RETINAL DISORDERS

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Vessel density, retinal thickness, and choriocapillaris vascular flow in myopic eyes on OCT angiography

Paolo Milani[1] · Giovanni Montesano[2,3] · Luca Rossetti[2] · Fulvio Bergamini[4] · Alfredo Pece[5]

Abstract

Purpose To investigate foveal avascular zone area, macular vascular density, choroidal thickness, and outer retina and choriocapillaris flow in myopic eyes by OCT angiography.

Methods Automated macular maps and flow calculations were retrospectively evaluated in 42 myopic and in 40 control eyes.

Results Myopic eyes presented lower whole superficial vessel density (46.4 ± 4.9 vs. $51.6 \pm 3.6\%$, $P < 0.0001$) and higher flow area in the outer retina (1.3 ± 0.2 vs. 1.1 ± 0.3 mm^2, $P = 0.0012$). Between the myopic and non-myopic eyes, no significant differences could be detected in the choriocapillaris perfusion area (1.9 ± 0.07 vs. 1.9 ± 0.05 mm^2, respectively; $P = 0.55$) and in the foveal avascular zone area (0.23 ± 0.1 vs. 0.26 ± 0.1 mm^2, respectively; $P = 0.12$). The spherical correction positively correlated with superficial vessel density and negatively correlated with outer retina perfusion ($P \leq 0.0021$). The superficial vessel density and the local retinal thickness positively correlated at all macular locations ($P < 0.005$), especially in the foveal region ($P < 0.0001$).

Conclusions Eyes with high myopia present reduced superficial vascular density and increased outer retina flow. Superficial vascular density and retinal thickness appear to be significantly correlated.

Keywords OCT angiography · Myopia · Choriocapillaris · Vessel density · Outer retina

Introduction

In the last few years, spectral domain (SD) optical coherence tomography (OCT) angiography devices have become commercially available and visualization of the superficial, deep macular vascular plexus and of the outer retinal layer is now commonly evaluated. Sequential acquisition of blood flow movement allows defined visualization of neovascular activity, but also parameters such as retinal vascular density maps and choriocapillary segmentation are gaining popularity among the researchers for the evaluation of pathophysiologic alterations in macular disease.

High myopia (HM) is one of the leading causes of visual impairment in many developed countries [1] because of its possible association with neovascularization, areas of macular chorioretinal atrophy, lacquer crack, and retinoschisis. Thus, to understand microvascular early, changes may be of clinical relevance. Although quantitative information from recent studies found that in HM the density of both the superficial and deep microvascular plexuses is significantly decreased and negatively correlated with the axial lengths [2, 3], less is known about choriocapillaris (CC). Thinner choroid is typically related to HM, and the presence of large areas of chorioretinal atrophy may further complicate choriocapillaris assessment, resulting in a challenge in some cases. Consequently, findings from some studies may be controversial. For example, the evaluation of choriocapillary flow is increased according to some researchers [4] but not according to others [5]. Moreover, although a reduction in macular vascular density has been described [2–4, 6], some clinical features such as the evaluation of the foveal avascular zone (FAZ) and outer retina flow variations have not been amply investigated to date.

It should be also considered that in most of the previous studies about HM, the microvascular characteristics were

✉ Paolo Milani
    dottpaolomilani@hotmail.com

1   Istituto Auxologico Italiano and Retina 3000 Eye Center, Milan, Italy

2   University of Milan-ASST Santi Paolo e Carlo, Milan, Italy

3   City, University of London, Optometry and Visual Sciences, London, UK

4   Istituto Auxologico Italiano, Milan, Italy

5   Melegnano Hospital and Retina 3000 Eye Center, Milan, Italy

investigated separately, and that calculation software external to the OCT angiography device was used for quantitative measurement.

Therefore, the aim of the present study is to assess macular microvascular features more comprehensively, along with CC blood flow and retinal thickness correlations in a group of myopic eyes using an advanced OCT angiography.

Materials and methods

This study was conducted in accordance with the tenets of the Declaration of Helsinki, and informed consent was obtained from each individual. The eyes of the patients, all Caucasians, presenting in Retina 3000 Eye Center, Milano, Italy, in 2016 with HM (refractive error $\geq -6D$) and the eyes of the controls (refractive error $0 \pm 2D$) were enrolled. Refraction data were converted to the spherical equivalent, which was calculated as the spherical dioptric power plus one-half of the cylindrical dioptric power. The complete ophthalmic examinations of all subjects were unremarkable, and the best corrected visual acuity was $\geq 20/25$. In particular, exclusion criteria were as follows: ocular hypertension, a history of any previous ocular disease or surgery, media opacities (corneal or lenticular opacities), and vitreoretinal disorders such as macular holes or macular puckers. Eyes with areas of chorioretinal or retinal pigment epithelium (RPE) atrophy affecting the macular region were also excluded because these conditions may frequently cause artifacts and alter quantitative analysis.

All participants underwent comprehensive ocular examination including autorefractometer, assessment, and slit-lamp biomicroscopy of the anterior and dilated posterior segment. Intraocular pressure was measured by applanation tonometry.

Optical coherence tomography angiography scans were obtained using the AngioVue, Angioanalytics, XR Avanti device (Software V.2016.1.0.26 Optovue Inc., Fremont, CA, USA) with the angio retina mode (3×3 mm). This OCT angiography is FDA approved and avails of the split-spectrum amplitude decorrelation algorithm (SSADA) that operates at 70,000 A scans per second to acquire volumes of 304 X 304 A-scans. Exclusion criteria for OCT angiography examinations were signal strength index < 55, low quality of images with severe artifacts because of poor fixation, and layer segmentation errors (provided automatically by the software).

The following parameters were evaluated: FAZ area, superficial vascular density, choroidal thickness, outer retina flow, and choriocapillaris flow.

Image selection and analysis

The AngioVue software included in the Avanti device can be used for several layouts with multiple retinal layers segmentations. In our study, the FAZ was calculated automatically in

mm^2 by the software using the "non-flow" measure function in correspondence to the macular superficial plexus visualization. The superficial vascular plexus is automatically segmented by the software from the inner limiting membrane (with an interface offset of 3 μm) to the inner plexiform layer (IPL) (with an interface offset of 16 μm). Using the "density" measure function, a map was automatically created that provided percentage of areas occupied by vessels in the whole macular area and in the fovea, parafovea, temporal, superior, nasal, and inferior macular areas (Fig. 1). The corresponding retinal thickness was also calculated automatically in micrometers. The blood flow was calculated in mm^2 by the "flow" automatic analysis function in a selected area of 3144 mm^2 centered on the fovea in the outer retina layer, segmented automatically from the IPL (with an interface offset of 72 μm) and the RPE (with an interface offset of 31) and in the choriocapillaris, segmented automatically from 31 to 59 μm inferiorly to the RPE (Fig. 2).

Statistical analysis

Effect magnitude and P values for factors and continuous variables were calculated using different linear mixed models. Random effects were used to account for correlations among clustered observations (two eyes from the same subject or multiple observations from the same eye). Two sets of multivariate linear models were used: the first set dealt with global variables, such as the global superficial vessel density, the choriocapillaris perfusion, and the outer retinal layer perfusion; the second set of models used topographical information to investigate any differential behavior in the superficial vessel density and retinal thickness at different locations of the retina (fovea, parafovea, superior, inferior, nasal, and temporal areas). In the latter, interactions were used to model and test different behaviors at the various locations. Only significant interactions ($P < 0.05$) were kept in the final models used for the analysis. All P values were calculated from the linear models using a t-type statistics on the effect estimates, as provided by the package lme4 for R. We only reported effect magnitude since correlation coefficients and R^2 indices are not univocally defined for mixed models. All calculations were performed in an R scripting environment (R Foundation for Statistical Computing, Vienna, Austria). Results are reported as mean ± SD (standard deviation) or estimate ± SE (standard error) according to whether they were raw calculations or marginal estimates from a model. In the topographical models, 95% confidence intervals are reported along with the estimates.

Results

A total of 42 myopic eyes from 37 individuals (12 men and 25 women, Caucasians) and 40 control eyes from 28

Fig. 1 Map of the vessel density and retinal thickness in a myopic and non-myopic eye (left and right, respectively). Using the "density" measure function, the AngioVue software can provide an automatically elaborated map that calculates the percentage areas occupied by superficial vessels in the whole macular area and in the fovea, parafovea, temporal, superior, nasal, and inferior macular portions. The corresponding retinal thickness included between the inner limiting membrane and the retinal pigment epithelium is also measured in micrometers
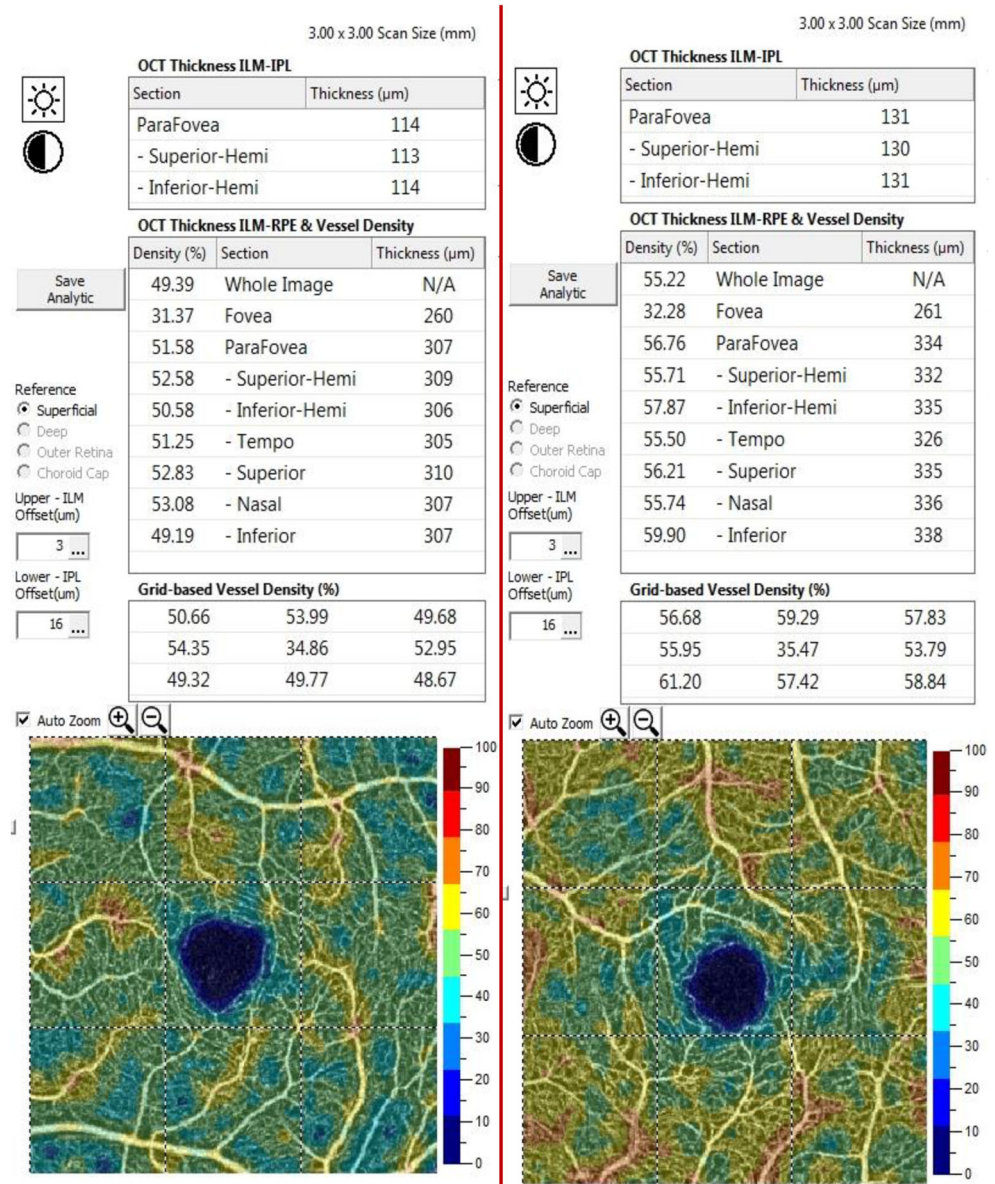

individuals (13 men and 15 women, Caucasians) were included. Demographics are reported in Table 1. Age was comparable between the two groups (51.85 ± 10.87 and 56.24 ± 16.64 years in the myopic and normal subjects, respectively; $P = 0.19$, mean $\pm$ SD). As expected, the spherical correction was significantly different between the two groups (-10.26 ± 3.83 diopters and -0.07 ± 1.44 diopters for the myopic and non-myopic eyes, respectively; $P < 0.0001$). Since there were more females in the myopia group, this is not a truly matched cohort.

Global analysis

We first analyzed the effect of myopia on the FAZ area, the whole superficial vessel density, the choriocapillaris, and the outer retina perfusion. The results are reported in Table 2. The effect of myopia was explored both in terms of differences between the two groups and in terms of correlation with the dioptric continuous value. The two analyses were performed separately to avoid correlation between the two predictor factors (group classification and spherical correction). Both analyses were corrected for age using a multivariate model. The effect of age as calculated in the analysis with the group classification was significant (negatively) for the whole superficial vessel density ($P = 0.006$), but not for the FAZ area, the choriocapillaris, and the outer retina perfusion ($P = 0.17$, $P = 0.92$, and $P = 0.3$, respectively). Myopic eyes presented a lower whole superficial vessel density (46.4 ± 4.9 vs. $51.6 \pm 3.6\%$, $P < 0.0001$) and higher flow area in the outer retina (1.3 ± 0.2 vs. 1.1 ± 0.3 mm^2, $P = 0.0012$). Between the

Fig. 2 Flow measurement in the outer retina and in the choriocapillaris of a myopic (top left and bottom left, respectively) and of a healthy individual (top right and bottom right, respectively). The circular area of 3144 mm^2 centered on the fovea is automatically delimited by the software that calculates in mm^2 the total area of multiple bright areas corresponding to the choriocapillary lobular meshwork where the blood flow can be detected by the OCT angiography device
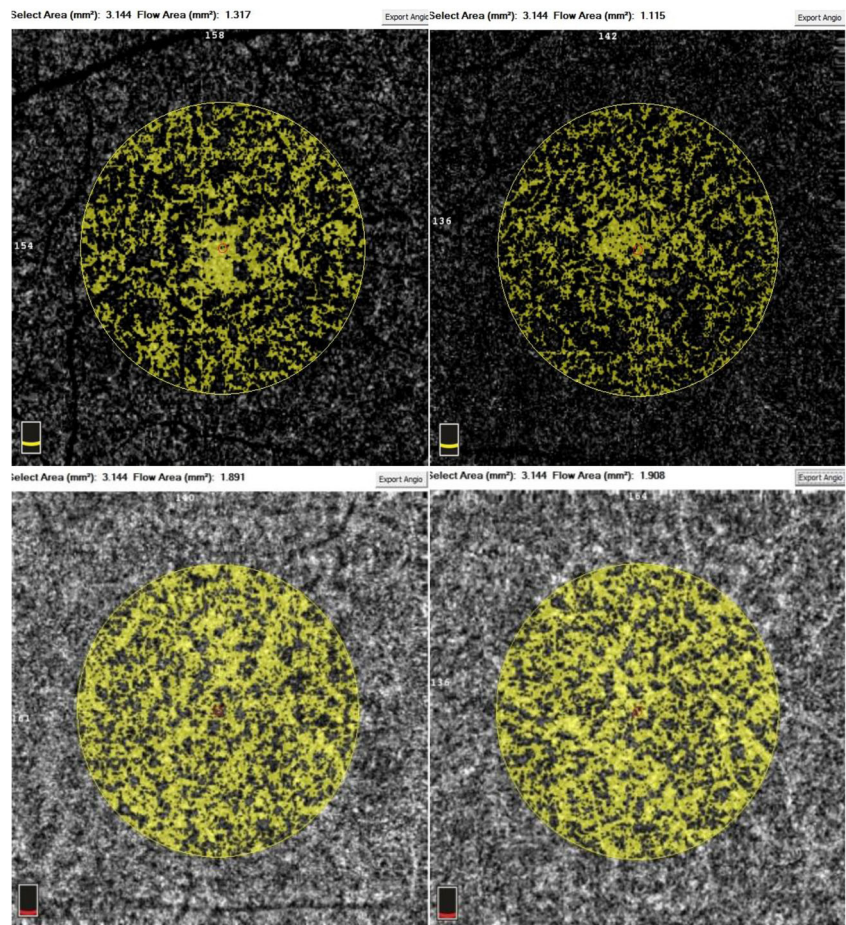
myopic and healthy eyes, no significant differences could be detected in the choriocapillaris perfusion area (1.9 ± 0.07 vs 1.9 ± 0.05 mm^2, respectively; $P = 0.55$) or in the FAZ area (0.23 ± 0.1 vs 0.26 ± 0.1 mm^2, $P = 0.12$). These findings were partially confirmed when the correlation with the spherical correction was explored, reporting a significant positive correlation with the superficial vessel density ($P < 0.0001$, meaning that vessel density decreased with more negative spherical values) and a significant negative correlation with the outer retina perfusion ($P = 0.0021$). Again, no significant correlation could be found between the spherical correction and the FAZ area or the choriocapillaris flow ($P = 0.12$ and $P = 0.07$, respectively).

Table 1 Demographics and descriptive statistics; values are reported as mean ± SD. Significant P values are in italics

Descriptive	Myopic	Normal	P
Patients, M/F	37, 12/25	28, 13/15	*0.37*
Eyes	42	40	
Diopters	-10.26 ± 3.83	-0.07 ± 1.44	*< 0.0001*
Age	51.85 ± 10.87	56.24 ± 16.64	0.19

Topographic analysis

We further characterized the differences in terms of retinal thickness and superficial vessel density at different retinal locations. The results are reported in Table 3. The retina was generally thicker in normal patients, but no statistically significant differences could be detected between the two groups at any location, except for the foveal region, where the myopic patients had a significantly thicker retinal thickness (273.62 ± 25.7 vs 257.87 ± 22.19 μm, $P = 0.0025$). On the other hand, we found a significantly reduced superficial vessel density in the myopic patients in all locations ($P < 0.001$), except in the foveal region, where no significant differences could be detected ($P = 0.45$).

As mentioned in the previous section, we analyzed the effect of myopia on retinal thickness and superficial vessel density by using the spherical correction as a continuous predictor (Table 4 and Fig. 3). Confirming the previous finding, the spherical correction was negatively correlated with the foveal thickness ($P = 0.01$) and positively correlated with the superficial vessel density at all locations ($P < 0.001$), except for the fovea ($P = 0.27$).

Table 2 Analysis of the parameters evaluated. Values are reported as mean ± SD for group mean, while estimate ± SE are used for continuous predictors. Significant *P* values are in italics. *FAZ* foveal avascular zone

Global statistics	Variables	Estimate	*P*
FAZ area	Age	0.0012 ± 0.0008	0.172
	Group		
	Myopic	0.23 ± 0.15	0.124
	Normal	0.26 ± 0.17	
	Diopters	0.51 ± 0.08	0.126
Whole superficial vessel density	Age	− 0.11 ± 0.04	*0.006*
	Group		
	Myopic	46.44 ± 4.9	*< 0.0001*
	Normal	51.65 ± 3.63	
	Diopters	0.51 ± 0.08	*< 0.0001*
Choriocapillaris perfusion area	*Age*	0 ± 0.0005	0.92
	Group		
	Myopic	1.95 ± 0.07	0.55
	Normal	1.94 ± 0.05	
	Diopters	− 0.003 ± 0.08	0.07
Outer retina perfusion area	Age	0.002 ± 0.002	0.3
	Group		
	Myopic	1.31 ± 0.21	*0.0012*
	Normal	1.1 ± 0.32	
	Diopters	− 0.019 ± 0.05	*0.002*

We then investigated the local correlation between the superficial vessel density and the local retinal thickness (Table 5 and Fig. 4). We found a significant positive correlation at all locations ($P < 0.005$), especially in the foveal region

($P < 0.0001$). We also explored interactions of the terms to investigate whether the thickness-density correlation could change between the myopic and normal patients, but no significant differences could be found ($P > 0.2$).

Discussion

The present study evidenced a reduced macular vascular density and a reduced outer retina flow in myopic eyes, but no significant differences between FAZ and CC flow areas measurements.

Consistently to previous reports [2–4, 6], in fact, we found that the whole macular vascular density is reduced in myopic eyes and it is correlated with the spherical equivalent ($P < 0.0001$, Table 2). This finding may be secondary to ocular elongation typically related to HM [2] or to reduced retinal blood flow as described by some authors using either the laser Doppler velocimetry technology [7–9] or the dynamic vessel analyzer software [10]. It has been also speculated that biomechanical stretching of the retina, the choroid, and the sclera can cause straightening and narrowing of the vessels and consequent capillary density reduction [4]. In our study, the macular vascular density was reduced in HM not only in the entire macular region but also in every portion of the macular area (topographic analysis, $P < 0.0005$, Table 3), except in the fovea ($P = 0.45$, Table 3) as confirmed by the analysis of the spherical correction used as a continuous predictor factor (Table 4). It is probable that the superficial vessel density in the foveal area is much lower in both myopic and non-myopic

Table 3 Analysis of the local differences at six retinal locations. Retinal thickness and superficial vessel density were compared between the two groups as marginal estimates using a single model. Significant *P* values are in italics

	Retinal thickness			Superficial vessel density		
	Mean	95% CI	*P*	Mean	95% CI	*P*
Fovea						
Myopic	273.62	267–280.23	*0.0025*	29.9	28.26–31.55	0.4573
Norm	257.87	250.44–265.31		30.83	28.99–32.66	
Parafovea						
Myopic	316.40	309.79–323.02	0.4587	48.58	46.94–50.23	*0.0001*
Norm	320.12	312.68–327.55		53.78	51.94–55.62	
Superior						
Myopic	322.47	315.86–329.09	0.6351	49.51	47.86–51.15	*0.0003*
Norm	324.85	317.42–332.28		54.21	52.37–56.05	
Inferior						
Myopic	313.83	307.21–320.45	0.1714	48.38	46.74–50.03	*< 0.0001*
Norm	320.73	313.29–328.16		54.81	52.97–56.64	
Nasal						
Myopic	321.19	314.57–327.8	0.8601	48.09	46.45–49.74	*0.0002*
Norm	322.07	314.64–329.5		52.89	51.06–54.73	
Temporal						
Myopic	307.64	301.02–314.26	0.2867	48.34	46.69–49.98	*0.0004*
Norm	313.00	305.56–320.43		53	51.17–54.84	

Table 4 Local correlations between retinal thickness and spherical correction (top) and between superficial vessel density and spherical correction (bottom). Significant *P* values are in italics. Units are reported on the top of each sub-table. % Density as percentage, *D* spherical correction as diopters, *μm* microns

	Slope	95% CI	*P*
Effect of spherical correction on local retinal thickness (μm/D)			
Fovea	− 1.2132673	− 2.044 to − 0.383	*0.01124447*
Parafovea	0.4157131	− 0.473 to 1.193	0.34100228
Superior	1.0123393	− 0.743 to 0.922	*0.02950621*
Inferior	0.5771462	− 0.04 to 1.626	0.19190971
Nasal	0.2845681	− 0.657 to 1.009	0.51129593
Temporal	0.6172083	− 0.433 to 1.233	0.16443866
Effect of spherical correction on superficial vessel density (%/μm)			
Fovea	0.114176	− 0.08 to 0.308	0.2656
Parafovea	0.4473889	0.253–0.641	*0.0003*
Superior	0.6010764	0.407–0.795	*< 0.0001*
Inferior	0.4995277	0.306–0.694	*0.0001*
Nasal	0.4373123	0.243–0.631	*0.0004*
Temporal	0.4839152	0.29–0.678	*0.0002*

individuals for the presence of the FAZ (Table 3). Likely, no significant differences were disclosed in the FAZ area measurements in both groups; in fact, the FAZ area showed to vary greatly among normal individuals according to age and other factors [11–14] and, consistently with our findings, no significant association with axial length has been reported to date [11, 15, 16].

Despite other studies [17, 18], a mild retina thinning was present in all the sections of myopic eyes but not with statistical significance, whereas thickening of the foveal area was found with statistical significance ($P = 0.0025$, Table 3). The increased foveal thickness in myopic eyes has been already reported [19–22], and Wu with associates postulated that elevation of the fovea may be secondary to mechanical stretching of the eyeball with internal limiting membrane flattening resulting in foveal elevation and panretinal thinning [19]. This evidence is confirmed by the analysis of the spherical correction as continuous predictor factor ($P = 0.011$, Table 4 top).

One interesting and unreported finding of our study is the positive correlation between the retinal thickness and the superficial vessel density in every portion of the macular area and especially in the fovea ($P < 0.005$ and $P < 0.0001$, respectively). This relationship is not influenced by the refractive status, and, accordingly, no differences between the myopic and control groups could be found ($P > 0.2$). Although it is possible that increased vascular density may cause increased retinal thickness, this feature may need further investigation.
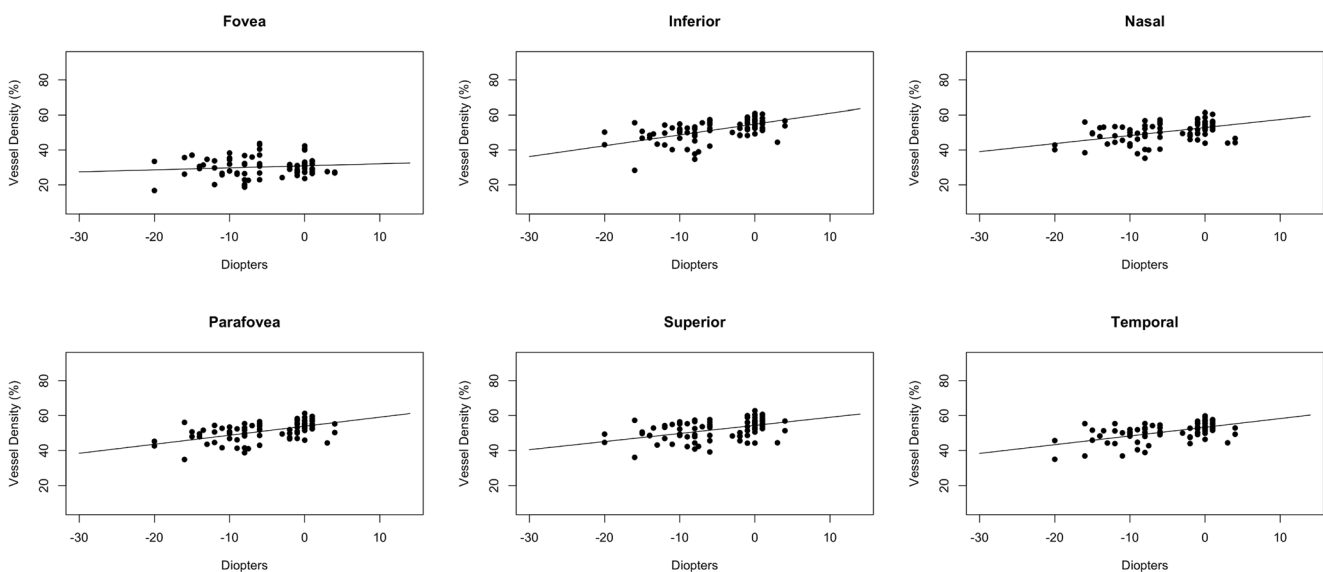

Fig. 3 Scatter plots and regression lines depicting the relationship between the local superficial vessel density and the spherical correction expressed in diopters at different locations

Table 5 Local correlations between local superficial vessel density and local retinal thickness. Significant *P* values are in italics. Units are reported on the top of each sub-table. % density as percentage, *μm* microns

Effect of local thickness on superficial vessel density (%/μm)

	Slope	95% CI	*P*
Fovea	0.129	0.101–0.157	*< 0.0001*
Parafovea	0.082	0.047–0.117	*0.0002*
Superior	0.076	0.037–0.115	*< 0.0001*
Inferior	0.075	0.039–0.11	*0.0001*
Nasal	0.066	0.031–0.102	*0.0003*
Temporal	0.058	0.019–0.098	*0.0041*

The V.2016.1.0.26 version of the AngioVue software can provide measurement of the blood flow in two automatically segmented retinal layers, the outer retina (between the IPL and the RPE), and the CC (31 μm posterior to the RPE). In both cases, the resulting elaboration is a granular image constituted by dark and bright adjacent areas corresponding to the absence or presence of blood flow, respectively, as detected by the tool. Flow measurement is expressed in terms of mm^2 within a selected area of 3144 mm^2 automatically centered on the fovea. Although this kind of flow evaluation is relatively new and therefore needs to be validated and compared, our study showed increased flow in the outer retina of myopic eyes, with a positive correlation to the degree of myopia and independent of age (Table 3). However, this interesting finding should be interpreted with caution because the automatic projection-artifact removal algorithm may be affected by minor superficial vessel density in myopic eyes, resulting in an augmented preservation of deeper vascular layer images. It is also

inconsistent with the only two studies that investigated quantitative changes in both the outer retina density and flow: vessel density was found independent of axial length and to decrease with older age [15], and vascular flow showed no significant differences between myopic and healthy individuals [5]. In these studies, which included Chinese individuals instead of Caucasians, the measurements were evaluated in percentage maps and not in mm^2 and were calculated using external software. These factors could explain the discrepancies. Mo and associates even found lower flow in myopic than in emmetropic eyes [5], but the presence of areas of chorioretinal atrophy in their series should have altered this measurement because of underestimation due to the shadowing effect caused by the lesions. We specifically excluded eyes with pathological fundus changes in our enrollment protocol.

On OCT angiography, the typical CC granular imaging reflects the anatomical meshwork of densely packed and interconnected capillaries that functions in a lobular mode in terms of blood flow [23]. Investigation of myopic CC is limited and complicated by extensive thinning of the choroid, typically related to this condition, progressing with age and the degree of myopia [4, 24–26]. This probably accounts for the different findings from other, previous studies where CC flow was found reduced [4, 5] or unchanged [15]. We were not able to identify significant measurable flow alteration in the CC associated with myopia ($P = 0.55$, Table 2) as enhanced by the spherical equivalent used as a continuous factor ($P = 0.07$, Table 2). The similar value in CC perfusion in both groups is a surprising finding, especially if considering the reduced retinal vascular density and retinal thickness. However, measurements may depend on the choroidal level of segmentation, on the SSADA technology limitations and may also differ if
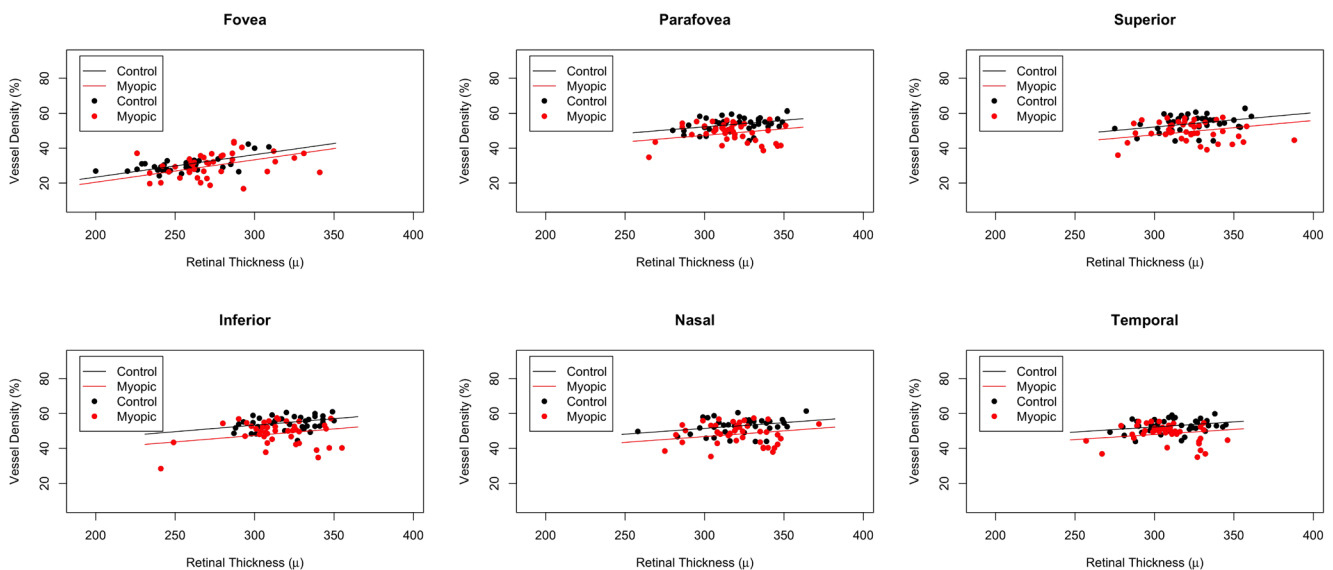
Fig. 4 Scatter plots and regression lines depicting the relationship between the local superficial vessel density and the local retinal thickness at different locations both in normal subjects (black dots and lines) and myopic patients (red dots and lines)

considering either flow-void number/size or density percentages. In fact, Al-Sheikh and associates found in myopic CC a decreased total number of flow voids, but an increased average total flow-void area versus the control group [4]. Similarly, Nicolo and associates showed a different spatial distribution of the vascular flow within the entire choroid in central serous chorioretinopathy, as the flow area at the level of CC was significantly smaller than at the deeper choroid, probably as a compensatory mechanism [27].

The impact of age on our series appears significantly inversely correlated only to the whole retinal vascular density, in agreement with other studies [14, 15], presumably because of physiologic age-related loss in vascularity. Aging does not seem to affect flow neither of the outer retina nor of the CC.

We acknowledge that some limitations affect this study: first, its retrospective design, single center, and monoracial background. Accuracy, sensitivity, and reproducibility of OCT angiography-derived maps are currently under investigation and continuously ameliorated, but artifacts may still alter measurements on some occasions, especially in HM [28]. Significant variability exists in FAZ and capillary density measurements among different machines and techniques [29]. The deep location of the choriocapillaris may have been associated with a loss in spatial resolution owing to the reduced penetration of the OCT signal beyond the RPE. Evaluation data of the CC might therefore have been less precise than those of the intraretinal vascular networks. Also, it could have been interesting to evaluate vessel density maps of the deep capillary plexus and of the choriocapillaris; however, these automatic elaborations were not available in the software at the time of the study and are particularly affected by artifacts and segmentation errors, resulting in poor reproducibility.

Overall, this paper presents some potential interesting points too. Using the device's automated software provided by the company, it is the first study to describe quantitative features of the outer retina flow in Caucasians with HM and is presumably the first to assess the relationship between superficial vascular density and retinal thickness in a group of myopic and non-myopic individuals. Future studies may clarify this relationship and further investigate the role of choriocapillary flow.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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