agreement with our results. We found that (74.7%) of cases with IS/OS disruption had both SCP and DCP NP while 25.2 % of them had DCP NP alone.

We also found a strong association between IS /OS disruption and decreased BCVA, long duration of DM, severity of DR. There was almost an agreement among studies about that. **Scarinci *et al.*** [20]**, Nesper *et al.*** [22]**, Hareedy *et al.*** [23] **and Abd Elhamid** [24] all have stated that there is strong relation between the integrity of photoreceptor layer& BCVA. This was agreed with our results so it seems that the status of IS/OS disruption could be an important predictor of VA.

As expected our study showed that, there was a highly statistically significant difference between both groups as regard mean duration of diabetes (p-value<0.001) so it seems that presence of ischemia increases with duration of DM**.** Ali, stated that the macular perfusion is markedly affected by diabetes duration [25]. This which was consistent with our results. Though the relation between IS /OS disruption and severity of diabetic retinopathy was investigated in many researches. Our results showed highly statistically insignificant results regarding disease severity. This was consistent with **McAnany and Park** [26] who found photoreceptor layer disruption in early stages of DR.

CONCLUSION

It could be concluded that using OCT/OCTA, this study showed that macular photoreceptor layer disruption in patients with diabetic retinopathy is co-localized to areas of capillary non-perfusion at the level of DCP. This is important in highlighting the contribution of the DCP to the photoreceptors integrity as well as the outer retina in diabetic macular ischemia.

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