Evaluation of Early Retinal and Choroidal Microvascular Changes in Type 2 Diabetes Patient Without Retinopathy

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ABSTRACT

Purpose: To investigate changes in retinal vascular plexuses and choriocapillaris in patients with type 2 diabetes mellitus (DM) without diabetic retinopathy (DR) using optical coherence tomography angiography (OCTA).

Methods: A total of 48 DM and 48 healthy control subjects were included. Mean superficial and deep vessel density (SVD, DVD) and flow in superficial and deep layers, choriocapillaris (CC) and FAZ area were measured by OCTA for analysis. Also, patients were categorized into two groups as high-risk (≥ 5 years) and low-risk (< 5 years) according to the duration of DM.

Results: SVD did not change in eyes without DR, but DVD significantly decreased when compared to healthy controls ($p< 0.05$). Both superficial and deep layer's flow did not change in diabetic patients who had a significant enlargement in FAZ area. CC flow area and CC thickness did not change in DM patients ($p> 0.05$). The mean DVD and FAZ area were correlated with HbA1c levels and the duration of DM. Comparison between the high-risk (20 patients) and low-risk groups (28 patients) revealed significant difference in superficial and deep layer's flow, CC and FAZ area ($p<0.05$). Also, SVD and DVD measurements of the DM patients were significantly different between high-risk and low-risk groups for all macular regions ($p<0.05$ for all).

Conclusions: OCTA can show the damage in patients without any clinically significant DR before the clinical manifestation in diabetic patients. Our results suggested that OCTA might be a promising tool for periodic screening of diabetic patients without DR.

Key Words: Diabetic retinopathy, HbA1c, Optical coherence tomography angiography, Type 2 diabetes, Vascular plexus.

INTRODUCTION

Diabetic retinopathy (DR) is the leading cause of visual impairment and blindness in people with diabetes and affects nearly 35% of all diabetic patients worldwide.[1] Early detection and treatment of DR is critical to prevent vision loss. Fluorescein angiography (FA) is the standard imaging modality for the diagnosis and follow-up of DR, and typical findings include microaneurysm, extended foveal avascular zone (FAZ), areas of ischemia due to capillary occlusion, and neovascularization.[2]

Because FA is an invasive procedure with dye injection, it can lead to serious side effects such as anaphylaxis and renal or cardiovascular complications, as well as less serious side effects like nausea/vomiting and back pain.[3] Although not providing very detailed images of the retinal structures, it provides an overlapping image of the superficial and deep retinal microvascular structures because the image from each layer is two-dimensional. Therefore, it is not possible to evaluate the retinal layers separately.

OCT angiography (OCTA) is a new technique that allows non-invasive, fast and dye-free imaging of the retinal and choroidal microvascular map at high resolution.[4] In the near future, OCTA instruments will widely take place to evaluate retinal and choroidal vascular structures in some clinical conditions such as age-related macular degeneration, central serous retinopathy and DR.[5,6] There is discordance between studies on retinal vascular measurements by OCTA in diabetic patients without clinically determinant retinopathy. There are different studies reporting decrease in both SVD and DVD or a decrease only in DVD; enlargement of FAZ or no significant change in FAZ area.[7-15]

The aim of this study was to evaluate retinochoroidal vascular structures by OCTA in diabetic patients without any significant signs of DR clinically.

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MATERIALS AND METHODS

This cross-sectional study analyzed 48 eyes of 48 diabetic patients (men/women:24/24; mean age 49.5±14.1 [41-70 years) without DR and 48 age and gender matched controls (men/women:25/25; mean age:48.5±13,1 [44-70 years). All individuals had been evaluated by two experienced retina subspecialists for the clinical signs of diabetic retinopathy. Mean HbA1c level was 7.9 (5.5-9.2)mg/dl.

The study was performed at Ekol Eye Hospital, Department of Ophthalmology in Izmir, Turkey. Informed consent forms were obtained from all patients and the study was approved by the Research Ethics Committee of Alaattin Keykubat University Hospital (registration number: 4-7). All subjects had normal biomicroscopy and fundoscopy findings. Subjects were tested for best corrected visual acuity (BCVA), intraocular pressure (IOP), and refractive error.

Patients with type 2 diabetes mellitus (DM) and healthy control subjects were recruited from Ekol Eye Hospital, Department of Ophthalmology Outpatient Clinic who presented between February 2018 and june 2018. For both patient and control groups, exclusion criteria were as follows: any other ocular disease that may affect ocular circulation (e.g., glaucoma, age-related macular degeneration, retinal vascular occlusion, macular edema, DR, previous ocular surgery or laser photocoagulation), refractive error < −6 diopters, and any other chorioretinal disease, intraocular surgery, eye trauma, blood pressure exceeding 150/100 mmHg and IOP > 21 mmHg, use of any systemic medication other than diabetes treatment or eye drops except artificial tears, corneal opacity, or cataract over grade I. Patients with grade I cataract or who used artificial tear drops were included.

Optical Coherence Tomography Angiography Measurements

XR Avanti AngioVue spectral domain OCTA (Software Version 2015.1.1.98, Optovue Inc, Fremont, CA) is a device which obtains volumetric scans of 304 ×304 A-scans at 70,000 A-scans per second, using a light source of 840 nm and an axial resolution of 5 µm. The OCTA system based on split-spectrum amplitude-decorrelation angiography algorithm which uses blood flow as intrinsic contrast.[16] Optovue Angio-Vue system technology allows for quantitative analysis. For measurement of retinal density, a 6×6 mm macular angiogram of superficial layer was analyzed using Optovue software with density function. Automatic segmentation was performed using the viewing software to generate en face projection images of the superficial capillary plexus (SCP) and deep capillary plexus (DCP). The SCP en face OCTA image was segmented using an inner boundary 3 µm below the internal limiting membrane and an outer boundary 16 µm below the inner plexiform layer and the DCP image 16µm to 70 µm below the inner plexiform layer. Outer retina is described as 70 µm below the inner plexiform layer and 30 µm below the retinal pigment epithelium.[17] The flow area was defined as the percentage of area occupied by vessels in a 6×6 mm square region of interest centered in the center of the FAZ. Angio-Vue software automatically outputs the flow area value within the region of interest (Figure 1.A). Vessel density is calculated as the percentage of area occupied by vessels and microvasculature in the selected region. The vessel density was separately calculated in five regions (fovea, temporal, superior, nasal and inferior) based on the Early Treatment Diabetic Retinopathy Study contour (Figure 1.B). This tool works both on SCP and DCP. To measure CC flow area, a 6×6 mm macular angiogram of the CC layer (from retinal pigment epithelium with a retinal pigment epithelium off-set of 31µm to the deeper layer with a retinal pigment epithelium off-set of 59 µm) was analyzed using Optovue software with flow function.[17] Flow area of CC was calculated automatically as vessel areas of CC divided by selected areas (Figure 1.C). Avascular area is a significant area (larger than the normal gap between capillaries) devoid of flow signal on an en face angiogram. On the OCTA of macula, the FAZ produces a normal avascular area. FAZ and central foveal thickness (CFT) are measured automatically using OCTA (Figure 1.D). Subfoveal choroidal thickness (SFCT) defined as the distance between the hyper-reflective line corresponding to the base of the RPE and the hyper-reflective line corresponding to the chorioscleral interface was measured three times by two independent observers with manual calipers in the horizontal and vertical sections beneath the fovea and average values were recorded and taken into analysis.

Statistical Analysis

One eye from each subject was randomly selected for analysis. Statistical analysis was performed using SPSS for Windows 21.0 (SPSS Inc, Chicago, IL). For each continuous variable, normality was determined using Kolmogorov–Smirnov test. All parameters showed normal distribution. Categorical variables were analyzed using chi-square test. OCTA measurements of the groups were compared using independent t-test. Correlation coefficients were calculated to assess between HbA1c, duration of the disease and vessel density in diabetic patients. P value < 0.05 was considered as statistically significant.

RESULTS

Mean BCVA on Snellen chart was 0.88±0.11 in the diabetic patients and 0.94±0.09 in the healthy subjects. The

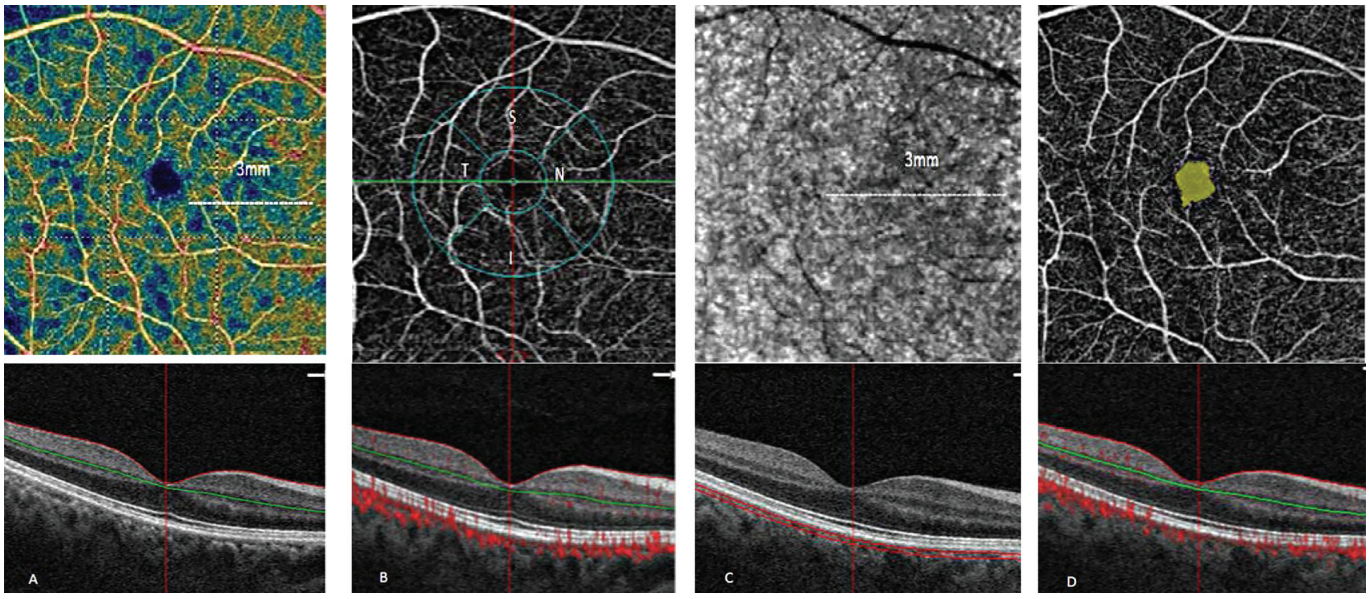

Figure 1. *Macular perfusion parameters of a 6mm×6mm angiography scan size using OCTA. A. The flow area within a 3-mm radius is represented by the color yellow. B. The vessel density of five areas of interest, including the fovea (1-mm diameter) and temporal, inferior, nasal, and superior quadrants (1-mm annular ring); (C) the choroidal capillary flow area within a 3-mm radius is represented by the color yellow; (D) the FAZ is automatically delineated using the included software and represented by the color yellow.*

difference in BCVA between the groups was not significant (P:0.653). There was no significant difference between the diabetic patients and healthy subjects in terms of age or gender (P>0.05 for both). The duration of diabetes ranged between 1 to 12 (7.5±3.41) years.

This cross-sectional study analyzed total of 48 (48 eyes) diabetic patients aged 49.5±14.1 (41-70) years old and 48 (48 eyes) age-matched healthy controls 48.5±13,1 (range: 44-70) years old. There were no differences between the study and control groups in terms of age, spherical equivalent (SE), axial length (AL), systolic blood pressure (SBP), diastolic blood pressure (DBP), and IOP. Demographic data and HbA1c levels for both groups are demonstrated in Table.1.

Macular flow area including superficial retinal flow area (SFA), deep flow area (DFA) and CC flow area measurements of the diabetic patients were not significantly different than controls (P>0.05 for all, independent t-test) (Table.2). FAZ area was significantly increased both in deep and superficial layers in diabetic patients (deep; p=0.011 and superficial; p=0. 0.021) (Table.2).

SVD of the diabetic patients was not significantly different in all macular region (foveal, parafoveal, temporal, superior, nasal, inferior) than controls (P>0.05), but DVD measurements for all macular regions was significantly

Table 1. *The Demographic and clinical data of the diabetic patients and controls.*

	Diabetic patients (n =48)	Control group (n =48)	P value
Age (years)	49.5±14,1 (41-70)	48.5±13,1 (44-70)	0,831
SBP (mmHg)	119.75±5.9 (105-130)	115.61±5.8 (100-130)	0,652
DBP (mmHg)	81.8±4.6 (70-90)	77.8±3.3 (70-90)	0.702
IOP (mmHg)	14.4±1.3 (10-18)	13,8±1.2 (10-19)	0.315
SE (D)	0.288±0.48 (-5.00, 3.00)	0.224±0.43 (-5.00, 2.75)	0.254
AL (mm)	23.11±0.68 (22.0-24.8)	23,92±0.55 (22.03-24.2)	0.796
HbA1c (mg/dl)	7.9 (5.5-9.2)	4.4 (3.5-5.6)	**0.0001**
Duration of DM (years)	7.5±3.41(1-12)	-	-

Spherical Equivalent (**SE**), Axial Length (**AL**), Systolic Blood Pressure (**SBP**), Diastolic Blood Pressure (**DBP**), and intraocular pressure (**IOP**); Values are mean ± SD (range:min-max)

Table 2. *Macular Perfusion in diabetic patient and Controls.*

	Diabetic patients n:48	Control Group n:48	P value
Superficial retinal flow area (mm^2)	16.007±0.94	16.311±0.85	0.364
Deep retinal flow area (mm^2)	13.455±0.28	13.712±0.38	0.320
CC flow area (mm^2)	18.024±0.86	18.127±0.63	0.162
FAZ area (Superficial, mm^2)	0.352±0.011	0.311±0.010	**0.021**
FAZ area (Deep, mm^2)	0.359±0.013	0.319±0.018	**0.011**
Superficial vessel density (%)			
Fovea	35.422±1.33	36.002±1.88	0.637
Parafovea	55.113±1.11	55.871±1.35	0.281
Temporal	55.792±1.33	56.201±1.24	0.179
Superior	56.661±0.84	57.060±0.84	0.203
Nasal	56.892±1.00	56.992±1.12	0.456
Inferior	56.021±1.21	56.828±1.07	0.108
Deep vessel density (%)			
Fovea	36.014±0.54	37.666±0.54	**0.012**
Parafovea	54.209±1.02	57.638±0.43	**0.027**
Temporal	53.113±1.86	56.499±1.18	**0.022**
Superior	53.278±1.97	56.914±0.69	**0.016**
Nasal	53.404±0.88	56.308±0.97	**0.014**
Inferior	52.701±1.31	55.975±1.69	**0.001**

decreased in diabetic patients than controls ($p<0.05$) (Table.2). The boxplot analysis representing the DVD measurements for all macular regions in study and control groups are shown in Figure 2.

CFT and SFCT values of the diabetic patients were not significantly different than controls (p=0,408, p=0,641; respectively).

Whether correlations between macular perfusion parameters (SFA, DFA, and CC flow area), FAZ area, SVD, DVD (foveal, parafoveal, temporal, superior, nasal, inferior) and HbA1c and the duration of disease had been revealed in diabetic patients. Spearman correlations between macular perfusion parameters (foveal, parafoveal, temporal, superior, nasal, inferior), SFA, DFA and CC flow area, SVD (except foveal area) and HbA1c and the duration of disease in diabetic patients were not statistically significant, but DVD of diabetic patients was correlated with HbA1c and the duration of disease significantly. Detailed Spearman correlation analysis are given in Table.3. Correlation analysis of flow parameters and the duration of disease and HbA1c (p values with Spearman's correlation coefficient tests. r values, Spearman's correlation coefficient is a measure of a relationship power between the two variables).

Diabetic patients are categorized into two subgroups as high-risk (≥5 years) and low-risk (<5 years) groups in terms of the duration of disease based on the previous studies.[18,19] Comparison between the high-risk (20 patient) and low-risk groups (28 patients) revealed statistically significant difference between the two risk groups for SFA, DFA, CC measurements and FAZ area ($p < 0.05$) (Table.4). Also, SVD and DVD was significantly decreased in high-risk diabetic patients than low-risk ones for all macular regions (foveal, parafoveal, temporal, superior, nasal, inferior) ($p<0.05$ for all) (Table.4).

In diabetic patients, visual acuity was significantly associated with vessel density (SVD; r=-0.44, p=0,027 and DVD; r=-0.57, p=0,021) and FAZ area (superficial; r=0.65, p=0,012 and deep r=0.81, P= 0.01).

DISCUSSION

It is already known that many biochemical and vascular changes occur in the retinal tissue of diabetic patients. In

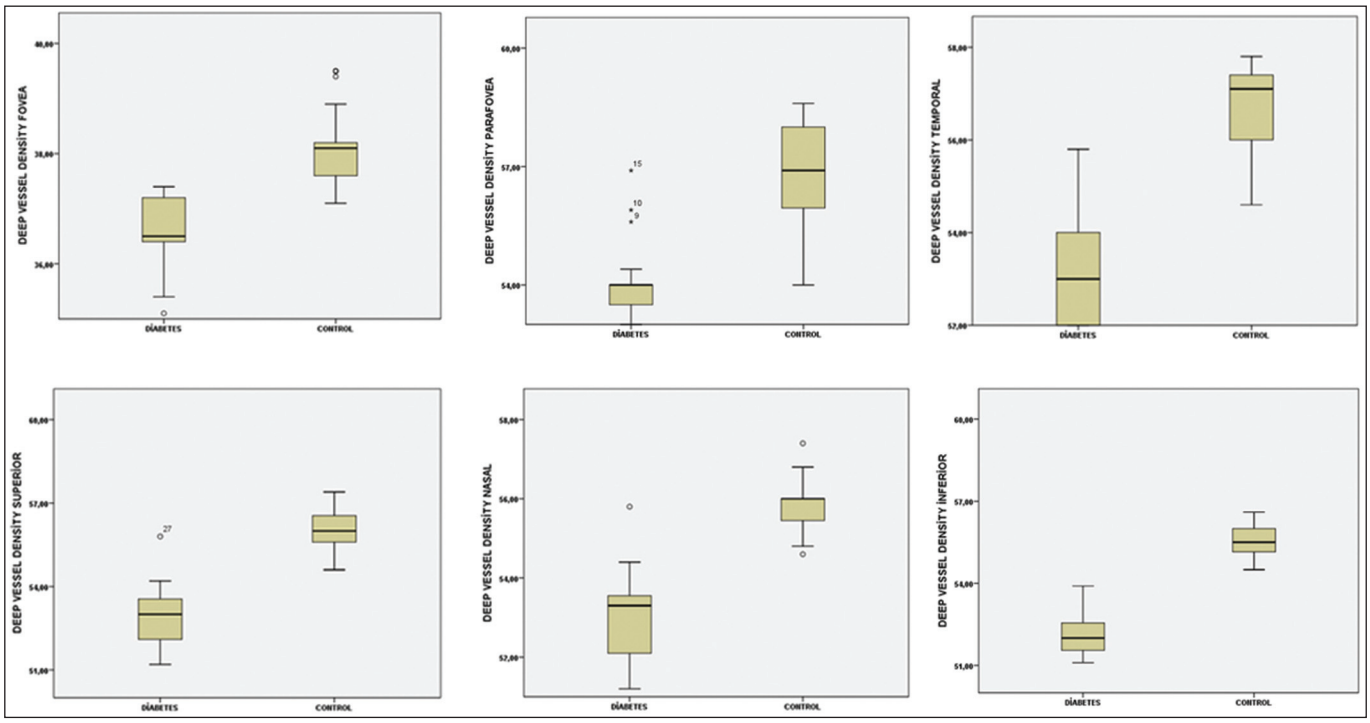

Figure 2. *The boxplot analysis representing the DVD measurements for all macular regions in study and control groups are shown.*

this study, retinal and choroidal vascular structures were evaluated using OCTA, a new, non-invasive, dye-free imaging method in patient with diabetes without DR.

In this study, superficial capillary plexus (3-15 µm deeper from the retina surface), which is crucial to ganglion cell layer nutrition, had been evaluated as flow area and vascular density. SVD and flow area values were not significantly different in diabetic patients than non-diabetic controls. Outer retina (15-70 µm deeper from the retina surface) and deep capillary plexus which consists of photoreceptors had been evaluated as deep retinal flow area and DVD. DVD was significantly decreased, but deep retinal flow was not significantly different in diabetic patients.-We did not observe any significant difference in CC flow area and SFCT, which reflects the situation of the choroidal vascular structure, between the two groups. Furthermore, the FAZ area in both superficial and deep layers was significantly enlarged in diabetic patients. Superficial, deep and CC flow did not reveal any difference in both groups.

Using OCTA, it is possible to detect microvascular alterations in the superficial, intermediate, and deep vascular layers of the retina. Superficial and deep vascular layers and FAZ area had been evaluated in previous studies. Dimitrova et al.[7] demostrated that both superficial and deep layer's vessel density was reduced in 29 diabetic patients without retinopathy when compared with 33 healthy individuals by OCTA imaging. Cao et al.[8] revealed that vessel density in superficial, deep and choriocapillaris was significantly decreased in 71 diabetic patients without DR when compared with 67 healthy controls. Scarinci et al.[9] reported that DVD was significantly decreased although no significant difference was detected in SVD in diabetics in their study comparing 23 healthy individuals and 20 type I diabetic patients without retinopathy. Simonett et al.[10] reported decreased DVD despite no significant change in SVD in 28 patients with type I DM (9 with mild non-proliferative DR, 19 without DR) accordant to Scarinci's study and Carnevalli et al.[11]

Our study is compatible with the studies that reports decrease in DVD by Scarinci, Simonett and Carnevalli; but discordant to the findings which demonstrates no significant decrease in SVD as in studies by Dimitrova and Cao. Retinal arterioles move to deep retinal layers to form intermedier vascular plexus after creating the superficial vascular plexus. Afterwards this vascular structure goes deeper in a perpendicular way to form a second deep plexus and turn to venular system.[20] This anatomical distribution results in a structure in which arterioles are dominant in superficial layers and venules are dominant in deeper. Detection of the first OCTA findings in deep vascular layers is in accordance with the occurrence of initial retinopathy in deep retinal layers as a sign of venous damage such as venous beading and venous dilatation. There are studies demonstrating the increase in resistance of retinal venous out-flow before the onset of DR in diabetic patients, this exhibits valuable confirmation compatible with the etiopathogenesis of the reasons of the occurrence in deep

Table 3. *Correlation analysis of flow parameters and the duration of disease and HbA1c. p values with Spearman's correlation coefficient tests. r values, Spearman's correlation coefficient is a measure of a relationship power between the two variables.*

	Duration of DM		HbA1c	
	p	r	p	r
Superficial retinal flow area (mm^2)	0.241	-0.555	0.541	-0.321
Deep retinal flow area (mm^2)	0.128	0.379	0.640	-0.412
CC flow area (mm^2)	0.512	-0.406	0.327	-0.522
FAZ area (Superficial, mm^2)	**0.041**	**0.602**	**0.031**	**0.714**
FAZ area (Deep, mm^2)	**0.021**	**0.708**	**0.037**	**0.708**
Superficial vessel density (%)				
Fovea	**0.014**	**-0.512**	**0.044**	**-0.630**
Parafovea	0.297	-0.954	0.118	-0.187
Temporal	0.312	-0.540	0.279	-0.560
Superior	0.478	-0.541	0.362	-0.191
Nasal	0.293	-0.472	0.315	-0.222
Inferior	0.338	-0.189	0.305	-0.797
Deep vessel density (%)				
Fovea	**0.004**	**-0.721**	**0.001**	**-0.607**
Parafovea	**0.007**	**-0.801**	**0.004**	**-0.578**
Temporal	**0.004**	**-0.459**	**0.001**	**-0.654**
Superior	**0.001**	**-0.354**	**0.002**	**-0.507**
Nasal	**0.001**	**-0.274**	**0.004**	**-0.354**
Inferior	**0.001**	**-0.514**	**0.003**	**-0.377**
Central Foveal Thickness	0.501	-0.102	0.504	-0.288
Subfoveal Choroidal Thickness	0.741	-0.189	0.602	-0.325
DM: Diabetes mellitus				

vascular plexus.[21,22] In experimental ischemic retina rat models created with high pressure, it was demonstrated that vascular damage starts in deep retinal layers in early periods.[23] In diabetic rat models produced with streptozosin, local acidosis and capillary drop-out secondary to it and damage in retina mostly intensify in deep retinal layers and choriocapillaris.[24] Outcomes of superficial and deep retinal flow in our study, revealed the deterioration of deep vascular layer and this finding is compatible with previous clinical and experimental studies.

In the current study, both superficial and deep FAZ area was larger in diabetic patients than in healthy subjects. Di et al.[12] found that the horizontal radius and vertical radius of the FAZ were significantly increased in eyes with any stage of DR compared to controls, but no significant difference was observed between the eyes of diabetic patients without clinical retinopathy and healthy individuals. Salz et al.[13] compared OCTA and FA findings in the eyes of diabetic patients and healthy subjects and reported that as the DR grade increases, the FAZ area and perifoveal intercapillary area also increase. In the same study it was reported that diabetic patients without retinopathy had larger FAZ and perifoveal intercapillary area when compared with healthy subjects. Takase et al.[14] measured FAZ area with OCTA and found enlarged FAZ area in diabetic patients, regardless of the presence or absence of DR. Choi et al.[15] demonstrated enlarged FAZ area by OCTA in eyes without DR in their study consisting of 9 diabetic patients with proliferative DR, 29 with non-proliferative DR, 51 without retinopathy and 63 healthy controls. There is some discrepancy with regard to FAZ area in studies evaluating diabetic patients without retinopathy and healthy individuals. There are reports demonstrating enlarged FAZ area both in superficial and deep layers besides the studies reporting no significant change, enlargement in diabetic macular edema, correlation or no relation with the stage of the DR.[7,9,16-18,25-29] Lubers et al.[30] revealed reduced red blood cell velocity, narrowed capillary vessel diameters, and decreased capillary vessel density in histopathologic examination of diabetic patients.

Table. 4. *Comparison of flow parameters between high-risk and low-risk groups in diabetics patients.*

	High-risk group (≥5 years) n:20	Low-risk group (<5 years) n:28	P value
Superficial retinal flow area (mm^2)	13.812±0.35	14.428±0.83	**0.022**
Deep retinal flow area (mm^2)	13.333±0.31	14.322±0.28	**0.025**
CC flow area (mm^2)	16.717±0.40	17.555±0.41	**0.041**
FAZ area (Superficial, mm^2)	0.353±0.22	0.321±0.018	**0.044**
FAZ area (Deep, mm^2)	0.358±0.011	0.323±0.016	**0.013**
Superficial vessel density (%)			
Fovea	34.384±1.55	35.102±1.25	**0.021**
Parafovea	53.117±1.97	54.258±1.33	**0.015**
Temporal	53.286±0.63	55.975±1.29	**0.019**
Superior	53.678±1.28	56.060±0.43	**0.016**
Nasal	53.494±0.52	55.692±1.88	**0.024**
Inferior	53.413±0.97	55.814±1.37	**0.011**
Deep vessel density (%)			
Fovea	36.322±0.77	37.187±0.73	**0.038**
Parafovea	55.274±1.31	56.301±0.23	**0.033**
Temporal	53.193±1.37	55.374±1.95	**0.014**
Superior	54.362±1.34	55.888±0.39	**0.022**
Nasal	52.916±0.85	55.943±0.90	**0.018**
Inferior	52.273±1.53	54.103±1.51	**0.016**
Central Foveal Thickness	235.843±12,3	238.929±19.9	0,578
Sub Foveal Choroidal Thickness	320.289±11.9	325.912±15.44	0,637

FAZ area is an indicator of inner retinal perfusion within the macula.[31] The ischemic state of the macula corresponds to the destruction of the FAZ border and enlargement secondary to it.[31,32] These findings which are supported by our in vivo observations of decreased vascular density and increased FAZ area in the deep capillary plexus of diabetic patients. Our findings of FAZ enlargement and reduced the vessel density before the development of retinopathy may be suggest microaneurysm prior to retinopathy or vasculopathy.

The choroidal abnormalities on FA in diabetic eyes include microaneurysms, dilatation and obstruction of the choriocapillaris, vascular remodelling with increased vascular tortuosity, vascular dropout, areas of vascular non-perfusion and choroidal neovascularization.[33] In the present study, there were no significant differences in subfoveal or mean choroidal thickness between diabetic patients and healthy subjects. Furthermore, flow measured by OCTA did not vary among healthy subjects. There are previous studies reporting that in diabetic patients, even those without DR, choroidal circulation is reduced, decreases are in correlation with DR grade or is unchanged at early stages and decreases at later stages.[34-36] Though not definitively proven, the general opinion is that a correlation exists between choroidal thickness and retinopathy.[37,38]

It is not clear if visual acuity and vessel density or FAZ area is correlated. There are reports that revealing FAZ area is correlated with visual acuity in patients with early DR and it has been proposed that FAZ enlargement may have utility in the follow-up of these patients.[39] We also found a significant correlation between FAZ area (superficial and deep) and visual acuity in diabetic patients, which supports this hypothesis. In addition to dimension, alterations in FAZ shape are also known to occur in diabetic patients. Some studies showed significant association between visual acuity and FAZ parameter or vessel density.[29,40] Furthermore, in a larger study group, there was a statistically significant negative correlation between the logMAR VA and the vessel density in the both superficial and deep layers, whereas another study found a weak correlation between SVD and VA.[26,41]

Another findinds in this study, HbA1c was positively correlated with FAZ area (superficial and deep) and negatively correlated with DVD. In previous studies,

however, associations between HbA1c and macular microcirculation parameters have been inconsistently described.[7,8] In patients either without or with background retinopathy, Sander et al.[42] found a significant correlation between HbA1c and perifoveal intercapillary area, but not with FAZ surface. Bhanushali et al.[28] found higher spacing between large vessels in the superficial layer in eyes with DR and showed that the higher spacing is significantly correlated with HbA1c levels. Gozlan et al.[29] performed a multivariate analysis and showed a positive correlation between HbA1c and FAZ parameters (grade, surface and perimeter). Our results support the suggestion that there is a correlation between HbA1c levels and deep vascular layer's flow in diabetic patients even without any finding of DR.

In the UK, population based studies involving patients with type 2 DM estimated cumulative incidence of DR to be 26.0% at 4 years 38.1–41.0% at 6 years.[19] Based on previous studies, we had categorized our diabetic patients into two subgroups as high-risk (≥ 5 years) and low-risk (< 5 years) according to the duration of the disease.[18,19] Comparison between the high-risk and low-risk groups revealed statistically significant difference between the groups in terms of superficial retinal flow area, deep flow area, CC parameters and FAZ area. Also, SVD and DVD parameters of the diabetic patients were significantly different between high-risk and low-risk groups for all macular regions (foveal, parafoveal, temporal, superior, nasal, inferior). To the best of our knowledge there is no previous report evaluating the retinal microvasculature in both low- and high-risk groups. We think that the results from the comparison of low- and high-risk groups in our study, supplies new arguments to previous prevalence studies by Thomas et al.[18] and Younis et al.[19] which reports that the duration of DM is the major risk factor for retinopathy development and the reports by Raman et al.[43] and Kostev et al.[44] pointing out that the duration of diabetes is correlated with the deterioration in retinal microvascular structure.

Limitations of our study are the small sample size and the cross-sectional design of it. Longitudinal studies in large groups are needed to confirm our preliminary results. There are previous studies evaluating retinal circulation in mixed type 1 and type 2 diabetic patient groups without DR, the homogeneity of our study group with type 2 diabetic patients may reflect more specific results to one type of DM. Our findings suggesting worse macular microcirculation in high-risk diabetic patients than low-risk diabetic patients must be evaluated in further OCTA assisted studies.

OCT angiography is capable of imaging the two major layers of the retinal vasculature without dye injection. Our data show that OCTA was able to detect changes in the different retinal layers and FAZ area. We believe that OCT angiography may be superior to FA, especially for the evaluation of the FAZ and both superficial and deep retinal layers in diabetic patient. The diagnosis of retinal and choroidal diseases will be revolutionized by OCTA; however, it is not yet clear to what extent it will replace FA. Further studies with larger patient groups will clarify the role of OCTA findings in the diagnosis, treatment, screening and prognosis of DR.

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