Detection of subclinical microvascular changes in patients with type 2 diabetes mellitus without diabetic retinopathy according to the different gender group

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ABSTRACT

Purpose: We aimed to compare retinal microvascular changes occurring in different sex groups in type 2 diabetes mellitus (DM) patients without diabetic retinopathy (DR) with optical coherence tomography angiography (OCTA) measurements.

Materials and Methods: This study included one eye of 48 different patients with type 2 DM who did not have any DR findings. Through the OCTA measurements of the patients, foveal avascular zone (FAZ) area (mm²), FAZ perimeter (mm), foveal density (FD), central macular thickness (CMT), and vascular density (VD) measurements were taken for superficial capillary plexus (SCP) and deep capillary plexus (DCP).

Results: When the DM group and the control group were compared, the mean FD was found to be statistically significantly lower in the diabetic group (p=0.02). SCP perifovea, perifovea temporal, nasal and inferior VD mean scores were statistically significantly lower in the diabetic group (p=0.04, p=0.04, p=0.02, p=0.03). The mean DCP parafovea, parafovea temporal and nasal VD (%) were found to be statistically significantly lower in the diabetic group as well (p=0.04, p=0.02, p=0.01). When males and females with DM were compared, SCP fovea and DCP fovea VD (%) values were found to be statistically significantly lower in females than males (p=0.01, p=0.02).

Conclusion: It was shown that FD and VD are affected by OCTA findings in DM patients without clinically detectable DR. In addition, it was detected that microvascular changes started earlier in females than in males. Therefore, it is thought that OCTA can be used for screening in diabetic patients.

Keywords: Diabetes mellitus, Diabetic retinopathy, Optical coherence tomography angiography, Optical coherence tomography.

INTRODUCTION

Diabetic retinopathy (DR) is a chronic disease that threatens vision by affecting the capillary structures that provide oxygen and other nutrients to the retinal tissues.[1] Due to the increasing prevalence of Type 2 Diabetes mellitus (DM), the prevalence of DR tends to increase as well.[2] The most effective way to prevent vision loss in DR is regular blood glucose monitoring, early diagnosis of DR through community screenings, and effective DR treatment in time.[3]

Optical coherence tomography angiography (OCTA) is a new, non-invasive method aimed at visualizing retinal microcirculation.[4] OCTA is able to assess the superficial and deep vessel density in the macular capillary plexus and the foveal avascular region in these layers.[5] Moreover, OCTA provides high-resolution images of retinal and choroidal microvascular blood flow and structure, which helps identify the presence of DR and disease progression.[6]

In recent studies, the role of OCTA has been examined, especially in patients with DR.[7-9] However, detecting

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retinal microvascular change in Type 2 DM patients before DR occurs is vital for the course of the disease, and there are a limited number of studies on this subject.[10] In addition, in the light of the information that was obtained from the literature review, OCTA findings in Type 2 DM patients were not evaluated separately in these studies in terms of sex. Therefore, this study aimed to detect retinal microvascular changes with OCTA at an early stage in type 2 DM patients without diabetic retinopathy by comparing them with the control group data according to different sex groups.

MATERIALS AND METHODS

In this retrospective study, one eye from 48 different patients with type 2 DM and without DR findings was included. They had to have come to XXXX Hospital Ophthalmology Department Retina Unit for control purposes between January 2019 and October 2019. A total of 95 eyes, including an eyefrom 47 healthy individuals with similar characteristics to the patient group, were included.The eye with high OCTA image quality was included in the study. Ethics committee approval for the study was obtained from the Ethics Committee of XXXX with the decision number 2019/2162 dated 22.11.2019 and was performed in accordance with the principles of the Declaration of Helsinki.

Demographic characteristics of the patients and information about their HbA1c values were obtained from the files of the patients and their records in the diabetes outpatient clinic, the data files of the control group and the data recorded in the system.

Both in the healthy group and the group with DM, those with additional retinal diseases such as retinal vascular occlusive disease, hypertensive retinopathy, central serous chorioretinopathy, senile macular degeneration; those who had previous intraocular surgery, laser surgery, those with corneal or lens opacity that would prevent the fundus from being visualized, glaucoma and optic neuropathy, and those with a diagnosis of additional systemic disease (hypertension) or without present HbA1c values were excluded from the study. Patients with high quality OCTA images, individuals of similar age and sex, those with spherical and cylindrical refractive errors between +3 and -3 diopter, and those with the best corrected visual acuity (BCVA) Snellen chart and a decimal value of 1.0 were included in the study. Fundus examinations of the patients were recorded from the patient files.

OCTA Measurement Parameters

After pupil dilation was achieved with 1% tropicamide and 2.5% phenylephrine, measurements were taken with AngioVue (RTVue-XR ®, Fremont, California, USA; software version 2018.1.0.37), a bimodal OCT system that can display patients' structural and vascular measurements together, and then evaluated. In the study, 6x6 mm OCTA images were preferred. Of the images, those with signal strength and quality of 7/10 and above were taken into evaluation (Figure 2).

Foveal Avascular Zone (FAZ) Area (mm²), FAZ Perimeter (mm), Foveal Density % (FD) Measurement

With the FAZ scaling application of the device, FAZ area (mm²), FAZ perimeter (mm) and foveal density (FD) (%) were automatically measured by selecting the "Retina" measurement (Figure 1). FD is defined as the vascular density (%) around the FAZ, in the area surrounded by a circle at a distance of 300 microns around the FAZ.[11,12]

Central Macular Thickness (CMT) Measurement

CMT measurement, the distance between the inner limiting membrane (ILM) and retinal pigment epithelium (RPE) layer, was taken automatically by the device by selecting the Quickvue module in OCTA. Quadrants were formed by automatically fitting the fovea-centered zone map defined by ETDRS. The 3X3 mm image taken with OCTA was divided into a 1 mm ring centered on the fovea and a 3 mm concentric ring surrounding it divided into 4 (5 zones).

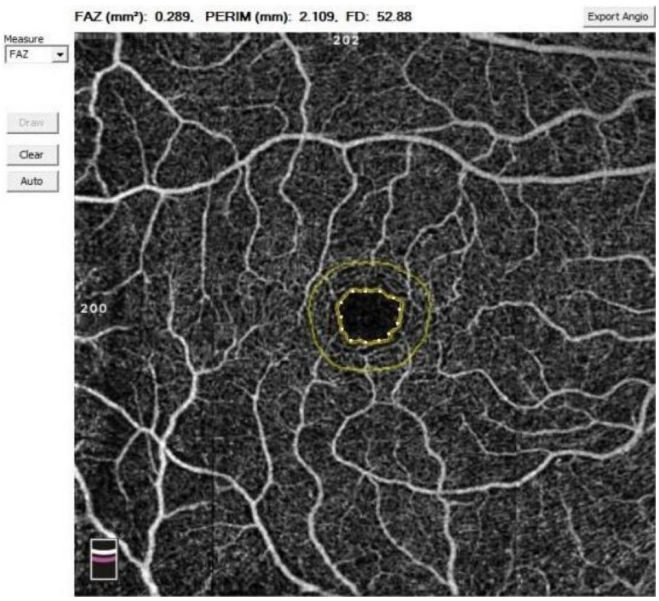

Figure 1: *Measurement of FAZ in OCT-A.*

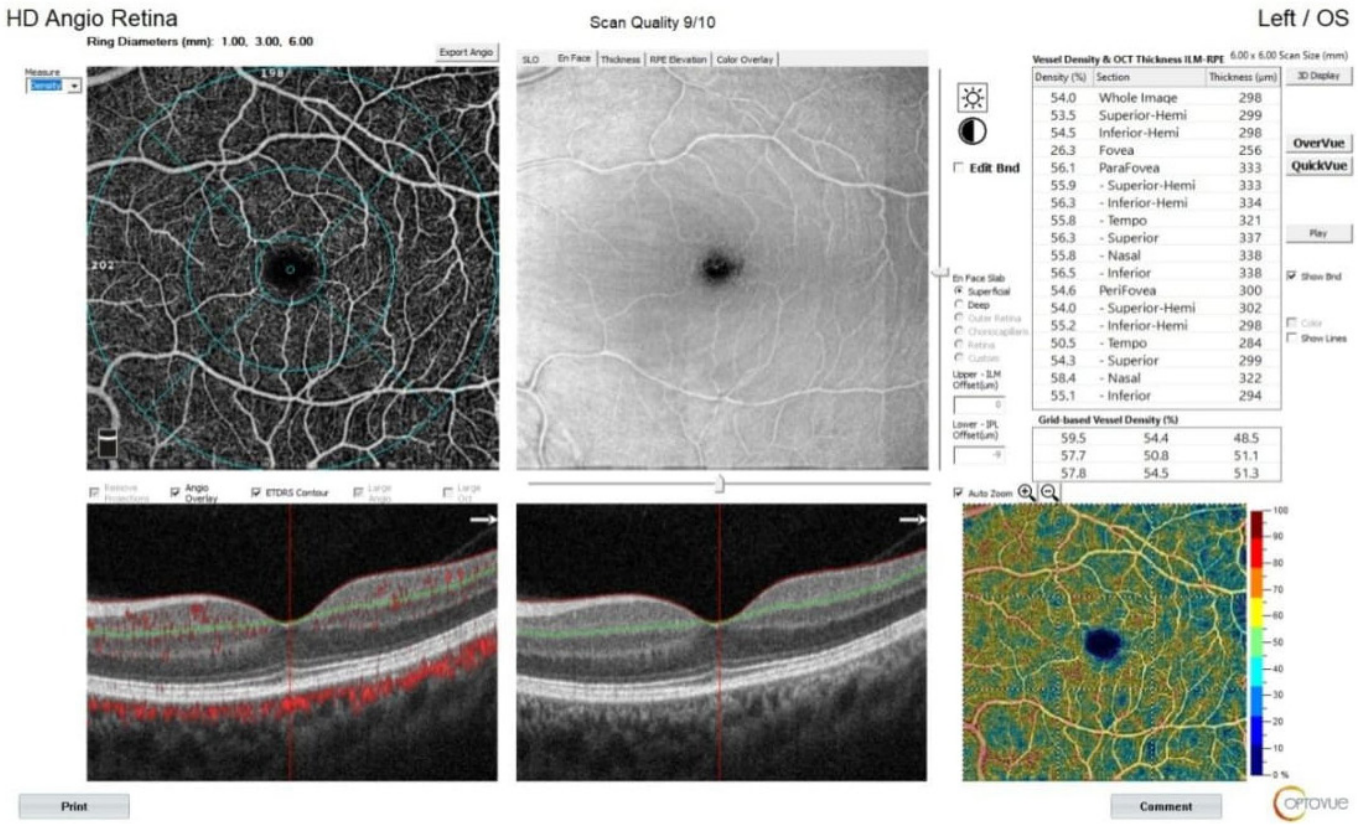

Figure 2: *Measurement of Vascular Density in OCTA.*

Statistical Analysis

In this retrospective study, descriptive statistical analyzes such as mean, percentile and standard deviation were used in order to examine the demographic data of the participants with and without DM. The Chi-Square test was performed for categorical variables, and Independent Samples t test was used for mean values in order to compare the medical measurements of people with and without DM. The Pearson Correlation Analysis was performed in order to examine the relationships between medical measurements. Normal distribution hypothesis was met for Independent Samples t test and Pearson Correlation Analysis. IBM SPSS 22.0 was used for analyzes. Significance level was taken as $p<0.05$ for all analyzes.

RESULTS

The mean age of the participants was 56.25±8.43 years. A total of 27 (57.4%) of the diabetic patients were female, and measurements were taken from the right eye of 20 participants (41.7%). Out of the group of non-diabetic patients, 24 (50%) were female, and measurements were taken from the right eye of 25 (53.2%) participants (Table 1). It was found that the mean age of the participants with and without diabetes was not statistically significantly different (t=1.80, p=0.076). In addition, it was found that the difference in ratios of sex (p=0.26) and eye measurement (X^2=1.27, p=0.26) between the two groups were not statistically significant.

It was observed that the difference in mean FAZ (mm²) and FAZ perimeter (mm) values were not statistically significant between participants with and without diabetes (p=0.83, p=0.87, respectively). In addition, the mean FD (%) between the two groups was found to be statistically significantly reduced in the diabetic group (p=0.02) (Table 1). Furthermore, the mean values of perifovea, and temporal, nasal and inferior VD (%) of the perifovea in the superficial capillary plexus (SCP) were found to be statistically significantly reduced in the diabetic group (p=0.04, p=0.04, p=0.02, p=0.03, respectively). In the deep capillary plexus (DCP), parafovea, and temporal and nasal VD (%) of parafovea were found to be statistically significantly reduced in the diabetic group (p=0.04, p=0.02, p=0.01, respectively) (Table 1).

It was found that the mean FAZ (mm²) and perimeter value (mm) between males and females with diabetes were statistically significantly different (p=0.006, p=0.008, respectively) (Table 2). SCP fovea and DCP fovea VD (%) values were found to be statistically significantly different

Table 1: *Characteristics of the study sample.*			
Variables	**DM(+) (n=48)**	**Control (n=47)**	***p***
Age (years)	53.3±7.3	56.3±8.4	0.07
Gender			
Female, n (%)	27 (57.4)	24 (50.0)	0.46
Male,n(%)	21 (42.6)	23 (50.0)	
HbA1c (%)	8.0±2.2	5.4±0.3	**<0.001**
OCT-A Parameters			
FAZ area (mm²)	0.3±0.1	0.3±0.1	0.83
FAZ perimeter (mm)	2.1±0.5	2.1±0.4	0.87
Foveadensity (%)	52.9±4.5	55.0±3.9	**0.02**
Superficial capillary plexus, Vascular density (%)			
Retina	49.3±3.1	50.5±2.9	0.06
Superior	49.9±3.2	50.5±3.1	0.35
Inferior	49.2±3.2	50.5±3.0	**0.03**
Fovea	19.3±7.1	19.0±6.4	0.85
Parafovea	51.8±3.4	52.7±3.8	0.21
Temporal	51.9±3.4	52.9±3.7	0.19
Nazal	50.6±3.9	52.0±3.8	0.09
Superior	52.6±4.5	53.6±4.7	0.31
Inferior	51.9±3.9	52.5±4.6	0.58
Perifovea	49.9±3.1	51.2±3.0	**0.04**
Temporal	46.1±3.4	47.5±3.6	**0.04**
Nazal	53.7±3.3	55.1±2.8	**0.02**
Superior	50.2±3.6	51.7±3.8	0.07
Inferior	49.7±3.5	51.3±3.3	**0.03**
Deep capillary plexus, Vascular density (%)			
Retina	49.9±5.3	51.1±4.7	0.25
Superior	50.4±5.6	51.6±4.5	0.30
Inferior	49.5±5.2	50.7±4.9	0.25
Fovea	35.2±8.3	36.5±7.5	0.44
Parafovea	53.7±3.8	55.4±3.7	**0.04**
Temporal	55.1±3,9	56.8±3.5	**0.02**
Nazal	54.4±3.7	56.4±3.7	**0.01**
Superior	53.2±4.8	54.8±4.5	0.08
Inferior	52.1±4.8	53.4±4.7	0.21
Perifovea	51.4±5.7	52.3±5.0	0.40
Temporal	54.1±4.8	55.1±3.9	0.29
Nazal	50.1±6.5	50.6±5.7	0.70
Superior	51.4±6.4	52.6±5.7	0.35
Inferior	50.1±6.5	51.5±6.4	0.29

Abbrevations: FAZ, Fovea avascular zone; HbA1c, glycated haemoglobin; OCT, Optic cohorence tomography; OCT-A, Optic cohorence tomography-anjiography
Categorical variables were indicated as number (%) and determined by the Chi-square test .
Numerical variables with normally distrubuted were indicates as mean ± standart deviation and determined by t-test.
Values given in bold indicate statistically significant results ($p < 0.05$).

Table 2: *Comprasion of OCT-A parameters between different gender groups*			
Variables	**Diabetes Mellitus (n=48)**		***p***
	Female (n=24)	**Male (n=24)**	
HbA1c, (%)	7.4 ±1.3	8.5 ±2.7	0.28
OCT-A Parameters			
FAZ area(mm²*)*	0.3±0.1	0.2±0.1	**0.006**
FAZ perimeter (mm)	2.2±0.3	1.9±0.5	**0.008**
Foveadensity (%)	53.9±4.1	51.7±4.6	0.112
Abbrevations: FAZ, Fovea avascular zone; OCT-A, Optic cohorence tomography-anjiography Numerical variables with normally distrubuted were indicates as mean ± standart deviation and determined by t-test. Values given in bold indicate statistically significant results (p < 0.05).			

between males and females with diabetes (p=0.01, p=0.03, respectively).

It was determined that FAZ (mm²) and perim (mm) mean values between men and women in the control group were not statistically significant (p=0.667, p=0.739, respectively). VD was not significant at any stratum between men and women in the control group.

According to the Pearson Correlation Analysis, there was no statistically significant correlation between age, HbA1c, FAZ (mm²), FAZ perimeter (mm), FD (%), foveal thickness (µm) of the diabetic participants (p>0.05). It was observed that FAZ (mm²) value had positive correlation with FAZ perimeter (mm) and FD (%) (r=0.98, p<0.001), (r=0.49, p<0.001, respectively). FAZ Perimeter value was found to be positively correlated with FD (%) (r=0.51, p<0.001) (Table 3).

DISCUSSION

In this study, it was observed that diabetes-related changes occurred in the retinal microcirculation of type 2 DM patients without DR, and FD was affected before FAZ measurements. In addition, it was found that the parafovea in DCP, temporal and nasal VD of the parafovea, perifovea in the SCP, temporal, nasal and inferior VD of the perifovea were significantly reduced in the diabetic group compared to the control group. It was shown through this data that in both SCP and DCP of diabetic patients, VD is affected. It was also found that in diabetic patients, microvascular changes started earlier in females than in males. To the best of our knowledge, this is one of the first studies in which Type 2 DM patients were evaluated separately by OCTA according to sex in order to detect microvascular change at an early stage.

It remains unclear which sex is more susceptible in the early stage of DR. In the study conducted by Lee et al., in which they investigated the risk factors for retinal microvascular disorder in patients with type 2 DM and without DR, no significant difference was found between the DM and control groups in terms of age and sex in the OCTA data.[13] Unlike this study, there are also studies showing that females are more likely to have DR.[14-16] A study of 120,000 cases from Germany and Australia showed that females were more likely to have DR than males.[14] Similarly, studies from the UK and Japan have shown that women tend to have greater reductions in visual acuity compared to men.[15,16] However, unlike these studies, there are some studies from the United States and

Table 3: *Corelation analysis in diabetic patients*						
Variables	**Fovea density**		**FAZ area**		**FAZ Perimeter**	
	r	*P* value	r	*P* value	r	*P* value
Age (years)	-0.25	0.08	-0.02	0.92	-0.01	0.99
HbA1c (%)	-0.22	0.12	-0.23	0.11	0.23	0.11
FAZ area (mm²*)*	**0.49**	**<0.001**	-	-	**0.98**	**<0.001**
FAZ perimeter (mm)	**0.51**	**<0.001**	**0.98**	**<0.001**	-	-
Foveadensity (%)	-	-	**0.49**	**<0.001**	**0.51**	**<0.001**
Abbrevations: FAZ, Fovea avascular zone; HbA1c, glycated haemoglobin. Values given in bold indicate statistically significant results (p < 0.05).						

India which indicate that males are at risk for DR.[17,18] This cross-study inconsistency highlights the need for further research on the relationship between DR and sex. In the present study, unlike the studies mentioned above, it was shown that microvascular changes in type 2 DM patients without DR development started earlierfemales. We can speculate that this situation may have arisen with the effect of hormonal and genetic factors in women. In order for the findings of this study to be generalizable, prospective cohort observational studies are needed.

Yu et al.reported that the superficial FAZ was greater in women than in men.[19] Samara et al. in his study, although the FAZ dimensions were larger in women (superficial FAZ 0.272 vs 0.258 mm2, P = 0.55 deep FAZ 0.429 mm2 0.480 p=0.13), no significant difference was found between the genders.[20] The effect of gender on FAZ size was not clear in previous studies. In line with this, in our study, no significant change was found in the FAZ and FD values of the control group. We think that the reason for this situation may be the low number of participants included.

Thanks to OCTA's ability to layer the macula and retinal tissue close to the macula, excluding the peripheral retina, it can take separate sections from the vascular plexuses (superficial and deep) in the macula, and retinal microcirculatory pathology can be detected at an early stage.[21] A recent cross-sectional study found that VD in DCP in OCTA was lower in diabetic patients without DR than in non-diabetics. In addition to these findings, it was suggested that parafoveal capillary nonperfusion in DCP is an early manifestation of DR.[22] Another recent study suggested that VD reduces in DCP and SCP when DR is present.[23] In the study by Lee et al., diabetic patients without clinical signs of DR were found to have lower VD in SCP and DCP, and a larger FAZ area compared to healthy control group.[13] In the present study, the VD of the parafovea and temporal and nasal layers of parafovea of DCP; and the VD of perifovea and temporal, nasal and inferior layers of perifovea of SCP were found to be significantly reduced in diabetic patients compared to the control group. However, further research is needed to evaluate the role of OCTA in detecting early signs of DR in diabetic patients.

OCTA helps detect the retinal vascular abnormalities, including areas of capillary nonperfusion, FAZ changes and disruption of choriocapillaris flow.[24] In a recent study, the FAZ area was evaluated with OCTA in a study that included patients with type 2 DM without clinical signs of DR, patients with nonproliferative diabetic retinopathy, and a healthy control group. A statistically significant enlargement of FAZ was shown in the other two groups compared with non-diabetic eyes.[25] Unlike these studies, in another study, no significant difference was found in the FAZ area when the diabetic patients and the control group were compared.[6] Similarly, there was no statistically significant difference between the diabetic patients and the control groups in the present study in terms of the mean values of FAZ area in the whole retina. Due to the different results obtained in the studies, it can be said that FAZ measurements cannot be a sensitive biomarker for the detection of early microvascular changes in patients with diabetes.[26,27,28] However, the FAZ scaling application in the new version of OCTA allows for a separate measurement of a more specific parameter, FD.[23] In a recent study, FD was found to be lower in diabetic patients without DR compared to the control group.[6] Similarly, no significant difference was observed in the FAZ area in the present study, but FD was found to be significantly reduced in diabetic patients compared to the control group. This may indicate that a decrease in FD, an indicator of macular perfusion before FAZ is impaired, may be a more sensitive measurement than FAZ.

The limitations of this study are the small number of patients and that it is a cross-sectional study. In addition, the measurement of microvascular changes in the peripheral retina is limited since the 6x6 mm measurement in OCTA includes the posterior pole retina. Another disadvantage was that OCTA could not identify blood flow below the lowest detectable velocity, so areas defined by OCTA as capillary nonperfusion may be areas of slow or turbulent flow.

CONCLUSION

In conclusion, it was shown in the present study that of the OCTA findings, FD and VD are affected in diabetic patients without diabetic retinopathy findings. Therefore, it is thought that OCTA can be used for screening in diabetic patients. It was also observed that females experience earlier onset of microvascular changes among diabetic patients. Prospective, randomized and controlled studies with larger numbers of patients are needed to elucidate the relationship between OCTA data and vascular changes in diabetes.

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