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Original article

The Role of Optical Coherence Tomography Angiography to Assess Retinal Perfusion of Non-Proliferative Diabetic Retinopathy

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Abstract

Background: Diabetic retinopathy (DR) is one of the leading causes of visual impairment and blindness in patients aged 20-47 years. Clinically, DR has two stages: non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). The aim of this work was to assess retinal microvasculature abnormalities in different stages of non-proliferative diabetic retinopathy using optical coherence tomography angiography. **Methods:** This cross-sectional case control study was carried out on 90 eyes of 55 subjects attending outpatient clinic of Ophthalmology department (35 of healthy non-diabetic, 15 of mild NPDR, 27 of moderate NPDR and 13 of severe NPDR). **Results:** At 3x3 size scan of OCTA, FAZ and PERIM were significantly more enlarged in case group compared to the control group (both $p<0.001$) however, superficial and deep VD% were significantly lower in case group compared to the control group (both $p<0.001$). There was a significant difference among the three subgroups (mild, moderate and severe) as regards FAZ, superficial and deep VD% (all $p <0.001$). **Conclusions:** OCT angiography can be effectively and efficiently used in diagnosis and follow up of non-proliferative diabetic retinopathy. In the presence of NPDR, OCTA shows progressive increase of FAZ area and reduction of VD in both superficial and deep plexus at increasing DR severity.

Keywords: Optical Coherence Tomography Angiography, retinal perfusion , Non-Proliferative Diabetic Retinopathy.

Introduction

Diabetic retinopathy (DR) is one of the leading causes of visual impairment and blindness in patients aged 20-47. It affects one-third of the over 460 million diabetic patients worldwide. DR results from the long-term effect of hyperglycaemia on the microvasculature of the eye[1,2].

Clinically, DR is divided into two stages: non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) [3].

NPDR represents the early stage of DR. It is further subclassified as mild, moderate, or severe based on clinical features like microaneurysms, hemorrhage, exudates and vascular abnormalities [4]. Despite the importance of NPDR staging for risk stratification and surveillance planning, current grading criteria are subjective, based on qualitative features, and are susceptible to clinician judgment and individual clinical presentation of the patient [5]. NPDR severity status is associated with the risk of further progression to PDR which is a more advanced stage of DR. PDR is characterized by neovascularization [6].

Visual impairment in diabetes is usually related to three different mechanisms: diabetic macular edema, complications of retinal neovascularization (mainly vitreous hemorrhage and retinal detachment), and diabetic macular ischemia (DMI) [7].

Traditionally, patients with diabetic retinopathy were monitored with serial fundus ophthalmoscopy in conjunction with ancillary testing, including fluorescein angiography (FA), to assess for areas of neovascularization, retinal edema and non-perfusion [8].

While FA remains a gold-standard adjunctive test, it requires the injection of dye. Therefore it is not suitable for all patients, including those who have poor venous access and allergy to fluorescein (which may include anaphylaxis) [9].

Optical coherence tomography angiography (OCTA) is a rapid, non-invasive imaging technique that has been used to assess retinal perfusion in DR by detecting motions of erythrocytes and visualizing blood flow using serial optical coherence tomography B-scans [4]. The vascular changes on OCTA have been demonstrated to distinguish healthy eyes from eyes with diabetes and no DR, and to correlate with the severity of DR [10-12].

OCTA has also allowed quantitative measurement of non-perfused area of the macula and characterization of the three distinct capillary plexuses in the macula

(i.e., the superficial [SCP], the middle [MCP], and the deep capillary plexus [DCP]), which show unique pathologic changes in DR eyes [12-14].

The aim of this work was to assess retinal microvasculature abnormalities in different stages of non-proliferative diabetic retinopathy using optical coherence tomography angiography.

Subjects and Methods:

This cross-sectional case control study was carried out from April 2021 to May 2022 on 90 eyes of 55 subjects attending outpatient clinic of Ophthalmology department of Benha University Hospitals. Inclusion criteria were type of diabetic retinopathy (Mild, Moderate, and severe non-proliferative diabetic retinopathy), duration of diabetes (Not less than 5 years), refractive error (Range from -3D to +3D), Types of diabetes (Type 1 and type 2 diabetes), gender (both male and female) and age (All patients were above 18 years).

An informed written consent was obtained from the patients. The study was done after approval from the Ethical Committee Benha University and the Research Institute of Ophthalmology (No. Ms 2-1-2021).

Exclusion criteria were:

presence of media opacities preventing reliable retinal imaging and fundus examination, proliferative diabetic retinopathy, retinal detachment or vitreous haemorrhage, anterior segment pathology, history of glaucoma or optic nerve disease and vitreoretinal surgery or trauma, other macular diseases (macular hole, epiretinal membrane, age related macular degeneration).

On the basis of severity of non-proliferative diabetic retinopathy eyes were classified by dilated fundus examination and fluorescein angiography into four group (35 eyes of healthy non diabetic, 15 eyes of mild NPDR, 27 eyes of moderate NPDR and 13 eyes of severe NPDR).

All participants were subjected to: History taking, laboratory investigation (Glycated haemoglobin “HBA1C”, and random blood sugar), complete ophthalmic evaluation and investigations (Fundus photography, fundus fluorescein angiography and optical coherence tomography Angiography).

Complete ophthalmic evaluation

UCVA & BCVA measurement using Snellen chart with conversion to logMAR notation for statistical analysis. Refraction was measured by (Topcon Auto-refractometer RM 8900).

Anterior segment examination using slit lamp microscopy: Assessment of media clarity (cornea and crystalline lens i.e., no

corneal opacity or cataract). Excluding anterior segment diseases or surgeries that could affect study results (previous cataract or refractive surgeries are not excluded), Pupil examination, Intraocular pressure (IOP) measurement using Goldmann applanation tonometer, Posterior segment examination using binocular indirect ophthalmoscope with 20+D lense (to evaluate periphery of the retina) and indirect slit lamp Biomicroscopy (+90 volk lens) for detailed evaluation of posterior pole.

Fundus photography: using Topcon TRC-50DX Series camera

Fluorescein angiography: Digital retinal camera system (Spectralis HRA2, Heidelberg Engineering, Germany) was used for FA examination after pupillary dilatation with Tropicamide 1% eye drops to assess the grade of NPDR.

Optical Coherence Tomography Angiography (OCT-A) of the macula: all patients were subjected to (the RTVue XR Avanti, Optovue, Inc., OCT-A) after pupillary dilatation with Tropicamide 1% eye drops then data was collected:

OCTA of the superficial and deep networks was captured. SCP and DCP were distinctly evaluated using the automatic layers' segmentation. FAZ area was measured in both layers using software "Draw region" tool to outline FAZ area manually, and Software Automatically calculate the outlined area.

The protocol consisted of a sequence of 256 sections covering central 10° × 10° recorded in the high-resolution mode (512 A-scans) spaced by 6 μm between individual sections.

Statistical analysis

Statistical analysis was done by SPSS v26 (IBM Inc., Armonk USA). Quantitative variables were presented as mean and standard deviation (SD) and were compared by unpaired Student's t- test for the same group, student's t-test to compare mean of two groups and ANOVA test to compare mean of more than two groups. Categorical data was presented as frequency (%) and performed by using chi square test (X2-value) and Fisher exact test (FET). A two tailed P value < 0.05 was considered significant.

Results:

Table (1) shows distribution of all subjects according to sex and examined eye. **(Fig.1)** By comparing the case to control group, there was insignificant difference between both groups as regards sex, eye with NPDR, age, UCVA, BCVA. The mean of IOP was insignificantly different between both groups.

Table (1): Distribution of all subjects according to sex and examined eye, distribution of cases according to grade of DM, type and duration of the disease and Comparison between case and control groups according to sex, examined eye, age, UCVA, BCVA and IOP

		All group (90)		
Sex	**Male**	22 (24.5%)		
	Female	68 (75.5%)		
Eye	**Rt**	42 (46.7%)		
	Lt	48 (53.3%)		
		Case group (55)		
Grade of DM	**Mild**	15 (27.3%)		
	Moderate	27 (49%)		
	Severe	13 (23.7%)		
Type of DM	**Type I DM**	2 (3.7%)		
	Type II DM	53 (96.3%)		
Duration of DM (years)		18.07 ±6.20		
		Case group (55)	**Control group (35)**	**P value**
Sex	**Male**	16 (29.1%)	6 (17.15%)	0.157
	Female	39(70.9%)	29 (82.85%)	
Eye	**Rt**	27(49.1%)	15(42.9%)	0.643
	Lt	28 (50.9%)	20(57.1%)	
Age /year		52.17± 9.57	52.4±5.12	0.79
UCVA		0.468±0.164	0.0±0.0	----
BCVA		0.32±0.133	0.0±0.0	----
IOP		15.22±2.0	15.10±1.46	0.657

Data are presented as mean ± SD or frequency (%)

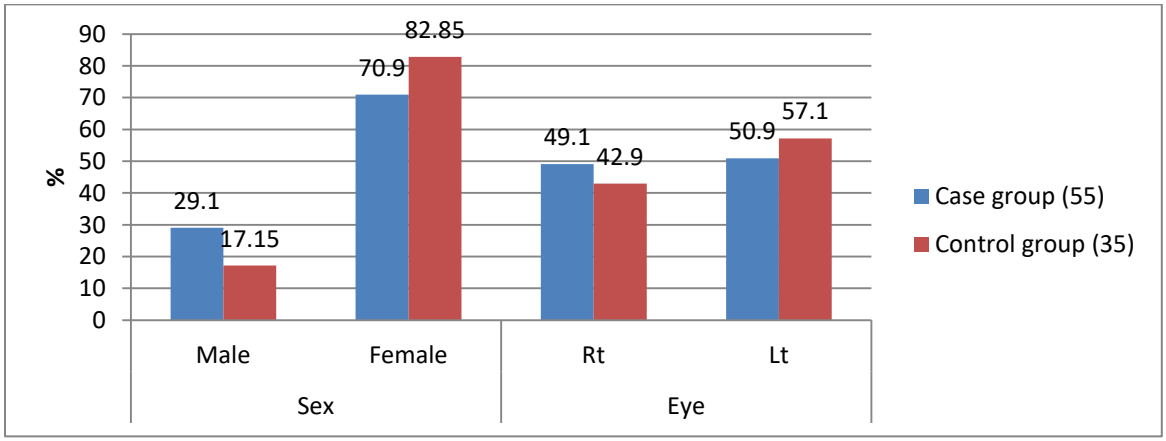

Fig.1: Distribution of subjects according to sex and examined eye

Table (2) shows that at 3x3 scan size of OCTA, FAZ and PERIM were significantly more enlarged in case group compared to the control group (both p<0.001). While FD, VD% of superficial and deep layers were significantly lower in the case group than the control group (all p <0.001). **(Fig.2)**

Table (2): Comparison between case and control groups according to FAZ, PERIM, FD, Superficial whole image VD%, Superficial Fovea VD %, Superficial Parafovea VD%, Superficial Parafoveal superior hemi VD%, Superficial Parafoveal inferior hemi VD%, Deep whole image VD%, Deep Fovea VD%, Deep Parafovea VD%, Deep Parafoveal superior hemi VD% and Deep Parafoveal inferior hemi VD%

	Case group (55)	Control group (35)	P value
FAZ	0.332± 0.107	0.127±0.02	<0.001*
PERIM	2.30± 0.69	1.34± 0.20	<0.001*
FD	42.38± 6.63	50.66± 5.33	<0.001*
Superficial whole image VD%	41.35± 5.41	47.61± 3.80	<0.001*
Superficial Fovea VD %	16.60±8.33	20.13±5.07	0.722
Superficial Parafovea VD%	42.17±5.72	50.85±4.17	<0.001*
Superficial Parafoveal superior hemi VD%	43.71±6.21	51.04±4.14	<0.001*
Superficial Parafoveal inferior hemi VD%	42.67±5.72	50.54±5.03	<0.001*
Deep whole image VD%	46.83±7.25	54.66±3.75	<0.001*
Deep Fovea VD%	31.01±9.41	33.81±7.78	0.124
Deep Parafovea VD%	48.06±7.49	56.90±3.60	<0.001*
Deep Parafoveal superior hemi VD%	48.83±7.84	57.40±3.89	<0.001*
Deep Parafoveal inferior hemi VD%	47.20±7.85	56.20±4.09	<0.001*

Data are presented as mean ± SD or frequency (%), *: significant P value

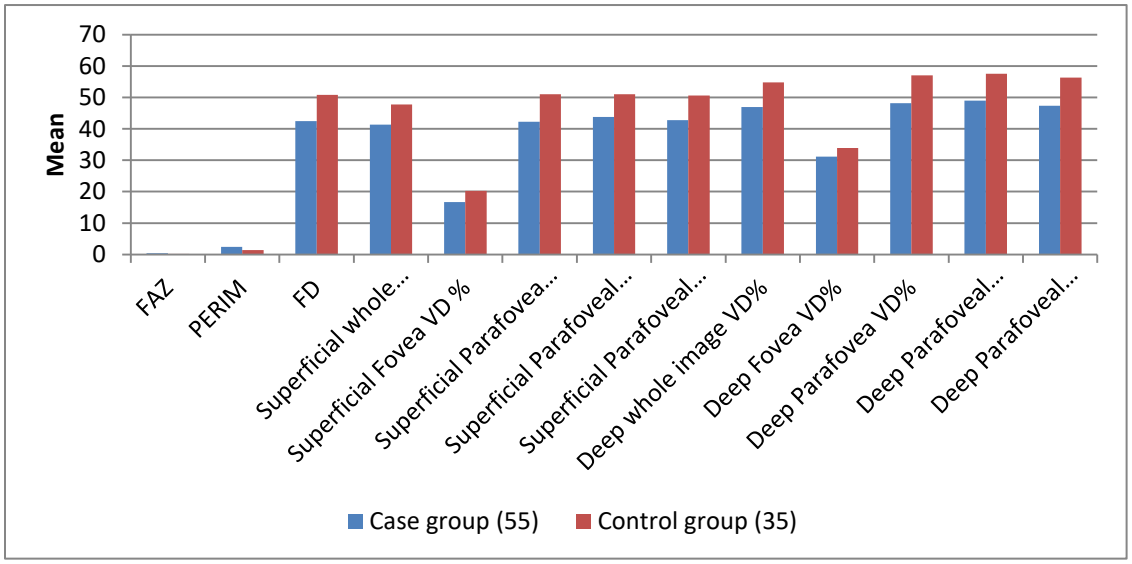

Fig.2: Comparison between cases and controls according to 3x3 scan size of OCTA

Table (3) shows that in the case group, there was a statistical insignificant difference among mild, moderate, and severe groups as regards sex, eye with NPDR, type of DM, treatment of DM and age. **(Fig.3)**

Table (4): Comparison between the cases subgroups according to sex, eye with NPDR and distribution of cases according to grade of DM, type and duration of the disease

Case group (55)		Mild (15)	Moderate (27)	Severe (13)	P value
Sex	**Male**	10 (66.7%)	4 (14.8%)	2(11%)	0.121
	Female	5(33.3%)	23 (85.2%)	15.4(84.6%)	
eye	**Rt**	7(46.7%)	14(51.9%)	6(46.2%)	0.764
	Lt	8 (53.3%)	13(48.1%)	7(53.8%)	
Type of DM	**Type I DM**	0(0%)	0(0%)	2(15.4%)	0.052
	Type II DM	15(100%)	27(100%)	11(84.6%)	
TTT of DM	**ORH**	7(46.7%)	16(59.3%)	2(15.4%)	0.052
	Insulin	8 (53.3%)	11(40.7%)	11(84.6%)	
Age /year		50.61±9.95	55.51±7.44	51.0±12.66	0.165

Data are presented as mean ± SD or frequency (%)

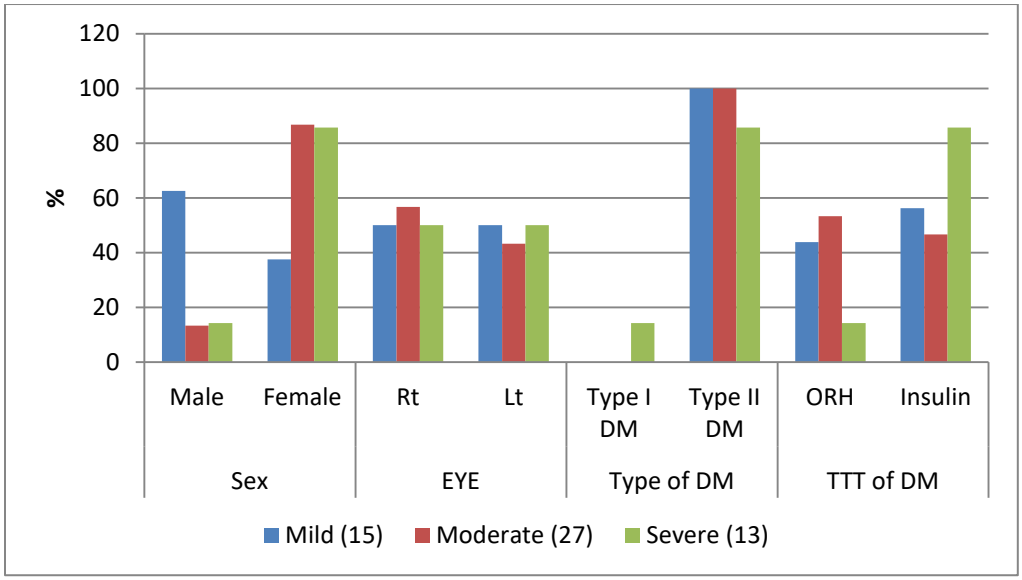

Fig.3: Comparison in between the cases subgroups according to sex, eye with NPDR, Distribution of cases according to grade, type and treatment of DM.

Table (5) shows that in the case group, there was a significant difference among the three groups as regards UCVA (logMAR); it was significantly higher in the moderate group than mild group (p= 0.011), significantly higher in the severe group than moderate group (p= 0.01), and significantly higher in the severe group than mild group (p <0.001). BCVA (logMAR) was significantly different among the three groups; it was significantly higher in the moderate group than mild group (p= 0.001), significantly higher in the severe group than moderate group (p= 0.004), and significantly higher in the severe group than mild group (p <0.001). IOP was

insignificantly different among the three case groups. **(Fig.4)**

Table (6): Comparison between the cases subgroups according to duration of DM, UCVA (logMAR), BCVA (logMAR), and IOP

Case group (55)	Mild (15)	Moderate (27)	Severe (13)	P value	Mild & moderate	Mild & severe	Moderate & severe
Duration of DM	16.12±6.55	18.22±6.0	19.62±6.01	0.175	0.242	0.105	0.481
UCVA (logMAR)	0.377±0.208	0.566±0.214	0.746±0.260	<0.001*	0.011*	<0.001*	0.01*
BCVA (logMAR)	0.214±0.166	0.411±0.168	0.603±0.217	<0.001*	0.001*	<0.001*	0.004*
IOP	13.29±0.76	16.02±1.48	16.05±2.26	0.231	0.243	0.434	0.831

Data are presented as mean ± SD, *: significant P value

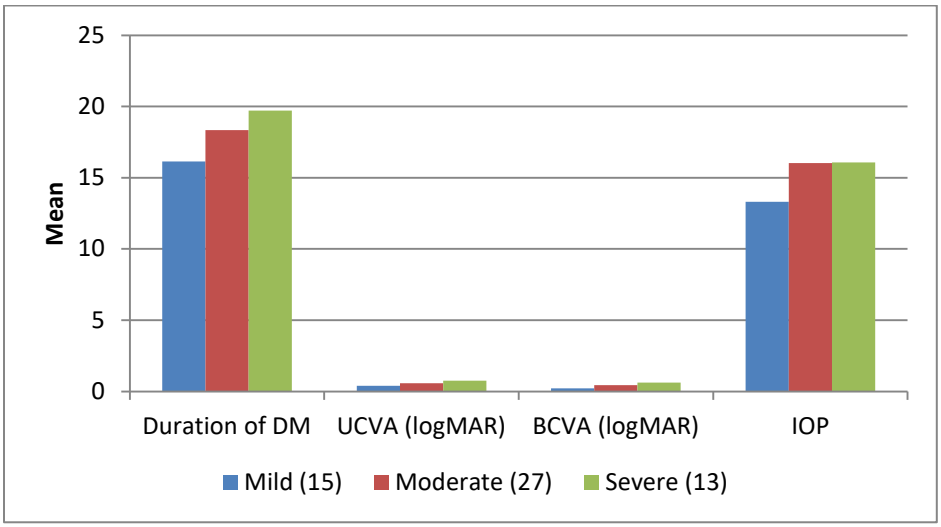

Fig.4: Comparison between the cases subgroups according to duration of DM, UCVA (logMAR), BCVA (logMAR), IOP.

Table (7) shows that there was a significant difference among the three groups as regards FAZ; it was significantly more enlarged in the severe group than moderate group (p <0.001), and significantly more enlarged in the severe group than mild group (p <0.001). PERIM was significantly different among the three groups; it was significantly more enlarged in the severe group than moderate group (p <0.001), and significantly more enlarged in the severe group than mild group (p <0.001). Superficial whole image VD% was significantly different among the three groups; it was significantly lower in the moderate group than mild group (p= 0.006), and significantly lower in the severe group

than mild group (p <0.001). Superficial Fovea VD% was significantly different among the three groups; significantly lower in the severe group than mild group (p= 0.002).

Superficial Parafovea VD% was significantly different among the three groups; it was significantly lower in the moderate group than mild group (p= 0.003), significantly lower in the severe group than moderate group (p= 0.031), and significantly lower in the severe group than mild group (p <0.001). Superficial Parafoveal superior hemi VD% was significantly different among the three groups; it was significantly lower in the moderate group than mild group (p= 0.012), and significantly lower in the severe group than mild group (p =0.001).

Superficial Parafoveal inferior hemi VD% was significantly different among the three groups; it was significantly lower in the moderate group than mild group (p= 0.006), significantly lower in the severe group than mild group (p <0.001) and significantly lower in severe group than moderate group(p=0.014). Deep whole image VD% was significantly different among the three groups; it was significantly lower in the severe group than mild group (p =0.013). Deep Fovea VD% was significantly different among the three groups; it was significantly lower in the moderate group than mild group (p= 0.043), significantly lower in the severe group than moderate group (p= 0.001), and significantly lower in the severe group than mild group (p <0.001). Deep parafovea VD% was significantly different among the three groups. It was significantly lower in severe group than mild group (p=0.020). Deep Parafoveal inferior hemi VD% was significantly different among the three groups; it was significantly lower in the severe group than mild group (p= 0.006). **(Fig.5)**

Table (8): Comparison between the cases subgroups according to FAZ, PERIM, FD, Superficial whole image VD%, Superficial Fovea VD%, Superficial Parafovea VD%, Superficial Parafoveal superior hemi VD%, Superficial Parafoveal inferior hemi VD%, Deep whole image VD%, Deep Fovea VD%, Deep Parafovea VD%, Deep Parafoveal superior hemi VD% and Deep Parafoveal inferior hemi VD%

Case group (55)	Mild (15)	Moderate (27)	Severe (13)	P value	Mild & moderate	Mild & severe	Moderate & severe
FAZ	0.218±0.071	0.300±0.071	0.430±0.151	<0.001*	0.14	<0.001*	<0.001*
PERIM	1.81±0.31	2.21±0.59	3.06±0.69	<0.001*	0.061	<0.001*	<0.001*
FD	44.50±7.43	42.06±7.11	40.88±4.01	0.322	0.234	0.160	0.630
Superficial whole image VD%	45.10±6.20	40.86±3.64	37.70±5.24	<0.001*	0.006	<0.001*	0.051
Superficial Fovea VD%	19.06±6.56	16.27±6.80	13.2±10.84	<0.001*	0.054	0.002*	0.116
Superficial Parafovea VD%	45.82±6.15	41.83±3.76	38.23±5.76	<0.001*	0.003*	<0.001*	0.031*
Superficial Parafoveal superior hemi VD%	45.10±6.20	42.34±4.03	38.10±7.63	0.002*	0.012*	0.001*	0.084
Superficial Parafoveal inferior hemi VD%	45.02±6.22	41.50±4.04	37.38±5.09	<0.001*	0.006*	<0.001*	0.014*
Deep whole image VD%	49.63±5.89	46.11±8.48	43.03±3.70	0.043*	0.254	0.013*	0.07*
Deep Fovea VD%	33.02±7.02	30.77±7.34	22.60±10.34	<0.001*	0.043*	<0.001*	0.001*
Deep Parafovea VD%	51.15±5.10	47.25±9.06	43.56±4.03	0.065	0.22	0.020*	0.128
Deep Parafoveal superior hemi VD%	51.73±6.62	48.20±9.48	45.15±4.02	0.295	0.553	0.130	0.23
Deep Parafoveal inferior hemi VD%	51.86± 3.80	47.31± 9.22	43.01±6.12	0.025*	0.143	0.006*	0.085

Data are presented as mean ± SD, *: significant P value

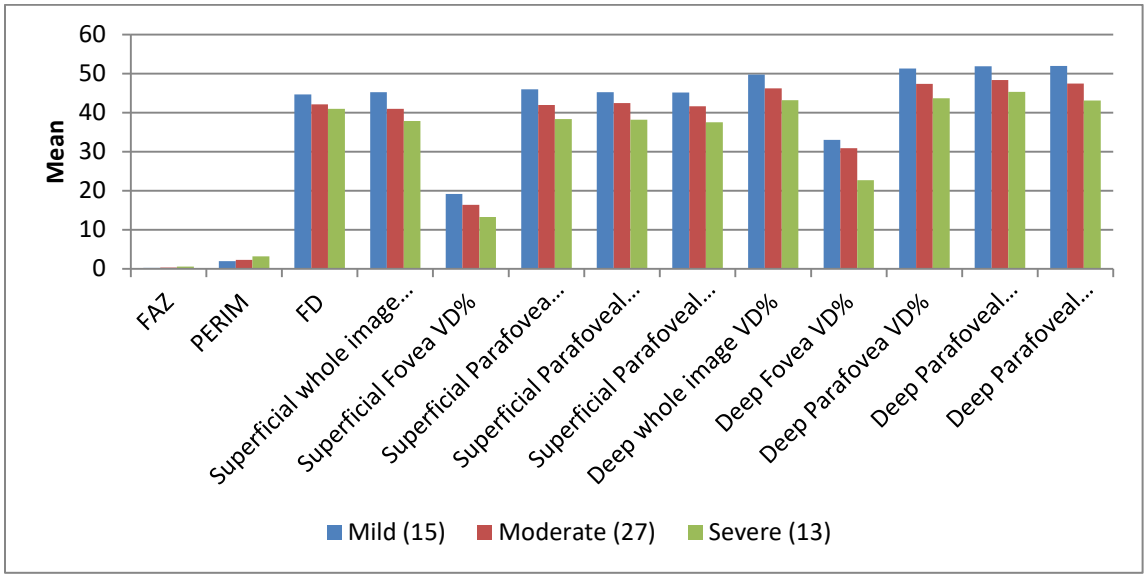

Fig.5: Comparison between cases subgroups according to 3x3 scan size of OCTA.

Discussion

Traditionally, patients with diabetic retinopathy were monitored with serial fundus ophthalmoscopy in conjunction with ancillary testing, including fluorescein angiography (FA) to assess for areas of neovascularization of the disc or elsewhere, retinal edema and non-perfusion [15].

In our study, at 3x3 scan size of OCTA, FAZ and PERIM were significantly more enlarged in case group compared to the control group (both p<0.001). While, FD, superficial and deep VD% were significantly lower in the case group than the control group (all p <0.001).

In agreement with our findings, a study included 64 patients in the NPDR group and 48 healthy control subjects for comparison. All subjects underwent ocular examination with visual acuity and wide-field fundus photos. They found that the FAZs was significantly enlarged in the NPDR group when compared with those in the control group (p = 0.001). The foveal vascular densities were significantly lower in the NPDR group than in the control group (p = 0.001). the vessel densities of the superior and inferior parafoveal areas in the DCP were significantly decreased in the NPDR group compared to those in the controls (superior/temporal/inferior/nasal: p = 0.006, p = 0.395, p = 0.034, and p = 0.079, respectively).but The parafoveal vascular density in the SCP did not differ significantly between the two groups

(superior/temporal/inferior/nasal; all p > 0.05).[16]

However, another study evaluated the changes in retinal vascular plexuses and choriocapillaris in DM patients without clinical DR and to compare them with healthy controls and to identify early preclinical biomarkers for DR using OCTA. Their prospective cross-sectional study included 68 eyes (34 eyes of type-2 diabetic patients without DR and 34 eyes of healthy controls). found the FAZ area had the same in both groups (0.41±0.23 mm2 in the healthy-control group vs. 0.42±0.15 mm2 in the DM group, P=0.98). The irregularities in the FAZ borders (loss of normal spider-web capillary pattern or adjacent nonperfusion areas) were documented in the eyes of the DM group (22/34=65%).[17]

In the present study, in the case group, BCVA (logMAR) was significantly different among the three groups; it was significantly higher in the moderate group than mild group (p= 0.001), significantly higher in the severe group than moderate group (p= 0.005), and significantly higher in the severe group than mild group (p <0.001).

Conforming to our findings, a study investigated microvascular parameters that are related to the severity of DR with OCTA. In total, 105 eyes from 105 diabetic patients were recruited in this prospective cross-sectional study, including 37 eyes with no clinical signs of DR (NoDR), 43 eyes with NPDR, and 25 eyes with PDR. Multivariate regression analysis was used to identify the best OCTA parameters that could distinguish DR severity among groups. The results showed that BCVA (logMAR) was significantly increased with the severity of DR (P < 0.05). [18]

There was a significant difference among the three groups as regards FAZ; it was significantly more enlarged in the severe group than moderate group (p <0.001), and significantly more enlarged in the severe group than mild group (p <0.001).

In our study, most parameters in superficial and deep capillary plexus were significantly different among the three groups; they were significantly lower in the moderate group than mild group, significantly lower in the severe group than moderate group, and significantly lower in the severe group than mild group (all p <0.05).

So, OCTA shows progressive increase of FAZ area and reduction of VD in both superficial and deep plexus at increasing DR severity.

Compatible to our results, a study included sixty eyes of 60 patients with treatment naïve NPDR (mild: 21, moderate: 21,

severe: 18), 23 eyes with diabetes and no retinopathy, and 24 healthy control eyes were enrolled. OCTA slabs were segmented into superficial (SCP), middle (MCP), and deep capillary plexus (DCP) and thresholded by a new method based on DCP skeletonized vessel length. The foveal avascular zone (FAZ) area, parafoveal vessel density (VD), and adjusted flow index (AFI) from all three capillary layers and the vessel length density (VLD) of the SCP were compared between each severity group, after adjusting for age and image quality. The results exhibited that SCP VD demonstrated significant differences between eyes with diabetes with no retinopathy and mild NPDR ($p = 0.001$ and $p < 0.001$, respectively), as well as between moderate vs. severe NPDR ($p = 0.004$ and $p = 0.009$, respectively).[19]

A recent study which included patients with anti-VEGF and PRP treatment demonstrated that the decreased DCP vessel density was primarily present in absent to early DR, whereas in eyes with advanced DR, the alteration of VD was mainly found in the superficial layer. A combined model of SCP FAZ area, DCP vessel density and acircularity was used to distinguish eyes with different severity of DR with a high ROC value [20]. In our study, DCP was also correlated with the severity of DR. This would indicate that loss of capillary density in the DCP may be an important pathological finding in the progression of DR, especially in the advanced stages.

So there is significant evidence that the density of vascular perfusion reduces with increasing severity of DR and that OCTA parameters can be used to identify these changes. It has also been demonstrated that vessel density is significantly reduced in NPDR eyes compared to controls, in both the SCP and DCP. However, as with FAZ measurements, there have been inconsistencies noted in the literature, particularly in relation to deep plexus analysis [21-23].

In the present study, both retinal changes in the superficial and deep capillary plexus were evaluated. A study evaluated OCTA images in patients with diabetic retinopathy in both the superficial as well as the deep capillary plexus utilizing 3×3 mm OCTA scans. They observed that areas of retinal non-perfusion were greater in the superficial than the deep capillary plexus and suggested that the deep capillaries could be relatively more spared compared to capillaries in the superficial plexus secondary to anatomical differences.[24]

Limitations: The grader was not blinded as to the relative size of the image being graded (3×3 mm or 6×6 mm). Relatively small sample size. Single center study.

Conclusions:

OCT angiography can be effectively and efficiently used in diagnosis of non-proliferative diabetic retinopathy. In the presence of NPDR, OCTA shows progressive increase of FAZ area and reduction of VD in both superficial and deep plexus at increasing DR severity. OCTA can be used for following up of NPDR patients, as it uses no contrast agent, being non-invasive, and its scans with high quality images and good perception of the deep retinal layers.

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