Comparison of Optical Coherence Tomography Angiography findings in Diabetic Patients and Healthy Subjects

Abdullah BEYOGLU[1], Yalcin KARAKUCUK[2], Aysegul COMEZ[1]

ABSTRACT

Purpose: The aim of this study is to compare superficial flow density (SFD), deep flow density (DFD), choriocapillaris flow density (CFD), superficial foveal avascular zone (SFAZ), deep foveal avascular zone (DFAZ), superficial vessel density (SVD) and deep vessel density (DVD) of advanced stage pre-proliferative Diabetic Retinopathy patients (PPDR) and normal subjects using optical coherence tomography angiography (OCTA)

Materials and Methods: 40 eyes of 40 advanced stage PPDR patients and 40 eyes of 40 normal subjects were included in this prospective study as study and control groups respectively. Each subject underwent a comprehensive ophthalmic assessment, and OCTA image was taken. The right eye of each participant was used in the study.

Results: There were no significant differences between the study and control groups in respect of age and gender (p>0,05) (Table 1). The mean SFD, DFD, CFD, SFAZ, DFAZ, SVD and DVD values were 1230.92±111.56 mm^2, 1185.33±156.15 mm^2, 1860.6±56.17 mm^2, 0.487±0.205 mm^2, 0.646±0.240 mm^2, % 47.50±3.15, % 52.38±3.54 in the diabetic group and 1520.22±38.31 mm^2, 1596.25±79.83 mm^2, 1962.7±26.96 mm^2, 0.283±0.057 mm^2, 0.340±0.054 mm^2, % 54.23±3.27, % 60.72±3.39 in the control group, respectively (Table 1). There were statistically significant differences between the two groups according to SFD, DFD, CFD, SFAZ, DFAZ, SVD and DVD measurements.

Conclusion: Diabetic maculopathy and ischemia can be evaluated with OCTA. As being a rapid and non-invasive procedure, OCTA is particularly helpful in the follow-up and treatment of retinopathy in the early stages, especially in newly diagnosed diabetic patients.

Key Words: Diabetic retinopathy, Optical coherence tomography angiography, Foveal avascular zone, Flow density, Vascular density.

INTRODUCTION

Diabetic retinopathy (DR) may lead to complications such as microangiopathy, hemorrhage, exudate, macular edema and neovascularization. Diabetic macular edema is the most common cause of visual impairment in developed countries, diabetic retinopathy is one of the most important causes of blindness.[1,2] Staging is applied based on the Early Treatment Diabetic Retinopathy Study (ETDRS), in which vascular changes resulting in abnormalities are considered. Nowadays, various devices are used to asses and stage of diabetic retinopathy.[3] One of the main methods used during evaluation of DR is fluorescein angiography (FA). This came into widespread use for ocular imaging in the 1970s and is the current gold standard method for retinal imaging.[4]

Although FA has a very important place in terms of treatment and follow-up in retinal diseases, it is an invasive method and may cause nausea, vomiting, pruritus and occasionally allergic reactions such as anaphylaxis.[1] The recently developed OCTA device has begun to be used in DR patients in terms of treatment and follow-up.[1,5] The device sends signals on erythrocytes in vascular structures to give information about blood flow. [6] The advantages of OCTA are being non-interventional, fast, reproducible and easy, thereby providing improvements in terms of treatment and follow-up.[1,7]

In this study, we aimed to evaluate the OCTA changes in advanced stage PPDR patients and compare them with individuals without any systemic or ocular pathology. Superficial flow density (SFD), deep flow density (DFD), choriocapillaris flow density (CFD) (Figure 1), superficial foveal avascular zone (SFAZ), deep foveal avascular zone

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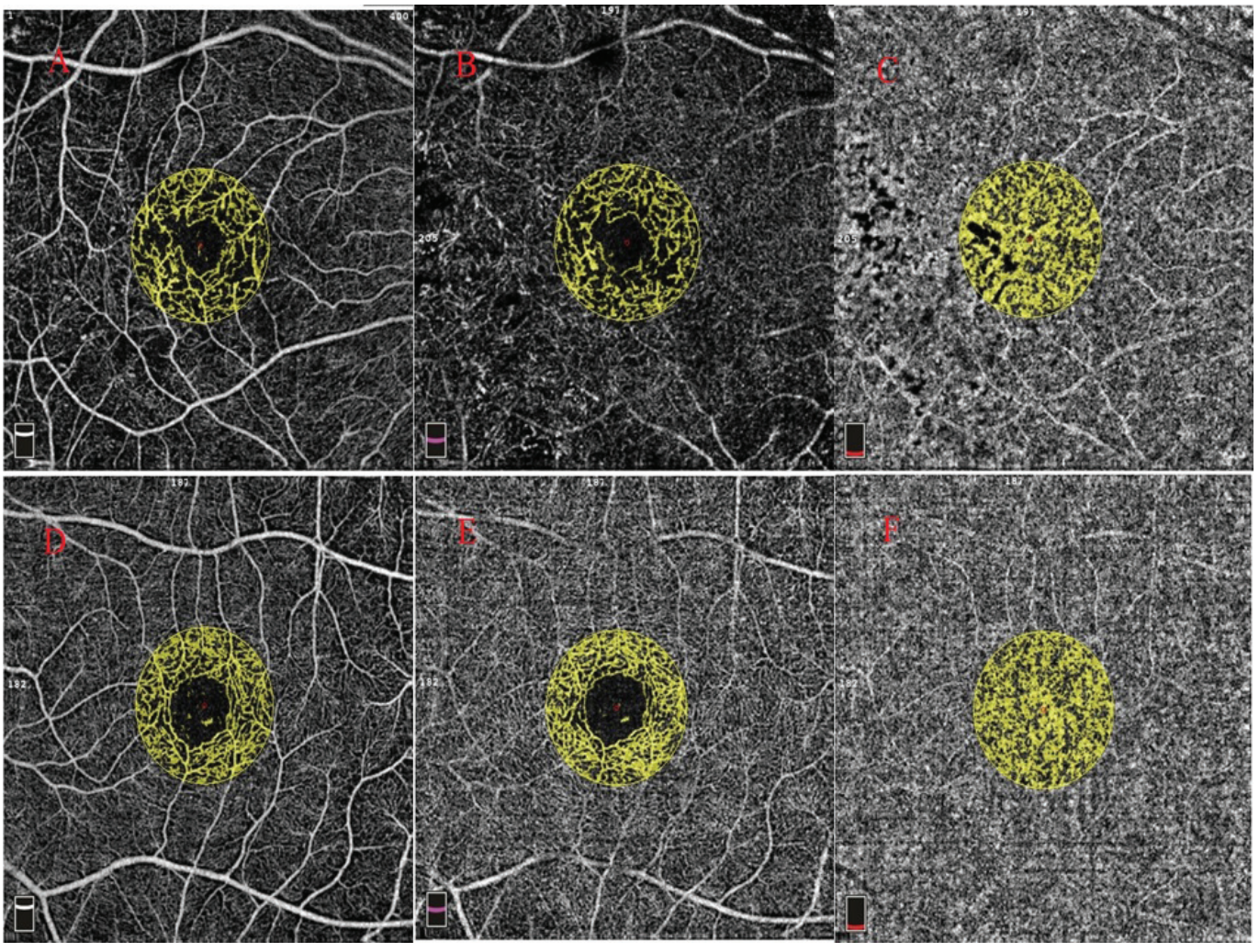

Figure 1. *Superficial (A), Deep (B), and Choriocapillaris (C) flow density decrease in diabetic eye's. Normal flow density (D, E, F) in healthy group.*

(DFAZ) (Figure 2), superficial vessel density(SVD) and deep vessel density (DVD) (Figure 3) were compared using the values in the OCTA images taken.

METHODS

In this cross-sectional, observational study, 40 advanced stage PPDRP patients without macular edema (22 (55%) females and 18 (45%) males)who were followed in Kahramanmaras Sutcu Imam University Hospital, ophthalmology department , retina section and 40 normal subjects 20 (50%) males and 20 (50%) females)who were seen in the ophthalmology policlinic of same hospital were evaluated. Advanced stage PPDRP was defined as: Diffuse hemorrhage in four quadrants of the retina, venous pilling in two or more areas, and presence of one or more IRMA in one or more quadrants as defined by EDTRS study group.[3] Normal subjects were defined as people without glaucoma, uveitis, corneal, retinal pathology and any history of ocular surgery.

The study was conducted in accordance with the tenets of the Declaration of Helsinki, and with the approval of the Ethics Committee of Sutcu Imam University Kahramanmaras, Turkey. Informed consent for participation in this study was obtained from each individual.

The patients with poor co-operation preventing a reliable examination, any history of ocular surgery, eye trauma, uveitis, dense media opacities, patients with glaucoma findings, those with any systemic disease other than diabetes mellitus, cystoid macular edema,diabetic macular edema, any history of systemic or ocular medication, and those who smoked or consumed alcohol excluded from study. In addition, patients with measurements of axial length (AL) ≤22 mm or >25 mm, who had a spherical refractive error more than 2 diopters and cylindric refractive error more than 1.5 diopters were excluded.

Study Measurements

Each subject underwent a comprehensive ophthalmic

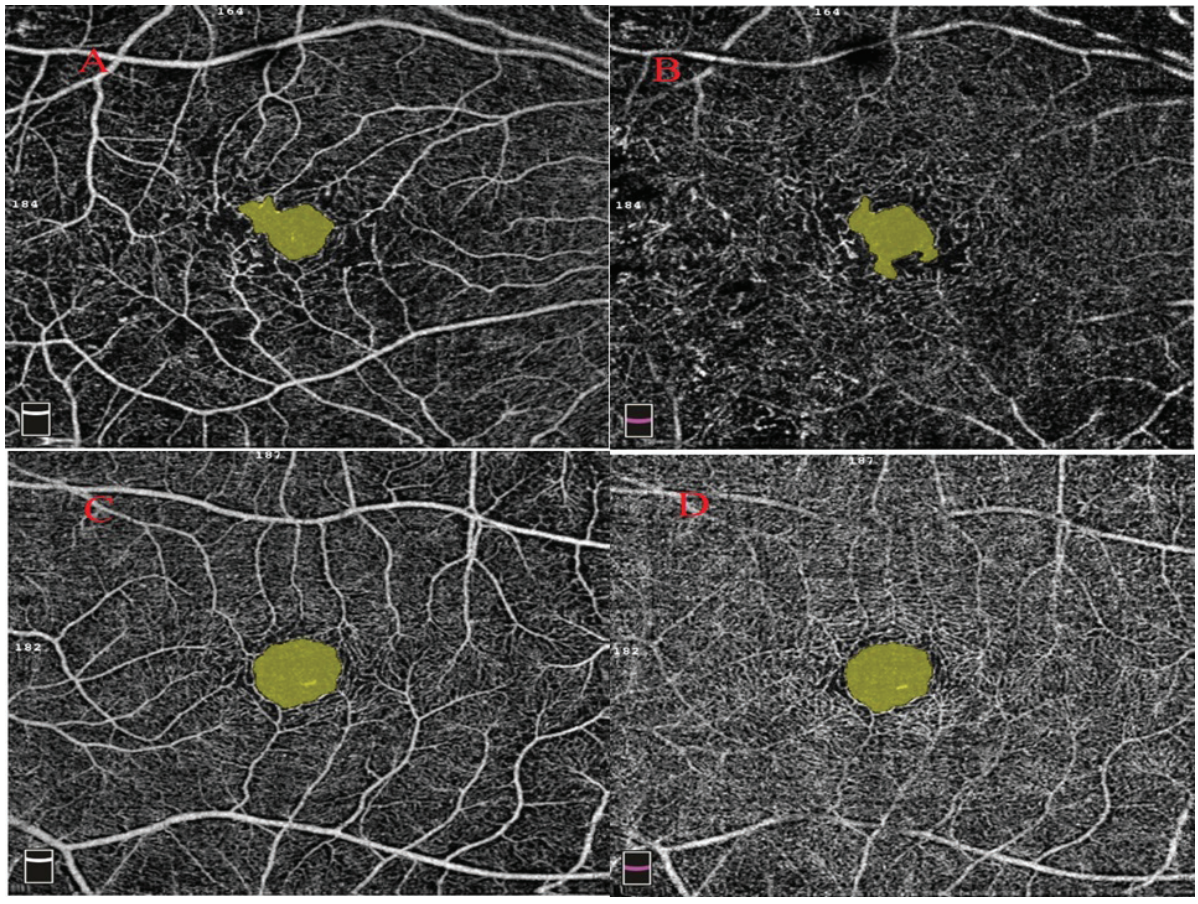

Figure 2. *In the diabetic eyes, superficial (A) and deep (B) FAZ increased compared to healthy eyes (C, D) and irregularities of the borders were observed.*

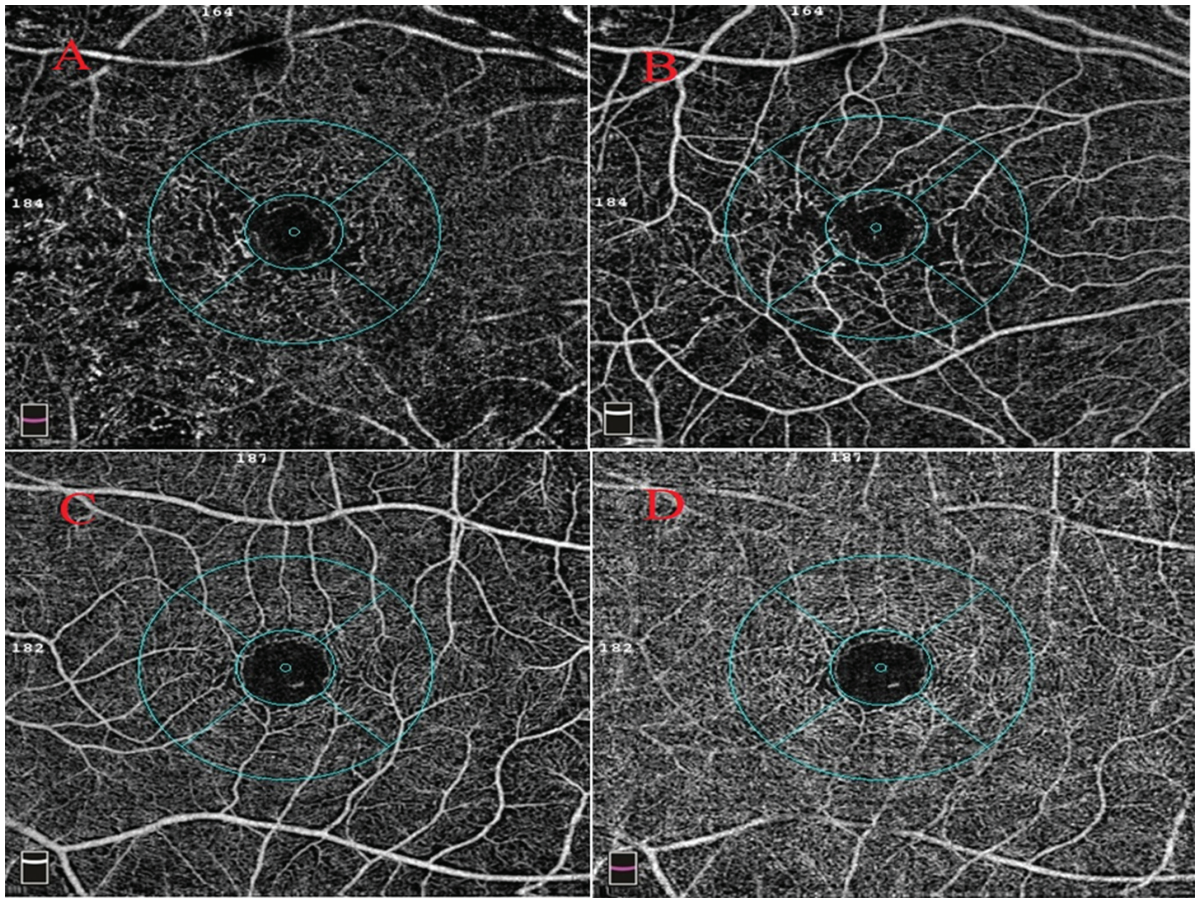

Figure 3. *Comparison of vascular density changes in normal eyes with diabetic eyes.*

assessment that included best-corrected visual acuity, slit-lamp biomicroscopy, air-puff tonometer, dilated fundus examination and OCTA imaging was performed. The measurements of octa images were taken at 6x6 mm to observe ischemic changes and vd at a wider angle. A combination of 1% tropicamide and 2.5% phenylephrine solution was used for pupil dilatation. The right eye of each participant was included in the study.

Optical coherence tomography angiography techniques

OCTA (XR Avanti AngioVue spectral domain OCTA (Software Version 2015.1.1.98, Optovue Inc, Fremont, CA) is a device which obtains volumetric scans of 304x304 A-scans at 70,000 A-scans per second, using a light source of 840 nm and an axial resolution of 5 mm. The OCTA system is based on a split-spectrum amplitude-decorrelation angiography algorithm using blood flow as intrinsic contrast. All OCTA scans were performed using AngioVue OCTA with A-scanning area of 6x6 mm.

Optovue Angio-Vue system technology allows for quantitative analysis. It provides numerical data about flow area or vessel density. For the measurement of retinal density, a 6x6 mm macular angiogram of the 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 retinal capillary plexus (SCP) and deep retinal capillary plexus (DCP). The SCF 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 16 µm to 70 µm below the inner plexiform layer. The outer retina is defined as 70 µm below the inner plexiform layer and 30 µm below the retinal pigment epithelium. The flow area was defined as the percentage area occupied by vessels in a 6x6 mm square region of interest centered in the center of the FAZ. AngioVue software automatically produces the flow area value within the region of interest.

Vessel density (VD) is calculated as the percentage area occupied by vessels and microvasculature in the selected region. The VD was separately calculated in five regions (fovea, temporal, superior, nasal and inferior) based on the ETDRS guideline. This tool works on both the SCP and DCP. For measurement of the CC flow area, a 6x6 mm macular angiogram of the choriocapillaris layer (from retinal pigment epithelium with a retinal pigment epithelium offset of 31 µm to the deeper layer with a retinal pigment epithelium offset of 59 µm) was analyzed using Optovue software with flow function. The CC flow area was calculated automatically as the vessel areas of CC divided by selected areas.[8] The data obtained were evaluated as surrounding SFD, DFD, CFD, SFAZ, DFAZ, SVD and DVD.

Statistical Analysis

Statistical analyses were made using Statistical Package for the Social Sciences for Windows vn 18.0 software. (SPSS, Inc., Chicago, IL, USA). Continuous data were stated as mean ± standard deviation (SD), and categorical data as number (n) and percentage (%). In the analysis of categorical data, the Chi-square test was used. Conformity of the data to normal distribution was evaluated with the Kolmogorov-Smirnov test. In the group comparisons, the Independent Student's t-test was applied to numerical data that met parametric assumptions and the Mann Whitney U-test was applied to numerical data that did not meet parametric assumptions. Pearson analysis was applied to determine relationships between parameters with normal distribution, and the Pearson's correlation coefficient was used for those that did not conform to normal distribution. A value of $p<0.05$ was accepted as statistically significant.

RESULTS

The mean age of the diabetic patients was 60.7±3.9 years (range 54 -68 years), and the mean age of the control group was 59.5±2.8 years (range 56- 66 years). There were no statistically significant difference between groups according to age(P=0.120) and gender (p=0.752). The mean SFD was lower in the diabetic group 1230.92±111.56 mm^2 compared to the control group 1520.22±38.31 mm^2 and the difference was statistically significant (p<0.001).The mean DFD was determined as 1185.33±156.15 mm^2 in the diabetic group and 1596.25±79.83 mm^2 in the control group and the difference was statistically significant (p<0.001). The mean CFD was determined as 1860.6±56.17 mm^2 in the diabetic group and 1962.7±26.96 mm^2 in the control group and the difference was statistically significant (p<0.001). The mean SFAZ was determined as 0.487±0.205 mm^2 in the diabetic group and 0.283±0.057 mm^2 in the control group and the difference was statistically significant (p<0.001). The mean DFAZ was determined as 0.646±0.240 mm^2 in the diabetes group and 0.340±0.054 mm^2 in the control group and the difference was statistically significant (p<0.001). The mean SVD was determined as 47.50±3.15 % in the diabetes group and 54.23±3.27 % in the control group and the difference was statistically significant (p<0.001). The mean DVD was determined as 52.38±3.54 % in the diabetes group and 60.72±3.39 % in the control group and the difference was statistically significant (p<0.001) (Table 1).

Table 1. *Comparison of mean OCTA values between advanced stage pre-prolierative diabetic Retinopathy patients and control group.*

	Diabetic Group	Control Group	*p*
SFD	1230.92±111.56	1520.22±38.31	***p<0,01***
DFD	1185.33±156.15	1596.25±79.83	***p<0,01***
CFD	1860.6±56.17	1962.7±26.96	***p<0,01***
SFAZ	0.487±0.205	0.283±0.057	***p<0,01***
DFAZ	0.646±0.240	0.340±0.054	***p<0,01***
SVD	47.50±3.15	54.23±3.27	***p<0,01***
DVD	52.38±3.54	60.72±3.39	***p<0,01***

Superficial flow density (**SFD**), Deep flow density (**DFD**), Choriocapillaris flow density (**CFD**), Superficial foveal avascular zone (**SFAZ**), Deep foveal avascular zone (**DFAZ**), Superficial vessel density (**SVD**) and Deep vessel density (**DVD**)

DISCUSSION

DR has become a serious public health problem throughout the world and may cause visual loss as a result of irregular glycemic control. [7-9] There are various current methods of identification and follow-up of DR. [3]FA and OCT devices are widely used in ophthalmology for treatment planning and the follow-up of DR patients. [1] OCTA was defined by Makita et al.[5], in 2006 and the use of it in ophthalmology has been increasing in recent years. One of the most important advantages is that it is non-interventional and repeatable. [1,5,7]

In a 2015 study by Hwang et al.[1], the FA images of 4 diabetic patients and 6x6 mm OCTA images were compared. It was reported that although FA and OCTA FAZ areas were similar, OCTA showed FAZ area more easily, provided more detailed information about it and was not affected by leakage. They also reported that capillary dropout, intra-retinal microangiopathy (IRMA) and the characteristic structures of arterioles were better evaluated in OCTA. Due to the slow down of blood flow, microaneurysms (MA) may not be detected on OCTA. On the other hand, structures evaluated as wide MA on FA were reported as small neovascularisation (NV) on OCTA images. It was stated that NV could be overlooked if imaging performed in a small area (6x6/20˚) and especially if a slight shadow artefact was present. It has been reported that OCTA can not be used instead of FA for planning of laser photocoagulation treatment for small leakages. In our study, images were obtained as described by previous authors. Expansions in the FAZ, capillary dropout and IRMA were seen more clearly, and fewer MA was determined compared to the fundus imaging.

In a study by Goudot et al.[7], which 22 diabetic patients with DR and no maculopathy and 22 healthy, non-diabetic patients were included, there were significant differences between groups in respect of flow, FAZ and VD. In our study, the difference between the flow, FAZ and VD values were found to be statistically significant in the study and control groups. The different results between our study and the study of Goudot et al.can be attributed to patient selection as diabetic patients without retinopathy had been included in the latter. Furthermore, unlike other studies in literature, when we evaluated flow and compared it between groups, we used CFD in addition to SFD and DFD. A significant difference was determined between the groups in respect of CFD.

Mastropasqua et al.[9], compared 60 diabetic patients of different grades with 20 healthy control subjects. Within the diabetic group, the patients were separated as non-DR, mild DR, moderate-severe DR and proliferative DR. In comparison with the control group, no statistically significant difference in FAZ and SVD was found in the non-DR and mild DR diabetic patients, whereas a significant difference was determined in the moderate-severe DR and proliferative DR sub-groups. Also, a statistically significant difference between the mild DR, moderate-severe, and proliferative DR groups and the control group was reported. In our study, statistically significant differences were determined between the advanced stage PPDRP patients and the control group in respect of FAZ, SVD and DVD.

In a study by Di et al.[11], a significant difference was determined between diabetic patients with and without DR and the control group in respect of FAZ expansion. Fretaberg et al.[12] also reported similar FAZ expansion using OCTA. In the current study, an increase was determined in the FAZ area, which was consistent with these previous findings.

Cao et al.[13], compared diabetic patients without DR and a healthy control group through evaluations of SVD, DVD, CVD and the SFAZ. A significant difference was determined between the groups in respect of VD, but the

difference in FAZ was not determined to be statistically significant. However, it was noted that there was an increased irregularity in the FAZ contours of the diabetic group. Recent studies have reported that this irregularity could be the first sign of damage in early stage diabetic patients[1,13].

In another study which compared diabetic patients without DR and a healthy control group, a statistically significant decrease in the diabetic group in respect of SVD and DVD[14]. Difference- In the current study, we reported a significant decrease in VD and a significant increase in FAZ area in the advanced stage PPDR patients. This suggests that even in patients with no clinical signs, FAZ area and VD are important parameters to be examined in follow-up of retinopathy and may help to define the improvement that can be obtained with strict diabetic regulation.

Coscas et al.[16], reported the findings obtained with OCTA from a comparison of diabetic patients of various grades and a healthy control group, and the importance of OCTA was emphasized in the treatment and follow-up of diabetic patients. In our study, we reported a significant increase in FAZ and a decrease in VD and flow in DR patients even when there were no severe clinical symptoms. With the application of strict diet and diabetes regulation protocols to these patients, it could be possible to obtain an improvement in prognosis without progression of DR to the proliferative stage. Further studies with larger sample sizes and a multi-disciplinary approach are needed. The main limitations of this study were its retrospective design and relatively low number of included eyes.

In conclusion, we documented several changes in PPDR patients such as a change in superficial and deep capillary plexus and CC flow, FAZ area and VD via OCTA which seems a promising device for diagnosis DR as it is non-invasive, repeatable, and has no known serious side effects.

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