• Clinical Research •

Identification of retinal thickness and blood flow in age-related macular degeneration with reticular pseudodrusen

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Abstract

● **AIM:** To investigate thickness characteristics and vascular plexuses in retinas with reticular pseudodrusen (RPD) as an early detection strategy for age-related macular degeneration (AMD).

● **METHODS:** This retrospective study included 24 subjects (33 eyes) with RPD and 25 heathy control subjects (34 eyes). The superficial capillary plexus (SCP) and the deep capillary plexus (DCP) of the retinal posterior poles were investigated with optical coherence tomography angiography (OCTA). Retinal thicknesses and vessel densities were analyzed statistically.

● **RESULTS:** The general retinal thicknesses of RPD eyes were significantly decreased (95%CI -14.080, -0.655; *P*=0.032). The vessel densities of DCP in RPD eyes were significantly increased in the global (95%CI 1.067, 7.312; *P*=0.027), parafoveal (95%CI 0.417, 5.241; *P*=0.022), and perifoveal (95%CI 0.181, 6.842; *P*=0.039) quadrants. However, the vessel densities of the SCP were rarely increased in the eyes with RPD.

● **CONCLUSION:** The thinning of retinas in the RPD group suggests a reduction in the number of cells. Additionally, the increased vessel density of the DCP in retinas with RPD indicates a greater demand for blood supply, possibly due to the hypoxia induced RPD compensation caused by RPD in the outer retina. This study highlights the pathological risks associated with RPD and emphasizes the importance of early intervention to retard the progression of AMD.

● **KEYWORDS:** reticular pseudodrusen; age-related macular degeneration; retinal thickness; retinal vessel density; optical coherence tomography angiography

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INTRODUCTION

Age-related macular degeneration (AMD) is one of the leading causes of impaired vision among the elderly and early diagnosis could be beneficial for the prognosis[1-2]. Recently, a specific subtype of early-stage AMD has been identified that includes reticular pseudodrusen (RPD)[3-4]. This subtype has been named reticular macular disease (RMD) by Smith *et al*[5]. RPD presents as a reticular lesion in color fundus photography and scanning laser ophthalmoscopy[3,5-6]. RPD shows the involvement of vitronectin, unesterified cholesterol, apolipoprotein E, and complement factors, such as complement factor H[7-8]. Optical coherence tomography (OCT) has shown that RPD is characterized by a type of abnormal deposit on the retinal pigment epithelium (RPE) that reaches deep into the photoreceptor layer. This pathological sediment is also called subretinal drusenoid deposits[6-7].

RPD has been identified as a high-risk factor in AMD progression[5,9-11]. It was reported that the visual acuity, dark adaptation, retinal sensitivity[11-14] and contrast sensitivity[13] of patients with prominent RPD were significantly impaired. It was also reported that the retinas were thinner in patients with RPD[15]. AMD accompanied by RPD was found to easily advance to end stage with geographic atrophy or choroidal neovascularization (CNV)[9,11]. PRD is assumed to disrupt the metabolism of retinal outer layers and the phagocytotic process of the RPE, resulting in impairment of photoreceptors[16]. However, the pathogenic mechanism of RPD is yet to be

clarified. Recently, Cicinelli *et al*[17] found a significant reduction in both the retinal superficial capillary plexus (SCP) and deep capillary plexus (DCP) using optical coherence tomography angiography (OCTA) in RMD patients. This aroused attention to the retinal blood supply in retinas with RPD. As mentioned previously, former studies focused only on a 3×3 mm^2 region of the fovea, which made it difficult to study and elucidate the circulation of RPD in the superior-temporal perifovea[18].

In this study, we explored characteristics of the retina in AMD accompanied by RPD and we imaged blood circulation with 6×6 mm^2 wide-angle OCTA. We investigated the retinal thickness and vessel density of patients with RPD to better uncover retinal alterations in a wider range that raise alarms for early intervention of AMD.

SUBJECTS AND METHODS

Ethical Approval This research was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (Ethical Committee Number: 2020K-25). All protocols were in compliance with the principles of the Declaration of Helsinki. All individuals who participated in the study understood the protocols and filled out the informed consent forms.

Patient and Public Involvement A total of 33 eyes of 24 subjects with RPD and 34 eyes of 25 healthy controls were recruited for this retrospective case-control study between July and October 2019 at the First Affiliated Hospital of Guangzhou Medical University in China.

The lesions of RPD were confirmed with spectral domain optic coherence tomography (SD-OCT) and identified when one or more hyperreflective mounds in the subretinal space were present between the RPE-Bruch's membrane complex and the ellipsoid zone or breaking through the ellipsoid zone, following the standards of former studies[11,19], in at least one of the images of the posterior pole B-scans (Figure 1). Wei YZ and Cheng H identified the existence of RPD in each fundus image. When the two examiners disagreed, the images were reviewed again and final decisions were made by consensus. A group of healthy subjects was enrolled as controls.

Exclusion criteria for both the RPD group and healthy eyes were as follows: 1) age<50y; 2) a history of vitreoretinal disease and surgery, such as diabetic retinopathy, macular hole, retinal vein occlusion, epiretinal membrane, and uveitis, geographic atrophy; 3) subjects with a spherical diopter less than -6.00 D or axial length greater than or equal to 26 mm; 4) subjects with significant media opacities that affected imaging with OCTA (scanning quality score <6).

All subjects were given a routine ocular examination that included best-corrected visual acuity, noncontact tonometry, refractive error, slit lamp fundus examination, SD-OCT (Spectralis OCT; Heidelberg, Germany), infrared (IR) imaging, and OCTA.

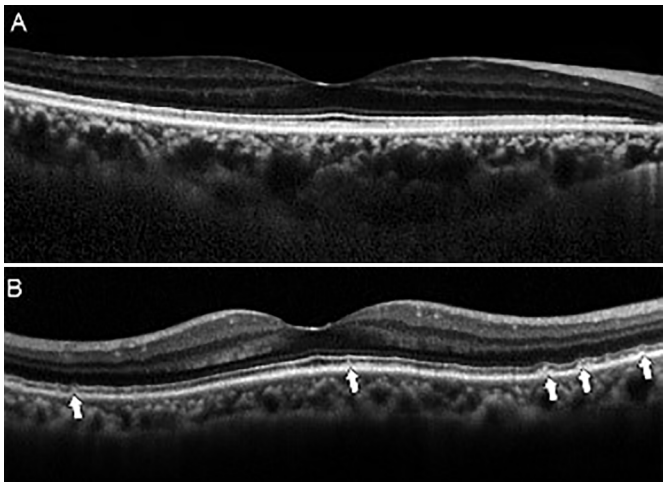

Figure 1 Spectral domain optic coherence tomography (SD-OCT) images of macular retinas A: Normal retina; B: Reticular pseudodrusen (RPD) were present as hyper-reflective mounds above the retinal pigment epithelium, contacting or breaking through the ellipsoid zone.

OCTA examinations were conducted in a darkroom with an AngioVue OCTA system (V.2017.1.0.151; RTVue-XR Avanti; Optovue, USA). The subject was assessed with OCTA after sitting quietly for five minutes. We chose the macular HD 6×6 mm^2 scan pattern with an 840 nm wavelength. The en-face OCTA images of SCP and DCP were automatically generated by the system. The SCP was segmented between the internal limiting membrane (ILM) and the external aspect of the inner plexiform layer. The DCP was segmented between the external aspect of the inner plexiform layer and below the outer plexiform layer[20]. The retinal thickness (ILM to RPE) was automatically measured and the examiners made corrections together if segmentation errors were present.

Variables included in the investigation were: 1) retinal thickness of the whole image; 2) superficial retinal global, foveal, parafoveal, and perifoveal vessel density; 3) deep retinal global, foveal, parafoveal, and perifoveal vessel density. The percentages of vessel densities were calculated as the vessel area with blood flow over the measuring area.

Statistical Analysis SPSS V.26.0 software (USA) was used for statistical analysis. The normality of the data distributions was assessed with a Shapiro-Wilk normality test. Differences between RPD and healthy retinas were calculated by means of independent samples *t*-tests or Chi-square tests. Data were expressed as the mean±standard deviation (SD) and 95% confidence interval (CI). *P* values less than 0.05 were deemed statistically significant.

RESULTS

Baseline Characteristics A total of 67 eyes were included in the analysis (33 eyes of 24 patients in the RPD group; 34 eyes

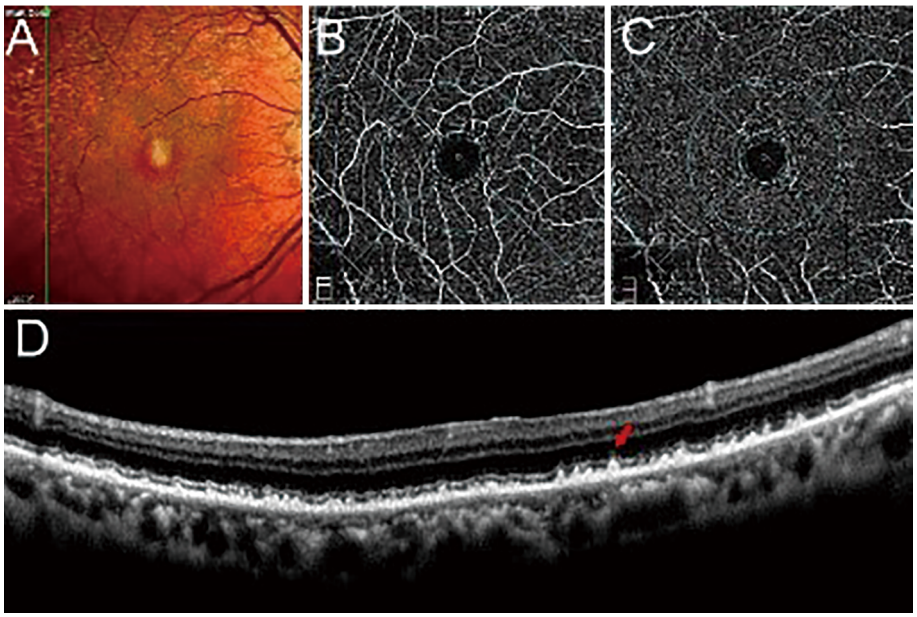

Figure 2 Optical coherence tomography angiography (OCTA) and optical coherence tomography (OCT) scan images of a 72-year-old female patient with reticular pseudodrusen (RPD) A: Scanning laser ophthalmoscope image showing a reticular pattern with blue-white appearance at the posterior pole; B, C: Correspond to 6×6 mm^2 HD OCTA images of the superficial capillary plexus (SCP) and deep capillary plexus (DCP), respectively; the blue rings (1, 3, and 6 mm in diameter) were automatically generated by software and were used to segment the region of interest into three fields: foveal, parafoveal, and perifoveal areas; D: Corresponding OCT image for the green line in A showing multiple hyper-reflective lesions above the retinal pigment epithelium and even breaking through the ellipsoid zone (red arrows).

of 25 patients in the heathy control group; the mean age was 64.67±9.708y). Demographic data of subjects were reported in Table 1. There was no significant difference between the two groups in age, gender, and eyes selected.

Anatomical Outcome The software automatically fitted a circle (1.0 mm in diameter) that was centered on the fovea, while the parafovea area was defined as a wide round annulus around the fovea between 1.0 and 3.0 mm in diameter and the perifovea was defined as a round annulus between 3.0 and 6.0 mm in diameter (Figure 2).

Table 2 shows the structural parameters and comparisons between the RPD group and control group. To confirm whether the vascular dysfunction was accompanied by retinal structural abnormalities, the retinal thicknesses were compared between the two study groups. The thickness from the ILM to the RPE appeared thinner in patients affected by RPD (95%CI -14.08, -0.65; *P*=0.032).

Quantitative analysis with OCTA centered on the posterior pole of the retina disclosed a statistically significantly higher deep mean vessel flow density (95%CI 1.07, 7.31; *P*=0.027) in the RPD group compared to the controls. However, the foveal vessel flow density did not show a difference in RPD compared with controls (95%CI -1.90, 4.89; *P*=0.382), in contrast to the parafoveal vessel flow density (95%CI 0.42, 5.24; *P*=0.022) and the perifoveal vessel flow density (95%CI 0.18, 6.84; *P*=0.039). The DCP density of the RPD group in the whole image and parafoveal and perifoveal regions were increased significantly. The global (95%CI -0.11, 4.01; *P*=0.063), parafoveal (95%CI -1.33, 4.80; *P*=0.063), and perifoveal (95%CI -0.15, 4.12; *P*=0.068) SCP density, though showing

Table 1 Demographic data of the RPD and control group

Characteristics	RPD group	Control group	*P*
Eyes/patients	33/24	34/25	-
Age (y)	64.33±10.40	65.00±9.13	0.741[a]
Gender (M/F)	15/18	15/19	0.912[b]
Eye (right/left)	21/12	17/17	0.260[b]

[a]Independent samples *t*-test; [b]Chi-square test. RPD: Reticular pseudodrusen.

Table 2 Quantitative comparison of thickness and retinal vessel density

Parameters	RPD group	Control group	95%CI	[a]*P*
Retinal thickness, μm	271.6±14.2	279.0±13.3	-14.08, -0.65	0.032
SCP vessel density, %				
Global	49.5±4.4	47.6±3.9	-0.11, 4.01	0.063
Foveal	18.3±5.7	17.2±6.8	-1.97, 4,19	0.476
Parafoveal	52.4±5.8	50.0±4.2	-1.33, 4.80	0.063
Perifoveal	50.9±4.5	48.0±4.2	-0.15, 4.12	0.068
DCP vessel density, %				
Global	51.8±6.0	48.3±6.5	1.07, 7.31	0.027
Foveal	32.6±7.2	31.1±6.7	-1.90, 4.89	0.382
Parafoveal	56.1±4.7	53.3±6.6	0.42, 5.24	0.022
Perifoveal	52.9±6.6	49.4±7.0	0.18, 6.84	0.039

[a]Independent samples *t*-test. RPD: Reticular pseudodrusen; CI: Confidence interval; SCP: Superficial capillary plexus; DCP: Deep capillary plexus.

an increasing trend, did not reach a statistically significantly difference between the two groups. In the regional sub-analysis, no statistically significant difference was observed in the foveal region (95%CI -1.97, 4.19; *P*=0.476).

DISCUSSION

Because there have been found to be linked to the pathological end stage of AMD, RPD have been attracting the attention of ophthalmologists in recent years. The blood supply system has been found to deform in retinas with RPD[17], therefore, OCTA is ideal for obtaining images of the vascular layers in the retina from the ILM to the choroid without dye injection. With automatic image analysis, the retinal vessel density can be calculated from the primary data of OCTA[21]. Former studies investigating RPD mainly focused on a small region of 3×3 mm^2 in the central posterior pole of the retina[15,17]. This limitation potentially impeded the profound recognition of the clinical features in retinas with RPD. In order to better understand the characteristics of RPD, we investigated the clinical parameters of the foveal, parafoveal, perifoveal, and global retina using a 6×6 mm^2 scanning map with OCTA in this retrospective study.

It is known that retinal nourishment is only supplied by the blood vessels of the inner retinal layer and the choroidal circulation system. The thickness of the retina reflects the status of the retinal blood supply to a certain extent[22-23]. It has been reported that the retinas with RPD were thinner and the choroidal vascular flow in RPD eyes was diminished[15,24-25]. In addition to what is known, our findings reveal a discrepancy in vascular flow among the different layers of the retina for the first time. In our study, thinning of the retinas with RPD indicates a decrease in retinal nourishment, which could be related to the reduced blood supply. However, increased vessel density in the DCP layer was also found, which presents a contradiction to the observed thinning retina. In this case, the contradiction could be explained by the anatomical characteristics of the retinas: RPD are located above the RPE layer and mainly influence the outer retina, while they also obstruct the nourishment supplies transported from the choroidal vascular flow through the RPE. Thus, the retinal thinning could have resulted from the primary decrease in nourishment in the outer retina, which induced a compensatory increase in the vessel density in the DCP.

While needing to maintain its high metabolic rate for phototransduction, the retina could be easily impaired by hypoxia resulting from an unstable blood flow. It was reported in a recent study that choroidal hypoxia could prominently induce RPD pathogenesis[26]. In another study, histologic abnormalities were found to occur in photoreceptors affected by RPD, which led to excessive secretion of vascular endothelial growth factor (VEGF)[27]. These results implied that RPD might be related to partial damage of the blood supply, which decreased the tissue oxygen content. Hypoxia is able to induce the expression of endothelial nitric oxide synthase and VEGF, which are involved in the increased permeability of vascellum and vasorelaxation in an impaired retina[28]. As VEGF is the major factor causing neovascularization, we hypothesize that the VEGF induced by choroidal hypoxia could diffuse from the outer retina to the inside layers and cause a significant increase in DCP. The SCP, however, is too distant to be influenced by VEGF from the outer retinal layer. These findings provide a possible explanation for the increase in DCP vessel density found in our study. It has also been reported that the RPD are associated with inflammatory disorders[8,29]. While the activation of microglial cells in retinas with RPD is related to angiogenesis[28], the increase in vessel density in retinas with RPD could be part of the inflammatory response. Moreover, some studies have found that the photoreceptors in RPD appeared to be dysfunctional, which led to the development of sub-retinal vascularization[7-8]. However, VEGF in each of the retinal layers has never been quantified. We will further verify this inference in the future by enriching our database and determining the appropriate timing for early therapeutic intervention.

Interestingly, a former study using OCTA found rarefaction in both SCP and DCP in the retinas with RPD[17], which conflicts with our results. This could be due to different inclusion criteria. In that study, the RPD in the cases were netlike structural and the measuring acreage was two-disc diameters away from the retinal posterior pole. The criterion in our study was the presence of one or more RPD on SD-OCT imaging, which was consistent with previous studies[24,30]. Another possible reason is the cases included in our study were in the early pathological process of the development of RPD, when a compensatory increase of DCP vessels could be at an initial fastigium. Though the increasing blood flow in DCP presented as a compensatory change to restore the reduced blood supply of the outer retina, reduction might still occur with a prolonged course of the disease. Decreased blood flow can be found beyond the RPD area in later states[15]. Ethnic variations may also account for the difference; the subjects included in our study were Chinese. Unlike with other ethnicities, choroidal neovascularization (CNV) is markedly common in Asian AMD patients[31-32].

In our study, we observed no significant change in retinal blood perfusion in the foveal area in the subjects with RPD, which is consistent with the results of Cicinelli *et al*[17]. This phenomenon in foveal blood flow was also seen in eyes with retinal atrophy[17] and adult-onset foveomacular vitelliform dystrophy[33]. The particular blood supply of the fovea by choroidal vessels, put forward by the study of Steinberg *et al*[34],

might also explain the unaffected vascular plexuses with RPD involvement. In their study, they suggested that impaired choriocapillaris blood flow in the process of forming RPD might be less likely in the fovea. It is also noteworthy that the basic vessel density is at a low level in the foveal region, which can possibly lead to undetectable vascular variations. Overall, it is conceivable that there are mechanisms preserving the fovea automatically, which shall be studied further in the future. In summary, all of these pathological changes give rise to greater dangers with advanced AMD and RMD becomes critical with CNV in Asian populations. Delaying the progression of AMD accompanied by RPD may be possible by developing strategies for anti-VEGF treatments as early intervention may prevent degenerating progression.

In conclusion, our study illustrated the pathological index of retinal thinning and increased retinal vessel density in DCP in retinas with RPD, revealing an abnormal blood supply induced by the very retinopathy. The thinning retinas revealed a decreased retinal blood perfusion came from choroid, which might lead to production of VEGF and inflammatory factors. Following, the increasing retinal blood circulation of DCP, could be a compensation resulted from neovascular factors produced in the outer retina. More attentions should be paid to the retinal pathogenesis brought by RPD, and there should be early intervention contributing to control the lesion progression from deteriorating into late-stage AMD, which would be promoting early detections and treatments for irreversible eye diseases.

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REFERENCES

1 Mitchell P, Liew G, Gopinath B, Wong TY. Age-related macular degeneration. *Lancet* 2018;392(10153):1147-1159.

2 Rubner R, Li KV, Canto-Soler MV. Progress of clinical therapies for dry age-related macular degeneration. *Int J Ophthalmol* 2022;15(1): 157-166.

3 Wightman AJ, Guymer RH. Reticular pseudodrusen: current understanding. *Clin Exp Optom* 2019;102(5):455-462.

4 Grewal MK, Chandra S, Gurudas S, Bird A, Jeffery G, Sivaprasad S. Exploratory study on visual acuity and patient-perceived visual function in patients with subretinal drusenoid deposits. *J Clin Med* 2020;9(9):2832.

5 Smith RT, Sohrab MA, Busuioc M, Barile G. Reticular macular disease. *Am J Ophthalmol* 2009;148(5):733-743.e2.

6 Spaide RF, Ooto S, Curcio CA. Subretinal drusenoid deposits AKA pseudodrusen. *Surv Ophthalmol* 2018;63(6):782-815.

7 Rudolf M, Malek G, Messinger JD, Clark ME, Wang L, Curcio CA. Sub-retinal drusenoid deposits in human retina: organization and composition. *Exp Eye Res* 2008;87(5):402-408.

8 Greferath U, Guymer RH, Vessey KA, Brassington K, Fletcher EL. Correlation of histologic features with *in vivo* imaging of reticular pseudodrusen. *Ophthalmology* 2016;123(6):1320-1331.

9 Agrón E, Domalpally A, Cukras CA, Clemons TE, Chen Q, Lu Z, Chew EY, Keenan TDL; AREDS and AREDS2 Research Groups. Reticular pseudodrusen: the third macular risk feature for progression to late age-related macular degeneration: Age-Related Eye Disease Study 2 Report 30. *Ophthalmology* 2022;129(10):1107-1119.

10 Wu Z, Fletcher EL, Kumar H, Greferath U, Guymer RH. Reticular pseudodrusen: a critical phenotype in age-related macular degeneration. *Prog Retin Eye Res* 2022;88:101017.

11 Monge M, Araya A, Wu L. Subretinal drusenoid deposits: an update. *Taiwan J Ophthalmol* 2022;12(2):138-146.

12 Zhang Y, Sadda SR, Sarraf D, *et al*. Spatial dissociation of subretinal drusenoid deposits and impaired scotopic and mesopic sensitivity in AMD. *Invest Ophthalmol Vis Sci* 2022;63(2):32.

13 Ooto S, Suzuki M, Vongkulsiri S, Sato T, Spaide RF. Multimodal visual function testing in eyes with nonexudative age-related macular degeneration. *Retina* 2015;35(9):1726-1734.

14 Corvi F, Pellegrini M, Belotti M, Bianchi C, Staurenghi G. Scotopic and fast mesopic microperimetry in eyes with drusen and reticular pseudodrusen. *Retina* 2019;39(12):2378-2383.

15 Ahn SM, Lee SY, Hwang SY, Kim SW, Oh J, Yun C. Retinal vascular flow and choroidal thickness in eyes with early age-related macular degeneration with reticular pseudodrusen. *BMC Ophthalmol* 2018;18(1):184.

16 Querques G. Reticular pseudodrusen: a common pathogenic mechanism affecting the choroid–Bruch's membrane complex and retinal pigment epithelium for different retinal and macular diseases. *Invest Ophthalmol Vis Sci* 2015;56(10):5914.

17 Cicinelli MV, Rabiolo A, Sacconi R, Lamanna F, Querques L, Bandello F, Querques G. Retinal vascular alterations in reticular pseudodrusen with and without outer retinal atrophy assessed by optical coherence tomography angiography. *Br J Ophthalmol* 2018;102:1192-1198.

18 Borooah S, Papastavrou V, Lando L, Han J, Lin JH, Ayyagari R, Dhillon B, Browning AC. Reticular pseudodrusen in late-onset retinal degeneration. *Ophthalmol Retina* 2021;5(10):1043-1051.

19 Querques G, Canouï-Poitrine F, Coscas F, *et al*. Analysis of progression of reticular pseudodrusen by spectral domain–optical coherence tomography. *Invest Ophthalmol Vis Sci* 2012;53(3):1264.

20 Campbell JP, Zhang M, Hwang TS, *et al*. Detailed vascular anatomy of the human retina by projection-resolved optical coherence tomography angiography. *Sci Rep* 2017;7:42201.

21 Spaide RF, Klancnik JM Jr, Cooney MJ. Retinal vascular layers imaged by fluorescein angiography and optical coherence tomography angiography. *JAMA Ophthalmol* 2015;133(1):45-50.

22 Ito H, Ito Y, Kataoka K, Ueno S, Takeuchi J, Nakano Y, Fujita A, Horiguchi E, Kaneko H, Iwase T, Terasaki H. Association between retinal layer thickness and perfusion status in extramacular areas in diabetic retinopathy. *Am J Ophthalmol* 2020;215:25-36.

23 Milani P, Montesano G, Rossetti L, Bergamini F, Pece A. Vessel density, retinal thickness, and choriocapillaris vascular flow in myopic eyes on OCT angiography. *Graefes Arch Clin Exp Ophthalmol* 2018;256(8):1419-1427.

24 Chatziralli I, Theodossiadis G, Panagiotidis D, Pousoulidi P, Theodossiadis P. Choriocapillaris' alterations in the presence of reticular pseudodrusen compared to drusen: study based on OCTA findings. *Int Ophthalmol* 2018;38(5):1887-1893.

25 Nesper PL, Soetikno BT, Fawzi AA. Choriocapillaris nonperfusion is associated with poor visual acuity in eyes with reticular pseudodrusen. *Am J Ophthalmol* 2017;174:42-55.

26 Viggiano P, Toto L, Ferro G, Evangelista F, Porreca A, Mastropasqua R. Choroidal structural changes in different intermediate AMD patterns. *Eur J Ophthalmol* 2021;32(1):460-467.

27 Spaide RF, Armstrong D, Browne R. Continuing medical education review: choroidal neovascularization in age-related macular degeneration--what is the cause? *Retina* 2003;23(5):595-614.

28 Kaur C, Sivakumar V, Foulds WS. Early response of neurons and glial cells to hypoxia in the retina. *Invest Ophthalmol Vis Sci* 2006;47(3):1126-1141.

29 Hu ML, Quinn J, Xue K. Interactions between apolipoprotein E metabolism and retinal inflammation in age-related macular degeneration. *Life (Basel)* 2021;11(7):635.

30 Ramon C, Cardona G, Biarnés M, Ferraro LL, Monés J. Longitudinal changes in outer nuclear layer thickness in soft drusen and reticular pseudodrusen. *Clin Exp Optom* 2019;102(6):601-610.

31 Wong CW, Wong TY, Cheung CM. Polypoidal choroidal vasculopathy in asians. *J Clin Med* 2015;4(5):782-821.

32 Yasuda M, Kiyohara Y, Hata Y, Arakawa S, Yonemoto K, Doi Y, Iida M, Ishibashi T. Nine-year incidence and risk factors for age-related macular degeneration in a defined Japanese population. *Ophthalmology* 2009;116(11):2135-2140.

33 Toto L, Borrelli E, Mastropasqua R, Di Antonio L, Mattei PA, Carpineto P, Mastropasqua L. Adult-onset foveomacular vitelliform dystrophy evaluated by means of optical coherence tomography angiography: a comparison with dry age-related macular degeneration and healthy eyes. *Retina* 2018;38(4):731-738.

34 Steinberg JS, Fleckenstein M, Holz FG, Schmitz-Valckenberg S. Foveal sparing of reticular drusen in eyes with early and intermediate age-related macular degeneration. *Invest Ophthalmol Vis Sci* 2015;56(8):4267-4274.