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Vascular and structural alterations of the choroid evaluated by optical coherence tomography angiography and enhanced-depth imaging optical coherence tomography in eyes with reticular pseudodrusen and soft drusen

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ABSTRACT

Background: To assess the vascularity of choriocapillaris and structural choroidal differences in eyes with reticular pseudodrusen (RPD) and soft drusen.
Methods: 21 eyes with RPD (group 1), 17 eyes with soft drusen (group 2), and 19 eyes as a control group (group 3) were included in this study. Choriocapillaris vascular density and flow area were measured by optical coherence tomography angiography. Total choroidal area, luminal area, stromal area, and lumen/stroma ratios were measured on optical coherence tomography B-scans converted to binary images.
Results: Mean choriocapillaris vascular density was higher in group 3 than other groups (group 1 vs 3, $p = 0.001$; group 2 vs 3, $p = 0.003$). Mean flow area in choriocapillaris was higher in group 3 than other groups (group 1 vs 3, $p = 0.001$; group 2 vs 3, $p = 0.001$). Mean luminal, stromal, and total choroidal areas decreased in group 1 and group 2 compared to controls ($p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively). The stroma ratio decreased in group 1 compared to group 3 ($p = 0.013$). The lumen ratio and lumen/stroma ratio increased in group 1 compared to group 3 ($p = 0.012$ and $p = 0.008$, respectively).
Conclusions: The choroid of eyes with RPD and soft drusen was affected in both choriocapillaris and whole choroid layer.

1. Introduction

Age related macular degeneration (AMD) is a disorder characterized by a progressive loss of central vision due to degenerative and neovascular changes in the macula. The prevalence of AMD has been estimated at approximately 8.7% and is predicted to affect 288 million in 2040 [1]. AMD is subclassified into the nonexudative 'dry' or atrophic form and the exudative 'wet' or neovascular form. Although, exudative AMD is the less frequent subtype, it is the leading cause of irreversible blindness in adults over 60 years old in developed countries.

Dry AMD constitutes 85–90% of all AMD cases and has a relatively better prognosis [2]. The pathogenesis of early-stage dry AMD is characterized by the thickening of Bruch's membrane due to lipid and protein accumulation. This process causes the formation of different types of drusen under the retinal pigment epithelium (RPE). In the late stages, the disease may progress to geographical atrophy [3].

Drusen are focal deposits of lipofuscin, photoreceptor debris, and inflammatory components between the basal lamina of the RPE and the inner collagenous layer of the Bruch membrane [4]. The drusen types associated with dry AMD are hard drusen, soft drusen, and reticular pseudodrusen (RPD). Hard drusen are small and are associated with a much smaller risk of vision loss than soft drusen which are larger, cluster together and have not very well defined edges. RPD is yellowish subretinal lesions and are more commonly found in the superotemporal quadrant of the macula [5]. RPD, also known as subretinal drusenoid deposits, represent a morphological change to the retina distinct from other subtypes of drusen by their location between the sensory retina and the RPE. Due to this locational difference, it was named as "pseudo"drusen. On histological examination, RPD has been shown to have distinct compositions in comparison to soft and hard drusen, suggesting different pathways of pathogenesis [6]. Although their etiology remains unclear, the presence of opsin within lesions, a high topographic

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association with areas of highest rod-photoreceptor concentration and functional deficits most pronounced within the scotopic range, has implicated rod photoreceptor dysfunction as a component of RPD [6]. These lesions have been identified as an independent risk factor for disease progression to choroidal neovascularizations or geographic atrophy [7,8].

Abnormal choroidal circulation may be involved in the development of AMD [9]. It has been suggested that the degree of choriocapillaris pruning is related to the number of drusen present [10]. Mullins et al. observed an inverse relationship between choroidal thickness and the density of deposits [10]. In addition, choriocapillaris density under drusen was 45% lower than in regions without drusen. Vascular dropout appears to be linearly related to the progression of AMD. Histopathologic analysis by Seddon et al. revealed higher choriocapillaris vascular loss for all stages of AMD compared to controls [11]. Histological analysis has shown that changes in the choroidal interstitial stroma can occur in eyes with AMD due to edema, fibrosis, and inflammation with cellular infiltration [12]. Recently, it was speculated that the vascular structure is profoundly compromised, especially in RPD cases [13,14].

Optical coherence tomography angiography (OCTA) provides high-resolution, three-dimensional angiograms of the retina and choroid and visualization of blood flow by detecting the motion contrast of erythrocytes [15]. The superiority of OCTA over dye-based angiography techniques is that it can show retinal and choroidal vascular as separate layers, and it is non-invasive since dye injection is not required.

Patients with RPD and soft drusen have decreased vascular density in the choriocapillaris compared to healthy individuals [16]. With the help of OCTA and binarized enhanced depth imaging optical coherence tomography (EDI-OCT) images, it may be possible to understand whether the vascular or stromal component of the choroid is more affected.

The main aim of this study was to assess the vascular and stromal changes in the choroid with OCTA and ImageJ in eyes with RPD and soft drusen.

2. Materials and methods

2.1. Patient selection

This study was a retrospective analysis of patients with a diagnosis of dry AMD. Patients with RPD (group 1) and soft drusen (group 2) were included in this study. A control group (group 3) was comprised of normal individuals without a history of any ocular disease or ocular surgery.

The diagnosis of RPD was made according to the following characteristics: punctate, irregular sinusoidal, or ring-shaped deposits in the fundus photographs; granular hyperreflective materials situated between the RPE layer and the ellipsoid zone on OCT; small lesions clustered in a reticular pattern and a variable target aspect with an isoreflective core surrounded by a hyporeflective halo on infrared reflectance imaging. The diagnosis of soft drusen was made according to the following characteristics: yellow-white colored and indistinct borders in the fundus photographs and dome-shaped mounds of deposit under the RPE on OCT.

The exclusion criteria were the presence of severe corneal opacities and dense lens opacities, geographic atrophy, signs of choroidal neovascularization, intravitreal anti-vascular endothelial growth factor therapy, and vitreoretinal surgery according to the medical history. All the procedures were performed in agreement with the principles of the Declaration of Helsinki. This study was approved by the Medical Ethical Committee of the Ankara University Faculty of Medicine (I1–55–20).

The primary outcome measure was the change in the choroid structure, which was evaluated as the total choroidal area, luminal area, and stromal area by ImageJ. The secondary outcome measure was alterations in the choriocapillaris vasculature.

2.2. Imaging and image analysis

Each patient underwent a best-corrected visual acuity evaluation, biomicroscopy, applanation tonometry, OCT, and OCTA. OCTA was performed to assess the retinal and choroidal vasculature using the RTVue XR spectrum field OCT device and AngioVue OCTA software (RTVue XR Avanti, Optovue, Inc., Fremont, CA). Two consecutive B scans covering 6 mm were completed to compute inter-B scan decorrelation with the split-spectrum amplitude-decorrelation angiography algorithm. The software (Optovue, Version 2015.100.0.35) offers automated segmentation of the retinal layers, and en face OCTA is then produced by decorrelation projection within the segmented slab. Images showing inadequate signals (i.e., a signal strength index < 60) were excluded. A 6×6-mm OCT angiogram was recorded for each patient. All control patients underwent the same examination protocol as the dry AMD group. Choriocapillaris vascular density measurements in the parafoveal region were calculated, and comparisons were made between groups. In addition, the flow area in the choriocapillaris was measured in a 1.5 mm radius area (Fig. 1).

Enhanced depth imaging mode of spectral domain OCT (Spectralis; Heidelberg Engineering, Inc., Heidelberg, Germany) was used for choroidal measurements. Binarization of the choroidal area was performed with ImageJ software (Version 1.50a; National Institutes of Health, Bethesda, MD, USA) (Fig. 2a, Fig. 2b). A 3000-μm wide area with margins of 1500 μm temporal to the fovea was selected. The choroidal area was defined from the RPE to the chorioscleral border, and the borders were set manually with the ImageJ ROI Manager. Three choroidal vessels with lumens > 100 μm were selected by the oval selection tool, and the average reflectivity of the luminal areas was determined. The Niblack method was used for the binarization of the choroidal image. Then, the image was converted to eight bits and adjusted by the Niblack auto local threshold. The luminal area was determined with the threshold tool. After adding the distance between the pixels, the choroidal area, luminal area, and stromal area were automatically calculated. The light pixels were accepted as the stromal area, and the dark pixels were accepted as the luminal area.

2.3. Statistical analysis

All comparisons between groups were statistically analyzed using SPSS 11.5 (SPSS Inc., Chicago, IL, USA). The normality of all data was tested by the Shapiro-Wilk test. The significance of the difference among all groups was investigated by one-way analysis of variance (ANOVA) and the Kruskal-Wallis test. Pairwise comparisons with the Tukey HSD and Bonferroni tests were used to evaluate which groups differed. Statistical significance was set at $p < 0.05$.

3. Results

In total, 21 eyes of 17 patients in group 1 (7 women and 10 men, mean age 69.7 ± 3.9 years), 17 eyes of 15 patients in group 2 (9 women and 6 men, mean age 69.9 ± 3.8 years), and 19 eyes of 10 healthy patients in group 3 (7 women and 3 men, mean age 67.8 ± 3.2 years) were included in the study. There was no significant difference between the groups in terms of age and gender distribution ($p = 0.642$ and $p = 0.448$, respectively). The demographic data of the patients and healthy controls are shown in Table 1.

The mean choriocapillaris vascular density in the parafoveal region was 65.3% ± 5.4 in group 1, 65.8% ± 4.8 in group 2, and 71.6% ± 3.5 in group 3. The mean choriocapillaris vascular density in the parafoveal region was significantly higher in group 3 than in group 1 and in group 2 (group 1 vs 3, $p = 0.001$ and group 2 vs 3, $p = 0.003$). There was no statistically significant difference between group 1 and group 2 ($p = 1.000$) (Table 2).

The flow area in the choriocapillaris in the 1.5 mm radius area was 4.345 ± 0.2 mm^2 in group 1, 4.354 ± 0.3 mm^2 in group 2, and 4.899 ±

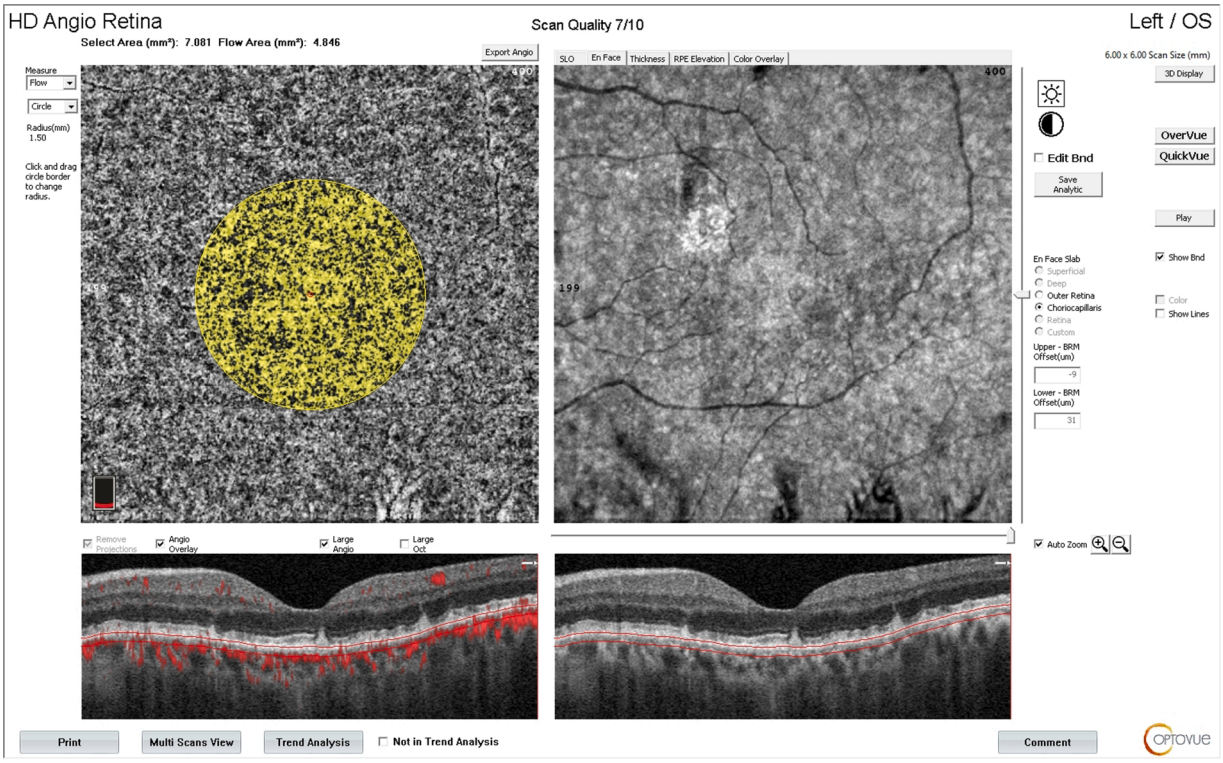

Fig. 1. A 64-year-old female with reticular pseudodrusen. Choriocapillary slab of the OCTA. The flow area (highlighted in yellow) is marked as a circle, centered on the fovea, with a radius of 1.5 mm. The automatically measured flow area of this case was 4.539 mm^2.

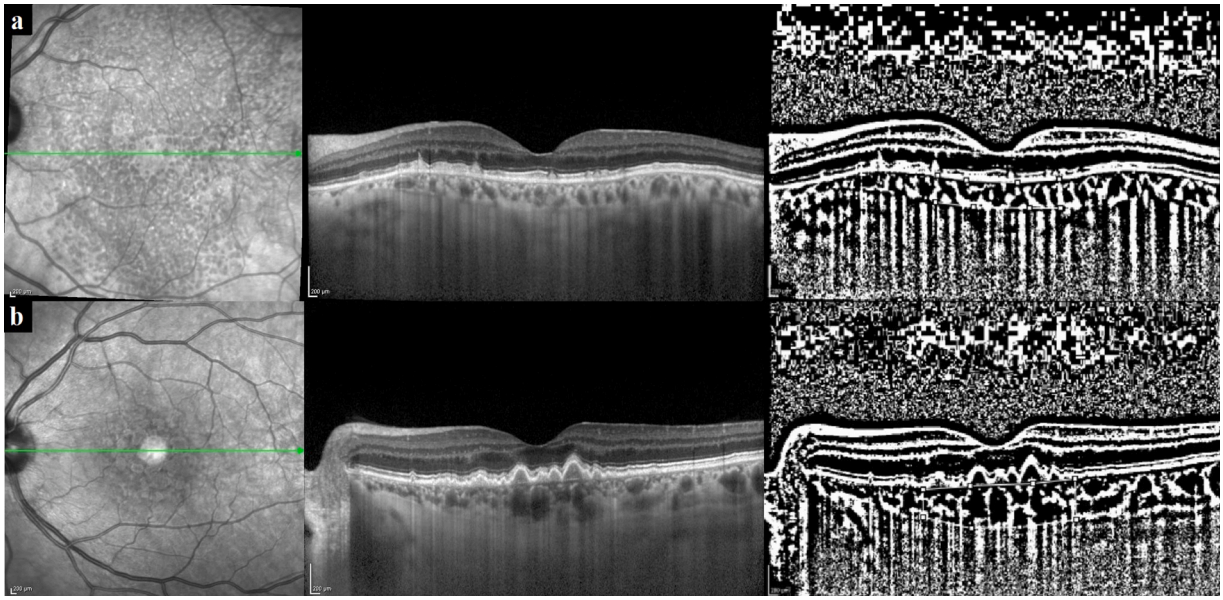

Fig. 2. EDI-OCT images and converted binary images using ImageJ with the area of interest in the choroid demarcated with a white line.
a: EDI-OCT image of an eye with reticular pseudodrusen. Binarized choroidal measurements revealed that the choroidal area was 0.641 mm^2 and lumen area was 0.491 mm^2. b: EDI-OCT image of an eye with soft drusen. Binarized choroidal measurements revealed that the choroidal area was 0.668 mm^2 and lumen area was 0.506 mm^2.

0.3 mm^2 in group 3. The flow area in the choriocapillaris in the1.5 mm radius area was significantly higher in group 3 than in group 1 and in group 2 (group 1 vs group 3, $p = 0.001$ and group 2 vs group 3, $p = 0.001$). The P values of these comparisons are shown in Table 2.

According to measurements made with ImageJ, the mean luminal area was 0.403 ± 0.1 mm^2 in group 1, 0.467 ± 0.1 mm^2 in group 2, and 0.657 ± 0.2 mm^2 in group 3. The mean stromal area was 0.123 ± 0.03 mm^2 in group 1, 0.151 ± 0.03 mm^2 in group 2, and 0.239 ± 0.07 mm^2 in group 3. The mean total choroidal area was 0.526 ± 0.1 mm^2 in group 1, 0.618 ± 0.1 mm^2 in group 2, and 0.897 ± 0.2 mm^2 in group 3. The mean luminal, stromal and total choroidal areas decreased in eyes with RPD and soft drusen compared to eyes in the control group. The stroma ratio was 0.237 ± 0.03 in group 1, 0.249 ± 0.03 in group 2, and 0.271 ± 0.03 in group 3. The stroma ratio decreased in eyes with RPD compared to

Table 1
The demographic data of the patients and healthy controls.

	Group 1	Group 2	Group 3	p-value
Eyes, n	21	17	19	
Age (Mean ± SD)	69.7 ± 3.9	69.9 ± 3.8	67.8 ± 3.2	0.642
Female/Male, n/n	7/10	9/6	7/3	0.448

SD: Standard deviation.

eyes in the control group ($p = 0.013$). The lumen ratio was 0.762 ± 0.03 in group 1, 0.750 ± 0.03 in group 2, and 0.728 ± 0.03 in group 3. The lumen/stroma ratio was 3.289 ± 0.5 in group 1, 3.082 ± 0.5 in group 2, and 2.744 ± 0.4 in group 3. The lumen ratio and lumen/stroma ratio increased in eyes with RPD compared to eyes in the control group. The P values of these comparisons are shown in Table 3.

4. Discussion

The pathophysiological mechanisms underlying the formation of RPD have not been accurately determined. Many factors have been implicated in RPD pathogenesis. In a histologic study by Arnold et al., there was significant loss of choroidal vessels in the Sattler layer and increased spacing between large choroidal veins, suggesting that fibrosis of the choroidal stroma and loss of vascularity were responsible for the development of RPD [17].

Recently, several researchers have reported that the choroidal thickness is decreased in eyes with RPD [18,19]. Querques et al. showed that the choroid of eyes with RPD was thinner than that of eyes with early AMD [18]. Switzer et al. reported that among patients with early AMD, those with RPD had a thinner choroid in the subfoveal region than those without RPD [19]. Spaide et al. hypothesized that RPD lesions were mainly caused by RPE dysfunction [20]. They reported that a reduction in RPE function might lead to dysfunction in the transport mechanism between the RPE and Müller cells. This condition results in an accumulation of the materials in the subretinal space. This accumulation can then lead to a reduction in photoreceptor metabolic activity, which they suggested may explain the choroidal thinning in eyes with RPD.

Corvi et al. compared the luminal and stromal area of the choroid in eyes with soft drusen and RPD by the binarization technique with ImageJ [21]. They showed a progressive thinning of the total choroidal area involving both the luminal and stromal areas in eyes with RPD. They reported that the mean total choroidal, luminal, and stromal area were more reduced in eyes with RPD than in eyes with soft drusen and control eyes. However, although our results showed that the mean luminal, stromal, and total choroidal areas decreased in AMD eyes with or without RPD compared to healthy control eyes, the differences between AMD groups (i.e., RPD and soft drusen) were not statistically significant. The reduction in the luminal, stromal, and total choroidal areas revealed by ImageJ might be explained by the secondary result of the lack of oxygen demand of the RPE or lack of vascular endothelial growth factor secretion due to RPE dysfunction [22].

In contrast to Corvi et al. we did not show a decrease in the lumen ratio in eyes with RPD compared to eyes in the other groups. In our study, the lumen ratio increased in eyes with RPD compared to eyes in the control group. Therefore, it may be speculated that compromised stroma in the RPD group might be more prominent than in the control group. Contrary to Corvi et al., in a larger series, it was shown that choridal vascularity index increased in eyes with RPD compared to the control group, and it was emphasized that the stromal component seems to show a relatively greater attenuation [23]. Arnold et al. showed that fibrosis of the choroidal stroma and loss of vascularity were responsible for the development of RPD, and the stroma was more fibrotic in the eye with an RPD pattern than the eye without an RPD pattern and the normal eye [17]. Therefore, it might be speculated that the whole choroid is compromised in AMD patients compared to normal eyes. According to our results, the ratio of stroma or lumen may vary, but which part is more affected is unclear.

Few studies in the literature have reported reduced perfusion using OCTA in the RPD group compared to healthy controls and soft drusen. The principal result of those studies was that the eyes with RPD presented large areas of choriocapillaris non-perfusion in OCTA compared to conventional drusen [24,25]. Although we showed that there was a decrease in the parafoveal choriocapillaris vessel density and the mean flow area in the choriocapillaris compared to healthy individuals in both groups, we could not find a difference between AMD subgroups. Therefore, speculation that the difference between RPD and soft drusen with imaging modalities still lacks good scientific evidence. Similar to

Table 2
Evaluation of choriocapillaris vascular characteristics with OCTA.

				p values ANOVA/ Kruskal–Wallis Test	Pairwise Comparisons		
	Group 1 (Mean ± SD)	Group 3 (Mean ± SD)	Group 3 (Mean ± SD)		Group 1 vs. Group 3	Group 2 vs. Group 3	Group 1 vs. Group 2
Mean choriocapillaris vascular density (%)	65.3% ± 5.4	65.8% ± 4.8	71.6% ± 3.5	< 0.001*	0.001*	0.003*	1.000
Flow area in the choriocapillaris in the 1.5-mm radius area (mm^2)	4.345 ± 0.2	4.354 ± 0.3	4.899 ± 0.3	< 0.001*	0.001*	0.001*	1.000

* SD: Standard deviation; *: Statistically significant P values.

Table 3
Choroidal structural characteristics evaluated with ImageJ.

Variables	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	Group 3 (Mean ± SD)	P values ANOVA/ Kruskal-Wallis Test	Pairwise Comparisons Group 1 vs. Group 3	Group 2 vs. Group 3	Group 1 vs. Group 2
Total choroidal area (mm^2)	0.526 ± 0.1	0.618 ± 0.1	0.897 ± 0.2	< 0.001*	< 0.001*	0.001*	0.417
Stromal area (mm^2)	0.123 ± 0.03	0.151 ± 0.03	0.239 ± 0.07	< 0.001*	< 0.001*	< 0.001*	0.259
Stroma ratio	0.237 ± 0.03	0.249 ± 0.03	0.271 ± 0.03	0.016*	0.013*	0.179	0.577
Luminal area (mm^2)	0.403 ± 0.1	0.467 ± 0.1	0.657 ± 0.2	< 0.001*	< 0.001*	0.005*	0.503
Lumen ratio	0.762 ± 0.03	0.750 ± 0.03	0.728 ± 0.03	0.016*	0.012*	0.176	0.581
Lumen/Stroma ratio	3.289 ± 0.5	3.082 ± 0.5	2.744 ± 0.4	0.011*	0.008*	0.174	0.501

* SD: Standart deviation; *:Statistically significant P values.

our results, Cicinelli et al. also described vascular changes not only at the choriocapillaris level but also at the choroidal level in patients with RPD, drusen, and a mixed phenotype [16]. They analyzed OCTA images through the ImageJ software. They showed that the choriocapillaris, the Sattler, Haller's, and the whole choroid vessel density decreased in all groups compared to those in healthy controls. Their results are consistent with our results even though we used the binarized technique on B-scan OCT instead of OCTA scans and could not differentiate all three layers of the choroid due to the segmentation problem in the enhanced depth imaging mode of OCT. This study also confirmed that choroidal vascular depletion occurs in patients with RPD and drusen in the early stages of dry AMD, and the choroidal layer shows dramatic alterations in its composition with a predominance of the stromal tissue on the vascular network. No statistically significant differences were found between the RPD and soft drusen groups.

A potential limitation of our study was the limited number of eyes included. The small sample was mainly due to the strict inclusion criteria for the soft drusen, RPD, and control groups and the exclusion of patients with geographic atrophy. In addition, patients with significant artifacts on OCTA imaging were excluded from our study.

5. Conclusion

OCTA can be used to visualize alterations in the choriocapillaris of patients with dry AMD. Our study showed impairment in the choriocapillaris with OCTA in patients with RPD and soft drusen compared to healthy patients. Additionally, accompanying findings showing decreased luminal, stromal, and total choroidal areas in eyes with RPD and soft drusen compared to control eyes may strongly indicate the possible role of choroidal vascular and stromal depletion in pathogenesis and progression of AMD. The fact that the degree of choriocapillaris pruning is associated with the number of drusen, an inverse relationship between choroidal thickness and drusen density, and a linear relationship between vascular loss and AMD progression support this view. Large trials are required to evaluate the structural and vascular changes and determine the blood flow in patients with dry AMD to understand underlying pathogenesis.

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Declaration of Competing İnterest

There is no declaration of interest.

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