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ARTICLE

Choroidal vascularity index in leptochoroid: A comparative analysis between reticular pseudodrusen and high myopia

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PURPOSE: To investigate the choroidal vascularity index (CVI) in patients affected by leptochoroid.

METHODS: Three distinct age-matched cohorts were collected: patients with reticular pseudodrusen (RPD) secondary to age-related macular degeneration, patients with high-myopia, and healthy controls. CVI was calculated in the subfoveal 6000 μm diameter area.

RESULTS: 54 eyes (54 patients) were included (18 eyes in each cohort). No statistical differences were disclosed in terms of age between controls, RPD patients ($p = 0.062$), and myopic patients ($p = 0.070$). Total choroidal area showed a different distribution among the 3 cohorts ($p < 0.001$), due to the reduction of luminal and stromal choroidal area in both RPD and myopic groups in comparison to controls ($p < 0.001$). Interestingly, CVI showed a different distribution between the 3 cohorts ($p < 0.001$). In detail, RPD group showed no changes in CVI in comparison to controls ($p = 1.000$), whereas the myopic group showed a higher CVI in comparison to both RPD group and controls ($p < 0.001$ in both analyses).

CONCLUSIONS: Different changes of the choroidal vascular and stromal components characterize the leptochoroid secondary to RPD eyes and high-myopic eyes. The relative greater impairment of the vascular area in RPD eyes in comparison to myopic eyes could be at the basis of the lower development of RPD in patients with high myopia.

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INTRODUCTION

"Leptochoroid" is defined as a choroidal thinning that characterizes several macular diseases [1–8]. A thinning of the choroidal layers and a reduction of the choriocapillaris perfusion were previously reported in different stages of non-neovascular (or dry) and neovascular age-related macular degeneration (dAMD and nAMD, respectively) [1–3, 9–11]. Of note, patients affected by reticular pseudodrusen (RPD) secondary to dAMD showed a greater reduction of choroidal thickness in comparison to patients affected by typical drusen [12–14], suggesting that RPD may be the result of choroidal atrophy and ischemia leading to photoreceptor outer segments disruption and accumulation above the retinal pigment epithelium (RPE) [12]. On the other hand, also patients affected by high myopia (HM) were characterized by a severe leptochoroid, but a lower prevalence of AMD and RPD. For this reason, several groups have suggested a protective role of HM on the development of dAMD [15–18]. However, no studies have elucidated the differences in choroidal structures between these two diseases characterized by a leptochoroid (i.e., RPD and HM).

Recently, the introduction of a new structural optical coherence tomography (OCT) tool, namely choroidal vascularity index (CVI), has allowed us to better investigate the choroidal changes, especially in the ratio between stromal and luminal area [19]. Several studies reported CVI alterations in patients affected by

dAMD [20–22]. However, to date, no studies examined the CVI alterations in leptochoroid associated with RPD in comparison to HM. The aim of this study is to investigate the CVI and other choroidal features in patients affected by RPD or HM featuring leptochoroid, in order to gather insights on the pathophysiology of these conditions. We selected RPD eyes due to the more severe degree of leptochoroid in this phenotype among intermediate AMD phenotypes [12–14].

METHODS

In this retrospective cohort study, patients affected by RPD secondary to dAMD (i.e., RPD group) or HM (i.e. myopic group) were collected in the Medical Retina & Imaging Unit of the Department of Ophthalmology of University Vita-Salute San Raffaele in Milan, Italy, between January 2020 and June 2020. The study was conducted in agreement with the Declaration of Helsinki for research involving human subjects. All subjects signed informed consent for retrospective studies that were approved by the Ethics Committee of San Raffaele Institute.

The present study consists of three distinct cohorts: RPD group, myopic group, and a group of healthy age-matched subjects (i.e., control group).

Inclusion criteria for the RPD group were: (1) age greater than 50 years, (2) diagnosis of RPD secondary to dry AMD (3) clear ocular media to ensure proper image quality. Exclusion criteria for the RPD group were: (1) presence of any retinal disorder other than AMD (e.g., diabetic retinopathy, retinal vein or artery occlusion, posterior uveitis), (2) presence of other

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Table 1. Main clinical features of the study population.

	Total population (n = 54)		RPD patients (n = 18)	Myopic patients (n = 18)		Healthy subjects (n = 18)		
	Mean ± SD	P value*	Mean ± SD	Mean ± SD	P value+	Mean ± SD	P value+	P value§
BCVA, LogMAR	0.12 ± 0.16	0.041	0.15 ± 0.13	0.17 ± 0.22	1.000	0.05 ± 0.05	0.152	0.054
Axial Length, mm	24.74 ± 1.68	<0.001	23.73 ± 0.61	26.71 ± 1.42	<0.001	23.78 ± 0.51	1.000	<0.001
CMT, μm	265 ± 21	0.027	256 ± 23	265 ± 19	0.503	274 ± 16	0.023	0.519
Subfoveal ChT, μm	188 ± 116	<0.001	187 ± 75	90 ± 84	0.004	286 ± 94	0.003	<0.001
Mean ChT, μm	178 ± 108	<0.001	179 ± 71	85 ± 83	0.002	270 ± 78	0.003	<0.001

n Number, *SD* Standard deviation, *RPD* Reticular pseudodrusen, *BCVA* Best-corrected visual acuity, *CMT* Central macular thickness, *ChT* Choroidal thickness.
Statistical Analysis Analysis of variance (ANOVA) for independent samples with Bonferroni post-hoc analysis.
*ANOVA for independent samples
+Comparison with RPD group
§Comparison with myopic group

AMD phenotype rather than RPD, (3) presence of MNV, (4) any previous retinal treatments (e.g., intravitreal injections, photodynamic therapy), (5) myopia greater than 6 dioptres (D) of sphere or 3D of the cylinder, and/or axial length >25.5 mm.

Inclusion criteria for the high myopic group were: (1) age greater than 50 years, (2) diagnosis of HM (defined as an axial length >25.5 mm or a refractive error > −6 D of spherical equivalent) [4], (3) clear ocular media to ensure proper image quality. Exclusion criteria for the myopic group were: (1) presence of any retinal disorder other than myopia (e.g., AMD, diabetic retinopathy, retinal vein or artery occlusion, posterior uveitis), (2) any previous retinal treatments (e.g., intravitreal injections, photodynamic therapy), (3) presence of myopic MNV.

Inclusion criteria for the control group were: (1) age greater than 50 years, (2) clear ocular media to ensure proper image quality. We excluded subjects with any retinal disorder and/or myopia greater than 6D of sphere or 3D of cylinder, and/or axial length >25.5 mm

If both eyes presented inclusion criteria, only one eye was included. The eye with the higher quality of structural OCT image was selected as the study eye. If both eyes have the same quality of OCT image, the included eye was selected by flipping a coin.

Clinical data of patients were recorded and reviewed. In detail, all patients underwent a complete ophthalmologic examination with a multimodal imaging approach as part of the standard clinical assessment of our Unit. We recorded best-corrected visual acuity (BCVA) using Snellen charts, infrared reflectance (IR), short-wave fundus autofluorescence (SW-FAF), structural spectral-domain OCT, and axial length measurement. All OCT examinations were performed using the enhanced depth imaging (EDI) OCT in order to achieve a good visualization of the choroid. OCT-angiography (OCT-A) and/or dye angiographies (i.e., fluorescein angiography [FA] and indocyanine green angiography [ICGA]) were also performed in case of clinical and multimodal imaging suspicion of MNV presence. IR, SW-FAF, structural OCT, FA, and ICGA were performed using the Spectralis HRA + OCT (Heidelberg Engineering, Heidelberg, Germany). OCT-A examinations were performed using PLEX® Elite 9000 (Carl Zeiss Meditec, Inc., Dublin, CA, USA). Axial length was measured using a noncontact biometry instrument (IOLMaster, Carl Zeiss Meditec AG, Jena, Germany).

Imaging analysis
Subfoveal choroidal thickness (ChT), mean ChT, and central macular thickness (CMT) were recorded. Two trained examiners (EB and GV) measured the distance from the Bruch's membrane to the sclerochoroidal interface in the subfoveal location (subfoveal ChT) and the mean value was used for statistical analyses. Furthermore, the ChT was also measured 500 and 1000 μm nasally and temporally to the fovea, and the mean value among the 5 measurements (subfoveal, 500 μm nasally, 1000 μm nasally, 500 μm temporally, and 1000 μm temporally to the fovea) was used in order to calculate the mean ChT. CMT was defined as the vertical distance from the Bruch's membrane and vitreoretinal interface. CMT was recorded with the Spectralis software (Heidelberg Eye Explorer, Version 1.9.14.0, Heidelberg, Germany) in the central 1 mm-diameter circle.

Horizontal and vertical B-scan of structural EDI OCT passing through the fovea were exported by the Spectralis Software. The choroidal parameters were analysed using a previously reported algorithm [23]. Briefly, the choroidal analysis involved automated binarization of an HD horizontal and vertical 6 mm OCT B-scan after defining the choroidal boundaries.

The Bruch-RPE junction and the sclerochoroidal junction were selected as the upper and lower boundary of the region of interest (ROI). Total choroidal area (TCA) was calculated as the total area of the ROI. Luminal choroidal area (LCA) was calculated as the dark pixels of the ROI after binarization. Stromal choroidal area (SCA) was calculated as the white pixels of the ROI after binarization. CVI was obtained as the ratio between LCA and TCA [23].

Statistical analysis
Statistical analyses were performed using SPSS Statistics Version 20 (IBM, Armonk, New York, USA). All values of descriptive analyses were expressed as means ± standard deviations for quantitative variables and as counts and percentages for categorical variables. In all patients, BCVA was converted to Logarithm of the Minimum Angle of Resolution (LogMAR) for statistical analysis. The agreement between individual measurements of subfoveal and mean ChT from both readers was performed using the intraclass correlation coefficient (ICC; 95% CI). Comparisons of BCVA, axial length, CMT, subfoveal ChT, mean ChT, TCA, LCA, SCA, and CVI between the 3 cohorts were performed using the Analysis of Variance (ANOVA) with Bonferroni post-hoc analysis. In all analyses, p-values <0.05 were considered statistically significant.

RESULTS
Patient demographics and main clinical features
A total of 54 eyes of 54 Caucasian patients (18 eyes for each group) were included in the study. Thirty-nine patients were females and 15 patients were males. The mean age of all patients was 71.2 ± 8.6 years (median 73.5; range 50–83 years). In detail, the mean age of controls (71.3 ± 7.0 years) did not show significant differences in comparison to myopic patients (65.4 ± 9.6 years; p = 0.062) and to RPD patients (77.0 ± 4.4 years; p = 0.070).

BCVA showed significant differences among study cohorts (p = 0.041). In detail, mean BCVA was between 20/25 and 20/32 Snellen equivalent in myopic and RPD patients (0.17 ± 0.22 LogMAR and 0.15 ± 0.13 LogMAR respectively), and between 20/20 and 20/25 Snellen equivalent (0.05 ± 0.05 LogMAR) in controls. Furthermore, also the mean axial length was different among study cohorts (p < 0.001). Indeed, myopic patients showed a greater axial length (26.71 ± 1.42 mm, range 25.58–30.36) in comparison to RPD patients (23.73 ± 0.61 mm, range 22.70–24.87, p < 0.001) and controls (23.78 ± 0.51 mm, range 22.72–24.66, p < 0.001). Of note, no difference in axial length was disclosed between the RPD group and controls (p = 1.000).

All main clinical features of the whole population and of each cohort are reported in Table 1.

Choroidal analysis
Analysing ChT among the three different cohorts, subfoveal ChT and mean ChT showed significantly different values among study

Table 2. Choroidal analysis of the RPD group, HM group, and controls.

	Total population (n = 54)		RPD patients (n = 18)	Myopic patients (n = 18)		Healthy subjects (n = 18)		
	Mean ± SD	P value*	Mean ± SD	Mean ± SD	P value+	Mean ± SD	P value+	P value§
LCA, mm² (mean ± SD)	0.4396 ± 0.2770	<0.001	0.3970 ± 0.0861	0.2415 ± 0.2086	0.096	0.6803 ± 0.2891	0.001	<0.001
SCA, mm² (mean ± SD)	0.2681 ± 0.1966	<0.001	0.2529 ± 0.0577	0.0982 ± 0.0905	0.003	0.4531 ± 0.2048	<0.001	<0.001
TCA, mm² (mean ± SD)	0.7077 ± 0.4688	<0.001	0.6499 ± 0.1383	0.3397 ± 0.2960	0.025	1.1334 ± 0.4896	<0.001	<0.001
CVI, % (mean ± SD)	64.48 ± 7.06	<0.001	61.10 ± 3.09	71.99 ± 6.84	<0.001	60.35 ± 3.01	1.000	<0.001

n Number, SD Standard deviation, RPD Reticular pseudodrusen, HM High myopia, LCA Luminal choroidal area, SCA Stromal choroidal area, TCA Total choroidal area, CVI Choroidal vascularity index

Statistical Analysis Analysis of variance (ANOVA) for independent samples with Bonferroni post-hoc analysis.

*ANOVA for independent samples
+Comparison with RPD group
§Comparison with myopic group

groups in both analyses ($p < 0.001$ in both analyses) (Table 1). Myopic patients showed a thinner subfoveal ChT and mean ChT in comparison to both the RPD group ($p = 0.004$ and $p = 0.002$, respectively) and controls ($p < 0.001$ in both analyses). Furthermore, RPD group showed a thinner subfoveal ChT and mean ChT in comparison to controls ($p = 0.003$ in both analyses). In detail, subfoveal ChT was $90 \pm 84\ \mu m$, $187 \pm 75\ \mu m$, and $286 \pm 94\ \mu m$ in myopic, RPD, and control groups, respectively, and $85 \pm 83\ \mu m$, $179 \pm 71\ \mu m$, and $270 \pm 78\ \mu m$ considering the mean ChT. Inter-observer variability between readers was excellent for all measurements [ICC = 0.962 (0.927–0.997)].

All binarized images were analysed in order to obtain the LCA, SCA, TCA, and CVI. Following the ChT trend, mean TCA was lower in myopic patients in comparison to RPD patients ($p = 0.025$) and to controls ($p < 0.001$) (Table 2) (Figs. 1–3). Moreover, the RPD group showed a lower TCA in comparison to controls ($p < 0.001$). In the analysis of the vascular and stromal choroidal area, the RPD group showed a lower value of both LCA and SCA in comparison to controls ($p = 0.001$ and $p < 0.001$, respectively) whereas, interestingly, no differences were disclosed considering the CVI ($p = 1.000$) (Figs. 1 and 3). On the other hand, the myopic group showed a lower value of both LCA and SCA in comparison to controls ($p < 0.001$ in both analyses) but a greater CVI in comparison to controls ($p < 0.001$) (Table 2) (Figs. 2 and 3). In other words, the SCA was greater impaired in comparison to LCA, resulting in an increased CVI.

Finally, comparing the RPD group with the myopic group, the latter showed a significantly lower SCA ($p = 0.003$) with a greater CVI ($p < 0.001$). All choroidal analyses were reported in Table 2.

DISCUSSION

In this study, using the CVI analysis, we have disclosed that the vascular choroidal area is impaired to a greater extent in the leptochoroid of RPD patients compared with HM patients.

The thinning of the choroid (i.e., leptochoroid) was previously reported in several diseases, including high myopia and different stages of dAMD [1–4]. Of note, the impairment of the choroidal thickness was greater in AMD patients affected by RPD in comparison to AMD patients affected by drusen [12–14]. On the basis of this finding, several groups supported the hypothesis that the progressive choroidal atrophy and vascular impairment led to the damage of photoreceptors, disruption of the photoreceptor outer segments, resulting in the accumulation of the waste materials above the RPE (i.e., development of RPD) [12–14]. This hypothesis was also supported by other authors that demonstrated a reduction of the perfusion density of the choriocapillaris below RPD [24, 25]. However, the reduction of the choroidal thickness could not be the only driver into the pathogenesis of RPD. Indeed, in another macular disease characterized by a severe leptochoroid, namely HM, the prevalence of RPD is lower in comparison to patients without HM, suggesting a protective role of HM in the development of dAMD [15–18]. Storey et al. [26] reported that amblyopic eyes due to anisometropia manifest decreased severity of AMD compared with non-amblyopic eyes in the same patient, supporting the protective role of high myopia in the development of dAMD. Furthermore, our group has displayed that myopic anisometropia manifests decreased rate of RPD presence compared with non-ambylopic eyes in the same patient (unpublished data).

In the last years, CVI has been proposed as a novel OCT-based parameter to quantify choroidal structural changes in different disorders, including AMD [19–22]. CVI allows disclosing in vivo specific alterations of the stromal and vascular area of the choroid, gathering insight into the pathogenesis of different diseases. In detail, several groups reported a reduced CVI in patients affected by iAMD and by GA [21, 22]. Velaga et al. [21] reported that CVI and other choroidal parameters are altered in patients affected by
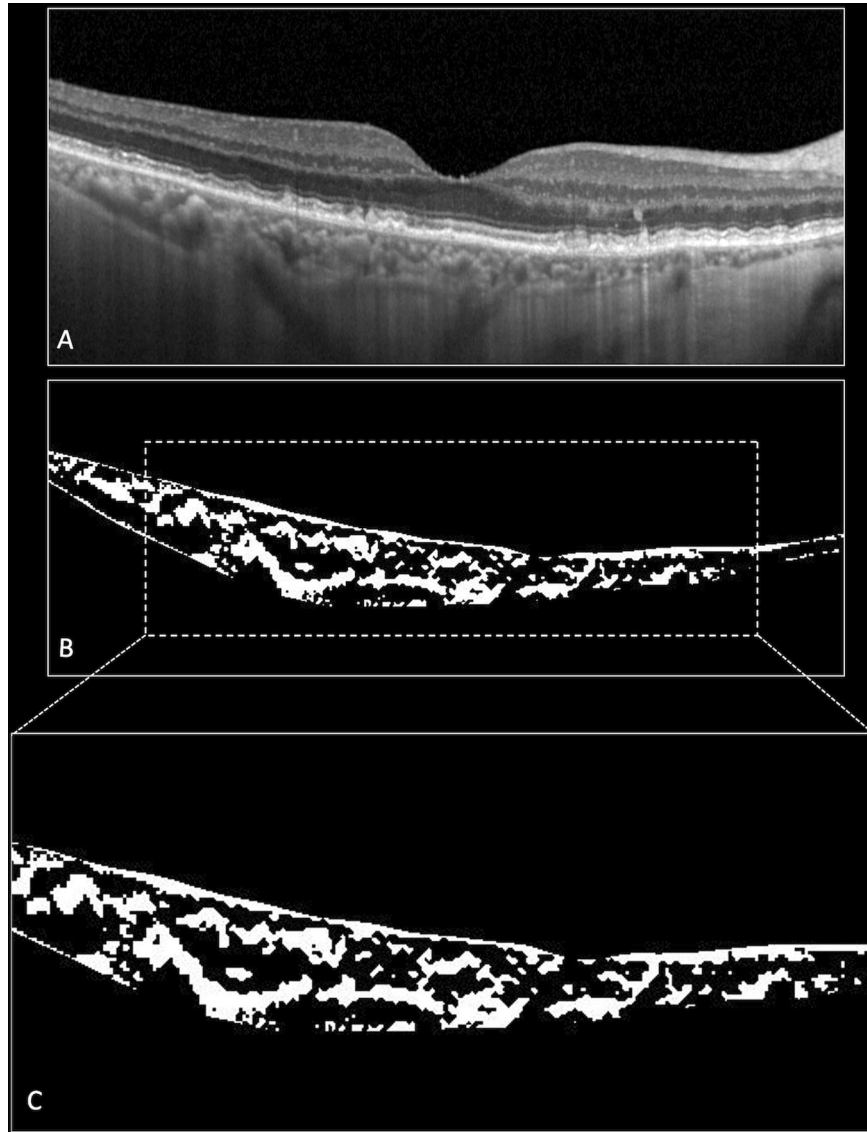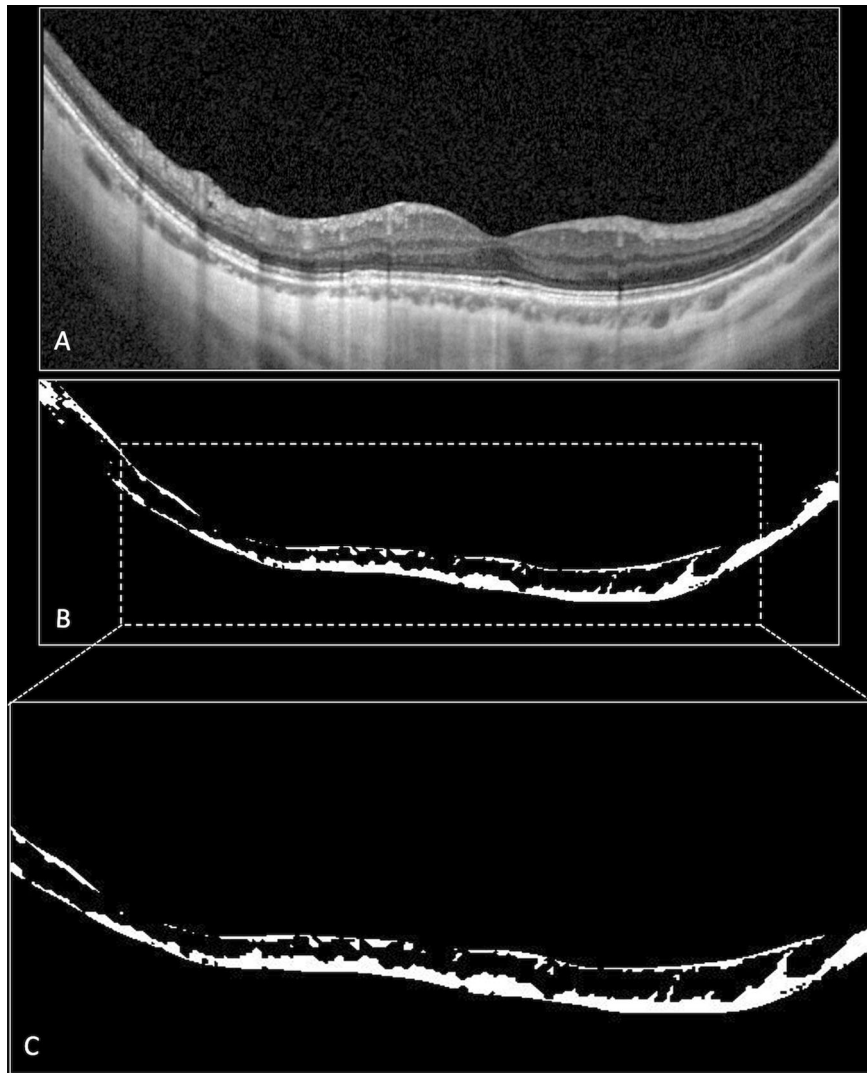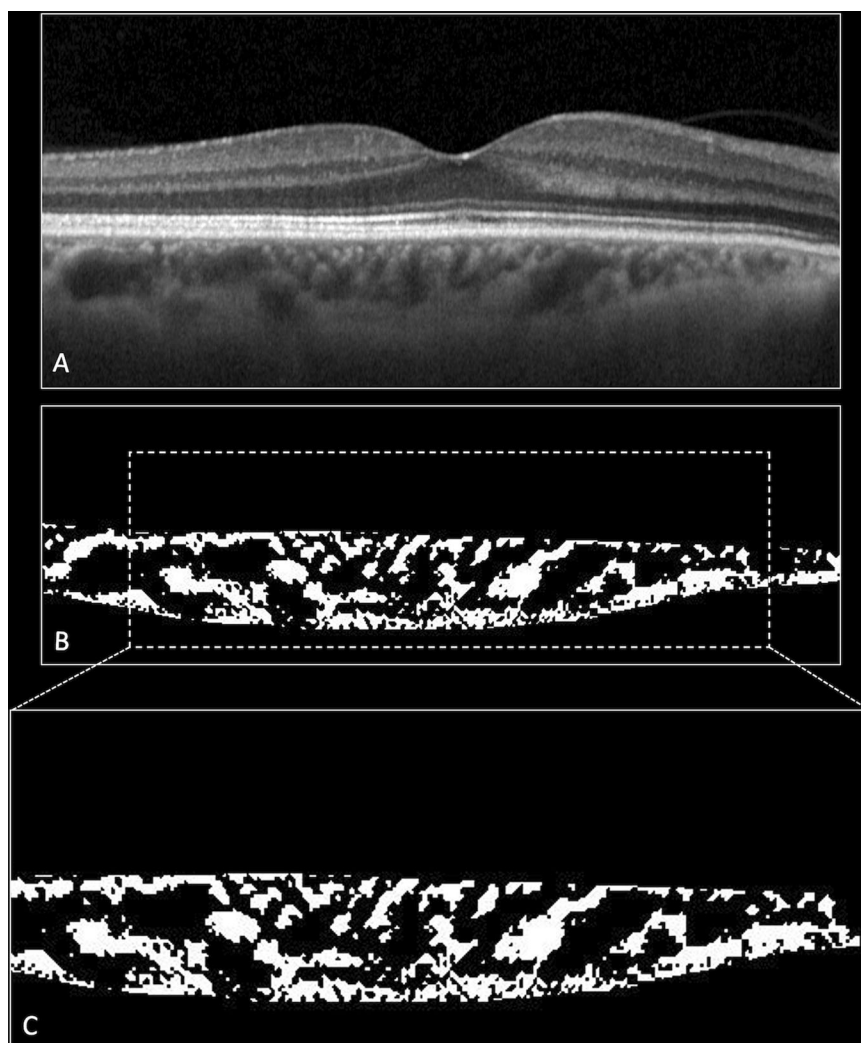
Fig. 1 Structural optical coherence tomography (OCT) and choroidal vascularity index (CVI) calculation of the right eye of a patient affected by reticular pseudodrusen. Structural b-scan OCT passing through the fovea (**A**) was binarized after defining the choroidal boundaries (**B**). A region of interest (ROI) of 6000 μm centred to the fovea was selected (**C**). The Bruch-RPE junction and the sclerochoroidal junction were selected as the upper and lower boundary of the region of the ROI. Dark pixels represent the luminal area, whereas white pixels the stromal area. CVI was calculated as the ratio between the luminal area and the total choroidal area.

iAMD eyes in comparison to controls. However, no studies have investigated and compared alterations of CVI in different diseases characterized by leptochoroid. Here, we compared, face to face, two cohorts of patients affected by leptochoroid (i.e., RPD and myopic groups), in order to disclose the possible different status of vascular and stromal areas of the choroid characterizing these two diseases. Based on our results, we disclosed a significant reduction of both vascular and stromal areas (i.e., LCA and SCA) in RPD and myopic groups in comparison to controls ($p = 0.001$ or $p < 0.001$ in all analyses). Interestingly, patients affected by high myopia showed a greater mean value of the ratio between vascular area and total choroidal area (i.e., CVI) in comparison to controls ($p < 0.001$) and to the RPD group ($p < 0.001$). In other words, although both RPD and HM eyes are characterized by a thinning of the choroid ($p < 0.001$ in the analyses of subfoveal and mean ChT in comparison to age-matched controls), myopic eyes showed a lower relative impairment of the vascular area in comparison to

eyes affected by RPD secondary to AMD, resulting in an increased CVI. Our findings could explain why patients affected by HM have a lower prevalence of RPD in comparison to patients without HM (i.e., protective role of HM on the development of dAMD). The greater impairment of LCA in RPD eyes in comparison to HM eyes could be of paramount importance in the pathogenesis of RPD development. Indeed, although a thinning of the choroid using structural OCT was reported on the basis of the RPD [12–14], we hypothesize that the main risk factor should be considered the reduction of the vascular area of the choroid due to the stromal replacement and not the entire ChT. Our hypothesis is supported by previously reported histological and in vivo data. Of note, McLeod et al. [27] reported that changes of choroidal interstitial stroma characterize the development of AMD in comparison to healthy patients analysing 11 post-mortem eyes. Furthermore, using in vivo imaging analysis, our group and others described that choroidal cytoarchitecture is profoundly altered in the setting of AMD

Fig. 2 Structural optical coherence tomography (OCT) and choroidal vascularity index (CVI) calculation of the right eye of a patient affected by high-myopia. Structural b-scan OCT passing through the fovea (**A**) was binarized after defining the choroidal boundaries (**B**). A region of interest (ROI) of 6000 µm centred to the fovea was selected (**C**). The Bruch-RPE junction and the sclerochoroidal junction were selected as the upper and lower boundary of the region of the ROI. Dark pixels represent the luminal area, whereas white pixels the stromal area. CVI was calculated as the ratio between the luminal area and the total choroidal area.

changes, with an altered ratio between the vascular component and the fibrous matrix [9, 28, 29]. In this setting, the fibrous matrix increases while the vascular component gradually reduces, inducing a different distribution of the choroidal vessels in iAMD patients [9]. Of note, these phenomena are greater in RPD patients among dAMD phenotypes, resulting in unique choroidal re-arrangements that take place in these patients [9].

Drawbacks of our study should be disclosed, mainly due to the relatively small sample size and the retrospective nature. Furthermore, we have not included a group with concomitant RPD and HM, but the prevalence of RPD in HM patients is uncommon. One can argue that we have not included patients with drusen secondary to dAMD. However, patients affected by drusen are not characterized by leptochoroid and it was yet reported that drusen eyes showed no CVI differences in comparison with healthy eyes [21].

Another possible limitation of the study is that, potentially, in thicker choroids, the different choroidal vascular layers (choriocapillaris, Sattler's, and Haller's) are better graphically represented

and this could be a bias in CVI evaluation comparing HM patients and patients affected by RPD. Indeed, in HM patients there is a greater loss of choriocapillaris and Sattler's layer in comparison to patients affected by RPD. However, a subanalysis of CVI separately for Sattler's and Haller's area could not be performed with reliability due to the alterations of the choroidal architecture in HM and RPD patients. Furthermore, it was demonstrated that CVI is not influenced by the ChT in healthy patients [30, 31].

On the other hand, also the strengths of this study should be kept in mind. First of all, we have compared three age-matched cohorts. Although Zhou et al. [30]. reported that CVI remained constant in all regions with age, matching the age of patients of the different cohorts allowed us to compare not only the CVI but also the ChT and the total volume of the choroid. Indeed, it is well known that ChT and the volume of the choroid are influenced by the age of patients. Secondly, the CVI analysis could be influenced by several factors. For this reason, we have used a previously reported and validated algorithm [23].

In conclusion, we have disclosed that CVI is a more sensitive biomarker in detecting choroidal changes associated with

Fig. 3 Structural optical coherence tomography (OCT) and choroidal vascularity index (CVI) calculation of the right eye of a healthy patient. Structural b-scan OCT passing through the fovea (**A**) was binarized after defining the choroidal boundaries (**B**). A region of interest (ROI) of 6000 μm centred to the fovea was selected (**C**). The Bruch-RPE junction and the sclerochoroidal junction were selected as the upper and lower boundary of the region of the ROI. Dark pixels represent the luminal area, whereas white pixels the stromal area. CVI was calculated as the ratio between the luminal area and the total choroidal area.

leptochoroid as compared to ChT. Using CVI, we have highlighted the difference in the stromal and vascular impairment in two different diseases characterized by leptochoroid (i.e., RPD and HM), providing insights for better understanding the pathogenesis of these diseases. The greater relative impairment of the vascular area in RPD eyes in comparison with HM could be on the basis of the lower incidence of RPD in HM eyes.

Summary Table
What was known before

- No studies investigated choroidal features in leptochoroid.

What this study adds

- In this study, reporting choroidal features in leptochoroid secondary to pseudodrusen in comparison to high-myopia, we proposed that relative lower vessel impairment in myopic eyes could explain the protective role of myopia on pseudodrusen development.

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