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Role of OCTA in the prognosis of dry-type AMD

E. KIRIKKAYA[1], S. KAYNAK[2]

[1]Department of Ophthalmology, Health Sciences University İzmir Tepecik Training and Research Hospital, İzmir, Turkey
[2]Department of Ophthalmology, Tınaztepe University School of Medicine and Retina Eye Center, İzmir, Turkey

Abstract. – OBJECTIVE: This study aimed to determine the prognostic value of Optical Coherence Tomography Angiography (OCTA) in dry-type age-related macular degeneration (AMD).

PATIENTS AND METHODS: Thirty-five eyes of 25 patients with dry-type AMD were included in the study. All patients underwent a complete ophthalmological examination. First and last foveal avascular zone (FAZ), foveal density (FD), FAZ perimeter, non-flow area (NFA), foveal (F)-parafoveal-perifoveal superficial and deep capillary plexus (SCP-DCP) vessel density (VD) OCTA measurements were recorded. Foveal thickness (FT), macular volume (MV), and choroidal thickness (CT) measurements with enhanced depth imaging (EDI) mode were made with Optical Coherence Tomography (OCT). The relationship of all parameters with the best corrected visual acuity (BCVA-logmar) was evaluated. A *p*-value <0.05 was considered statistically significant.

RESULTS: The mean age of the patients was 73.3±11.8 (45-91) years. There was a statistically significant difference between the first and last BCVA, FT, and FD. While FD and BCVA increased, FT was found to decrease statistically significant (*p*=0.002, *p*=0.001, *p*=0.045, respectively). The correlation of BCVA with other variables at the first and last visit was examined. There was a statistically positive correlation between BCVA and FAZ, FAZ perimeter, and NFA in the first and last measurements. In the second measurement, a statistically negative correlation was found between BCVA and MV, FT, superficial FVD, superficial FT, deep FT, superficial parafoveal VD, superficial parafoveal FT, deep parafoveal FT, deep parafoveal VD, and FD variables.

CONCLUSIONS: There are positive and negative correlations between OCTA parameters and BCVA in the SCP-DCP in dry-type AMD. OCTA has prognostic significance in dry AMD.

Key Words:
Dry AMD, OCTA, FAZ, Superficial capillary plexus, Deep capillary plexus.

Introduction

Age-related macular degeneration (AMD) is one of the most important reasons for vision loss in the older population. While it affects 10% of individuals over the age of 65, it increases to 25% after the age of 75[1]. It is classified as dry type (90%) characterized by pigment epithelial changes such as drusen deposition, retinal pigment epithelial (RPE) atrophy and/or hypertrophy, and wet type (10%) with choroidal neovascularization (CNV) accompanying these degenerative changes.

AMD is a multifactorial disease; genetic and various environmental risk factors play a role in the pathogenesis[1]. Although the effects of some of these risk factors are more pronounced (age, genetics, race, smoking), the effect of some other factors (gender, nutrition, obesity, cardiovascular diseases, diabetes and hyperglycemia, iris color, cataract and cataract surgery, refractive error, high optic disc cupping-disc ratio) are controversial[2].

In vivo imaging with Optical Coherence Tomography (OCT) has significantly enhanced the comprehension of early recognition, pathogenesis, disease progression, and treatment strategies of chorioretinal disorders, including AMD. Optical Coherence Tomography Angiography (OCTA) is a new imaging technique that ensures exhaustive visualization of the retinal vascular network by acquiring and processing the motion contrast of the erythrocytes in the vessel with consecutive OCT scans of a specific retinal area with high resolution. The procedure is noninvasive and can be repeated many times during the day[3-8].

OCTA can obtain a three-dimensional image of these vascular layers. Therefore, it is possible to measure the areas of neovascularization and the blood flow in these vessels quantitatively. Other than fundus fluorescein angiography OCTA can be used in the diagnosis of diseases that

Corresponding Author: Esin Kırıkkaya, MD; e-mail: kesintunca@yahoo.com

may affect the deep capillary plexus (DCP), which is located between the IPL and outer plexiform layer (OPL), that is, the outer border of the inner nuclear layer (INL). This is an extremely significant superiority, as it has been demonstrated that the most significant vascular alterations in retinal diseases are in DCP, and decreased perfusion, ischemia, and neovascularizations (NV) in DCP play a significant role in visual prognosis[8-12]. Chow et al[13] Showed the mean FAZ area of SCP to be 0.25 mm^2 (0.04 mm^2-0.48 mm^2) and the area of DCP FAZ to be 0.38 mm^2 (0.12 mm^2-0.66 mm^2) in healthy individuals; they reported that the difference was significant.

OCTA can give quantitative information about the vascular density ratios in the macular capillary plexuses, the foveal avscular zone (FAZ) properties, the capillary non-perfusion areas, and the flow areas of the choriocapillaris.

OCTA has been widely used in AMD. In non-exudative AMD, there is an increase in choriocapillaris flow voids with an increase in the number of drusen and reticular pseudodrusen[14,15]. There is a marked choriocapillaris flow impairment below geographic atrophy (GA) lesions, and there are also flow deficits at the margin of GA in many cases[16-18]. This remark that the changes in the choriocapillaris might precede RPE loss and expansion of GA.OCTA may detect non-exudative or silent type 1 NV in eyes that might be considered to have non-neovascular AMD[19].

In early AMD, there are no significant changes in the retinal vasculature. Nevertheless, the OCTA of the choriocapillaris demonstrates alterations that may not be associated only with aging. Choriocapillaris density is likely to decrease with age; on the other hand, a homogeneous and regular pattern of vasculature still exists.

In this study, we aimed to investigate the changes in dry-type AMD patients over time with OCTA and whether these changes can give us information about AMD progression and determine the prognostic value of OCTA in dry-type AMD.

Patients and Methods

This retrospective study was performed in adherence with the tenets of the Declaration of Helsinki and approved by the local ethics committee. Informed consent was obtained from all the study participants.

Thirty-five eyes of 11 female and 14 male patients with dry type AMD were included in the study. All patients underwent complete ophthalmological examination, including best corrected visual acuity (BCVA), intraocular pressure (IOP), and anterior and posterior segment examination. Best corrected visual acuity (BCVA) was evaluated with the Snellen visual acuity (VA) chart, and Snellen VA values were converted to logarithm of the minimum angle of resolution (logMAR). Patients with other eye diseases that might affect vision, including high myopia, corneal pathology, glaucoma, optic neuropathy, proliferative vitreoretinopathy, RD, and other retinal diseases, were excluded.

Various OCTA measurement parameters such as first and last automated FAZ, Foveal Density (FD), FAZ perimeter, non-flow area (NFA), foveal (F)-parafoveal-perifoveal SCP and DCP VD were recorded (Figure 1a-b; 2a-b) using OCTA Optovue RTVue XR Avanti SD-OCT [Software 2018.1.0.37, (CA, USA)] with 70000 A scans, 5 microns optical axial resolution, 15 microns transversal resolutions, 3 microns per sampled pixel, 2 mm axial imaging depth, 304x304 B-scans imaging volume, 209000 A-lines for total A-scans per volume, and 2.9 seconds acquisition per volume. 2018 software segments the retina into eight layers. The boundaries used to define these layers include the ILM, outer limit of the nerve fiber layer (NFL), outer limit of the IPL, outer limit of the inner nuclear layer (INL), outer limit of the OPL, inner/outer segment (IS/OS), apical boundary of retinal pigment epithelium (RPE), and Bruch's membrane. Automated Spectral Domain (SD) OCT foveal thickness (FT), macular volume (MV), and sub-foveal choroidal thickness (SFCT) measurements with enhanced depth imaging (EDI) mode were made using the Optovue RTVue XR Avanti SD-OCT (Software 2018.1.0.37, CA, USA) caliper from high-definition 18-line radial scans of the macula with line length of 10 mm and depth of 2.6 mm, each line consisting of 1,024 scans with 5-µm axial resolution and 15-µm lateral resolution, were performed. The horizontal division passing straight ahead of the center of the fovea was used for the measurement of SFCT. SFCT in the enhanced images was measured as the perpendicular distance between the outer portion of the hyper-reflective line matching to the RPE to the hyporefleictive line matching to the chorio-scleral junction. The measurement of SFCT was made manually by a single qualified

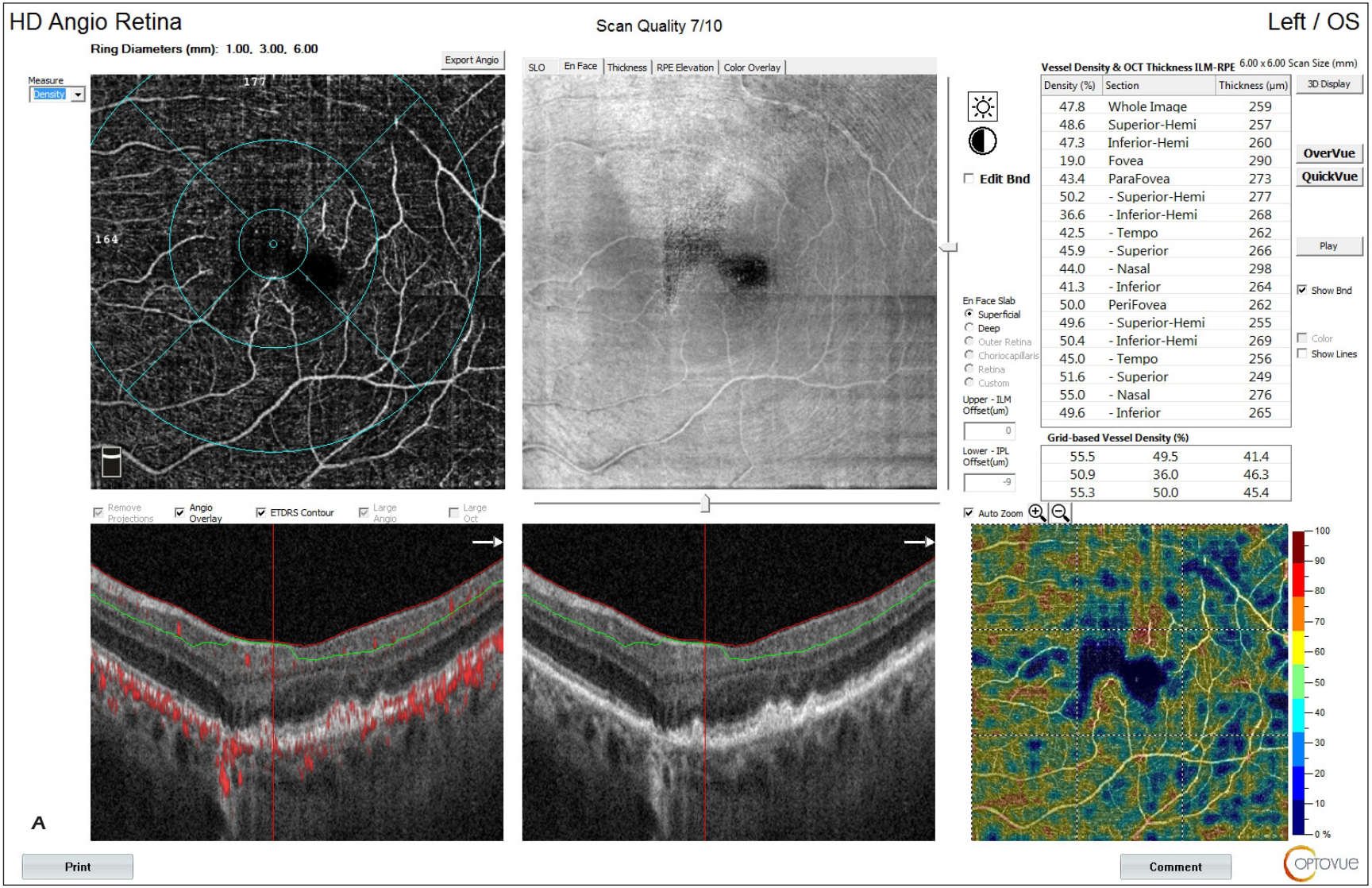

Figure 1. **A**, OCTA image of superficial capillary plexus at diagnosis.

Continued

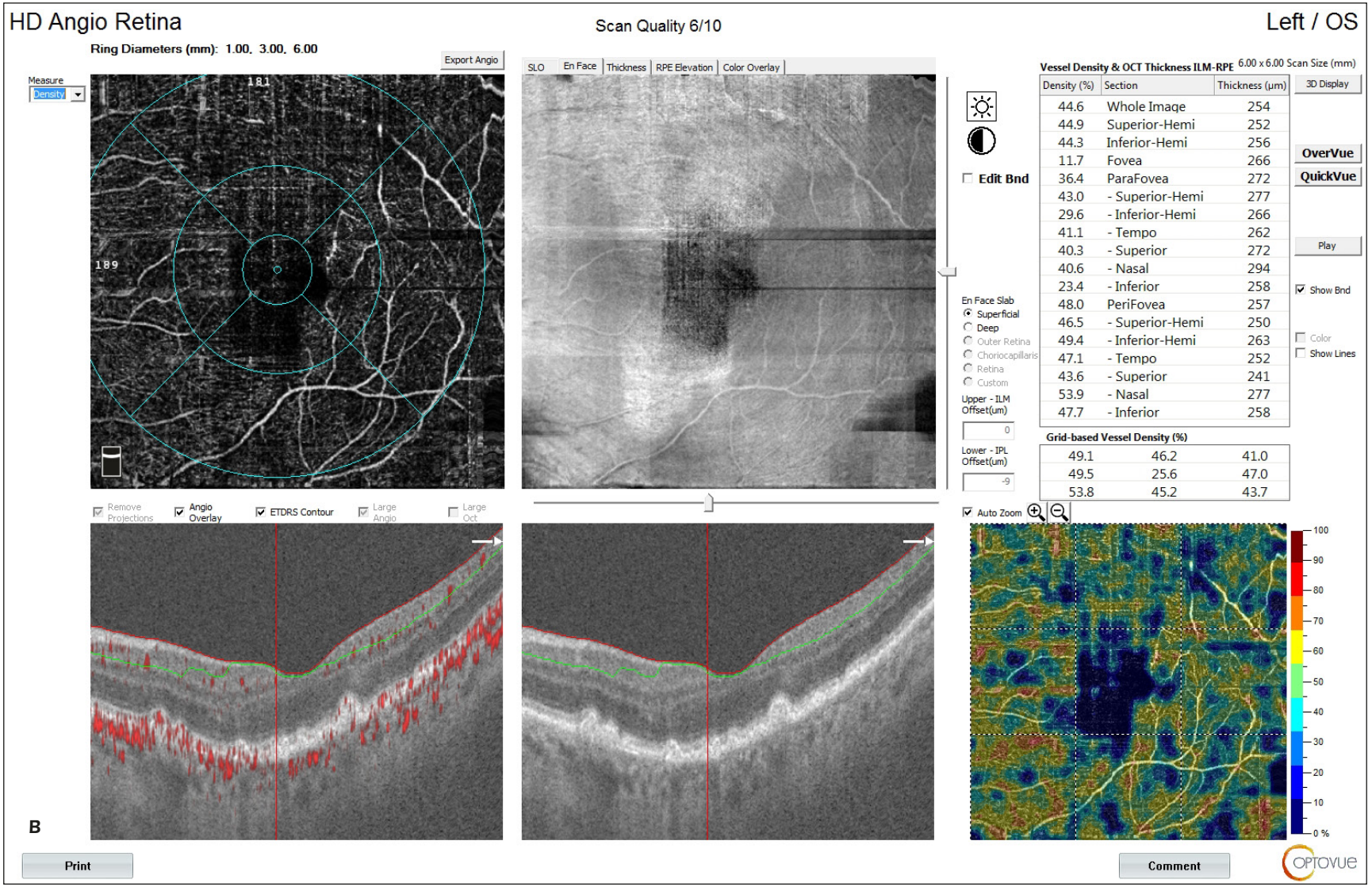

Figure 1 ***(Continued).*** **B**, OCTA image of superficial capillary plexus at last visit.

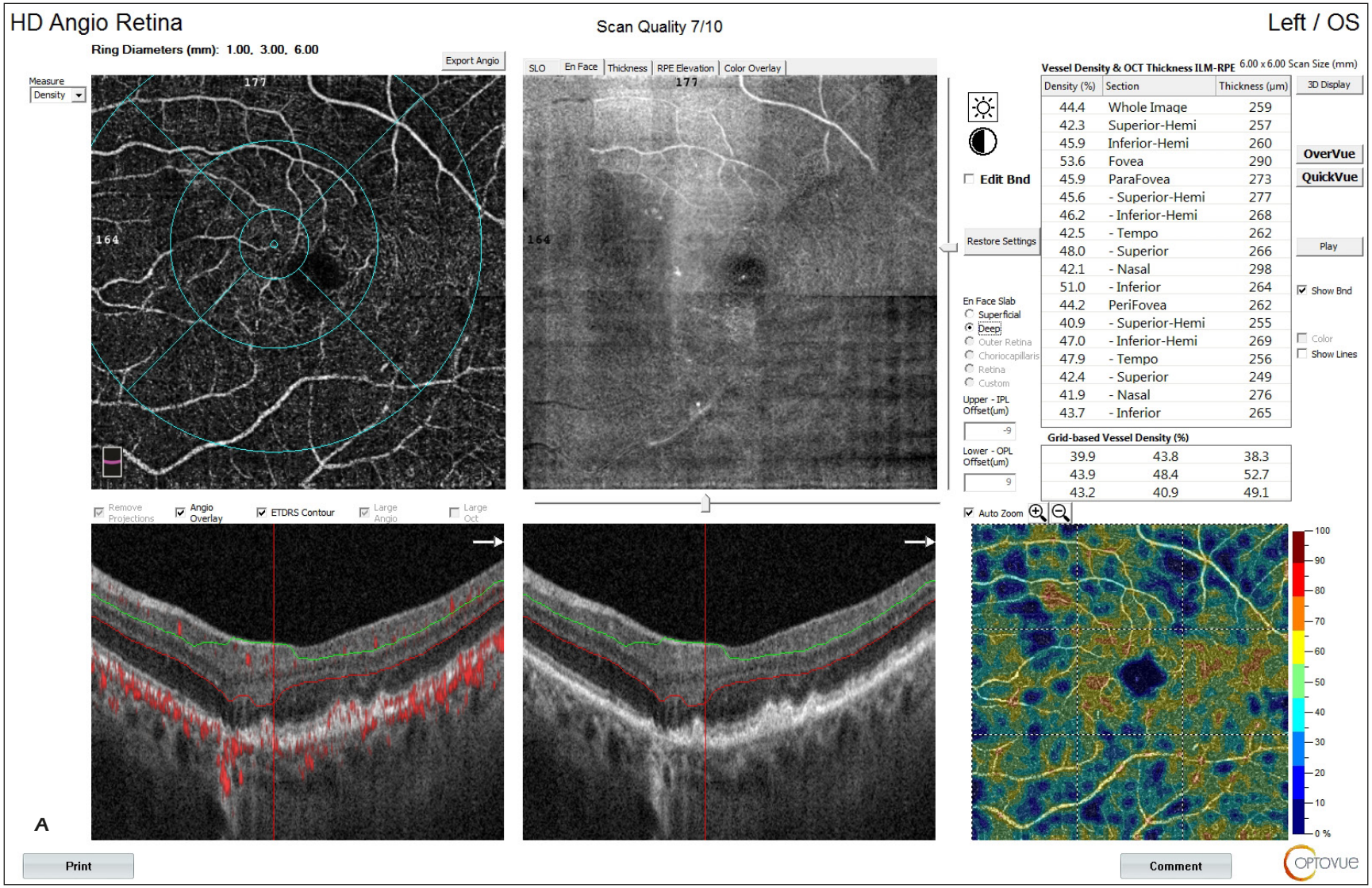

Figure 2. **A**, OCTA image of deep capillary plexus at diagnosis.

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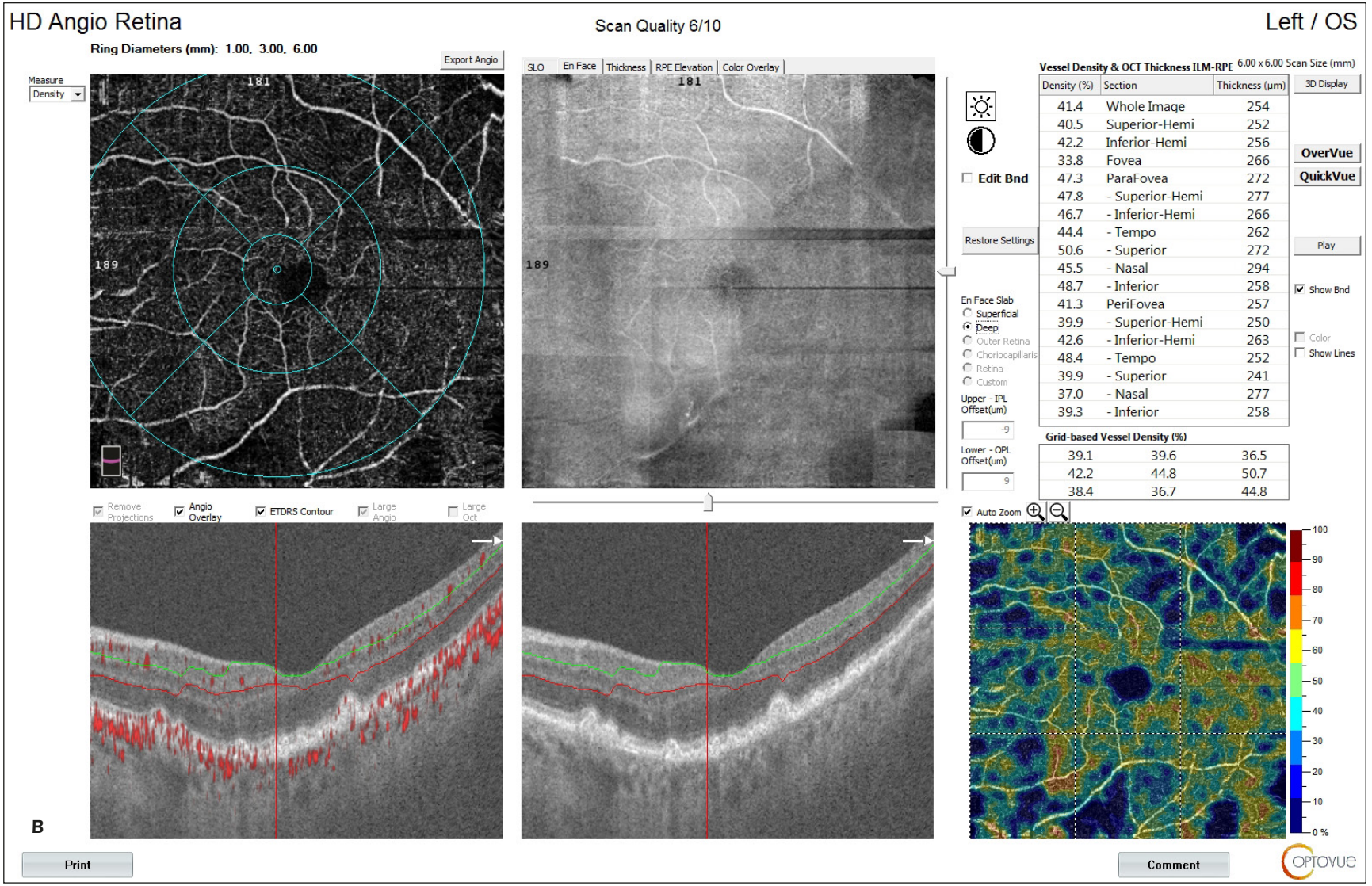

Figure 2. ***(Continued).*** **B**, OCTA image of deep capillary plexus at last visit.

doctor. Internal software used an averaging system to calculate the central macular thickness (MT) as the distance between the RPE and the ILM by preset algorithms. The relationship of all parameters with visual acuity (VA-logmar) was evaluated.

Statistical Analysis

The data were evaluated in the statistical package program of IBM SPSS Statistics Standard Concurrent User version 26 (IBM Corp., Armonk, NY, USA). Descriptive statistics were given as number of units (n), percent (%), mean±-standard deviation (), median, minimum and maximum values. The normal distribution of data and differences of numerical variables were evaluated with the Shapiro-Wilk test of normality. The differences between the first and last measurements were compared with the paired *t*-test. The correlation between BCVA and other variables at the first and last examinations was evaluated with Spearman correlation analysis. A *p*-value of <0.05 was considered statistically significant.

Results

The mean age was 73.3±11.8 years (45-91). The median follow-up period was 16 months (3-122). Eighteen right eyes, 17 left eyes, and 9 both eyes were affected by AMD. A statistically significant difference was found between the first and last BCVA, FT, and FD (p=0.001, p=0.002, p=0.045, respectively). While FD and BCVA were increasing, FT was found to decrease statistically significantly (Table I).

At the first and last examination, the correlations of BCVA with other variables were investigated (Table II). There was a statistically positive correlation between BCVA and FAZ, FAZ perimeter, and NFA. At the first examination, there was a statistically negative correlation between BCVA and the variables FT, Super VDF, Super F, Deep VDF, Deep F, Super paraf VD, Super paraf, Deep perif VD, Deep paraf, Deep paraf VD and FD. At the second measurement, there was a statistically negative correlation between BCVA and the MV, FT, Superf VDF, Superf F, Deep F, Sup paraf VD, Sup paraf, Deep paraf, Deep paraf VD and FD variables (Table II).

Table I. Comparison of first and last BCVA levels and OCTA measurements.

	Measurements		Statistics	
	First	Last		
	± ss	± ss	*t*	*p*
FAZ (mm²)	0.275 ± 0.118	0.314 ± 0.139	1.973	0.057
MV (mm³)	6.622 ± 0.514	6.562 ± 0.531	2.014	0.052
FT (µm)	231.9 ± 33.8	225.4 ± 33.8	3.402	0.002
CT (µm)	177.5 ± 46.9	173.8 ± 49.8	0.809	0.425
Super VDF	18.63 ± 8.92	18.39 ± 8.78	0.183	0.856
Super FT (µm)	232.6 ± 40.2	234.7 ± 41.5	0.531	0.599
Deep VDF	33.74 ± 9.87	35.24 ± 7.57	0.974	0.337
Deep FT (µm)	232.6 ± 40.2	234.7 ± 41.8	0.533	0.597
Super paraf VD	45.52 ± 6.47	44.83 ± 6.53	0.718	0.478
Super paraf T (µm)	284.9 ± 31.0	283.6 ± 34.7	0.506	0.616
Deep perif VD	45.46 ± 7.13	46.07 ± 7.36	0.583	0.564
Deep perif T (µm)	261.3 ± 22.7	259.8 ± 23.0	1.256	0.218
Super perif VD	46.07 ± 5.34	45.65 ± 5.48	0.600	0.553
Super perif T (µm)	261.3 ± 22.7	261.9 ± 22.1	0.240	0.812
Deep paraf T (µm)	284.0 ± 34.9	284.4 ± 31.4	0.165	0.870
Deep paraf VD	48.65 ± 5.28	49.72 ± 7.19	0.796	0.432
BCVA (logmar)	0.177 ± 0.316	0.392 ± 0.475	3.749	0.001
FD	46.0 ± 7.5	48.5 ± 6.6	2.088	0.045
FAZ Perim (mm)	2.106 ± 0.484	2.203 ± 0.485	1.237	0.225
NFA (mm²)	0.771 ± 0.451	0.871 ± 0.604	1.257	0.218

t: Paired *t*-test, FAZ: Foveal Avascular Zone, BCVA: Best Corrected Visual Acuity, MV: Macular Volume, FT: Foveal Thickness, CT: Choroid Thickness, FD: Foveal Density, Perim: Perimeter, NFA: Nonflow Area, VD: Vascular Density, F: Foveal, Super: Superficial, Paraf: Parafoveal, Perif: Perifoveal, T: Thickness.

Table II. Correlations between BCVA and OCTA measurements.

	BCVA			
	First		Last	
	rho	*p*	*rho*	*p*
FAZ (mm²)	**0.441**	**0.009**	**0.441**	**0.009**
MV (mm³)	-0.299	0.086	**-0.465**	**0.006**
FT (μm)	**-0.552**	**0.001**	**-0.700**	**< 0.001**
CT (μm)	-0.232	0.187	-0.254	0.147
Super VDF	**-0.413**	**0.015**	**-0.410**	**0.016**
Super FT (μm)	**-0.435**	**0.010**	**-0.414**	**0.015**
Deep VDF	**-0.458**	**0.007**	-0.290	0.096
Deep FT (μm)	**-0.435**	**0.010**	**-0.417**	**0.014**
Super paraf VD	**-0.371**	**0.031**	**-0.666**	**< 0.001**
Super paraf T (μm)	**-0.395**	**0.021**	**-0.561**	**0.001**
Deep perif VD	**-0.379**	**0.027**	-0.312	0.073
Deep perif T (μm)	-0.199	0.259	-0.220	0.212
Super perif VD	-0.246	0.161	-0.264	0.131
Super perif T (μm)	-0.199	0.259	-0.191	0.279
Deep paraf T (μm)	**-0.399**	**0.020**	**-0.561**	**0.001**
Deep paraf VD	**-0.406**	**0.017**	**-0.468**	**0.005**
FD	**-0.446**	**0.008**	**-0.526**	**0.001**
FAZ Perim (μm)	**0.438**	**0.009**	**0.548**	**0.001**
NFA (mm²)	**0.488**	**0.003**	**0.598**	**< 0.001**

t: Paired *t*-test, FAZ: Foveal Avascular Zone, BCVA: Best Corrected Visual Acuity, MV: Macular Volume, FT: Foveal Thickness, CT: Choroid Thickness, FD: Foveal Density, Perim: Perimeter, NFA: Nonflow Area, VD: Vascular Density, F: Foveal, Super: Superficial, Paraf: Parafoveal, Perif: Perifoveal, T: Thickness.

Discussion

Studies showed[20,21] functional changes such as prolonged choroidal filling in the choroid, which is remarkably related to areas of RPE atrophy, and demonstrated that drusen concentration is conversely related to choroidal blood volume and blood flow in early AMD. In another study[22], increases in CC flow voids, which are areas of decreased CC perfusion, compared to healthy age-matched controls, have been demonstrated with SD-OCTA in intermediate AMD. CC flow variations and flow voids seem to assume the predominant role in the pathogenesis of dry AMD. Outer retinal hypoxia caused by degeneration and functional deficits in the CC has been assumed to be the leading cause in the development of AMD.

In some studies[23-25], loss of choriocapillaris has been incriminated as a predictor of drusen or GA progression. The role of the choroidal vasculature in AMD is well understood, but the involvement of retinal vessels in AMD pathogenesis remains unclear[26,27]. OCTA studies[28,29] also demonstrated that retinal VD and FAZ were lower in eyes with non-exudative AMD than in normal eyes and proposed that a loss in retinal vascularity might be related to early AMD.

Toto et al[30] demonstrated that patients who were likely to develop GA had a decreased flow in SCP and injury of both the inner and the outer retina. In the literature, it was shown that decreased blood flow in the choroid and retina induces chronic ischemia in Bruch's membrane, RPE, and neuroretina, and differences in the DCP were not found. The construction of two vascular plexuses is different[31]. Toto et al[30] explained the reason for the protection of the DCP in intermediate AMD because of the different construction of two vascular plexuses. In intermediate AMD, alterations in SCP and DCP develop, which correlate directly with a reduction in CT, relatively preserved. Consistent with Toto et al[30], we also found alterations in SCP, but differently from their study, we found alterations in DCP as well as a reduction in CT, which was not statistically significant. Vaghefi et al[32] analyzed the VD of the CC and showed a significant decrease in VD with age and disease. Therefore, they concluded that CC VD

might ensure a biomarker of healthy aging and intermediate dry AMD[32]. Similar to Vaghefi et al[32], we also found a decrease in VD in SCP.

Lee et al[33] aimed to find the diversities in retinal perfusion that might be related to CNV in their study and used OCTA to compare retinal VD in non-exudative and exudative AMD. According to their study[33] eyes with exudative AMD might have decreased retinal capillary perfusion in the central macula, and the authors hypothesized the effect of retinal perfusion on the pathogenesis and treatment of exudative and non-exudative AMD[33].

According to Lee et al[33], across all eyes with AMD, the superficial retinal VD decreased with aging, as indicated in the previous studies[34,35]. In the study by Lee et al[33] it was shown that VD decreased in eyes with exudative AMD as compared with non-exudative AMD. They could not hypothesize if the lower retinal VD might increase the risk of formation of CNV or occur as a result of CNV formation in eyes with AMD[33]. Although they found variations in VD, they did not state any variation in FAZ area, circularity, or perimeter among exudative and non-exudative AMD. Their results were consistent with prior studies[36,37] demonstrating decreased VD but no variation in FAZ measurements among eyes with early or intermediate AMD and normal eyes. They demonstrated lower retinal VD and FAZ circularity in eyes with advanced AMD compared to those with intermediate AMD[33]. They also demonstrated slightly lower VD, larger FAZ perimeter, and reduced FAZ circularity in eyes with center-involving GA when compared to eyes without GA, but not those with non-central GA[33].

Their study focused only on the superficial rather than the intermediate or deep retinal capillary plexuses because the VD and FAZ parameters in the superficial layer have been well-approved using OCTA platform and are less likely to be affected by CNV pathology in the outer retinal layers[38-40]. Unlike Lee et al[33], we evaluated both superficial and deep vascular plexus and found variations both in SCP and DCP. Different from their study, we found variations in FAZ area, FAZ perimeter, and NFA. In our study, all three parameters were found to increase at the last examination, but the difference was not statistically significant. However, we did not evaluate neovascular AMD patients.

Concentrating on the retinal layers closer to the surface has the benefit of preventing the loss of signal and distortions caused by drusen and other AMD pathologies. It also helps to avoid any obscuring shadows that could affect the measurement of VD in the deeper retinal layers on OCTA[41,42].

With the development in diagnostic imaging, screening intermediate AMD populations at high risk for advanced form is becoming highly significant cause it may be approved for both therapeutic and prognostic reasons. Several publications[14,39,40] have demonstrated the important role of OCTA in the non-invasive identification of treatment-naive quiescent CNV in the setting of dry AMD, defined as type 1 neovascularization detected on FA and ICGA, with no signs of activity on OCT for at least 6 months[41,42].

Limitations

Our study has some limitations. We did not have a healthy control group, and we did not separate dry AMD patients into early and intermediate groups. Besides, our study group is small, although our inclusion criteria for patients were strict.

Conclusions

In conclusion, as far as we investigated the literature, our study is the first study declaring the OCTA alterations both in SCP and DCP in dry AMD patients, and our results support the fact that retinal hypoxia affects retinal vascularity and both vascular plexuses. According to our study, there are positive and negative correlations between OCTA parameters and BCVA in the SCP and DCP in dry AMD. OCTA has prognostic significance in dry AMD.

To sum up, dry AMD patients' alterations in the retina and choriocapillaris can be observed by using OCTA. These changes seem to be present during all stages of the disease. In the future, the capacity of OCTA to visualize the structure and flow disruptions of the choriocapillaris and retina could prove to be valuable in detecting and tracking the advancement of dry AMD, as well as monitoring the efficacy of therapies aimed at halting disease progression in dry AMD clinical trials. Our study should be supported with a larger series.

Conflict of Interest
The authors declare that they have no conflict of interests.

Ethics Approval
Approval was received from the Ethical Board of the local Committee of the Health Sciences University İzmir Tepecik Training and Research Hospital with number 2020/14-56/23.12.2020.

Informed Consent
Written informed consent was obtained from all the patients.

Availability of Data and Materials
The data is made available in the manuscript, figures, and tables.

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Authors' Contribution
All contributions belong to both authors.

ORCID ID
Esin Kırıkkaya: 0000-0003-1004-9492
Süleyman Kaynak: 0000-0001-5587-7238

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