RETINAL VASCULAR PLEXUSES' CHANGES IN DRY AGE-RELATED MACULAR DEGENERATION, EVALUATED BY MEANS OF OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY

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Purpose: To investigate alteration in superficial and deep retinal vascular densities and choroidal thickness, in patients affected by early and intermediate age-related macular degeneration (AMD).

Methods: All patients had undergone optical coherence tomography angiography (OCTA). All eyes were grouped into two stages: "early AMD" and "intermediate AMD." Outcome measures were superficial vessel density, deep vessel density, and choroidal thickness. A control group of healthy subjects was selected for the statistical comparisons.

Results: A total of 37 eyes of 37 dry AMD patients were enrolled for the study. Fourteen of 37 eyes were classified as having early AMD, the remaining 23 of 37 eyes were classified as being affected by intermediate AMD. Superficial and deep vessel densities were 39.21% ± 10.67% and 43.84% ± 11.57%, respectively, in the control group and 28.30% ± 10.73% and 36.41% ± 12.30%, respectively, in AMD patients ($P = 0.001$ and $P = 0.017$, respectively). Choroidal thickness was significantly reduced in AMD patients.

Conclusion: In the last years, several studies have reported vascular factors playing an important role in AMD pathogenesis. We demonstrated that both superficial and deep retinal plexuses are altered among patients affected by AMD. Interestingly, this alteration starts immediately at the intermediate AMD stage and also the choroidal thickness reduction.

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Age-related macular degeneration (AMD) is the leading cause of irreversible central vision loss in the Western world.[1]

It is known that two clinically recognized subtypes of AMD exist: nonneovascular (dry) AMD and neovascular exudative (wet) AMD.[2] Dry AMD is characterized by accumulations of lipo-glyco-proteinaceous deposits (drusen) and the degeneration of the retinal pigment epithelium. Geographic atrophy accompanies the advanced form of nonneovascular AMD and results in sclerosis of choriocapillaris, retinal pigment epithelium atrophy, and degeneration of the outer retinal layer.[2]

Many factors have been implicated in the AMD pathogenesis, such as inflammation, oxidative damage, ageing, genetic predisposition, and environmental elements.[3,4] In the last years, several studies have reported vascular factors playing an important role in AMD pathogenesis.[5–8] Indeed, there is a growing body of evidence that choroidal and retinal blood flows are diminished in AMD,[5–8] the latter aspect causing hypoxia associated with the progression of AMD.

Spectral domain-optical coherence tomography (SD-OCT) scans show bands that seem to correspond to the anatomical layers of the human retina, and allow seeing also the choroidal layers. Optical coherence tomography angiography (OCTA) has recently been developed

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to study retinal and choroidal microvasculature without need for the dye injection and has let us to study both the superficial and the deep retinal vascular plexuses.[9]

In the current study, we used an OCTA system based on a SD-OCT device using a split-spectrum amplitude decorrelation angiography (SSADA) algorithm. The main aim of this study was to investigate superficial and deep retinal vascular densities and choroidal thickness, in patients affected by early and intermediate AMD, to determine whether retinal vessel density and choroidal thickness are reduced in these patients.

Methods

Study Participants

We reviewed the charts of 40 consecutive patients affected by early and intermediate dry AMD who consecutively presented to the University Gabriele D'Annunzio Department of Ophthalmology, between December 2014 and April 2015. University Gabriele D'Annunzio Ethics Committee approved this study and all patients gave informed consent to the use of their data.

Criteria for inclusion were age ≥50 years old, best corrected visual acuity (BCVA) of at least 0.1 logarithm of the minimum angle of resolution (Snellen acuity of 20/25), and diagnosis of AMD in at least 1 eye. Exclusion criteria were evidence or history of neovascularization, presence of geographic atrophy, previous ocular surgery (included anti-VEGF therapy), any maculopathy secondary to causes other than AMD (including presence of an epiretinal membrane or vitreomacular traction syndrome), refractive error greater than three diopters (because it has been known that high myopia affect choroidal thickness[10]), and significant media opacities.

All patients had undergone a complete ophthalmologic examination, which included measurement of BCVA, intraocular pressure, fundus examination, colour fundus photography, fluorescein angiography, and OCTA. We considered only optical coherence tomography (OCT) scans without significant motion artefacts and with a signal strength index >60. Indeed, three patients had to be excluded from the analysis because none of the three acquired scans was both of good quality and without significant motion artefacts.

All eyes included in our present study cohort were grouped into two stages: "early AMD" and "intermediate AMD." The staging was based on the clinical AMD classification proposed by Ferris et al[11] in 2013 as follows: persons with medium drusen (63–125 μm), but without pigmentary abnormalities, should be considered to have "early AMD"; persons with large drusen (>125 μm) or with pigmentary abnormalities associated with at least medium drusen should be considered to have "intermediate AMD". No patients affected by late AMD (neovascular AMD or geographic atrophy) were considered for the analysis. Staging was determined both on fundus colour images and on OCT scans (to use the measuring tool to evaluate drusen width) by two independent investigators in a blind manner and all the discrepancies were resolved by consensus between these two observers.

A control group homogenous for age and sex was also included in the current analysis. All control subjects also underwent a complete ophthalmologic examination, including BCVA, intraocular pressure, fundus examination, and OCTA.

Outcome measures included: 1) superficial vessel density; 2) deep vessel density (DVD); 3) choroidal thickness.

Procedures

SD-OCT angiography with XR Avanti. XR Avanti AngioVue OCTA (Optovue Inc, Fremont, CA) is a device with a high speed of 70,000 axial scans per second, using a light source of 840 nm and an axial resolution of 5 μm. The AngioVue OCTA system based on split-spectrum amplitude decorrelation angiography algorithm (Version: 2015.100.0.13) uses blood flow as intrinsic contrast. Indeed, the flow is detected as a variation over time in the speckle pattern formed by interference of light scattered from RBC and adjacent tissue structure.[12] In addition, the SD-OCT tool was skilled of acquiring the standard structural OCT scans typically used by commercially available devices in the evaluation of AMD.

Before imaging, each subject's pupils were dilated with a combination of 0.5% tropicamide and 10% phenylephrine. Study participants underwent SD-OCT imaging following a protocol that included AngioVue OCT 3D volume set of 3 mm × 3 mm, consisting of 304 × 304 pixels in the transverse dimension. An internal fixation light was used to center the scanning area. The OCT signal position and signal quality were optimized by means of "Auto All" function, which performs in sequence the "Auto Z" to find the best position for obtaining the retina OCT image, the "Auto F" to find the best focus for the particular subject's refraction, and the "Auto P" to find the best polarization match for the particular subject's ocular polarization.

One FastX (horizontal raster) set and 1 FastY (vertical raster) set were performed for each acquisition scan. Each set takes approximately 3 seconds to complete. After the completion of the FastX and FastY sets, the software performed the motion correction technology to remove saccades and minor loss of fixation. Scans with low quality (i.e., if the subject

blinked or if there were much motion artefacts in the data set) were excluded and repeated until good quality was achieved. Three scans for each patient were captured, then the best one in quality (without significant motion artefacts and with a signal strength index >60) was considered for analysis.

Vascular layer segmentation. Vascular retinal layers were visualized and segmented as previously described.[12–15] To evaluate the superficial retinal plexus, we used a layer thickness of 60 microns from the inner limiting membrane, to include all the vessels of this plexus. Therefore, to visualize the deep retinal plexus we used a 30-micron thick layer from the inner plexiform layer, for the purpose of visualizing the plexus in it entirely. Two investigators checked the segmentation quality before testing vessel density.

Vessel density analysis. Objective quantification of vessel density was evaluated for each eye using the split-spectrum amplitude decorrelation angiography software. Quantitative analysis was performed on the OCTA en face images for each eye using the AngioVue software. The vessel density was defined as the percentage area occupied by vessels in a 3 mm × 3 mm square region of interest centered on the center of the foveal avascular zone (Figure 1). AngioVue software automatically outputs the flow area value within the region of interest.

The vessel density is calculated using the formula previously described,[16] as follows:

$$Vessel\ \ density = \frac{\int V \cdot dA}{\int dA},$$

where V is 1 when the OCTA value is above a background threshold and 0 otherwise. A is the area of interest.

Choroidal thickness. Cross-sectional SD-OCT scan (10 mm scan length, 3 mm scan depth) of macular region was performed using the XR Avanti SD-OCT (Optovue Inc, Fremont, CA). The obtained scan provides visualization of structures from deep choroid well into the vitreous, in a single B-scan. The images were shown and measured with the XR Avanti software. The choroid was measured in masked fashion from the outer portion of the hyper-reflective line corresponding to the retinal pigment epithelium to the inner surface of the sclera. Macular measurements of the choroid thickness were made in the subfoveal location and at 750 μm intervals from the fovea up to 1.5 mm nasal, 1.5 mm temporal, 1.5 mm superior, and 1.5 mm inferior from the center of the fovea (Figure 2).

Statistical Analysis

Statistical calculations were performed using Statistical Package for Social Sciences (version 20.0, SPSS Inc, Chicago, IL). The difference between healthy subjects (control group) and each AMD group was generated by conducting analysis of variance followed by Bonferroni post hoc test.

Univariate linear regression analyses were performed to evaluate the relationships between age, choroidal thickness, and vessel density.

The chosen level of statistical significance was $P < 0.05$.

Results

A total of 37 eyes of 37 AMD patients (16 males and 21 females; mean age 68.58 ± 7.69 years, range 51–82 years) were enrolled for the study (Table 1). Fourteen of 37 eyes were classified as having early

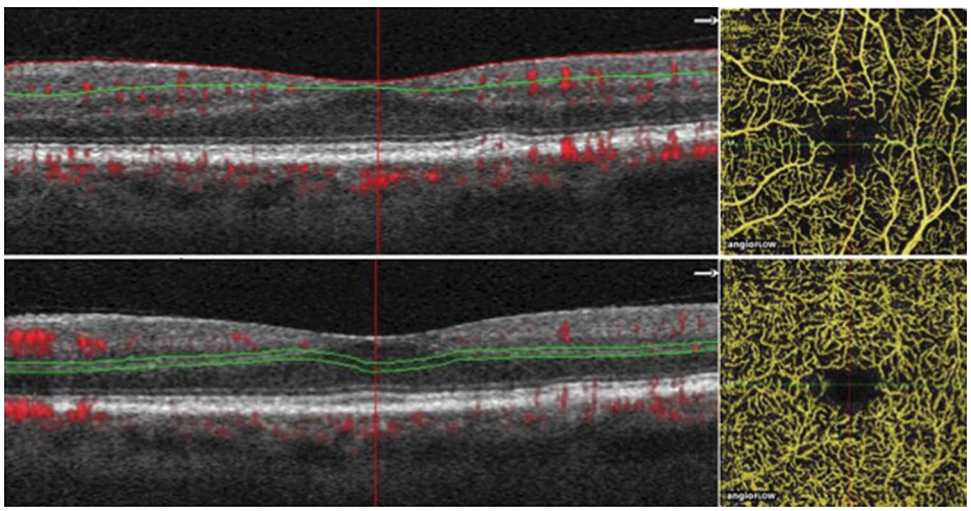

Fig. 1. Representative optical coherence tomography angiography macula 3 × 3 scan from an AMD patient. To evaluate the superficial retinal plexus (top figure), we used a layer thickness of 60 microns from the inner limiting membrane, to include all the vessels of this plexus. Moreover, to visualize the deep retinal plexus (bottom figure), we used a 30-micron thick layer from the inner plexiform layer, for the purpose of visualizing the plexus in it entirely.

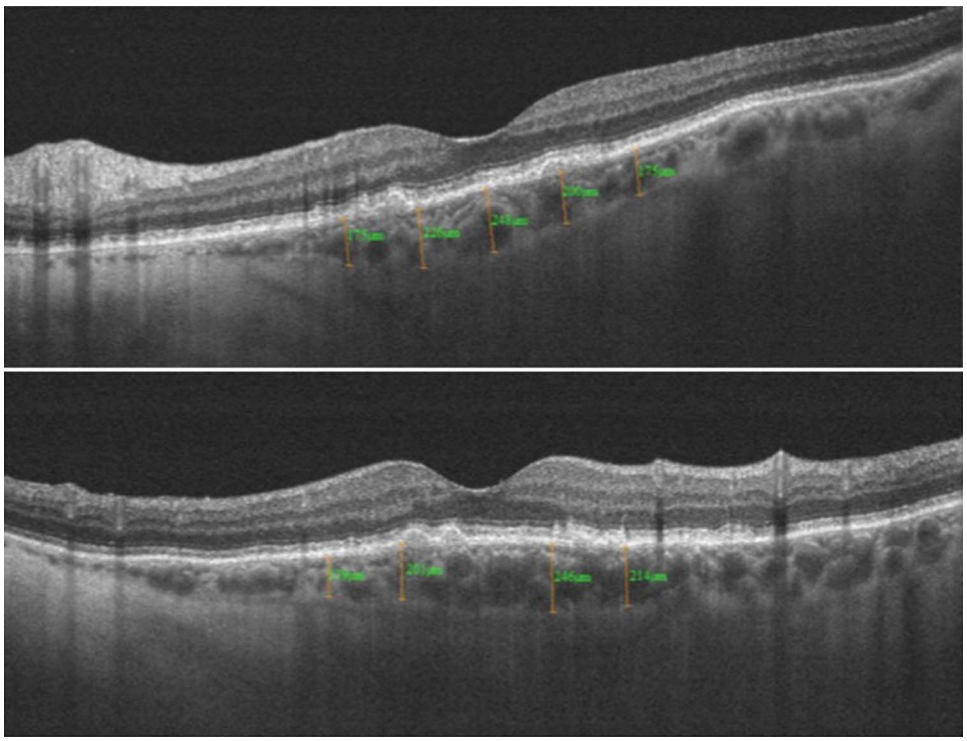

Fig. 2. Representative horizontal (top figure) and vertical (bottom figure) high-quality line scans through the fovea, from an AMD patient. The choroid was measured from the outer portion of the hyperreflective line corresponding to the retinal pigment epithelium to the inner surface of the sclera. These measurements were made at the subfoveal level and at 750 μm intervals from the fovea to 1.5 mm nasal, 1.5 mm temporal, 1.5 mm superior, and 1.5 mm inferior from the center of the fovea.

AMD and the remaining 23 of 37 eyes were classified as being affected by intermediate AMD (Table 1).

A control group of 21 eyes of 21 healthy subjects, homogenous for age and sex (9 males and 12 females; mean age 67.18 ± 14.15 years, range 44–83 years, P = 0.651 after the comparison with the AMD group) was selected for statistical comparisons (Table 1).

Mean BCVA was 0.03 ± 0.05 logarithm of the minimum angle of resolution (approximately Snellen acuity of 20/20) in healthy subjects and –0.01 ± 0.04 logarithm of the minimum angle of resolution (approximately Snellen acuity of 20/20) in AMD patients (P = 0.324) (Table 1).

Vessel Density Analysis

Superficial vessel density was 39.21% ± 10.67% in the control group and 28.30% ± 10.73% in patients affected by AMD (P = 0.001). Considering separately patients affected by early AMD and intermediate AMD, superficial vessel density was 33.80% ± 8.44% and 25.91% ± 10.89% in the 2 groups, respectively (P = 0.568 and $P < 0.0001$, after the comparison with the control group). Moreover, patients affected by intermediate AMD did not show a statistically significant reduction in superficial vessel density compared with patients with early AMD (P = 0.153) (Figures 1 and 3; Table 2).

Deep vessel density was 44.68% ± 10.50% and 36.09% ± 10.08% in the control group and in AMD patients (P = 0.017), respectively. Considering separately the two AMD groups, deep vessel density was 35.30% ± 6.11% in early AMD patients and 36.43% ± 11.50% in intermediate AMD patients (P = 0.353 and P = 0.057, after the comparison with the control

Table 1. Characteristics of Age-Related Macular Degeneration Patients and Controls

	AMD Patients (n = 37)			
	Overall Patients	Early AMD Patients (n = 14)	Intermediate AMD Patients (n = 23)	Controls (n = 21)
Age, years	68.58 ± 7.69	66.50 ± 6.55	69.47 ± 8.10	67.18 ± 14.15
Gender, n				
Male	13	4	9	8
Female	21	7	14	12
BCVA, LogMAR (Snellen equivalent)	0.03 ± 0.05 (~20/20)	0.02 ± 0.04 (~20/20)	0.03 ± 0.04 (~20/20)	–0.01 ± 0.04 (~20/20)

AMD, age-related macular degeneration; BCVA, best-corrected visual acuity (logMAR [logarithm of the minimum angle of resolution]); n, number of patients.

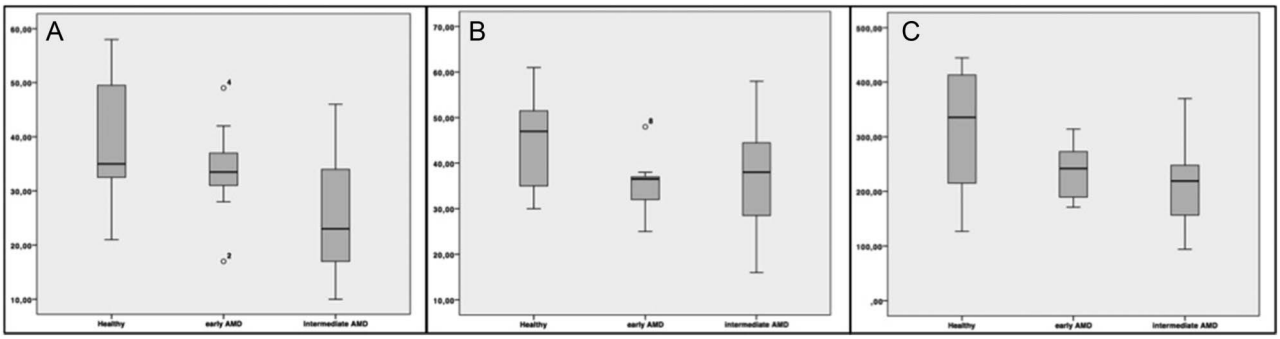

Fig. 3. Box plot showing superficial vessel density (**A**), deep vessel density (**B**) and subfoveal choroidal thickness (**C**) in AMD patients and healthy controls (each box shows the median, quartiles, extreme values, and missed values).

group). Moreover, no difference in deep vessel density was found between the two AMD patient groups (P = 0.782) (Figures 1 and 3; Table 2).

Choroidal Thickness Analysis

Comparing all AMD patients with healthy controls, choroidal thickness was significantly reduced (Table 2).

Evaluating separately early and intermediate AMD groups, choroidal thickness was significantly reduced in all the chosen testing points only in the intermediate AMD group (in early AMD patients, thinning reached statistically significance only in the 1,500 inferior and in the 750 superior measurements). Nevertheless, no difference was found between early AMD and intermediate AMD patients (Figures 2 and 3; Table 2).

Noise Analysis

Decorrelation can also be generated by bulk motion (causing noise). To be sure noise did not influence the analysis, as already shown by Wei et al,[17] we tested vessel density in the foveal avascular zone area. Indeed, because there is no retinal circulation in the foveal avascular zone, this method is an assessment of background motion noise. Foveal avascular zone vessel density was 0.01% ± 0.01% in early AMD patients, 0.03% ± 0.03% in intermediate AMD patients, and 0.03% ± 0.02% in healthy controls. After comparisons, no difference in foveal avascular zone vessel density was found among the groups (P = 0.287 for early AMD vs. intermediate AMD, P = 0.368 for early AMD vs. healthy controls, and P = 1.0 for healthy controls vs. intermediate AMD), the latter aspect suggesting noise not influencing results.

Central Macular Thickness Analysis

Central macular thickness was 223.90 ± 18.17 μm in the early AMD group, 189.21 ± 20.47 μm in the intermediate AMD group, and 219.58 ± 16.64 μm in the healthy group. We found a statistically significant difference between early and intermediate AMD patients ($P < 0.0001$) and between healthy controls and intermediate AMD patients ($P < 0.0001$).

Regression Analysis

Age was not associated with choroidal thickness, superficial, and deep vessel densities in AMD patients. Moreover, no correlation was found between central macular thickness and vessel density.

Discussion

In this retrospective study, we investigated retinal and choroidal vessel features in patients affected by early and intermediate AMD, by means of OCTA. Overall we found that both retinal vessels and choroidal vessels were altered in these patients.

In the last years, several authors have studied that choroidal vessels in patients affected by dry AMD due to abnormalities in choroidal circulation have been hypothesized to contribute to the development of AMD.[18–21] Many histologic studies, on eyes obtained postmortem from patients who had been affected by dry AMD, have shown a choroidal damage in these patients and have proved that both the choriocapillaris and the larger choroidal vessels being injured.[18–20] Moreover, optical coherence tomography imaging has allowed several authors to study choroidal thickness in AMD patients. Esmaeelpour et al[21] have demonstrated significant changes in Sattler's and Haller's choroidal layer thickness in relation to the progression of AMD. Interestingly, Lee et al[22] have recently shown that subfoveal choroidal thickness is closely related to the BCVA, the severity of nonexudative AMD, and the rate of geographic atrophy progression, giving choroidal thickness an important prognostic value. Moreover, all these studies have found choroidal thinning starting immediately at the intermediate AMD stage. Lee et al[22] have suggested that failing to

Table 2. Retinal Vessel Density and Choroidal Thickness in Age-Related Macular Degeneration Patients and Controls

	AMD Patients (n = 37)				*P*			
	Overall Patients	Early AMD Group (n = 14)	Intermediate AMD Group (n = 23)	Controls (n = 21)	AMD Patients Versus Controls	Early AMD Versus Controls	Intermediate AMD Versus Controls	Early AMD Versus Intermediate AMD
Superficial Vessel Density, %	28.30 ± 10.73	33.80 ± 8.44	25.91 ± 10.89	39.21 ± 10.67	0.001	0.568	<0.0001	0.153
Deep Vessel Density, %	36.09 ± 10.08	35.30 ± 6.11	36.43 ± 11.50	44.68 ± 10.50	0.017	0.353	0.057	0.782
Macular Choroidal Thickness, μm								
SF	211.51 ± 66.60	222.75 ± 50.49	204.22 ± 71.57	313.06 ± 111.76	0.001	0.132	0.003	0.544
1,500 μm N	175.13 ± 60.69	196.50 ± 55.11	170.95 ± 60.96	239.13 ± 88.86	0.011	0.296	0.017	0.678
750 μm N	211.96 ± 73.01	215.37 ± 79.92	209.39 ± 72.18	300.53 ± 106.96	0.002	0.112	0.008	0.969
750 μm T	228.13 ± 69.87	235.25 ± 81.20	225.91 ± 66.99	309.93 ± 109.78	0.004	0.232	0.015	0.955
1,500 μm T	197.42 ± 72.78	212.00 ± 80.80	194.82 ± 69.08	305.87 ± 120.88	0.001	0.211	0.002	0.974
1,500 μm S	213.25 ± 58.44	231.00 ± 52.29	207.34 ± 59.45	289.06 ± 83.96	0.001	0.268	0.002	0.831
750 μm S	217.64 ± 69.75	214.62 ± 68.52	218.69 ± 71.67	301.87 ± 88.17	0.001	0.037	0.006	0.944
750 μm I	216.93 ± 69.97	217.12 ± 47.95	216.87 ± 77.10	279.94 ± 96.24	0.014	0.236	0.045	1.000
1,500 μm I	197.03 ± 64.95	200.25 ± 61.90	195.91 ± 67.29	289.12 ± 103.41	0.001	0.044	0.003	1.000

Values were compared by one-way analysis of variance (ANOVA) followed by Bonferroni post hoc test.
AMD, age-related macular degeneration; I, inferior; N, nasal; SF, subfoveal; S, superior; T, temporal.

demonstrate a significant thinning among early AMD patients may suggest the potential time lag between the initial choroidal blood flow decreases in parallel with a subsequent anatomical thinning of the choroid. All these studies have supported the hypothesis that choroidal thinning and compromised choroidal circulation contribute to the development of AMD.

Our results confirmed that choroidal thickness is decreased in not-late stage AMD patients and that thinning starts from the intermediate stage.

To the best of our knowledge, no study that evaluates detailed features of retinal vasculature in early and intermediate AMD by means of an imaging approach exists.

Introduction of optical coherence tomography angiography has allowed the opportunity to image effectively two layers of the retinal vasculature without dye injection.[9] We used this new useful imaging tool to study both the superficial and the deep vascular layers in AMD patients.

It has been known that also retinal vasculature and choroidal vasculature are damaged in AMD eyes.[5,6] The Blue Mountains Eye Study,[5] by means of retinal photographs, has demonstrated that AMD is associated with retinal vessel changes (focal arteriolar narrowing and arteriovenous nicking). These results would not be surprising, because of systemic hypertension,[23] dietary fat intake,[24,25] and history of coronary, carotid, and peripheral vascular disease[26] are risk factors of AMD, as for vascular disease. The authors have then suggested that structural retinal vascular changes may contribute to AMD progression.

We demonstrated, for the first time, that both superficial and deep retinal plexuses are altered among patients affected by not-late stage AMD. Furthermore, evaluating separately patients affected by early AMD and intermediate AMD, superficial vessel density was significantly decreased only in intermediate AMD eyes. The latter aspect is very interesting because it shows retinal and choroidal vessel damages following the same trend in AMD, as the vascular injury starts immediately at the intermediate stage.

Moreover, Rogala et al[27] have recently shown, by means of SD-OCT, inner retinal layer thinning in dry AMD patients. However, the latter thinning was not significant at the early AMD stage. Then, further studies would be necessary to understand whether a relation between superficial retinal vessel density reduction and inner retinal layer thinning exists.

Our study has several limitations. The series presented here is relatively small. However, one should look at the current series in consideration of the strict inclusion criteria for AMD and control group, and similarity of groups with respect to the meaningful

characteristics such as age (which is known to affect the choroid measurements). Another limitation is we did not test the OCTA vessel density evaluation reproducibility, because this is a retrospective study. Finally, a further major limitation is that we used two different methods to study retinal and choroidal vessels. Several authors have already shown, by means of OCTA, a choriocapillaris vessel density reduction in AMD patients.[28,29] However, the OCTA choriocapillaris loss should be interpreted with caution because drusen could lead to an attenuation artefact confusing the evaluation.

In conclusion, we provided the first fully integrated study of retinal and choroidal blood supply in early and intermediate AMD patients and we showed that both choroid and retinal vessels were modified in these patients. This study raises many questions and prompts further investigation, including the evaluation of new therapeutic approaches targeted to reduce the retinal vessel damage progression.

Key words: age-related macular degeneration, AMD, choroid, choroidal thickness, optical coherence tomography angiography, retinal vessel, vessel density.

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