Original Article

Role of Optical Coherence Tomography Angiography in Predicting Risk of Progression of Diabetic Retinopathy

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ABSTRACT

Purpose: To determine the role of Optical Coherence Tomography Angiography (OCTA) in predicting risk of progression of diabetic retinopathy.

Study Design: Descriptive observational study.

Place and Duration of Study: Jinnah Post graduate Medical Center, Karachi, from June 2022 to June 2023.

Methods: Patients with type 1 or 2 diabetes were included. Base line investigations were done including Central subfield thickness and OCTA at first visit. Second visit was conducted at 6th month and patients were followed for 24 months. OCT images of poor quality, motion artifact, inaccurate partition of tissue layers and blurry images were excluded.

Results: Among 97 enrolled patients, 88 cases finished the complete 24-months follow up. Out of 88 patients, 16 (18.18%) patients showed progression of diabetic retinopathy (DR), 9 (10.22%) patients developed DME, two showed both DR and DME .In univariate analysis, greater FAZ area, reduced FAZ circularity, Fractal dimension (FD) and vessel density (VD) of the deep capillary plexus (DCP) were significantly related to the advancement in DR. Among these, FAZ area, VD, and FD remained significant in the multivariate analysis. Whereas, only decreased VD and FD of superficial capillary plexus (SCP) were significantly related to advancement in DR and DME.

Conclusion: Changes in OCTA parameters is significantly associated with progression of diabetic ocular complications including diabetic retinopathy and diabetic macular edema. High risk subjects can be identified by this method for more rigorous treatment.

Key Words: SD-OCT angiography, OCTA, diabetic retinopathy, diabetic macular edema, Deep capillary plexus, superficial capillary plexus.

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INTRODUCTION

Diabetic retinopathy (DR) is a major contributor to impaired vision and visual loss among diabetic patients. Around 75% of type 1 and 50% of type 2 diabetic patients become victim of DR.[1] Long standing diabetes, increasing age, elevated blood pressure and cholesterol, presence of co-morbidities, anemia, and a family history of DR are among the well-established risk factors of diabetic retinopathy.[2] DR is still highly prevalent in diabetic patients despite tremendous improvements in the management of risk factors and use of medications. About one-third of diabetic individuals develop DR, which distinctly rises beyond the age of 60 years.[3] A thorough systematic review

revealed no difference in prevalence of DR among males and females. The prevalence was forecasted to be 28.41%, 25.93%, and 28.95% in the diabetic population overall, in females, and in males respectively.[3] Diabetic macular edema occurs due to buildup of fluid in the macula of retina. The prevalence of DME ranges from 4.2% -14.3% in type 1 diabetic cases. Whereas it affects 1.4%-5.57% of patients with type 2 diabetes.[4]

Timely management of diabetes in eyes at risk of DR can stop development of severe vision loss.[5] The identification of individuals who are at danger of developing DR and DME and who can take advantage from more intensive therapies is a crucial step in decreasing the prevalence and overall treatment of DR. However, recognized risk indicators including the length of diabetes and glycated hemoglobin (HbA1c) levels are not enough to assess the likelihood of developing diabetic complications. For instance, only around 11% of the variation in DR development can be attributed to total glycemic exposure.[6]

OCTA is one of advanced imaging technologies that pictures the microvasculature of eye using repeated B-scans and identifies motion contrast without using intravenous dye. More importantly, it provides measurements of deep micro-vessels of the eye that dye based angiography could not provide.[7] Several quantitative OCTA measures, such as area and circulation of the foveal avascular region are discussed in former researches.[8,9] OCTA measurements, which represent early microvascular modifications in certain capillary plexuses, may be possible biomarkers for DR and DME since they may be observed in diabetic individuals even in the absence of clinical symptoms.[10]

Although literature shows significance of OCT parameters using cross sectional study model, very less is known regarding early detection of DR and DME progression using OCTA parameters. This research was designed to explore the role of quantitative OCTA parameters in predicting the risk of progression of DME and DR in diabetic patients. This will help us to identify high risk patients for more rigorous treatment.

METHODS

This prospective observational research was conducted at eye department of Jinnah Postgraduate Medical Center, Karachi from June 2022 to June 2023 for a period of one year after acquiring permission from institutional review board. Sample size was calculated via online Sample size calculator (CI: 95%, margin of error 5%, population proportion 50, population size 128) Diabetic patients were selected and followed up for 24 months after taking written informed consent. Patients older than 18 years, diagnosed with Diabetes Mellitus (either type 1 or type 2) and completed the study period were included. Patients with Proliferative diabetic retinopathy (PDR) at initial visit, past record of any eye surgery or laser treatment within 6 months, ungradable or poor quality OCTA images and concurrent eye diseases were excluded.

Research was carried out according to Declaration of Helsinki. Demographic features including age, gender, length of diabetes, age of patient at diagnosis of diabetes, type of diabetes, and area of residence were noted in a self-designed proforma. Base line investigations such as body mass index (BMI), HbA_{1C} %,Blood Pressure (BP), DR severity, and detailed eye examination including axial length, spherical equivalent, intraocular pressure (IOP), Visual acuity (VA), Central subfield thickness, slit-lamp examination, fundoscopy and spectral domain OCTA of all cases were carried out at their first visit. Second follow up was conducted at 6^{th} month. Patients were followed for a duration of 24 months. Follow up was continued on yearly basis in case of no DR or early NPDR, whereas patients developing moderate or severe NPDR were tracked up 6 monthly. Severity of DR was categorized using guidelines provided by international clinical diabetic retinopathy disease severity scale. Visual acuity was changed to the logarithm of minimum angle of resolution for statistics. OCT angiography of each patient was performed using SD-OCT (DRI OCT Triton; Topcon Inc, Tokyo, Japan). OCT images of poor quality, motion artifact, inaccurate partition of tissue layers and blurry images were excluded from research. Various OCT related parameters of images such as FAZ area and circulation, VD and FD were measured according to the methodology narrated by Tang et al.[9]

Retinal camera (TRC 50DX, Topcon Inc) was utilized to capture retinal fundus photographs after pupillary dilation. Photographs were graded for DR severity via the modified Airlie House classification system.[11] Retinal thickness was calculated by Cirrus HD-OCT (software version 9.5; Carl Zeiss Meditec, Dublin, CA).

Data was analyzed using SPSS version 23. For categorical data, frequency and percentages were

calculated while mean and standard deviation were given for continuous data. Association of OCTA related parameters to the risk of progression of DR and DME was determined by applying Cox proportional-hazards model.

RESULTS

Ninety seven patients (194 eyes) were enrolled in the present research. Nine patients did not finish study duration and were omitted from analysis. Mean age of the patients was 65 ± 1.6 years. Majority of the cases had mild NPDR(43.18%). Detailed features of baseline investigations of all patients are presented in Table 1.Out of 88 patients, 16 (18.18%) showed progress in DR and 9 (10.22%) patients developed DME. Two patients showed both DR and DME(DME occurred 7 months earlier to DR).

Table 2 presents association of OCTA to progression in DR complications. All OCTA parameters including FAZ area, FAZ circularity, FD and VD of the DCP were considerably related to the

Table 1: *Base line characteristics of patients (N=88).*

		DR severity	
Age (Years)		No	14(15.90%)
Range	56-77	Mild	38 (43.18%)
Mean	65 ± 1.6	Moderate	30(34.09%)
		Severe	6(.8%)
Mean age at diagnosis of Diabetes (Years)	53 ±4.1	**Axial length mm**	24.67 ± 0.12
Duration of Diabetes (Years)	10 ± 1.7	**Spherical equivalent diopter**	-1.09 ± 2.01
Type of Diabetes			
Type I	4(4.76%)	**Log MAR**	0.20 ± 0.14
Type II	84(95.45%)		
Gender			
Male	67(76.13%)	**Central subfield thickness µm**	249.89 ± 22.16
Female	21(23.86%)		
		OCT parameters	
		Superficial capillary plexus	
Residence		FAZ area mm^2	0.43 ± 0.09
Karachi	83(85.56%)	FAZ circularity	0.57 ± 0.07
Outsider	5(5.68%)	VD%	78.14 ± 3.13
		FD	1.66 ± 1.23
		Deep Capillary Plexus	
		FAZ area mm^2	1.12 ± 0.39
BMI kg/m^2	25.96 ± 2.05	FAZ circularity	0.44 ± 0.13
		VD %	36.78 ± 2.95
		FD	1.65 ± 0.03
HbA_{1C} %	8.23 ± 1.03	**BP mmHg**	110.32 ± 5.09

HbA1c = glycated hemoglobin; BMI= Body Mass index; logMAR= logarithm of the minimum angle of resolution; OCTA= OCT angiography ;FAZ = foveal avascular zone, VD= vessel density FD=fractal dimension

Table 2: *Association of OCT parameters to risk of Diabetic retinopathy.*

OCTA Parameters	HR (Univariate)	P-value	HR(Multivariate)	P-value
Superficial capillary plexus				
FAZ area per S.D increase	1.343	0.06	1.353	0.19
FAZ circularity Per S.D decrease	1.197	0.17	1.132	0.31
VD Per S.D decrease	1.268	0.01*	1.045	0.03*
FD per S.D decrease	1.324	0.01*	1.290	0.01*
Deep Capillary Plexus				
FAZ area per S.D increase	1.731	<0.001*	1.923	<0.001*
FAZ circularity Per S.D decrease	0.934	<0.05*	0.845	0.07
Vessel density Per . decrease	1.877	<0.001*	1.926	<0.001*
Fractal dimension Per S.D decrease	3.347	0.01*	3.998	0.03*

OCTA= OCT angiography; FAZ = foveal avascular zone; S.D= Standard Deviation; HR= Hazard ratio
VD= vessel density FD=fractal dimension

Table 3: *Association of OCT parameters to risk of diabetic macular edema.*

OCTA Parameters	HR (Univariate)	P-value	HR (Multivariate)	P-value
Superficial capillary plexus				
FAZ area per S.D increase	0.951	0.80	0.663	0.16
FAZ circularity Per S.D decrease	1.022	0.37	0.854	0.76
VD Per S.D decrease	1.748	0.04*	1.586	0.03*
FD per S.D decrease	1.422	0.03*	1.690	0.02*
Deep Capillary Plexus				
FAZ area per S.D increase	1.039	0.66	0.986	0.77
FAZ circularity Per S.D decrease	1.187	0.45	1.712	0.21
VD Per S.D decrease	1.221	0.41	1.034	0.23
FD Per S.D decrease	0.747	0.06	1.132	0.12

OCTA= OCT Angiography; FAZ = Foveal Avascular Zone; S.D= Standard Deviation; HR= Hazard Ratio, VD= Vessel Density FD=Fractal Dimension

progression of DR in univariate analysis. Amongst these, FAZ, VD, and FD still showed significant association in multivariate analysis after adjusting for established risk factors. Whereas, only VD and FD of SCP were found to be considerably related to the advancement in DR in both univariate and multivariate analysis.

Table 3 displays the association of OCTA parameters to DME development. In both the univariate and multivariate analysis, VD and FD of SCP were significantly related to the DME development. OCTA related parameters of DCP did not exhibit any significant association with diabetic macular edema.

DISCUSSION

Optical coherence tomography angiography (OCTA) has modernized the subject of ocular imaging in current years. OCTA provides a fast, non-invasive and comprehensive technique of capturing retinal and choroidal micro vessels making OCTA an attractive choice to trail the progress of DR and improvement in patients.[12]

Present study indicated various OCTA related parameters which can predict the future occurrence of diabetic retinopathy and macular edema such as diabetic patients with large FAZ area, lower circularity, lower VD and FD on DCP are linked to an increased threat of DR complications, while patients with decreased VD and FD on SCP are at increased danger of developing retinopathy and diabetic macular edema when observed for a duration of 2 years. The associations of these OCTA parameters to advancement in diabetic retinopathy and emergence of diabetic macular edema is independent of other well-known risk factors such as age, length of diabetes, levels of HbA1c, blood pressure, and grading stage of DR at first visit.

Large FAZ area is an important parameter to predict advancement in diabetic retinopathy in diabetic cases as reported by previous dye based studies.[13] The findings from other OCTA studies also reported similar results.[14,15]A negative relationship among FAZ circulation and DR complications has also been stated in literature further supporting our results.[16]

Present research indicated lower VD and FD of DCP as significant parameters to assess progression of DR. Nesper et al, and Li et al. also showed that lower VD at the parafovea of the SCP and DCP is associated with increased DR complications.[8,17] Nesper et al, described that VD at the DCP is more significantly linked to DR severity.[8] DCP provides blood supply to the outer plexiform membrane, an area of communiqué between horizontal cells and the internal portions of photoreceptors.[17] In some animal researches, the outer plexiform membrane was recognized to have maximum oxygen need in retina, making this area vulnerable to ischemic damage.[18]In humans, impairments in photoreceptors is closely related to non-perfusion in DCP, producing reduced retinal sensations.[19] Hence, alterations in blood supply at the DCP may indicate the initial symptoms and forecast the growth of DR. Onishi et al, evaluated the approximate blood supply at the capillary plexuses of retina termed as AFI (adjusted flow index).They observed that it does not decrease significantly at SCP as DR severity progresses. However, it decreases sharply at the MCP and DCP.[20] Ashraf et al, also examined the VD and Vessel length density (VLD) of retinal capillary plexuses using OCTA. They observed that early DR mainly affects the MCP and DCP, while

DR in advanced stage more affects the SCP.[21] Zahid et al, measured FD at the SCP and DCP and stated that diabetic patients with DR had considerably decreased FD as compared to control cases.[22] However, Sun et al. observed diabetic patients for a period of 2 years and concluded that large FAZ area, VD and FD of DCP forecast advancement in DR complications and VD of SCP predict DME.[23] You et al, after a follow-up of 1 year concluded that diabetic patients with greater avascular regions in the SCP at initial examination were more associated to progression of DR.[24] Also Greig et al, testified that a greater FAZ regions and lower VD in the temporal area at initial examination can forecast the danger of DR advancement. This study consisted of 1 year follow-up duration.[25]

In this study, DME formation was significantly related with VD and FD of the SCP. Fluid production in eyes may initiate from the SCP that passes through the retina and absorbs in Müller cells and DCP. Damage to blood-retinal barrier resulting into enhanced outflow of blood from the SCP can adversely impair the fluid-removing abilities.[7]

Results of present study provide evidence to use OCTA to predict progression of DR and help practitioners in early detection of ocular complication of DM.

CONCLUSION

Changes in OCTA parameters are significantly associated to later advancement in diabetic retinopathy and diabetic macular edema. High risk subjects can be identified by this method for more rigorous treatment.

Conflict of Interest: Authors declared no conflict of interest.

Ethical Approval: The study was approved by the Institutional review board/Ethical review board **(TUF/IRB/205/23).**

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Authors Designation and Contribution

Arifa Farooq Ghazipura: Consultant Ophthalmologist: *Concepts, Design, Literature search, Data acquisition, Data analysis, Manuscript preparation, Manuscript editing, Manuscript review.*

Najeeb Ullah Achakzai; Consultant Ophthalmologist: *Design, Literature search, Data acquisition, Statistical analysis, Manuscript preparation, Manuscript review.*

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