Association Between Oct-Based Microangiography Perfusion Indices and Diabetic Retinopathy Severity in Patients with Diabetes in Pakistan

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ABSTRACT

Objective: To assess the relationship between capillary perfusion of retinal vessels and severity of diabetic retinopathy with the help of Optical Coherence Tomography angiography.

Study Design: Cross-sectional study.

Place and Duration of Study: Armed Forces Institute of Ophthalmology, Rawalpindi Pakistan, from Feb 2020 to Apr 2021.

Methodology: Seventy-three eyes of 37 subjects suffering from diabetes had their imaging done with Rtvue Avanti OCT angio system. Socio-demographic and clinical data was gathered. Subjects were divided into three groups depending upon the severity of diabetes. The perfusion index (PI) was taken as percent area coverage by retinal vessels with the flow.

Results: Out of a total of 73 eyes, 31 (42.5%) had none to mild Non-Proliferative Diabetic Retinopathy, 19 (26%) with moderate to severe Non-Proliferative Diabetic Retinopathy and 23 (31.5%) with Proliferative Diabetic Retinopathy. The mean age of the participants was 58.09 ± 10.32 years, with best corrected visual acuity as 0.35 ± 0.35 and Blood Sugar Random as 200.46 ± 70.71. BCVA showed a significant positive correlation with Perfusion Index (p=0.026). No significant association/relationship was found between the severity of diabetic retinopathy and perfusion index in this data (p=0.26).

Conclusion: No statistically significant relationship was found between Perfusion Index (PI) and severity of diabetic retinopathy.

Keywords: Diabetes, Optical coherence tomography angiography, Perfusion index, Retinopathy.

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INTRODUCTION

Diabetic retinopathy is the leading cause of vision loss and preventable blindness globally.[1] Approximately 2.6 million people are suffering from visionthreatening diabetic retinopathy. People who have diabetes are at risk of developing sight-threatening ocular diseases, including glaucoma, cataract, and diabetic macular oedema.[2] According to International Diabetes Federation, the number of people with diabetic retinopathy is suspected to increase to 700 million in 2045.[3]

Diabetic retinopathy is strongly associated with microvascular changes. The most important role in the pathogenesis of retinal microvascular damage is hyperglycemia. In addition, increased blood glucose levels cause blood vessels to dilate, leading to certain retinal blood flow changes that are perceived to be the earliest response.[4] Therefore, estimation of capillary perfusion and measurement of perfusion areas is essential in the pathogenesis of diabetic retinopathy.

Fluorescein angiography (FA) has been used as the first-line tool for measuring retinal capillary perfusion. However, it is invasive and needs an intravenous injection of fluorescein dye.[5] Fluorescein angiography provides details of retinal circulation and is helpful in the diagnosis and management of a variety of retinal disorders. Fluorescein angiography is invasive and of no use for patients with poorly dilating pupils and hazy media.[6] Based on duration, need for medical intervention, and ultimate outcomes, adverse reactions after FFA are categorized as mild (nausea, vomiting), moderate (syncope, pyrexia), or severe (anaphylaxis, Myocardial infarction).[7]

OCT-Angiography (OCT-A) has the benefit of not being invasive, and the imaging method does not include the use of dye. OCT-A has an advantage over FFA in measuring superficial and deep capillary plexus that is helpful in the diagnosis of exact location and details of pathology.[8] OCT-A is particularly valuable in managing diabetic retinopathy as changes at the microvascular level characterize the disease. OCT-A is superior to others as it picks up microvascular changes long before clinically evident. OCT-A is a convenient screening method because it accurately measures the non-perfused and microvasculature changes.[9,10] The characteristic features of DR using OCTA have been evaluated in many studies, but the

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relationship between perfusion indices and diabetic retinopathy severity has not been known before. Our study aimed to assess how retinal vascular perfusion is associated with DR severity with the help of OCTA.

METHODOLOGY

This cross-sectional study was carried out at the Armed Forces Institute of Ophthalmology, Rawalpindi, Pakistan, between February 2020 to April 2021 after approval from Institutional Ethical Committee (IERB Approval Certificate No: CPSP/REU/OPL-2018-124-1906). The study was carried out in accordance with the guidelines of the Declaration of Helsinki.

Inclusion Criteria: Patients with diabetes, of either gender were included in the study.

Exclusion Criteria: Patients of age age <20 years, those with a history of any previous vitreoretinal surgery, and those with another retinal vascular disease. Images having poor signal strength and severe motion artefacts were excluded from the study.

With the help of the WHO sample size calculator, the sample size was calculated with a confidence interval of 95%, which came out to be 62 eyes (Diabetic Retinopathy prevalence is 4-6%).[11]

We recruited 73 eyes of 37 patients. Three groups were selected from the patient population based on their severity of diabetes, and the sample was collected from these groups randomly. After informing subjects about the study, written and informed consent was taken from all subjects. Subjects were dilated with 0.5% tropicamide, after which images were obtained using OCTA.

Thirty-seven subjects (73 eyes) had undergone imaging with a spectral-domain optical coherence tomography (SD-OCT) AngioVue Imaging System (RTVue XR Avanti, Optovue Inc., Fremont, CA, USA). This device uses a split-spectrum amplitude-decorrelation angiography (SSADA) algorithm. The volumetric scans of 304 × 304 A-scans at a speed of seventy thousand A-scans per second in approx 3 seconds are obtained by the device.[12] To achieve images of retinal vessels, the repeated B-scan protocol was implemented. As a result, two repeated B-scans were acquired, with the total time for a single acquisition being 3 secs, not including the adjustment time.

In our study, we acquired OCTA images of size 6 × 6 mm with the help of the RTVue XR Avanti system (Optovue). Each output set has a horizontal-priority (fast-x) and a vertical-priority (fast-y) raster OCT volume, and are joined consequently by the AngioVue programming using 3D orthogonal registration technique (motion correction technology, or MCT), subsequently eliminating mass movement and producing a combined OCTA image for all measurements with diminished movement.[13]

The fovea was in the centre of the image in each en face projection of retinal circulation. The alignment of retinal circulation was done so that image was segmented into two regions, inner and outer.[14]

The central 1 mm diameter circle was the foveal region. The inner ring has a radius of 1–3 mm, while the outer ring has 3–6 mm radii.15 The Perfusion Index (PI) definition is the "percent coverage of the area by retinal vessels with the flow".

Statistical Package for Social Sciences (SPSS) version 23.0 was used for the data analysis. Descriptive statistics were performed in percentage and frequency for qualitative variables (gender, NPDR severity groups), and Mean ± SD was calculated for quantitative variables (BCVA, PI). Inferential statistics were applied in the form of one-way ANOVA between DR severity groups and socio-demographic characteristics of the participants to identify the relationship between them. Pearson correlation was applied between PI and DR and background characteristics to identify any significant association. The *p*-value of ≤0.05 was deemed significant.

RESULTS

Out of the total 73 eyes examined, the overall descriptive statistics were presented in Table-I.

Table-I: Descriptive Statistics of Socio-demographic and clinical characteristics of patients' eyes.

Variables	Values
Age (Mean ± SD)	58.09 ± 10.32 years
Best Corrected Visual Acuity (Mean ± SD)	0.35 ± 0.35
Blood Sugar Random (Mean ± SD)	200.46 ± 70.71 mg/dl
Perfusion Index Inner Ring (Mean ± SD)	38.49 ± 16.50%
Perfusion Index Outer Ring (Mean ± SD)	40.23 ± 12.22 %
Gender n (%)	
Male	51 (69.9%)
Female	22 (30.1%)
Insulin use n (%)	
Yes	32 (43.8%)
No	41 (56.2%)

Out of 73 eyes, 51 (69.9%) were males. Most of the eyes examined were of participants not using insulin 41 (56.2%). The mean age of the participants was 58.09 ± 10.32 years, with Best-corrected visual acuity as 0.35

± 0.35 and Blood sugar random as 200.46 ± 70.71 mg/dl. The perfusion index (PI) of the inner ring measured in these eyes was 38.49 ± 16.50 %, and that of the outer ring was 40.23 ± 12.22%.

Out of total of 73 eyes were taken (n=31) 42.5% none–mild NPDR, (n=19) 26% moderate-severe NPDR and (n=23) 31.5% PDR and their Perfusion indices were performed. The socio-demographic and clinical characteristics of these 73 eyes as per Diabetic Retinopathy groups were presented in Table-II.

DISCUSSION

In this study, we have found out that there is a significant difference in mean BCVA among diabetic retinopathy severity groups. Also, mean blood sugar levels show significant differences among the three diabetic retinopathy severity groups. In addition, a significant association was found between insulin use and diabetic retinopathy severity groups. This study demonstrated no significant association or relationship between diabetic retinopathy severity and PI.

Table-II: Socio-demographic and clinical characteristics of patients.

Variables	None to Mild (n=31) 42.5%	Moderate to Severe (n=19) 26%	Proliferative Diabetic Retinopathy (n=23) 31.5%	*p*-value
Age (Mean ± SD)	55.5 ± 13.89	59.68 ± 7.12	60.26 ± 5.28	0.185
Best Corrected Visual Acuity (Mean ± SD)	0.12 ± 0.24	0.34 ± 0.30	0.67 ± 0.28	<0.001
Blood Sugar Random (Mean ± SD)	172.09 ± 62.08	204 ± 66.66	235 ± 70.88	0.003
Perfusion Index inner ring (Mean ± SD)	34.93 ± 14.44	41.05 ± 15.16	41.17 ± 19.70	0.289
Perfusion Index outer ring (Mean ± SD)	38.64 ± 11.31	42.40 ± 11.80	40.60 ± 13.87	0.570
Gender n (%)				
Male	19 (13.87%)	17 (12.41%)	15 (10.95%)	0.091
Female	12 (8.76%)	2 (1.46%)	8 (5.84%)	
Insulin Use n (%)				
Yes	7 (5.11%)	8 (5.84%)	17 (12.41%)	0.001
No	24 (17.52%)	11 (8.03%)	6 (4.38%)	

The result showed a significant difference in mean Best Corrected Visual Acuity among Diabetic Retinopathy severity groups (p=0.001). Similarly, there was a significant difference in mean BSR levels among the DR severity groups (p=0.003). A significant association was identified between DR severity groups and use of Insulin (p=0.001)

The association of the mean Perfusion Index was measured with the clinical characteristics of the patients presented in Table-III.

Table-III: Association (Pearson Co-relation) of mean PI with clinical characteristics of patients.

Variables	Correlation co-efficient	*p*-value
Age	0.21	0.064
Best Corrected Visual Acuity	0.26	0.026
Blood Sugar Random	0.05	0.629
Insulin	0.06	0.578
Severity of Diabetic Retinopathy	0.13	0.26

Out of all the variables of Age, Best Corrected Visual Acuity, Blood Sugar Random, Insulin use and Diabetic Retinopathy severity, only BCVA showed a significant positive correlation with PI (p=0.026). There was no significant association/relationship found between Diabetic Retinopathy severity and PI in this data (p=0.26).

Optical coherence tomography angiography has already played a vital role in imaging the microvascular changes of diabetic retinopathy. Our study reveals further advantages of OCT angiography not available with older imaging systems. It provides the measurement of blood flow in both deep and superficial retinal and choroidal capillary layers.[15]

Weinhaus *et al,*[16] and Snodderly *et al,*[17] worked on animal models to study the images taken by FFA. This study revealed that fluorescein angiography could not consider the images of deeper vascular layers of the retina. On the other hand, OCTA has a unique feature that can image both inner and outer capillary networks. Hence the study concluded that OCT angiography contributes to a more precise measurement of retinal vasculature than FFA.

Two important components of diabetic retinopathy evaluation are the measurement of capillary perfusion and non-perfused areas.[18] Nowadays, the best way of measuring retinal perfusion is FFA. However, the ETDRS trial revealed a variation in measurements between different observers.[18] Thus, a reliable method is required to measure retinal capillary perfusion.

Many types of research have been carried out to measure the extent of capillary non-perfusion in

diabetic retinopathy. A study by Ishibazawa *et al,* described that OCT angio could visualize microaneurysms and retinal ischemia, enabling a detailed view of every layer of the retinal capillaries.[19]

In a retrospective study using OCTA and FFA, Couturier et al. carried out a study with 14 patients of diabetic retinopathy in whom changes of diabetic retinopathy in both superficial and deep capillary layers were measured. The capability of OCTA to evaluate capillary nonperfusion came out to be better.[20]

Agemy *et al*, chose twenty-one control and fifty-six diabetic eyes, and OCTA did imaging. This study concluded a statistically notable difference between the capillary perfusion of control and patients with diabetes. Our study was similar to this one in scanning techniques as both used Avanti RTVue-XR spectral-domain OCT system.[15]

Few kinds of research may explain no significant association between DR and capillary perfusion. In a study by Grunwald *et al,* mild background retinopathy was associated with increased blood flow.[21] Increased blood flow with increasing severity of retinopathy was also found by Feke *et al.* In PDR, retinal perfusion increases due to thickening of the capillary basement membrane.[22]

There was not found to be any change in retinal blood flow velocity, foveal avascular zone, and capillary density between patients with diabetes with and without macular oedema, and both subgroups had reduced capillary blood velocity than controls.[23,24] As previously, there was no such study done in Pakistan. Our study will contribute to a better understanding of diabetic retinopathy at the microvascular level with the help of new optical coherence tomography angiography.

LIMITATIONS OF STUDY

Our study has numerous limitations. Participants of our study belong to the South Asian population mainly. There is a possibility that the perfusion index varies in different races, and more research is required to assess changes in PI among different racial groups. Another limitation in our study was patients with PDR with poor vision who could not fixate properly, giving rise to motion artefacts and poor analysis of retinal blood flow. OCTA can provide highquality scans of the macula and optic disc but not the pos-terior pole. Just a single OCTA system was being used in our study, so our results may not be generalizable to others. Another limitation was that our study included the macular region and perfusion loss in the periphery was not assessed.

CONCLUSION

Our study concludes that OCT angiography is a valuable, non-invasive system for measuring perfusion index quantitatively, which will be helpful in the clinical staging of the disease and its management.

Conflict of Interest: None.

Authors' Contribution

TBT: Data collection, drafting the manuscript, WM: Conception, Final Approval of manuscript, AA: Data analysis.

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