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QUANTITATIVE ANALYSIS OF RETINAL MICROVASCULAR CHANGES IN OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY OF DIABETIC RETINOPATHY

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ABSTRACT

***Introduction**: Diabetic Retinopathy (DR) is a common microvascular complication in patients with Diabetes Mellitus (DM) that can cause visual impairment and blindness in adult populations. Retinal microvascular changes, reflecting capillary drop out, non perfusion, and retinal ischemia seen in patients with DM can be assessed not only qualitatively, but also quantitatively with the introduction of a new, non invasive imaging modality Optical Coherence Tomography Angiography (OCTA), avoiding potential advese risks that can occur with the use of dye-injection imaging technique. We quantified retinal microvascular changes in healthy control eyes and Diabetic Retinopathy using OCTA.*

***Methods**: A cross sectional study included 13 eyes of 9 patients with DR, consists of 11 eyes with Non Proliferative Diabetic Retinopathy (NPDR) and 2 eyes with Proliferative Diabetic Retinopathy (PDR) and 5 eyes of 5 age-matched controls. Participants were imaged with commercial OCTA device (CIRRUS HD-OCT 5000 Angioplex). We analyzed in the Superficial Capillary Plexus (SCP) the following OCTA parameters : Vessel Density (VD), Foveal Avascular Zone (FAZ) area, and FAZ circularity.*
***Result**: Normal eyes had a higher mean VD, FAZ circularity (p >0.05) and lower mean FAZ area (p <0.05) in the SCP compared with the DR (NPDR + PDR) group. If we excluded the PDR eyes from the analytic data, mean VD and FAZ area were found to be lower in control group, and mean FAZ circularity was higher. However, no quantitative parameters were statistically significant between control group and NPDR group.*

***Conclusion**: Microvascular changes in DR can be assessed with the use of Optical Coherence Tomography Angioraphy, which is non invasive and provides high quality of images acquired from the chosen level of retina.*

Keywords: Diabetic Retinopathy, Optical Coherence Tomography Angiography, Vascular density, Foveal Avascular Zone

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INTRODUCTION

Diabetic Retinopathy (DR) is a deliberating retinal microvascular complication of diabetes that remains the leading cause of visual impairment and blindness in working adult populations. This is a growing issue as the number of people living with diabetes increases. A meta analysis from 35 population based study conducted worldwide estimated global prevalence of DR among patients with diabetes to be 35.4% and 10.2% patients living with vision-threathening diabetic retinopathy. Diabetic retinopathy can be asymptomatic until the disease progress and there is significant irreversible damage and vision loss. Therefore, Early detection and proper treatment are particularly essensial to prevent sight threathening complications from diabetic retinopathy.[1,2]

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Retinal microvascular alteration caused by diabetes results in capillary drop out and decreased blood flow. Further nonperfusion and ischemia lead to an increased expression of angiogenic growth factors and development of pathogenic neovascularization that subsequently lead to the development of advanced-stage DR and Diabetic Macular Edema (DME). The importance of clinical understanding the microvascular changes in different stages of DR could provide essensial information regarding retinal perfusion status and the possibility to develop advanced stage and vision-threathening DR.[3–5]

Optical Coherence Tomography Angiography (OCTA) is a new, non invasive high resolution depth-resolved imaging technique that allowed us to study three dimensional microvascular changes in each retinal layer.[3,4,6,7] Qualitative and quantitative studies using OCTA on DR have shown alteration of retinal microvasculature and foveal avascular zone (FAZ) that can be seen even in patients with diabetes without clinically detectable diabetic retinopathy compared to healthy subject, suggesting that microvascular damage occurred before any visible sign of DR developed. These changes become more apparent as the DR progress. [5,8–12] With this advanced , non invasive technique, we aim to identify progressive changes in DR and provide quantification data on retinal microvascularity in diabetic patients.

METHODS

This is a cross-sectional study on Subjects with non proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) along with healthy subjects were recruited from the vitreoretinal department, Cicendo Eye Hospital National Eye Center between 17th and 24th January 2018. Inclusion criteria for DR subjects were patients age > 18 years, history of diabetes melitus (DM), presence of DR (NPDR or PDR), and good quality OCTA images. Exclution criteria were patients with other retinal diseases, such as retinal vascular occlusive disease, hypertensive retinopathy, age related macular degeneration, optic nerve diseases such as glaucoma and optic neuropathy, history of high refractive error and media opacity such as dense cataract or vitreous hemorrhage. Eyes with poor quality images on OCTA (signal strength below 6, image defocus or blur, and significant motion artifacts) due to unstable fixation or medium opacities that could confound the analysis were also excluded. For healthy subjects, we included patients with normal eyes and no history of systemic diseases. Level of retinopathy was determined by the treating physician using the International Diabetic Retinopathy Severity Scale.

Optical Coherence Tomography Angiography images were obtained with the CIRRUS high-definition OCT 5000 Angioplex instrument (Carl Zeiss Meditec, Dublin, CA), using the Optical Microangiography (OMAG) algorithm software. The device performed 68.000 A-Scans per second using 6x6 mm area surrounding the fovea. The effect of motion artifacts were minimized using FastTrack tracking system.[13]

Volumetric data sets for analyzing retinal microvasculature were applied to the Superficial Capillary Plexus (SCP), with Inner Limiting Membrane (ILM) as the inner surface and Inner Plexiform Layer (IPL) as the outer surface. Vascular Density (VD) was defined as the total length of perfused vasculature per unit area in the region of measurement. Foveal Avascular Zone refers to significant area devoid of flow signal that normally would be vascular.[13]

First, we compared the OCTA parameters between control group and diabetic group (NPDR + PDR). Second, we excluded PDR subjects, leaving NPDR subjects in the diabetic group.

STASTISTICAL ANALYSIS

All statistical analysis were performed using SPSS statistics. Saphiro wilk tests were used to determine if data were distributed normally. Independent T test and Mann-whitney U test were used for comparative data analysis. P-values less than 0.05 were considered statistically significant.

RESULTS

Of a total of 24 eyes of 17 patients imaged for this study, 6 were excluded due to signal strength below 6 and poor quality images, leaving a total of 18 eyes of 14 study participants (9 patients with DR and 5 healthy age-matched control). The study included 11 eyes with NPDR, 2 eyes with PDR and 5 healthy control eyes. The overall patients demographic characteristics are reported in table 1.

Table 1. **Demographic Patients Data of Diabetic and Healthy subjects**

Subjects Characteristic	DR	Healthy
No. of subjects, n	9	5
No. of eyes, n	13	5
Male : Female	6 : 3	4 : 1
Age, mean ± , y	53.5 ± 6.1	56.8 ± 10.6
Age range, y	43-66	51-73
Duration of DM mean ± y	5.6 ± 3.5*	
DR type, n (%)		
NPDR	11 (84.6%)	
PDR	2(15.4%)	

Abbreviations : DM, diabetes melitus; DR, diabetic retinopathy; NPDR, non proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

∗ Data not available in 4 patients

Table 2 shows the average VD, FAZ area, and FAZ circularity of SCP for diabetic, including NPDR and PDR group (NPDR+PDR) and control group. Mean vessel density was 16.27 ± 1.98 mm^{-1} in diabetic and 16.28 ± 1.96 mm^{-1} in control group (p = 0.998). FAZ area was 0.32 ± 0.18 mm^2 for diabetic and 0.20 ± 0.07 mm^2 in control group (p = 0.035), and mean FAZ circularity was 0.64 ± 0.13 and 0.67 ± 0.05 (p = 0.606) for diabetic and control group, respectively.

Table 2**. OCTA Parameters for Each Study Group (NPDR + PDR) and control group**

Parameters (SCP)	Diabetic group n = 11	Control group n = 5	P value
Vessel Density (mm^{-1})	16.83 ± 1.44	16.28 ± 1.96	.533
FAZ area (mm^2)	0.27 ± 0.10	0.19 ± 0.07	0.155
FAZ circularity	0.64 ± 0.17	0.65 ± 0.09	0.502

Abbreviations :
SCP, superficial capillary plexus; FAZ, fovea avascular zone
*****Mann –Whitney U test
[+] Statistically significant

Vessel Density and FAZ perimetry were not statistically different between both groups. however, FAZ area was significantly enlarged in DR eyes.

Average VD, FAZ area, and FAZ circularity of SCP for NPDR group and control group are reported in table 3. Mean VD was 16.83 ± 1.44 mm^{-1} for diabetic and 16.28 ± 1.96 mm^{-1} for control group (p= 0.533). Mean FAZ area was 0.27 ± 0.10 mm^2 and and 0.19 ± 0.07 mm^2 for diabetic and control group (p= 0.155), respectively. FAZ circularity was 0.64 ± 0.17 in diabetic and 0.65 ± 0.09 in control group (p= 0.502). None of these parameters were statistically significant between both groups.

Table 3. **OCTA Parameters for Each Study Group (NPDR group and control group)**

Parameters (SCP)	Diabetic group n = 13	Control group n = 5	P value
Vessel Density (mm^{-1})	16.27 ± 1.98	16.28 ± 1.96	.998
FAZ area* (mm^2)	0.32 ± 0.18	0.20 ± 0.07	.035+
FAZ circularity	0.64 ± 0.13	0.67 ± 0.05	.606

Abbreviations : SCP, superficial capillary plexus; FAZ, fovea avascular zone

DISCUSSION

Vascular changes have been the main interest of study in diabetic retinopathy, as the disease is primary a microangiopathy. Characterization of the microvascular alteration is considered important related to prognosis for vision loss and progression of the DR.[4–6] Vessel density measurements estimate the degree of capillary loss over an area, is known to be decreased in DR. Fovea avascular zone is a unique area in the macula which has the highest density of cone photoreceptor, specializing for high acquity vision. In diabetics, the FAZ is enlarged due to vascular disitegrity and can be used as an indicator of non-perfusion which could estimate the degree of ischemia of central retina, and has been linked with the visual prognosis of DR.[5,11,14–16]

Optical Coherence Tomography Angiography allowed us to study both qualitatively and quantitatively three dimensional microvascular changes in DR without the need of dye injection.[3,4,6] A pilot study by Ishibazawa et al[16] reported the clinical use of OCTA in detecting microaneurysm,capillary nonperfusion, and neovascularization in DR. Recent quantitative and qualitative studies on DR using OCTA have shown alteration in FAZ and the retinal microvasculatures both in the superficial and deep capillary plexus, compared to the normal eye.[8–11,16–18]

Dimitrova et al[10] and Adhi M et al[19] reported that vessel density in superficial and deep capillary plexuses of diabetic patients without DR are decreased compared to the healthy subjects, as well as the FAZ area that reported to increased in size in these patients, reflecting that microvascular changes in diabetic retinopathy have occurred before the clinical manifestations developed.[4,10,19]

In this study, we evaluated quantitative analysis of retinal SCP VD and FAZ on OCT in eyes with DR. From table 2, we reported that there were no significant difference between VD and FAZ circularity in SCP of healty eyes and diabetic eyes, including NPDR and PDR subjects. These findings are not consistent with findings from another studies reporting lower VD in DR eyes when compared to healthy subjects.[8,9,17,18] Rodolfo et al[11] reported that alteration of vessel density was present earlier in the Deep Capillary Plexus (DCP) compared to the SCP. Study by Peter et al[18] also proposed that DCP VD showed the strongest correlation with DR severity emphasizing the important role of the DCP in DR. Moreover, several previous studies also reported that microaneurysms, the earliest sign of microvascular changes in DR, were found primarily in DCP, sggesting the primary involvement of DCP in retinal microvascular diseases.[4,19]

In contrast to other studies that have shown that FAZ circularity decreases with increasing DR severity[5,8], our study found no significant changes of FAZ circularity between both groups. However, we found statistically significant enlargement of FAZ area in diabetic group. Conrath et al[14], on qualitative and quantitative analysis of FAZ in DR, reported that, in diabetics, FAZ size increased with advancing retinopathy stage. Both parameters of the FAZ represents capillary drop out, non perfusion, and retinal ischemia has been reported to correlate with visual prognosis in DR.[5,14]

From table 3, we analyze microvascular parameters by excluding eyes with PDR, Neither VD nor FAZ parameters were significantly different between both groups. As previously reported by several authors, the increase of FAZ size is more significant in the later stage of DR compared to the earlier stages of DR, and it can be used to ascertain its progression level.[11,14] This may explain the finding from table 3, where FAZ area was not significantly different from NPDR subjects.

This study has several limitations. The sample size was relative small and the study was not large enough to account for confounding factors such as duration of diabetes, gender, or level of blood glucose control and other systemic factors. Further study with a large number of patients is warranted to adequately evaluate the technology as a biomarker.

Even with these limitations, our study demonstrates that retinal microvascular changes in DR based on OCTA can be analyzed quantitatively.

The quantification of OCTA data propose a promising new field of study and will expected to be useful in the future as an objective marker of DR progression.

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