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Perivenular Capillary Loss: An Early, Quantifiable Change in Macular Telangiectasia Type 2

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Purpose: To evaluate differences in parafoveal vascular density surrounding arterioles and venules in type 2 macular telangiectasia (MacTel).

Methods: Thirty-seven eyes (20 subjects) diagnosed with MacTel and 16 healthy eyes (10 subjects) were imaged with optical coherence tomography angiography between March 2016 and June 2019 in this single-center, observational, cross-sectional study. Arterioles and venules were manually identified, and perivascular density was generated using a custom MATLAB code. The primary outcome measure was the ratio of periarteriolar to perivenular vascular density (arteriovenous [A/V] capillary ratio) in the superficial and deep capillary plexuses across MacTel stages. The main secondary outcome measures were overall parafoveal vascular density (VD), periarteriolar VD, and perivenular VD.

Results: In the superficial capillary plexus (SCP), the A/V capillary ratio was significantly higher in MacTel subjects than controls (0.914 vs. 0.892; $P = 0.0044$). The greatest differences occurred between controls and nonproliferative MacTel subjects without optical coherence tomography evidence of disease ($P = 0.0055$). A/V capillary ratios progressed in a nonlinear fashion with MacTel severity, increasing from nonproliferative disease (0.912) to intraretinal proliferative disease (0.931), then decreasing in subretinal proliferative disease (0.905). Parafoveal VD in the SCP was lower in MacTel subjects than controls only in subretinal proliferative disease ($P = 0.0130$).

Conclusions: The A/V capillary ratio of the SCP is a quantifiable metric of vascular pathology in MacTel that occurs earlier than decline in parafoveal VD. Elevated A/V capillary ratios in MacTel are consistent with an early, disproportionately perivenular disruption in the SCP.

Translational Relevance: Findings inform MacTel pathogenesis through revealing early perivenular capillary loss and offer a new quantitative metric for earliest stage MacTel.

Introduction

Macular telangiectasia type 2 (MacTel) is a bilateral macular disease causing progressive visual impairment. Müller cell dysfunction induces photoreceptor loss, vascular changes develop, and central vision loss slowly progresses.[1,2] Distinctive juxtafoveal microvascular changes are key findings in MacTel.[3] Early vascular findings include right-angle venules and telangiectatic capillaries.[3] Later vascular anomalies include enlargement of the foveal avascular zone, decrement in parafoveal vascular density (VD), and ultimately neovascularization.[3–5]

Yannuzzi et al. classified MacTel into either nonproliferative or proliferative stages based on evidence of subretinal neovascularization on clinical examination, fluorescein angiography (FA), and optical coherence tomography (OCT).[6] Proliferative MacTel may be further subclassified by the depth of neovascularization whether in the outer retina[5] or subretinal.[7] The most recently validated comprehensive staging system for MacTel is an OCT-based classification scheme (stages 0–6), based on several factors that were shown to be most relevant to the progression of disease, including ellipsoid loss, presence of pigment, hyperreflective foci, and neovascularization (Chew EY, et al. IOVS 2019;60:ARVO Abstract 1335).

Parafoveal VD is a quantitative metric for retinal capillary loss and can be assessed using optical coherence tomography angiography (OCTA).[4,8,9] Patients with MacTel have been shown to have a lower parafoveal VD in the superficial capillary plexus (SCP) and deep capillary plexuses (DCP) when compared with healthy controls.[4,8,10] Topographical changes in parafoveal VD have also been documented in MacTel, with lowest parafoveal VD found in the temporal parafovea.[9] The course of these parafoveal VD changes as MacTel progresses remains unknown.

Differences between arteriole-adjacent and venule-adjacent parafoveal VD are also poorly understood in MacTel. Arteriovenous differences have been evaluated in other retinal disorders, namely diabetic retinopathy.[11] In the healthy retina, vascular densities are much lower surrounding arterioles than venules,[12] so to detect subtle relative arteriovenous changes in diabetic retinopathy, the authors proposed the concept of an arteriovenous ratio, representing arteriolar-adjacent nonperfusion divided by venular-adjacent nonperfusion.[11] In diabetic retinopathy, arteriolar-adjacent nonperfusion has been shown to be the greatest contributor to overall nonperfusion, with venular-adjacent nonperfusion playing a larger role as disease progresses.[11]

The presence of peculiar yet characteristic right-angle venules[3,13] offers reason to believe arteriovenous (A/V) differences exist in MacTel. We have recently shown that there is an intricate relationship between photoreceptor loss and markers of vascular change, such as DCP telangiectasia.[14] Moreover, there is almost complete overlap between photoreceptor loss and neovascularization in MacTel,[5] so it is plausible that similar processes are reflected in A/V capillary changes.

In this study, we aim to identify whether arteriolar-adjacent or venular-adjacent patterns exist in parafoveal VD in MacTel in comparison to A/V capillary patterns of healthy controls. We hypothesized that the venular-adjacent parafoveal VD would be lower (and therefore A/V capillary ratios would be higher) in MacTel patients than healthy controls and that this pattern would worsen with increasing disease stage.

Methods

Subjects

Thirty-seven eyes from 20 patients with MacTel along with 16 eyes from 10 healthy control subjects were included in this cross-sectional, observational study. Patients were diagnosed with MacTel between March 2016 and June 2019 in the Department of Ophthalmology at Northwestern University in Chicago, IL. Written informed consent was obtained from all participants. This research was performed in accordance with the Health Insurance Portability and Accountability Act regulations and followed the tenets of the Declaration of Helsinki.

During one clinical visit, subjects underwent OCTA imaging of both eyes as well as fundus fluorescein angiography (FFA), fundus autofluorescence, and color fundus photography, as clinically indicated. MacTel diagnosis was made based on characteristic examination findings, such as parafoveal translucency, inner retinal crystals, dilated capillaries, and nontapering right angle venules, in concert with characteristic patterns on FFA, such as telangiectasias with hyperfluorescence in late phase. During the visit, all subjects underwent a full ophthalmologic exam, including best corrected Snellen visual acuity, expressed in the LogMAR scale for the purposes of this study. OCTA imaging was performed under ambient room lighting and all eyes were dilated before imaging. Subjects with an image quality index 7 or above were considered eligible for the purposes of this study.

MacTel subjects were grouped based on presence and location of neovascularization into three classes: nonproliferative, outer retinal proliferative, and subretinal proliferative. For validation purposes, subjects were staged using the recently proposed and validated OCT-based classification focusing on ellipsoid loss, pigment, hyperreflective foci, and neovascularization (Chew EY, et al. IOVS 2019;60:ARVO Abstract 1335). Specific criteria are listed in Supplemental Table S1.

OCTA Protocol

We used the RTVue-XR Avanti system (Optovue Inc., Fremont, CA, USA) to image all subjects, acquiring 3 mm x 3 mm OCTA scans. RTVue-XR Avanti captures two consecutive B-scans at each location and 304 A-scans at a rate of 70,000 scans/s. The system uses a light source centered at 840 nm with a bandwidth of 45 mm. RTVue-XR Avanti uses split-spectrum amplitude-decorrelation angiography software (version 2017.1.0.151) and generates angiographic flow information by quantifying the difference in OCT amplitude between consecutive B-scans. We reduced superficial capillary projection by using the built-in RTVue-XR Avanti 3D projection artifact removal software.

Image Analysis

A single masked reviewer graded subjects by assessing presence and depth of neovascularization on cross-sectional OCT with flow overlay. Eyes with evidence of vessels on cross-sections that were disrupting retinal pigment epithelium/Bruch's with an identifiable en face network of tangled vessels were defined as subretinal proliferative eyes, whereas those with evidence of vessels on cross-sections in the avascular layers of the outer retina with an identifiable en face network of tangled vessels were defined as outer retinal neovascular eyes. Those with neither were considered nonproliferative eyes. We used default segmentation parameters to study the macular capillary beds as en face angiograms of the SCP and DCP. Default segmentation of the SCP is from the inner limiting membrane to 55 µm above the inner plexiform layer (IPL). Default segmentation of the DCP is from 6 µm above the IPL to 50 µm below the IPL. We imported angiograms of SCP and DCP into Photoshop software (Adobe systems, San Jose, CA, USA) to manually outline isolated arterioles and venules.

Arterioles and venules visualized on the en face OCTA images of the SCP were manually identified and outlined in red and blue in Photoshop, respectively. To differentiate arterioles from venules, fundus photography and FFA were referenced. The presence of capillary-free zones surrounding arterioles, the concept of arteries not crossing arteries (and vice versa), and that venules topographically overlie vortexes in the DCP were also used to confirm the vessel identities using en face OCTA. Recent studies have validated the use of these techniques with en face OCTA to identify vasculature as arterial versus venular.[15,16] Images consisting of SCP vessel outlines were imported into a custom MATLAB software to quantify arteriolar-adjacent and venular-adjacent parafoveal VD for the SCP and DCP.

Quantification of Vascular Density

We used a custom MATLAB software (MathWorks, Natick, MA, USA) similar to prior work to identify vascular density within a defined radius (0.2 mm) surrounding SCP arterioles and venules on the OCTA images, set to maximize intervessel capillary space and minimize arteriovenular capillary zone overlap.[11] Figures 1 and 2 illustrate our methods for manual vessel isolation and automatic quantification of arteriovenous vascular density in healthy and MacTel eyes, respectively.

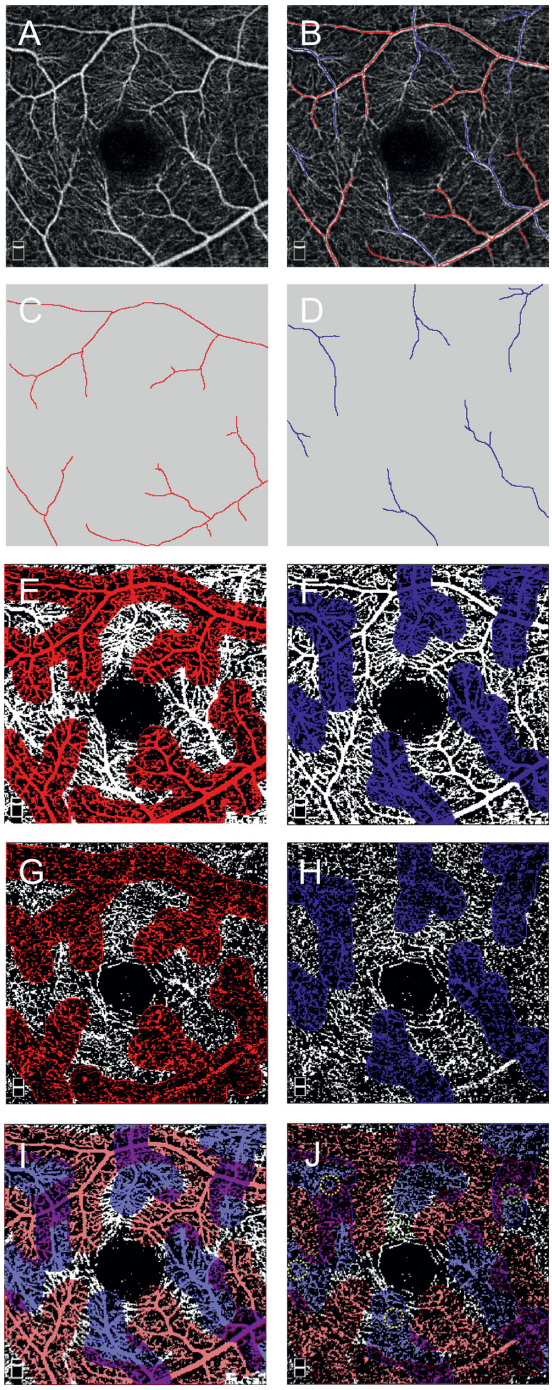

Figure 1. Arteriovenous vascular densities and methods of quantification visualized on OCT angiography in a healthy subject. Right eye of a healthy 66-year-old woman. (A) Superficial capillary plexus is shown. (B) Superficial capillary plexus with arterioles (red) and venules (blue) are labelled. (C,D) Arterioles and venules, respectively, from the superficial capillary plexus are isolated. (E,F) Periarteriolar (red) and perivenular (blue) vascular distributions are isolated on contrast-enhanced images of the superficial capillary plexus. (G,H) Periarteriolar (red) and perivenular (blue) vascular distributions from the superficial capillary plexus are superimposed on contrast-enhanced images of the deep capillary plexus. (I,J) Periarteriolar (red), perivenular (blue), and overlapping (purple) vascular distributions derived from the superficial vasculature are

Table 1. Demographics, Visual Acuities, and Disease Stages Between Control and MacTel Groups

	Control Group; N/Mean ± SD (range)	MacTel Group; N/Mean ± SD (range)	*P* Value
Subjects	10	20	
Eyes	16	37	
Age (y)	60.9 ± 9.1 (42–75)	60.6 ± 9.9 (43–85)	0.9230
Sex			
Male	4	14	
Female	12	23	
Visual acuity			
LogMAR	0.01 ± 0.08 (-0.1 to 0.2)	0.27 ± 0.25 (-0.1 to .9)	**0.0002**
Snellen	20/20 (20/15-20/30)	20/36 (20/16-20/160)	
Stage			
Nonproliferative		13	
Outer retinal Proliferative		9	
Subretinal proliferative		15	

Statistical considerations: groups were compared using two-tailed *t* tests ($P < 0.05$ in bold font).
MacTel, macular telangiectasia type 2; SD, standard deviation.

Statistical Analysis

We generated overall, arterial-adjacent, and venular-adjacent parafoveal VD in the SCP and DCP in all subjects and evaluated differences across MacTel stages. We calculated parafoveal VD arteriovenous capillary ratios (A/V capillary ratios), defined as arterial-adjacent parafoveal VD divided by venular-adjacent parafoveal VD. We subsequently evaluated differences across MacTel stages using analysis of variance (ANOVA) with Tukey post hoc analyses. We performed all statistical analyses using JMP 14.0 software (SAS Institute, Cary, NC, USA) and the statistically significant level was set at $P < 0.05$.

Results

Subject demographics and visual acuity for all subjects and MacTel disease stages are reported in Table 1. OCT-based Chew et al. disease stages are listed in Supplemental Table S1 and Supplemental Figure S1. Mean A/V capillary ratio in the SCP was higher in MacTel subjects (0.914) than healthy controls (0.892; $P = 0.0044$), as shown in Figure 3. Representative examples of healthy and MacTel arteriovenous vasculature are shown in Figures 1 and 2, respectively.

The SCP A/V capillary ratio varied by disease stage, as shown in Figure 4. Mean A/V capillary ratios increased with disease stage in subjects without subretinal neovascularization: healthy controls (0.892), nonproliferative MacTel (0.912), and intraretinal proliferative MacTel (0.931). Mean A/V capillary ratio normalized in subretinal proliferative MacTel (0.905). Significant differences were found between groups (ANOVA; $P = 0.0075$). After post hoc analysis, the A/V ratio in intraretinal proliferative MacTel was significantly higher than in healthy subjects ($P = 0.0043$). As shown in Supplemental Figure S2, using Chew et al. OCT-based staging, mean A/V capillary ratios increased from healthy subjects (0.892) to stages 0–2 (0.925), then declined in stages 3–5 (0.914) and stage 6 (0.905). Significant differences were found across groups (ANOVA; $P = 0.0175$). After post hoc analysis, the A/V ratio in stages 0–2 were found significantly higher than in healthy subjects ($P = 0.0133$). As shown in Figure 5, there was a significant difference in A/V capillary ratios between MacTel stage 0 (nonproliferative subjects without ellipsoid loss, pigment, or hyperreflective foci) and healthy controls ($P = 0.0055$).

Between-group and within-group differences in vascular density and associated metrics are shown in Table 2. Mean parafoveal VD was significantly lower in the SCP than in the DCP within MacTel subjects as a group ($P < 0.0001$) and control subjects as a group ($P < 0.0001$). Mean parafoveal VD (SCP and DCP) among all MacTel subjects were similar to healthy control subjects (MacTel: 38.23% and 48.67%

←
superimposed on the superficial capillary plexus and deep capillary plexus, respectively; venular vortices are circled in yellow and those that do not correlate with the superficial perivenular distribution are circled in green. A/V capillary ratios = 0.864 (SCP), 0.954 (DCP). DCP, deep capillary plexus; OCT, optical coherence tomography; SCP, superficial capillary plexus.

Table 2. Superficial and Deep A/V Capillary Ratios and Perivascular Capillary Densities in Control and MacTel Groups

	Control Group	MacTel Group	*P* Value
A/V capillary ratio			
SCP	0.892	0.914	**0.0044**
DCP	0.958	0.955	0.6680
P value (within group)	**<0.0001**	**<0.0001**	
Periarterial parafoveal VD			
SCP	40.09%	38.28%	0.2357
DCP	49.49%	48.99%	0.7683
P value (within group)	**<0.0001**	**<0.0001**	
Perivenular parafoveal VD			
SCP	44.89%	41.89%	0.0591
DCP	51.62%	51.32%	0.8546
P value (within group)	**0.0014**	**<0.0001**	
Overall parafoveal VD			
SCP	40.34%	38.23%	0.1994
DCP	49.13%	48.67%	0.7777
P value (within group)	**<0.0001**	**<0.0001**	

Statistical considerations: groups were compared using two-tailed *t* tests ($P < 0.05$ in bold font).

A/V capillary ratio, arteriolar parafoveal VD/venular parafoveal VD; DCP, deep capillary plexus; SCP, superficial capillary plexus; VD, vascular density.

vs. healthy: 40.34% and 49.13%; $P > 0.05$). However, mean SCP parafoveal VD in subretinal proliferative MacTel subjects was lower than in healthy control subjects (35.57% vs 38.23%; $P = 0.0130$). Within each group, the mean perivenular SCP parafoveal VD significantly exceeded mean periarteriolar SCP parafoveal VD (MacTel: 41.89% vs. 38.28%; $P = 0.0016$, healthy: 44.89% vs. 40.09%; $P = 0.0133$).

Discussion

In this study, we evaluated the A/V capillary ratio as a quantifiable metric to assess and understand early capillary change in MacTel. In accordance with our hypothesis and as shown in Figure 3, we found an elevated A/V capillary ratio in MacTel. We interpret capillary loss in MacTel to be venular predominant, as trends in Table 2 suggest that the higher A/V capillary ratio in MacTel is more likely caused by a decrease in perivenular VD than an elevation in periarteriolar VD. This adds greater detail to prior work demonstrating a decreased overall parafoveal vascular density in MacTel.[4,8,10] Furthermore, we found that the increase in A/V capillary ratio occurs before this decrease in overall parafoveal VD, which was only significantly decreased among our advanced MacTel subjects with OCTA evidence of subretinal neovascularization. As shown in Figure 5, the A/V capillary ratio is elevated very early in disease, in subjects without other OCT metrics of disease progression, such as ellipsoid loss, pigment, or hyperreflective foci.

The elevated A/V capillary ratio in MacTel fits within the current understanding of MacTel pathophysiology. The initial insult in MacTel is believed to be the loss of supportive Müller cells, with ensuing neurodegeneration believed to be intricately linked to vascular changes in MacTel.[1,2] In mice, selective ablation of Müller cells has been shown to induce photoreceptor apoptosis and subsequent intraretinal neovascularization.[2] In human eyes, the area of photoreceptor loss has been shown to topographically overlie areas of intraretinal neovascularization[5] and display a stage-specific topographical relationship with DCP telangiectasia.[14] Neurodegeneration is known to induce vascular change, however, markers of vascular pathology, such as DCP telangiectasia, are often found before markers of neurodegeneration, such as visible photoreceptor loss.[14] A proposed mechanism for this phenomenon is that subclinical photoreceptor damage and subsequent aberrant signaling may induce overlying telangiectasia.[14] Through this process, photoreceptor damage may also induce an abnormal venular architecture in MacTel, marked quantitatively by the elevated A/V capillary ratio and qualitatively by the presence of angled venules,[3,13] as visualized

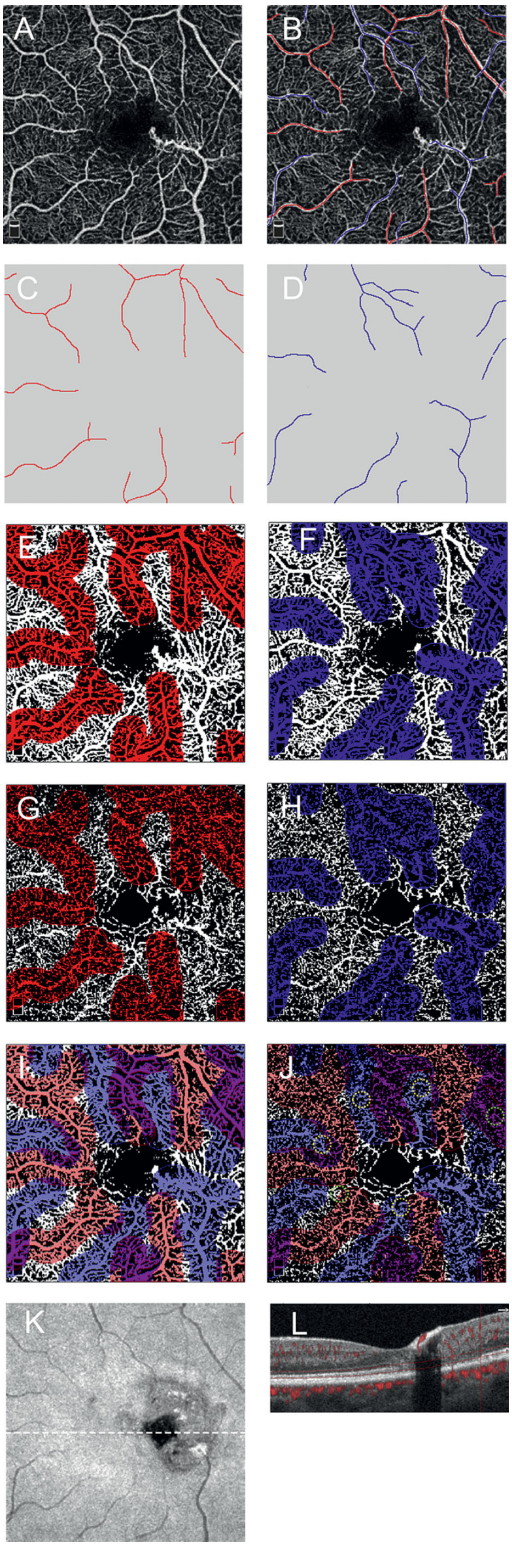

Figure 2. Arteriovenous vascular densities and methods of quantification visualized on OCT angiography in a subretinal proliferative MacTel subject. Left eye of a 49-year-old woman. (A) The superficial capillary plexus shows a dilated, angled venule invading the foveolar avascular zone. (B) Arteriolar (red) and venular (blue) outlines are labelled on the superficial capillary plexus. (C,D) Arterioles and venules, respectively, from the superficial capillary plexus are isolated. (E,F) Periarteriolar (red) and perivenular (blue) vascular distributions are isolated on contrast-enhanced images of the superficial capillary plexus. (G,H) Periarteriolar (red) and perivenular (blue) vascular distributions from the superficial capillary plexus are superimposed on contrast-enhanced images of the deep capillary plexus. (I,J) Periarteriolar (red), perivenular (blue), and overlapping (purple) vascular distributions derived from the superficial vasculature are superimposed on the superficial capillary plexus and deep capillary plexus, respectively; venular vortices are circled in yellow and those that do not correlate with the superficial perivenular distribution are circled in green. A/V capillary ratios = 0.904 (SCP), 0.968 (DCP). (K) En face image of ellipsoid zone shows noncentral loss represented by dark areas; dotted line represents the location of cross-sectional OCT. (L) Cross-sectional OCT shows large venule corresponding to area of pigment. A/V, arteriovenous; DCP, deep capillary plexus; MacTel, macular telangiectasia; OCT, optical coherence tomography; SCP, superficial capillary plexus.

in Figure 2. We propose that underlying photoreceptor damage, through inducing overlying telangiectasia, may predominantly affect venular capillary beds.

The relationship between A/V capillary ratio and MacTel stage also warrants further discussion. As shown in Supplemental Figure S2 referencing Chew et al. OCT-based staging, our results indicate that the increase in A/V capillary ratio in early MacTel (stages 0–2) progressively disappears with advancing MacTel (stages 3–6), making those stages indistinguishable from control eyes with normal A/V capillary ratios. We interpret these results to suggest that capillary loss is venular-predominant in early MacTel; however, as disease progresses, arterioles may become more involved. We propose the A/V capillary ratio may be more useful as an early diagnostic marker of MacTel rather than a metric for disease progression. The nonlinear change with disease progression and insignificant within-group differences in A/V capillary ratio across disease stages precludes utility of this parameter as a prognostic or monitoring biomarker beyond earliest stage MacTel. Of note, our data suggest that A/V capillary ratio changes are more prominent in the SCP, without significant differences in the DCP (Table 2). Although the DCP harbors many important vascular changes in MacTel[14,17,18] and may even present before alterations in the SCP, we were not able to detect arteriovenous differences at that capillary level in this study. It is possible that our sample size of 37 eyes may have been too small to detect subtle A/V differences in the DCP. Our lack of findings in the DCP may also be explained by the more complex vascular architecture of the DCP,[19,20] and in particular, the presence of centrally draining vortex veins. This difference in vascular architecture may limit the degree to which the superficial perivascular distributions can be correlated to the DCP. Figures 1 and 2 highlight this potential limitation by illustrating how the center

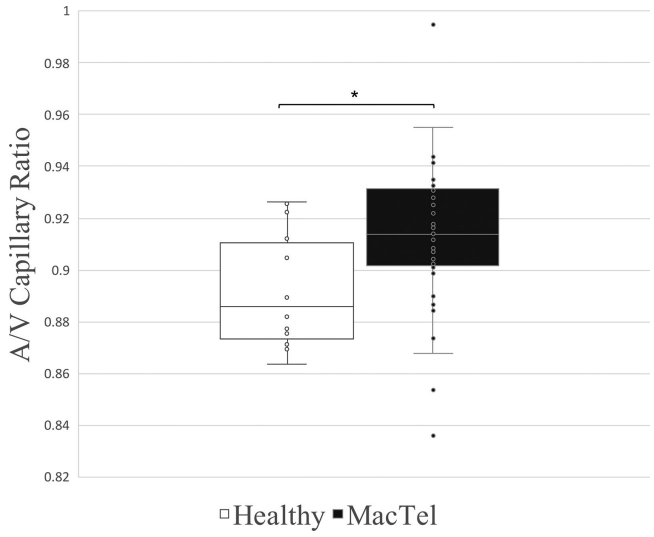

Figure 3. Higher A/V capillary ratio in MacTel than in healthy controls. Box plots indicate that parafoveal A/V capillary ratios in superficial capillary plexus are significantly higher in MacTel subjects (0.914) than healthy control subjects (0.0892; $P = 0.0044$). A/V, arteriovenous; MacTel, macular telangiectasia.

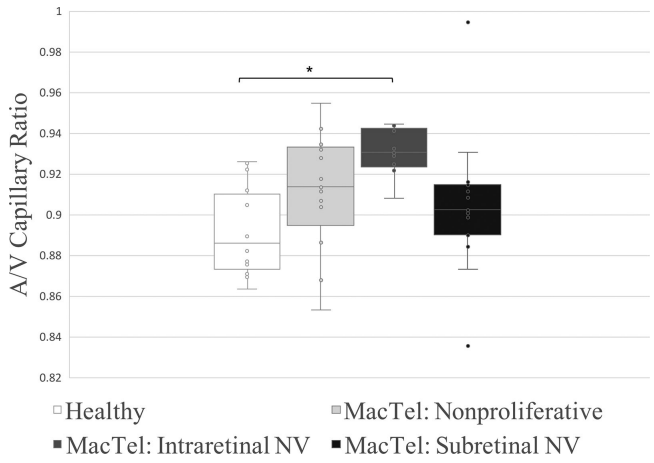

Figure 4. Progression of A/V capillary ratio with MacTel stage. Box plots indicate parafoveal A/V capillary ratios in the superficial capillary plexus for healthy controls, nonproliferative MacTel, intraretinal NV MacTel, and subretinal NV MacTel. Significant differences exist between groups (analysis of variance; $P = 0.0075$). Post hoc analyses show mean A/V capillary ratios are significantly higher in intraretinal NV MacTel (0.931) than in healthy controls (0.892; $P < 0.0043$). A/V, arteriovenous; MacTel, macular telangiectasia; NV, neovascular.

of some vortex veins (circled in green) deviate from the superficial perivenular distribution, suggesting they could be draining into smaller venular branches that overlap with larger arterioles.

This work should be understood with further consideration of its strengths and weaknesses. Our study is the first to evaluate and quantify A/V capillary differences in MacTel. Through automated methods,

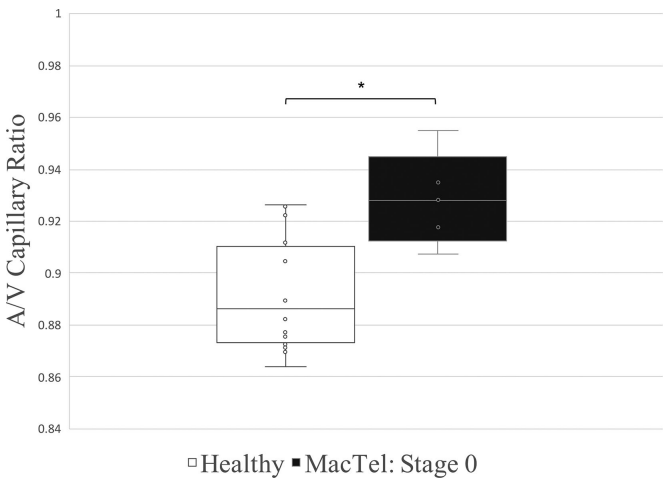

Figure 5. Higher A/V capillary ratio in earliest stage MacTel (stage 0) than in healthy controls. Box plots indicate that parafoveal A/V capillary ratios in the superficial capillary plexus are significantly higher in stage 0 MacTel (0.929) than in healthy controls (0.892; $P = 0.0055$). For reference, stage 0 refers to MacTel in the absence of OCT evidence of photoreceptor loss, macular pigmentary deposits, hyperreflective foci, or neovascularization. A/V, arteriovenous; MacTel, macular telangiectasia; OCT, optical coherence tomography.

we identified an objective, quantitative marker (the A/V capillary ratio) for the earliest stages of MacTel before signs of disease on OCT. On the other hand, our study is limited by a small sample size of 37 eyes from 20 patients. Although gender differences are not known in MacTel, we recognize that a slight female preponderance exists comparing our MacTel and control cohorts. Furthermore, in our quantification of peri-vessel vascular density, we did not adjust for overlapping vascular areas. Instead we considered these zones twice, in the arteriolar and venular distributions. Future studies evaluating arteriovenous vascular density may benefit from adjusting for these areas of overlap. Moreover, our study design was cross-sectional, so we could not evaluate longitudinal A/V capillary ratio changes. We encourage future studies to delineate A/V differences as disease progresses over time to further inform vascular pathogenesis. We also encourage future studies to validate the A/V ratio as a diagnostic marker in early stages of MacTel.

In summary, our data suggest that the A/V capillary ratio may function as a useful metric to detect subtle vascular changes in early MacTel and propose that early capillary loss is venular-predominant. This metric defines one of the earliest changes in MacTel, which, along with DCP telangiectasia, may ultimately play an important role in therapeutic MacTel trials designed to target the earliest stages.

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