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Retinal Microvasculature Density Alteration in Type 2 Diabetes with and without Retinopathy using Optical Coherence Tomography Angiography

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Abstract

Introduction: Diabetic retinopathy is characterized by neurodegenerative features associated with extensive vascular changes. It is a leading cause of blindness because hyperglycemia weakens retinal capillaries, resulting in leakage of blood into the surrounding space. This bleeding can result in the formation of scar tissue, which can cause tractional retinal detachment and maculopathy.

Purpose: To describe retinal microvascular changes measured via Optical coherence tomography angiography OCTA in patients with diabetes and different severity of diabetic retinopathy DR, and to evaluate the effect of systemic metabolic and vascular risk factors on retinal capillary density and morphologic characteristics.

Materials and Methods: A total of 58 subjects (19 females, 39 males) were recruited from a tertiary Hospital. They were divided into three groups based on stages of DR: group 1: comprise 26 diabetics without retinopathy. Group 2: comprise 22 diabetic patients with Non-Proliferative Diabetic Retinopathy (NPDR). Group 3: comprise 10 diabetic patients with Proliferative Diabetic Retinopathy (PDR). The age ranging from 40-70 years. All patients undergone detailed ocular examinations including one image from both eyes by OCTA AngioVue from Optovue to scan microvasculature densities at different layers around the macula.

Results: There was highly statistical significant difference ($P < 0.001$) between the 3 groups for vessel density in the superficial and deep retinal layers in normal eyes and different DR grades. Otherwise, there was no statistically significant difference in the outer retina and the choroid capillary density among the three groups as normally no blood flow in outer retina and choroidal capillaries disappear at foveal slope.

Conclusion: We document structural changes in the retinal microvasculature associated with severity of DR. Optical coherence tomographic angiography is a new non-invasive tool to quantify the retinal capillary microvasculature to study diabetes and its complications. Optical coherence tomographic angiography has the potential to be used in larger epidemiologic and clinical studies, including interventional trials, to directly visualize the microvasculature that was previously not accessible in a noninvasive manner.

Keywords: Deep density; Diabetic retinopathy; Microvasculature; OCTA; Superficial density

Introduction

Diabetes Mellitus (DM) is one of the fastest-growing health problems in the world, which is now reaching to epidemic proportion in some countries [1]. Saudi Arabia ranks the second highest in the Middle East, and is seventh in the world for the rate of diabetes [2]. It is estimated that around 7 million of the population are diabetic and almost around 3 million have pre-diabetes. DM has been found to be related to high mortality, morbidity and vascular complications [3]. One of the most frequent microvascular complications known to be a leading cause of blindness is diabetic retinopathy (DR) [4]. Type-2 diabetes accounts for approximately 90% of the population. They comprise a larger proportion of those affected with DR [5]. Recent studies in Saudi Arabia showed high prevalence of DR in different regions as Madinah (34.5%), Taif (33%) and Jazan (28.1%) [6]. DR characterized by neurodegenerative features associated with extensive vascular changes. The DR developed from chronic hyperglycemia, results in weakening of retinal capillaries and leakage of blood into the surrounding space [7].

Hyperglycemia results in increased production of Reactive Oxygen Species (ROS) in islet cells. Therefore, the b-cells that comprise low level of antioxidants become extremely vulnerable to oxidative stress leading to microvascular and macrovascular complications [8]. The alteration in retinal microvasculature in DR is linked with oxidative stress through increasing the transcriptional activation of vascular endothelial growth factor, inflammatory mediators, and advanced glycation end-product formation. However, the oxidative stress process contributes to inhibition of antioxidant enzyme mainly of glutathione peroxidase, Superoxide dismutase and catalase. Generally, total antioxidant status has been shown to be significantly lower in patients with proliferative retinopathy than in diabetic's not developing retinopathy [7]. The study aimed to describe retinal microvascular changes measured via Optical coherence tomography angiography OCTA in patients with diabetes and different severity of diabetic retinopathy DR, and to evaluate the effect of systemic metabolic and vascular risk factors on retinal capillary density and morphologic characteristics.

Methods

A total of 58 subjects aged 40 - 70 years old who had type 2 diabetes with and without retinopathy were eligible for this study. They were divided into three groups based on stages of DR: group 1: comprise 26 diabetics without retinopathy. Group 2: comprises 22 diabetic patients with non-proliferative diabetic retinopathy (NPDR). Group 3: comprises 10 diabetic patients with Proliferative Diabetic Retinopathy (PDR). Subjects with chorioretinitis scars, posterior uveitis, ocular hypertension, glaucoma and previous ocular surgery, age related macular degeneration, or any macular diseases were excluded from this study.

All patients underwent detailed ocular examinations including the following: 1. Visual acuity by Snellen chart 2. Refraction using autorefractometer 3. Slit lamp examination 4. IOP measurement 5. Fundus bio microscopy 6. One image from both eyes by Optical coherence tomography angiography OCTA (AngioVue, RTVue-XR; Optovue). The pictures were performed on a scan area of 3 X 3 mm^2 generated from the superficial, deep retinal vascular plexuses centered on the fovea in addition to the outer retina and choroid capillary density. The thickness on area 3x3 mm^2 was generated from Internal Limiting Membrane to The Retinal Pigment Epithelium Layers (ILM-RPE).

Ethical Consideration

The study was approved by the concerned Ethical Committee. Its protocol was explained to each participant at the time of recruitment and informed consent was obtained according to the Declaration of Helsinki.

Statistical Analysis

Statistical Analyses were performed by using Graph Pad Prism 7. All variables were expressed as Mean ± Standard deviation. Shapiro- Wilk tests were used to determine if demographic data distributed normally. Macular vascular densities and thickness were analyzed between 3 diabetic groups using one-way ANOVA test. A P value < 0.05 is considered statistically significant.

Results

Demographic Data and Medical history

Shapiro- Wilk tests showed that the data were normally distributed ($P>0.05$). Of a total of 116 eyes imaged for this study, 13 were excluded due to poor image quality and artifacts on OCTA images, leaving a total of 103 eyes of 58 study diabetic participants. The study included 48 eyes of 26 patients with DM without DR, 41 eyes of 22 patients with NPDR, and 14 eyes of 10 patients with PDR. Among those 58 subjects, there were 39 males (67%) and 19 females (32%). The mean (SD) age was 51.4 (22.38) in diabetic without DR group, 58.4 (26) in NPDR group and 62 (32.03) in PDR group with all ranging from 40-70 years old. The hypertension and dyslipidemia were presented in the majority of the subjects. The overall demographic and disease-related characteristics are reported in (Table 1).

Table 1: Demographic data and medical history.

	No DR	NPDR	PDR
Subjects	26	22	14
Eyes (n)	48	41	10
Age (mean±SD)	51.4±23.38	58.2±26	62±32.03
Sex F/M	8/18	6/16	5/5
Hypertension Yes/No	15/11	12/10	10/4
Dyslipidemia	21/15	16/6	6/4

Ocular History, Functional, and Anatomical Characteristics

The NPDR group was 6 mild, 8 moderate and 8 severe NPDR. The duration of diabetes was significantly different ($P=0.0005$) between the groups with mean (SD) of 8.52 (7.14), 13.59 (4.08) and 16.8 (4.61) years in NDR, NPDR and PDR groups respectively.

There was no significant difference in Hemoglobin A1c (HBA1c), High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL) and total cholesterol in all groups. Summary of ocular and systemic characteristics are summarized in (Table 2).

Table 2: Ocular and systemic characteristics.

	No DR	NPDR	PDR	P value
VA	0.9427±0.1584	0.8063±0.2549	0.6529±0.2516	<0.0001**
SE (Diopter)	0.2027±1.686	-0.8243±1.832	0.5357±2.221	0.564
IOP (mmhg)	18.02±2.832	19.32±2.752	20.21±2.887	0.0160 *
HBA1c %	8.23±1.78	8.59±1.91	8.7±2.16	0.8203
HDL (mg/dl)	39.71±12.23	52.09±17.92	42.8±8.9	0.0887
LDL (mg/dl)	113.2±41.52	113.9±46.71	83.6±25.56	0.3487
Cholesterol (mg/dI)	159.7±57.63	148.6±70.41	141.3±42.39	0.8354

*Significant
**Highly significant

Micro Vascular Density Group Comparison Analysis

There was highly statistical difference ($P < 0.001$) between the 3 groups for vessel density in the superficial and deep retinal layers in normal eyes and different DR grades. The eyes with non-diabetic retinopathy had higher vessel density compared with NPDR and PDR eyes. In the deep vessel density, only the fovea showed no statistical significant difference (P=0.3381) among groups (Tables 3 and 4). The mean density was decreased with severity of DR. In the superficial and deep vascular plexus, all the densities of the 9 regions were lowest in the PDR group except for the fovea and the superior regions in deep vessel density were lower in the NPDR. Otherwise, there was no statistically significant difference in the outer retina and the choroid capillary density among the three groups as normally no blood flow in outer retina and choroidal capillaries disappear at foveal slope. The outer retina and choroid capillary densities are presented in (Tables 5 and 6).

Table 3: Superficial Vascular Plexus Densities (SVP).

Superficial vessel density (%), mean±SD	No DR	NPDR	PDR	P value
Whole image	46.79±5.08	44.13±4.28	42.3±4.57	0.0024**
Fovea	27.59±5.51	25.07±5.14	22±4.12	0.0015**
Para fovea total	48.8±5.81	45.88±4.7	43.75±5.18	0.0027**
Sup. Hemi	48.91±5.88	45.68±4.99	43.67±6.15	0.0024**
Inf. Hemi	48.65±5.89	48.65±5.89	43.83±4.64	0.0081**
Temporal	48.43±6.22	46.53±4.61	43.69±4.22	0.0045**
Superior	48.43±6.22	46.03±5.60	43.35±6.68	0.0158**
Nasal	49.35±6.11	46.41±5.87	43.69±5.85	0.0041**
Inferior	48.61±6.14	46.35±5.7	44.25±5.75	0.0338*

Table 4: Deep Vascular Plexus Densities (DVP).

Deep vessel density (%), mean±SD	No DR	NPDR	PDR	P value
Whole image	54.85±3.03	50.03±5.07	49.56±4.43	0.0084**
Fovea	24.59±5.83	22.64±7.97	23.67±9.48	0.3381

Parafovea	58.53±3.13	52.98±5.79	51.39±5.32	<0.0001**
Sup.hemi	58.89±3.006	53.06±6.27	51.48±5.33	<0.0001**
Inf.hemi	58.16±4.01	52.88±6.09	51.17±5.42	<0.0001**
Temporal	57.45±4.34	51.54±6.42	50.35±5.89	<0.0001**
Superior	58.95±3.88	45.15±7.10	53.19±5.81	<0.0001**
Nasal	59.18±3.67	52.92±6.36	51.3±6.53	<0.0001**
Inferior	58.57±4.40	53.32±7.77	50.56±5.60	<0.0001**

Table 5: Outer Retinal Vascular Densities.

Outer vessel density (%), mean±SD	No DR	NPDR	PDR	P value
Whole image	44.31±5.32	44.99±4.37	46.66±4.36	0.2793
Fovea	57.66±7.78	57.46±6.33	56.85±9.47	0.9399
Parafovea	42.86±5.79	43.28±4.66	45.82±4.66	0.209
Sup.hemi	42.83±5.76	43.71±4.71	46.01±5.33	0.1466
Inf.hemi	42.85±5.96	43.59±5.14	45.66±4.33	0.2402
Temporal	42.83±5.90	44.55±4.46	45.72±4.6	0.1159
Superior	43.15±5.93	43.71±5.21	45.81±6.32	0.3133
Nasal	42.39±6.17	43.1±5.08	46.09±5.72	0.1068
Inferior	42.98±6.09	43.6±6.28	45.83±4.51	0.2993

Table 6: Choroidal vascular densities.

Outer vessel density (%), mean±SD	No DR	NPDR	PDR	P value
Whole image	65.09±2.20	64.09±3.96	64.59±1.77	0.2891
Fovea	64.2±4.27	64.74±5.05	63.48±4.13	0.6529
Parafovea	65.52±2.53	64.12±4.25	64.38±2.12	0.1245
Sup.hemi	65.49±2.42	64.28±4.25	64.43±2.27	0.1946
Inf.hemi	65.47±3.17	63.95±4.97	64.33±2.14	0.1731
Temporal	65.55±3.43	64.42±4.52	65.55±3.435	0.2938
Superior	65.62±3.00	64.53±4.94	64.29±2.16	0.3096

Foveal and Parafoveal Thickness Analysis

The thickness of the fovea and parafovea in all regions showed statistically significant difference (P=0003) in NPDR compared to the NDR and PDR groups respectively (Table 7). The thickness was highest in the NPDR group (Figure 1).

Table 7: Foveal and Parafoveal Thickness (µm).

Thickness (µm), mean±SD	No DR	NPDR	PDR	P value
Fovea	252.8±25.44	306±89.95	252.9± 54.95	0.0003**

Parafovea	317.8±22.69	337.2±46.03	310.7±31.98	0.0113*
Sup.hemi	317.5±22.37	335.2± 41.46	310.7±28.34	0.0116**
Inf.hemi	317.6± 23.22	337.1±56.68	310.3±37.17	0.0373**
Temporal	307.9±27.79	337.1±63.17	300.9±41.24	0.0053**
Superior	321.5± 21.51	338.2± 50.97	313.2±30.35	0.0379**
Nasal	320.6± 21.79	336.4± 36.07	310.9±30.24	0.007**
Inferior	319.9±23.12	342.3±56.84	311.9±39.51	0.0157**

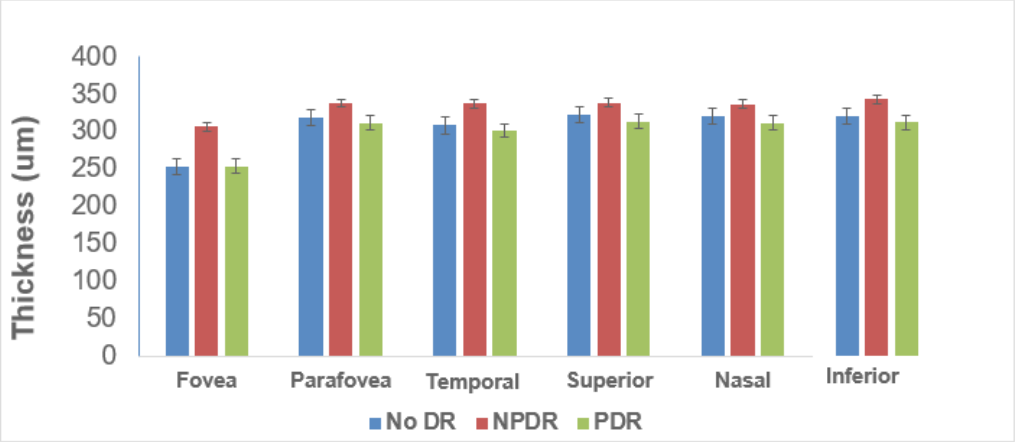

Figure 1: Foveal and Para Foveal thickness (ILM-RPE) in three diabetic groups.

Discussion

Over the past decades, Fluorescein Angiography (FA) remains the gold standard procedure. However, it has limitations, the most common being fluorescein injection, which can trigger severe reactions such as anaphylactic shock [9]. The OCTA is a new, time efficient, noninvasive tool to provide detailed quantification assessment of the retinal capillary microvasculature to study diabetes [10]. In this study we re-evaluated several significant previous findings to understand and prove the structural changes at the macula and choriocapillaris in DR. Our findings of superficial and deep vessel density showed a stronger correlation with DR severity, SVP and DVP densities that were decreased with increased severity level of DR similar to the those reported in Nesper et al and Agemy, et al. [11,12].

We observed the difference in Foveal Avascular Zone (FAZ) between DM without DR, NPDR and PDR. Increased FAZ is correlated with worsening of DR severity as proved while analysing the foveal superficial and deep microvascular densities. These results fit well the results of previous studies [11]. Previous studies reported that choriocapillary vessel density in DR and NDR tend to be decrease at the parafoveal region [13]. In contrast, our results showed no significant difference in choriocapillary density in both foveal and parafoveal areas between groups. On the agreement of Galina, et al. findings, there were no statistically significant differences in foveal thickness between the NDR and PDR groups [14], except for NPDR group that revealed higher thickness because most of the patients had macular edema.

Conclusion

We document structural changes in the retinal microvasculature associated with severity of DR. Optical coherence tomographic angiography is a new non-invasive tool to quantify the retinal capillary microvasculature to study diabetes and its complications. It has the potential to be used in larger epidemiologic and clinical studies, including interventional trials, to directly visualize the microvasculature that was previously not accessible in a noninvasive manner.

Author Disclosure Statement

The authors declare no potential conflicts of interest with respect to the authorship, and/or publication of this article.

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