

Radial Peripapillary Capillary Alterations in COVID-19: Insights from Optical Coherence Tomography Angiography – A Systematic Review

Triantafillos Loutroukis¹, Pamela D Moore², Robert Kuchen^{1*}

¹ Department of Ophthalmology, University Hospital Zurich, University of Zurich, 8091 Zurich, Switzerland.

² Faculty of Medicine, University of California, San Diego, CA 92093, USA.

Abstract

This review explores the potential of optical coherence tomography angiography (OCTA) to assess the radial peripapillary capillary (RPC) network in individuals infected with SARS-CoV-2, with the aim of understanding COVID-19-related microvascular changes in the retina. A comprehensive search of the PubMed database was conducted to identify original research and review articles that utilized OCTA to visualize the RPC network and quantify its parameters in COVID-19 patients. Current evidence suggests that COVID-19-associated systemic hypoxia, inflammatory processes, and hypercoagulability can compromise the RPC network. Alterations in RPC metrics were detectable both during the acute phase of infection and several months post-infection. Notably, reductions in RPC parameters were associated with subsequent thinning of the retinal nerve fiber layer, indicating potential long-term retinal and optic nerve involvement. OCTA provides a non-invasive means to evaluate retinal microvascular integrity in patients with a history of COVID-19. Monitoring RPC network parameters over time may help identify ischemic or inflammatory sequelae affecting the retina, optic nerve, and choroid, highlighting the importance of ocular follow-up in this population.

Keywords: COVID-19, Optical Coherence tomography angiography, SARS-CoV-2, Radial peripapillary Capillary network

Corresponding author: Robert Kuchen
E-mail: Robertkuchen1968@gmail.com

Received: 11 March 2025

Revised: 12 June 2025

Accepted: 19 June 2025

How to Cite This Article: Loutroukis T, Moore PD, Kuchen R. Radial Peripapillary Capillary Alterations in COVID-19: Insights from Optical Coherence Tomography Angiography – A Systematic Review. Bull Pioneer Res Med Clin Sci. 2025;4(1):126-36. <https://doi.org/10.51847/wGIOEpd65q>

Introduction

In late 2019, a novel coronavirus was identified in the respiratory tract of patients presenting with interstitial pneumonia in Wuhan, China. This virus was subsequently named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing the disease termed coronavirus disease 2019 (COVID-19). By March 2020, COVID-19 had escalated into a global pandemic. Clinical presentations of SARS-CoV-2 infection vary widely, from asymptomatic cases to severe atypical bilateral interstitial

pneumonia. Pathophysiological mechanisms include hyperactivation of the immune response, vascular endothelial injury, and heightened coagulability [1].

The primary cellular receptor for SARS-CoV-2 is angiotensin-converting enzyme 2 (ACE2), expressed in alveolar and intestinal epithelial cells, arterial smooth muscle, and other organs. Notably, ACE2 is also present in ocular tissues, including the choroid and retinal layers such as ganglion cells, vascular endothelium, Müller cells, and photoreceptors [2]. ACE2 is found in glial and neuronal cells of the central nervous system (CNS) [3]. Additionally, neuropilin-1, expressed in the choroid and

retina, serves as an alternative receptor facilitating viral entry [4, 5].

In severe COVID-19, systemic hypoxia may have profound effects on the retina and CNS, both highly metabolically active and sensitive to oxygen deprivation. Hypoxic injury can lead to degeneration of retinal ganglion cells and their axons forming the optic nerve [6]. Optical coherence tomography (OCT) is a noninvasive imaging technique capable of producing high-resolution cross-sectional images of the retina, choroid, and optic nerve, with quantitative and qualitative correlation to histology. OCT angiography (OCTA), an extension of conventional OCT, enables visualization of microvascular networks, including macular vessel density (VD) and the radial peripapillary capillary (RPC) network, located between the inner limiting membrane (ILM) and the retinal nerve fiber layer (RNFL) [7]. OCTA has been applied in systemic conditions such as diabetes, CNS disorders, and carotid artery stenosis [8–12].

The objective of this review is to summarize current evidence on OCTA assessment of the RPC network in COVID-19 patients, addressing early and long-term changes, optic disc blood flow regulation, hypoxia-related effects on the optic nerve, and relationships between RPC metrics, RNFL thickness, and COVID-19 treatment.

Materials and Methods

A Boolean search of the PubMed database was performed to identify original research articles and case reports published between January 2020 and November 2023. The search terms included “radial peripapillary capillary density,” “optical coherence tomography angiography,” and “optic nerve head.” Selection criteria emphasized methodological quality, relevance to the topic, citation count, sample size, and innovative methodology. From the retrieved articles, studies most pertinent to RPC changes in COVID-19 were included in the review.

Radial peripapillary capillary network and OCTA

The RPC network comprises capillaries supplied by the central retinal artery and neighboring retinal arterioles, delivering oxygen and nutrients to the superficial optic nerve head and retinal ganglion cell axons in the peripapillary region [13, 14]. The anterior optic disc and lamina cribrosa receive blood from short posterior ciliary arteries and the Zinn-Haller arterial circle, while the posterior lamina cribrosa is supplied by peripheral pia arteries and additional short posterior ciliary branches [15, 16].

OCTA provides a noninvasive, layer-specific assessment of retinal and optic nerve microvasculature, enabling measurement of VD and visualization of the RPC network. Both spectral-domain (SD) and swept-source (SS) OCT systems are available, with en-face OCTA allowing

segmentation and analysis of individual vascular layers [14, 17, 18]. Peripapillary scans typically cover a 4.5×4.5 mm area centered on the optic disc, with RPC density calculated in four quadrants: superior, nasal, temporal, and inferior (**Figure 1, 2**).

SD-OCT devices generally operate at an A-scan rate of ~70,000 scans/sec, repeating B-scans to generate decorrelation signals for flow detection. SS-OCTA, with higher A-line rates (~100 kHz) and deeper penetration, enables precise segmentation of retinal and optic nerve vascular plexuses and quantitative assessment of VD (**Figure 3**) [14, 19, 20].

The RPC network resides between the RNFL and ILM, closely following the orientation of superficial nerve fibers [21]. Dysfunction in RPC parameters has been implicated in glaucoma and retinal or optic nerve vascular diseases, and conventional fluorescein angiography cannot reliably visualize this network [22, 23]. Studies in healthy individuals demonstrate a positive correlation between RPC density and RNFL thickness, with higher RPC density associated with thicker RNFL, particularly around the optic disc [24, 25]. The RPC network extends ~8 mm from the temporal edge of the optic disc but is absent within ~1 mm of the fovea, decreasing gradually toward the temporal periphery [25]. OCTA allows automatic segmentation and quantification of the RPC network, facilitating layer-by-layer analysis for both clinical and research purposes [23, 24, 26].

Quantitative evaluation of RPC network capillary density is expressed as the proportion of the examined area occupied by blood vessels. The software automatically aligns the Early Treatment Diabetic Retinopathy Study (ETDRS) inner circle with the optic disc, and divides the RPC network into four quadrants—superior, nasal, temporal, and inferior—centered on the optic disc for automated analysis [27].



Figure 1. Color image of the right eye fundus in a COVID-19 patient with the optic nerve head in the

central part; swept-source OCT Triton (author's archive)

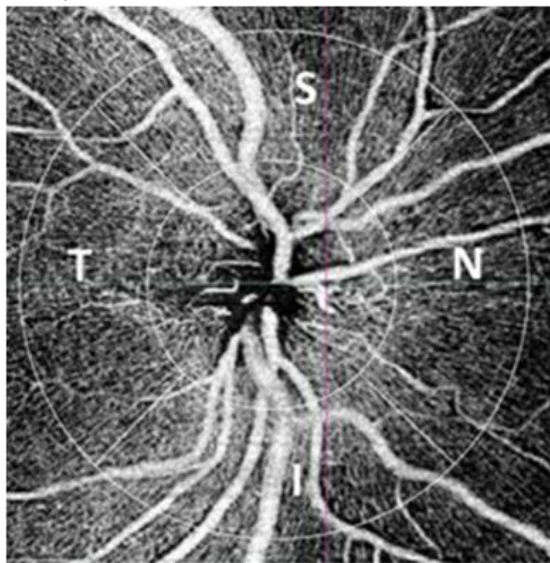


Figure 2. An OCTA image of the optic nerve head in the right eye in a COVID-19 patient; swept-source OCT Triton (author's archive)

Abbreviations: S - superior, N - nasal, T - temporal, I - inferior.

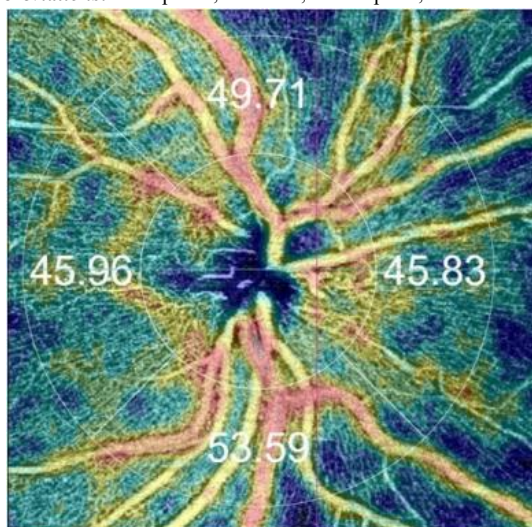


Figure 3. An OCTA map of radial peripapillary capillary (RPC) vessel density (VD) in the right eye in a COVID-19 patient; swept-source OCT Triton (superior RPC = 49.71 %; nasal RPC = 45.83 %; temporal RPC = 45.96 %; inferior RPC = 53.59 %) (author's archive)

Regulation of optic disc blood flow

Blood supply to the retina and optic nerve is tightly controlled by multiple autoregulatory mechanisms. Pressure autoregulation maintains stable blood flow despite fluctuations in intraocular or mean arterial pressure, independent of sympathetic nervous activity. Metabolic autoregulation adjusts blood flow in proportion to local tissue metabolic demand, ensuring consistent oxygen delivery while responding to changes in arterial carbon dioxide levels, similar to cerebral circulation [28].

Laser Doppler flowmetry studies in healthy subjects demonstrated that in most participants, optic disc perfusion remained constant until intraocular pressure rose acutely to 45 mmHg, indicating a wide autoregulatory plateau. Similar findings were observed in retinal circulation. However, some individuals showed no autoregulatory plateau, with blood flow declining linearly in response to decreased ocular perfusion [29]. Anatomical variations in optic nerve head vasculature exist, but their effect on autoregulatory capacity remains unclear [30, 31]. Animal studies suggest that increased metabolic demand may enhance vasodilatory responses and elevate the risk of optic nerve ischemia [32–37]. In humans, however, data on optic nerve perfusion under high metabolic demand are lacking. In glaucoma, reduced optic nerve blood flow combined with upregulation of nitric oxide synthase isoforms may contribute to neurodegeneration [38].

Perfusion of the optic nerve is also sensitive to systemic oxygen and carbon dioxide levels. Hypercapnia increases optic nerve blood flow more markedly than in the retina or brain [39].

Impact of hypoxia on the optic nerve in COVID-19

Retinal hypoxia primarily damages retinal ganglion cells, while photoreceptors and the outer plexiform layer are nourished by the choroid, and ganglion cells rely on the central retinal artery's superficial and deep capillary plexuses. Ganglion cell axons converge to form the optic nerve, where apoptosis or necrosis can occur. Hypoxia triggers the expression of hypoxia-inducible factor 1 α (HIF-1 α) and downstream targets such as vascular endothelial growth factor (VEGF) and nitric oxide synthase. Increased VEGF disrupts the blood-retinal barrier and contributes to retinal edema, while excess nitric oxide and glutamate release promote ganglion cell death. Concurrently, proinflammatory cytokines and free radicals exacerbate cellular injury. These mechanisms are observed in conditions including retinal vascular occlusions, diabetes, COPD, carotid artery stenosis, Takayasu arteritis, hyperviscosity syndromes, and trauma-related retinopathy, as well as in glaucoma [40–42].

Reduced RPC parameters in COVID-19

Abrishami *et al.* [7] investigated retinal vascular changes in 25 COVID-19 patients (mean age 41.5 ± 10.5 years) versus 22 healthy controls (mean age 36.7 ± 7.3 years). OCTA evaluation (RTVue XR Avanti, Optovue, AngioVue) was performed a mean of 20.3 ± 2.9 days after symptom resolution. The study found significant reductions in peripapillary small vessel VD, particularly in the inferior nasal and temporal quadrants, and in all-vessel density in the inferior sector, compared with controls. Conversely, intradiscal small vessel VD was elevated, likely reflecting optic nerve head swelling and congestion. Reduced RPC parameters may indicate SARS-CoV-2

neuroinvasiveness, consistent with animal studies reporting optic nerve inflammation and retinitis pigmentosa, and supported by clinical observations of Guillain-Barré and Miller-Fisher syndromes [43–45].

Ocular complications of COVID-19

Postmortem examinations have confirmed SARS-CoV-2 presence in retinal tissue, with ACE2 receptors detected in the retina and CNS [2, 3]. Thus, COVID-19 can result in retinal and optic nerve pathology. Flow-mediated dilation (FMD), a marker of endothelial function measured via brachial artery reactivity, is impaired in conditions predisposing to cardiovascular disease and may predict subclinical organ damage [46].

Savastano *et al.* [47] assessed FMD and OCTA-derived RPC parameters in 82 post-COVID-19 patients (mean age 52.9 ± 13.5 years). Pathological FMD ($<7\%$) was observed in 37.8% of patients and was associated with reduced RPC perfusion and density, indicating early endothelial dysfunction mediated by excessive immune responses and ACE2-dependent vascular damage [48–50].

A separate study of 40 patients evaluated six months post-COVID-19 hospitalization showed persistent reductions in RPC parameters compared with 40 healthy controls (mean age ~ 49 years), despite the absence of ophthalmic symptoms during acute infection. These findings suggest thrombotic microangiopathy contributes to long-term retinal microvascular impairment, highlighting the potential of OCTA as a noninvasive biomarker for vascular dysfunction following SARS-CoV-2 infection [51].

In a study conducted by Ugurlu *et al.* [52], COVID-19 patients were categorized into neurological, non-neurological, and asymptomatic groups. The cohort included 129 hospitalized COVID-19 patients (mean age 42.3 ± 13.8 years) and 130 healthy controls (mean age 44.9 ± 12.4 years). Ophthalmologic assessments were

performed between 29 and 45 days after a positive PCR test. Global RPC measurements (Tonoref III, Nidek RS-3000 Advance OCT, Bunkyo City, Japan) were significantly reduced in all COVID-19 patient groups compared with controls (neurological: $p = 0.001$; non-neurological: $p = 0.002$; asymptomatic: $p = 0.001$). Sub-analysis of RPC quadrants revealed that superior RPC density was also significantly lower in all patient groups versus controls ($p = 0.001$, $p = 0.001$, $p < 0.001$, respectively), as was inferior RPC density ($p < 0.001$, $p \leq 0.001$, $p < 0.001$, respectively), highlighting consistent peripapillary microvascular alterations across disease subtypes [52].

Guemes-Villahoz *et al.* [53] investigated RPC changes in a pediatric population. The study included 27 children (mean age 11.96 ± 3.8 years) examined 4–8 weeks post-SARS-CoV-2 infection and 45 healthy age-matched controls (mean age 11.02 ± 2.0 years). All patients were asymptomatic visually. Peripapillary perfusion density and flux index (FI) were measured using OCTA (Zeiss Cirrus 5000-HD-OCT Angioplex). The FI quantifies the number of red blood cells traversing a retinal vessel cross-section per unit time, calculated as the total area of perfused vasculature relative to a defined region. Notably, children with COVID-19 demonstrated significantly higher FI across all four quadrants compared with controls ($p < 0.001$). The underlying cause of this finding is unclear but may relate to developmental differences in retinal structure between children and adults, as well as individual variations in immune response to SARS-CoV-2 infection [53–56]. Supporting this, Yuan *et al.* [57] reported age-dependent differences in the immune response to SARS-CoV-2, and variations in ACE2 expression between children and adults may influence viral distribution in organs, including vascular endothelium [58].

A summary of data on RPC parameters obtained by OCTA in various studies are presented in **Table 1**.

Table 1. Radial peripapillary capillary parameters obtained with OCTA in different studies. Summary of OCTA Studies on RPC Parameters in COVID-19 Patients

Study	COVID-19 Patients (n, Mean Age \pm SD, years)	Healthy Controls (n, Mean Age \pm SD, years)	Timing of OCTA Examination	OCTA Instrument	Key Findings on RPC Parameters
Abrishami <i>et al.</i> [7]	n = 25, 41.5 \pm 10.5	n = 22, 36.7 \pm 7.3	Mean 20.3 \pm 2.9 days (range 13–29 days) post-symptom resolution	RTVue XR Avanti, Optovue, AngioVue	Significant reduction in vessel density (VD) in COVID-19 patients: entire peripapillary superficial vascular (SV) VD ($p = 0.032$), inferior nasal SV VD ($p < 0.001$), inferior temporal SV VD ($p = 0.004$), and grid-based VD in the inferior sector ($p = 0.023$). Higher intradiscal SV VD in COVID-19 patients ($p = 0.021$).
Savastano <i>et al.</i> [47]	n = 82, 52.9 \pm 13.5	—	1 month post-hospital discharge	Zeiss Cirrus 5000-HD-OCT, Angioplex	RPC perfusion-flow index (RPCP-FI) correlated with flow-mediated dilation (FMD) ($p = 0.027$) and was significantly lower in patients with pathological FMD ($<7\%$) ($p < 0.001$).
Cennamo <i>et al.</i> [51]	n = 40, 49.7 \pm 12.6	n = 40, 48.6 \pm 12.2	6 months post-hospitalization	RTVue XR Avanti,	Significantly lower RPC parameters in COVID-19 patients vs controls ($p < 0.001$). Significant

				Optovue, AngioVue	correlations between whole-image RPC and retinal nerve fiber layer (RNFL) thickness ($p = 0.001$) and intra-image RPC and RNFL ($p = 0.012$).
Ugurlu <i>et al.</i> [52]	$n = 129$, 42.3 ± 13.8	$n = 130$, 44.9 ± 12.4	29–45 days post-positive SARS-CoV-2 PCR test	Nidek RS-3000, RS-3000 Advanced OCT	Significantly lower global RPC in neurological, non-neurological, and asymptomatic COVID-19 groups vs controls ($p = 0.001$, $p = 0.002$, $p = 0.001$, respectively). Superior and inferior RPC measurements also significantly lower in these groups ($p \leq 0.001$).
Guemes-Villahoz <i>et al.</i> [53]	$n = 27$, 11.96 ± 3.8	$n = 45$, 11.02 ± 2.0	4–8 weeks post-SARS-CoV-2 diagnosis	Zeiss Cirrus 5000-HD-OCT Angioplex	Flow index (FI) significantly higher in all four peripapillary quadrants in children with COVID-19 vs controls ($p < 0.001$).
Savastano <i>et al.</i> [59]	$n = 80$, 52.9 ± 13.5	$n = 30$, 48.5 ± 13.4	1 month post-SARS-CoV-2 infection	Zeiss Cirrus 5000-HD-OCT Angioplex	Reduced RPC perfusion-density (RPCP-PD) in COVID-19 patients vs controls ($p = 0.041$). Lower RPCP-FI in patients with hypertension ($p < 0.001$). Age inversely correlated with RPCP-FI ($p < 0.001$) and RPCP-PD ($p < 0.01$). Lower RPCP-FI and RPCP-PD in patients treated with lopinavir/ritonavir ($p < 0.001$) or antiplatelet drugs ($p = 0.004$ and $p = 0.003$). Significant correlation between RNFL thickness and RPCP-FI/PD ($p < 0.001$).
Burgos-Blasco <i>et al.</i> [60]	$n = 90$, 55.48 ± 8.93	$n = 29$, 52.83 ± 8.49	4 and 12 weeks post-hospitalization	Zeiss Cirrus 5000-HD-OCT Angioplex	Significant differences in RPC parameters between COVID-19 patients and controls. No correlation between RPC parameters and clinical parameters, disease severity, or blood test results.

Notes:

- OCTA: Optical Coherence Tomography Angiography
- RPC: Retinal Peripapillary Capillary
- VD: Vessel Density
- SV: Superficial Vascular
- FMD: Flow-Mediated Dilation
- RNFL: Retinal Nerve Fiber Layer
- RPCP-FI: RPC Perfusion-Flow Index
- RPCP-PD: RPC Perfusion-Density
- p-values indicate statistical significance of differences or correlations.
- "-" indicates no data available for healthy controls in the study

Abbreviations: SD – standard deviation, AV – all vessels, FI – flux index, FMD – flow-dependent dilation, OCTA – optical coherence tomography angiography, RNFL – retinal nerve fiber layer, RPC – radial peripheral capillary, RPCP-FI – perivascular plexus radial capillary flow index, RPCP-PD – perivascular plexus radial capillary-perfusion density, VD – vessel density, SV – small vessels.

Effect of treatment on RPC parameters and correlations between RPC and RNFL in COVID-19 patients

Savastano *et al.* [47] investigated retinal microvascular changes using OCTA (Zeiss Cirrus 5000-HD-OCT Angioplex) in COVID-19 patients one month after hospital discharge. The study included 80 patients (mean age 52.9 ± 13.5 years) and 30 healthy controls (mean age 48.5 ± 13.4 years). The peripapillary radial capillary plexus density (RPCP-D) was significantly lower in COVID-19 patients compared with controls ($p = 0.041$). Patients with hypertension exhibited reduced RPCP flow index (RPCP-FI) ($p < 0.001$), while both RPCP-FI and RPCP-D showed an inverse correlation with age ($p < 0.001$ and $p < 0.01$, respectively).

During hospitalization, patients receiving lopinavir/ritonavir or antiplatelet therapy had lower RPCP-FI and RPCP-D values (lopinavir/ritonavir: $p < 0.001$; antiplatelet therapy: $p = 0.004$ and $p = 0.003$, respectively). A strong linear correlation was observed

between mean retinal nerve fiber layer (RNFL) thickness and both RPCP-FI and RPCP-D ($p < 0.001$). Comorbidities included hypertension (23.8 %), diabetes (42.5 %), and autoimmune diseases (23.8 %). Medications administered included lopinavir/ritonavir (33.8 %), darunavir/ritonavir (43.8 %), hydroxychloroquine (68.8 %), azithromycin (35 %), antiplatelet therapy (7.5 %), and heparin (41.3 %). These findings suggest that perivascular microcirculation of the RNFL is impaired in hospitalized COVID-19 patients, emphasizing the importance of retinal perfusion for ganglion cell function and homeostasis [61]. In glaucoma, RPC density has been shown to correlate with RNFL thickness and visual field index, and reductions in RPC density may serve as an early indicator of glaucomatous changes on OCTA [62–65]. Similar associations between RPC parameters and visual outcomes have been observed in non-arteritic ischemic optic neuropathy, where lower RPC density and flow index correspond to diminished visual acuity and field loss [66–68]. In COVID-19 patients, antiplatelet therapy was also linked with decreased RPCP-FI and RPCP-D values.

The role of platelets in endothelial injury is complex; low platelet counts due to bone marrow suppression or autoimmune mechanisms increase mortality fivefold in COVID-19, whereas elevated platelet counts are observed in sepsis or ARDS, likely driven by increased thrombopoietin levels in pneumonia [69–72].

The observed reduction in RPCP parameters among patients treated with lopinavir/ritonavir may reflect potential vascular endothelial effects of antiviral therapy, though this has not been corroborated by other studies. Similarly, systemic corticosteroids have not been conclusively shown to affect retinal vascular endothelium [47].

Cennamo *et al.* [51] reported significant correlations between whole-image RPC and RNFL thickness ($p = 0.001$) and between intra-image RPC and RNFL ($p = 0.012$) using the Optovue Angiovue system. Immunohistochemical studies have demonstrated ACE2 receptor expression in the ciliary body, choroid, retina, and retinal pigment epithelium, suggesting a route for SARS-CoV-2-mediated vascular injury [73, 74]. Clinically, COVID-19 patients have been reported to develop retinal lesions including cotton wool spots, hemorrhages, and sectoral ischemia, likely attributable to microthrombotic events [75–78]. The anatomical colocalization of the RPC network and RNFL provides a plausible explanation for the observed correlations between these parameters [13].

Long-Term Follow-Up of RPC parameters in COVID-19 patients

Burgos-Blasco *et al.* [60] evaluated 90 COVID-19 patients (mean age 55.48 ± 8.93 years) at 4 and 12 weeks post-hospitalization using OCTA (Zeiss Cirrus 5000-HD-OCT Angioplex), comparing their findings with 29 healthy controls (mean age 52.83 ± 8.49 years). Despite severe acute respiratory distress syndrome during hospitalization, none of the patients reported visual symptoms. Contrary to some previous studies, no significant differences in RPC parameters were observed between COVID-19 patients and controls. Furthermore, RPC values did not correlate with disease severity, clinical markers, or laboratory parameters. Within the COVID-19 cohort, 8 patients (8.9 %) had diabetes, 25 (27.8 %) had dyslipidemia, and 26 (28.9 %) had hypertension. Diabetes was identified as the strongest determinant affecting RPC parameters, with a 1.4 % reduction in global RPC in diabetic patients compared with non-diabetic patients. Weak negative correlations were also noted between RPC parameters, hemoglobin levels, and age. Overall, the study concluded that any retinal endothelial damage induced by SARS-CoV-2 does not appear to persist long-term and is not directly associated with disease severity [60].

Previous investigations by the same group identified reduced macular perfusion on OCTA in COVID-19 patients, particularly in those with elevated D-dimer levels

[79]. The apparent discrepancy in RPC findings may be attributed to the relatively sparse presence of small vessels in the peripapillary region in the current cohort [60]. Since OCTA has demonstrated sensitivity in detecting vascular changes in systemic and ocular diseases, further studies with larger cohorts and extended follow-up periods are warranted [80]. A three-month interval between imaging sessions was chosen due to the potential for thromboembolic complications during this period; however, no such events were observed. This suggests that peripapillary vascular damage may be reversible, and the risk of glaucomatous progression in this cohort appears low, though future reassessment is recommended [60].

Study limitations

Comparisons across studies are limited by the use of varying OCTA systems (spectral-domain vs. swept-source), different devices (e.g., Zeiss vs. Optovue), and distinct analytical algorithms. Additionally, systemic vascular comorbidities such as diabetes and hypertension can independently affect RPC parameters by compromising central retinal and optic nerve perfusion. Even preclinical diabetes has been associated with reduced RPC density [47, 81, 82]. Gomez *et al.* [83] also demonstrated that macular and peripapillary vessel density (VD) can be influenced by hypercholesterolemia, systemic arterial hypertension, and diabetes, with macular VD affected by age and sex, while peripapillary VD was less influenced. Other studies have similarly reported no significant association between age and peripapillary VD [84, 85].

While current OCTA technology enables assessment of RPC parameters, results should be interpreted cautiously. Ophthalmologists should consider comorbid vascular diseases prior to evaluating RPC density, and further research is necessary to draw definitive conclusions.

Conclusions

This review highlights the impact of SARS-CoV-2 infection on retinal, choroidal, and optic nerve vascularization, demonstrating that COVID-19 can alter RPC parameters. Multiple studies report reductions in RPC density among COVID-19 patients compared with healthy controls, with lower RPC values correlating with subsequent thinning of the RNFL. OCT and OCTA provide noninvasive means to monitor retinal and optic nerve health post-infection. For patients with reduced RPC or RNFL parameters, a history of SARS-CoV-2 infection should be considered. Long-term monitoring is essential to understand the potential ischemic consequences for the optic nerve, retina, and choroid and to evaluate the enduring effects of COVID-19 on ocular vascular integrity.

Acknowledgments: None.

Conflict of interest: None.

Financial support: None.

Ethics statement: None.

References

1. Perico L, Benigni A, Casiraghi F, Ng LFP, Renia L, Remuzzi G. Immunity, endothelial injury and complement-induced coagulopathy in COVID-19. *Nat Rev Nephrol.* 2021;17:46–64. <https://doi.org/10.1038/s41581-020-00357-4>
2. Choudhary R, Kapoor MS, Singh A, Bodakhe SH. Therapeutic targets of renin-angiotensin system in ocular disorders. *J Curr Ophthalmol.* 2017;29:7–16. <https://doi.org/10.1016/j.joco.2016.09.009>
3. Zhou Z, Kang H, Li S, Zhao X. Understanding the neurotropic characteristics of SARS-CoV-2: from neurological manifestations of COVID-19 to potential neurotropic mechanisms. *J Neurol.* 2020;267:2179–84. <https://doi.org/10.1007/s00415-020-09929-7>
4. Cantuti-Castelvetri L, Ojha R, Pedro LD, Djannatian M, Franz J, Kuivanen S, et al. Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity. *Science.* 2020;370:856–60. <https://doi.org/10.1126/science.abd2985>
5. Fernández-Robredo P, Selvam S, Powner MB, Sim DA, Fruttiger M. Neuropilin 1 involvement in choroidal and retinal neovascularisation. *PLoS One.* 2017;12:e0169865. <https://doi.org/10.1371/journal.pone.0169865>
6. Mesentier-Louro LA, Shariati MA, Dalal R, Camargo A, Kumar V, Shamskhov EA, et al. Systemic hypoxia led to little retinal neuronal loss and dramatic optic nerve glial response. *Exp Eye Res.* 2020;193:107957. <https://doi.org/10.1016/j.exer.2020.107957>
7. Abrishami M, Daneshvar R, Emamveridian Z, Shoeibi N, Sedighi S, Saeidi Rezvani T, et al. Optic nerve head optical coherence tomography angiography findings after Coronavirus Disease. *J Ophthalmic Vis Res.* 2021;16:9749. <https://doi.org/10.18502/jovr.v16i4.9749>
8. Anaya J-M, Rojas M, Salinas ML, Rodríguez Y, Roa G, Lozano M, et al. Post-COVID syndrome. A case series and comprehensive review. *Autoimmun Rev.* 2021;20:102947. <https://doi.org/10.1016/j.autrev.2021.102947>
9. Kitazawa K, Deinhardt-Emmer S, Inomata T, Deshpande S, Sotozono C. The transmission of SARS-CoV-2 infection on the ocular surface and prevention strategies. *Cells.* 2021;10:796. <https://doi.org/10.3390/cells10040796>
10. Dong J, Chen R, Zhao H, Zhu Y. COVID-19 and ocular complications: a review of ocular manifestations, diagnostic tools, and prevention strategies. *Adv Ophthalmol Pract Res.* 2023;3:33–8. <https://doi.org/10.1016/j.aopr.2022.11.001>
11. Hu K, Patel J, Swiston C, Patel BC. Ophthalmic manifestations of Coronavirus (COVID-19). Tampa, FL, USA: StatPearls Publishing; n.d.
12. Guduru A, Martz TG, Waters A, Kshirsagar AV, Garg S. Oxygen saturation of retinal vessels in all stages of diabetic retinopathy and correlation to ultra-wide field fluorescein angiography. *Invest Ophthalmol Vis Sci.* 2016;57:5278. <https://doi.org/10.1167/iovs.16-20190>
13. Ma X, Hua R. Optic nerve head injury and optical coherence tomography angiography. *Quant Imaging Med Surg.* 2021;11:4497–503. <https://doi.org/10.21037/qims-20-1218>
14. Spaide RF, Klancnik JM Jr, Cooney MJ. Retinal vascular layers imaged by fluorescein angiography and optical coherence tomography angiography. *JAMA Ophthalmol.* 2015;133:45. <https://doi.org/10.1001/jamaophthalmol.2014.3616>
15. Na KI, Lee WJ, Kim YK, Jeoung JW, Park KH. Evaluation of optic nerve head and peripapillary choroidal vasculature using swept-source optical coherence tomography angiography. *J Glaucoma.* 2017;26:665–8. <https://doi.org/10.1097/ijg.0000000000000684>
16. Onda E, Cioffi GA, Bacon DR, van Buskirk EM. Microvasculature of the human optic nerve. *Am J Ophthalmol.* 1995;120:92–102. [https://doi.org/10.1016/s0002-9394\(14\)73763-8](https://doi.org/10.1016/s0002-9394(14)73763-8)
17. Lei J. Compared the results of the RPC parameter from Spectralis, Optovue, Triton OCT instruments. They showed that the reproducibility of the results was high. n.d.
18. N.d. <https://doi.org/10.1038/s41598-018-36279-2>. [Accessed 3 March 2024].
19. Lee CW, Cheng HC, Chang FC, Wang AG. Optical coherence tomography angiography evaluation of retinal microvasculature before and after carotid angioplasty and stenting. *Sci Rep.* 2019;9:51382. <https://doi.org/10.1038/s41598-019-51382-8>
20. Jia Y, Bailey ST, Wilson DJ, Tan O, Klein ML, Flaxel CJ, et al. Quantitative optical coherence tomography angiography of choroidal neovascularization in age-related macular degeneration. *Ophthalmology.* 2014;121:1435–44. <https://doi.org/10.1016/j.ophtha.2014.01.034>
21. Henkind P. Radial peripapillary capillaries of the retina. I. Anatomy: human and comparative. *Br J*

- Ophthalmol. 1967;51:115–23.
<https://doi.org/10.1136/bjo.51.2.115>
22. Alterman M, Henkind P. Radial peripapillary capillaries of the retina. II. Possible role in Bjerrum scotoma. *Br J Ophthalmol.* 1968;52:26–31.
<https://doi.org/10.1136/bjo.52.1.26>.
23. Yu PK, Cringle SJ, Yu DY. Correlation between the radial peripapillary capillaries and the retinal nerve fibre layer in the normal human retina. *Exp Eye Res.* 2014;129:83–92.
<https://doi.org/10.1016/j.exer.2014.10.020>
24. Yu PK, Balaratnasingam C, Xu J, Morgan WH, Mammo Z, Han S, et al. Label-free density measurements of radial peripapillary capillaries in the human retina. *PLoS One.* 2015;10:e0135151.
<https://doi.org/10.1371/journal.pone.0135151>
25. Mase T, Ishibazawa A, Nagaoka T, Yokota H, Yoshida A. Radial peripapillary capillary network visualized using wide-field montage optical coherence tomography angiography. *Invest Ophthalmol Vis Sci.* 2016;57:OCT504.
<https://doi.org/10.1167/iovs.15-18877>
26. Tan PEZ, Balaratnasingam C, Xu J, Mammo Z, Han SX, Mackenzie P, et al. Quantitative comparison of retinal capillary images derived by speckle variance optical coherence tomography with histology. *Invest Ophthalmol Vis Sci.* 2015;56:3989.
<https://doi.org/10.1167/iovs.14-15879>
27. Lee JY, Kim JP, Jang H, Kim J, Kang SH, Kim JS, et al. Optical coherence tomography angiography as a potential screening tool for cerebral small vessel diseases. *Alzheimer's Res Ther.* 2020;12:638.
<https://doi.org/10.1186/s13195-020-00638-x>
28. Harris A, Thomas A, Ciulla A, Chung HS. Regulation of retinal and optic nerve blood flow. *Arch Ophthalmol.* 1998;116:1491–5.
<https://doi.org/10.1001/archophth.116.11.1491>
29. Pillunat LE, Anderson DR, Knighton RW, Joos KM, Feuer WJ. Autoregulation of human optic nerve head circulation in response to increased intraocular pressure. *Exp Eye Res.* 1997;64:737–44.
<https://doi.org/10.1006/exer.1996.0263>
30. Hayreh SS. Factors influencing blood flow in the optic nerve head. *J Glaucoma.* 1997;6:412–25.
<https://doi.org/10.1097/00061198-199712000-00012>
31. Hayreh SS. The 1994 Von Sallman Lecture. The optic nerve head circulation in health and disease. *Exp Eye Res.* 1995;61:259–72.
[https://doi.org/10.1016/s0014-4835\(05\)80121-6](https://doi.org/10.1016/s0014-4835(05)80121-6)
32. Neely KA, Ernest JT, Goldstick TK. Retinal tissue oxygen tension in normoxic cats under enflurane anesthesia. *Invest Ophthalmol Vis Sci.* 1995;36:1943–6.
33. Buerk D, Riva G, Cranstoun CE. Frequency and luminance-dependent blood flow and K⁺ ion changes during flicker stimuli in cat optic nerve head. *Invest Ophthalmol Vis Sci.* 1995;36:2216–22.
34. Van V, Riva T. Variations in blood flow at optic nerve head induced by sinusoidal flicker stimulation in cats. *J Physiol (Lond).* 1995;482:189–202.
35. Buerk DG, Riva CE, Cranstoun SD. Nitric oxide has a vasodilatory role in cat optic nerve head during flicker stimuli. *Microvasc Res.* 1996;52:13–26.
<https://doi.org/10.1006/mvre.1996.0040>
36. Michelson G, Langhans MJ, Groh MJ. Perfusion of the juxtapapillary retina and the neuroretinal rim area in primary open angle glaucoma. *J Glaucoma.* 1996;5:91–8.
<https://doi.org/10.1097/00061198-199604000-00003>.
37. Riva CE, Grunwald JE, Petrig BL. Reactivity of the human retinal circulation to darkness: a laser Doppler velocimetry study. *Invest Ophthalmol Vis Sci.* 1983;24:737–40.
38. Neufeld AH, Hernandez MR, Gonzalez M. Nitric oxide synthase in the human glaucomatous optic nerve head. *Arch Ophthalmol.* 1997;115:497–503.
<https://doi.org/10.1001/archophth.1997.01100150499009>
39. Harris A, Anderson DR, Pillunat L, Joos K, Knighton RW, Kagemann L, et al. Laser Doppler flowmetry measurement of changes in human optic nerve head blood flow in response to blood gas perturbations. *J Glaucoma.* 1996;5:258–65.
<https://doi.org/10.1097/00061198-199608000-00008>
40. Kaur C, Foulds WS, Ling EA. Hypoxia-ischemia and retinal ganglion cell damage. *Clin Ophthalmol.* 2008;2:879–89.
<https://doi.org/10.2147/opth.s3361>
41. Costa VP, Harris A, Stefánsson E, Flammer J, Krieglstein GK, Orzalesi N, et al. The effects of antiglaucoma and systemic medications on ocular blood flow. *Prog Retin Eye Res.* 2003;22:769–805.
[https://doi.org/10.1016/s1350-9462\(03\)00064-8](https://doi.org/10.1016/s1350-9462(03)00064-8)
42. Wax MB, Tezel G. Neurobiology of glaucomatous optic neuropathy: diverse cellular events in neurodegeneration and neuroprotection. *Mol Neurobiol.* 2002;26:45–55.
<https://doi.org/10.1385/MN:26:1:045>
43. Seah I, Agrawal R. Can the Coronavirus disease 2019 (COVID-19) affect the eyes? A review of coronaviruses and ocular implications in humans and animals. *Ocul Immunol Inflamm.* 2020;28:391–5.
<https://doi.org/10.1080/09273948.2020.1738501>
44. Su XW, Palka SV, Rao RR, Chen FS, Brackney CR, Cambi F. SARS-CoV-2-associated Guillain-Barre syndrome with dysautonomia. *Muscle Nerve.* 2020;62:E48–9.

45. Fernández-Domínguez J, Ameijide-Sanluis E, García-Cabo C, García-Rodríguez R, Mateos V. Miller-Fisher-like syndrome related to SARS-CoV-2 infection (COVID-19). *J Neurol*. 2020;267:2495–6. <https://doi.org/10.1007/s00415-020-09912-2>
46. Thijssen DHJ, Black MA, Pyke KE, Padilla J, Atkinson G, Harris RA, et al. Assessment of flow-mediated dilation in humans: a methodological and physiological guideline. *Am J Physiol Heart Circ Physiol*. 2011;300:H2–12. <https://doi.org/10.1152/ajpheart.00471.2010>
47. Savastano MC, Santoro L, Crincoli E, Fossataro C, Gambini G, Savastano A, et al. Radial peripapillary capillary plexus perfusion and endothelial dysfunction in early post-SARS-CoV-2 infection. *Vision*. 2022;6:26. <https://doi.org/10.3390/vision6020026>
48. Maruhashi T, Soga J, Fujimura N, Idei N, Mikami S, Iwamoto Y, et al. Endothelial dysfunction, increased arterial stiffness, and cardiovascular risk prediction in patients with coronary artery disease: FMD-J (Flow-Mediated Dilation Japan) Study A. *J Am Heart Assoc*. 2018;7:e008857.
49. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the ‘Cytokine Storm’ in COVID-19. *J Infect*. 2020;80:607–13. <https://doi.org/10.1016/j.jinf.2020.03.037>
50. Yan T, Xiao R, Lin G. Angiotensin-converting enzyme 2 in severe acute respiratory syndrome coronavirus and SARS-CoV-2: a double-edged sword? *FASEB J*. 2020;34:6017–26. <https://doi.org/10.1096/fj.202000782>
51. Cennamo G, Reibaldi M, Montorio D, D'Andrea L, Fallico M, Triassi M. Optical coherence tomography angiography features in post-COVID-19 pneumonia patients: a pilot study. *Am J Ophthalmol*. 2021;227:182–90. <https://doi.org/10.1016/j.ajo.2021.03.015>
52. Ugurlu A, Agcayazi SB, Icel E, Budakoglu O, Unver E, Barkay O, et al. Assessment of the optic nerve, macular, and retinal vascular effects of COVID-19. *Can J Ophthalmol*. 2023;58:570–6. <https://doi.org/10.1016/j.jcjo.2022.06.016>
53. Guemes-Villahoz N, Burgos-Blasco B, Perez-Garcia P, Fernández-Vigo JI, Morales-Fernandez L, Donate-Lopez J, et al. Retinal and peripapillary vessel density increase in recovered COVID-19 children by optical coherence tomography angiography. *J AAPOS*. 2021;25:325.e1–6. <https://doi.org/10.1016/j.jaapos.2021.06.004>
54. Fernández-Vigo JI, Kudsieh B, Shi H, Arriola-Villalobos P, Donate-López J, García-Feijóo J, et al. Normative database and determinants of macular vessel density measured by optical coherence tomography angiography. *Clin Exp Ophthalmol*. 2020;48:44–52. <https://doi.org/10.1111/ceo.13648>
55. Ahn HC, Son HW, Kim JS, Lee JH. Quantitative analysis of retinal nerve fiber layer thickness of normal children and adolescents. *Kor J Ophthalmol*. 2005;19:195–200. <https://doi.org/10.3341/kjo.2005.19.3.195>
56. Sunita M, Manisha S, Sanjeev M, Ravi K, Aarzoo J, Ajai A. Anatomical and clinical characteristics of paediatric and adult eyes. *Natl J Clin Anat*. 2021;10:5–9.
57. Yuan Y, Wang QP, Sun D, Wu ZB, Peng H, Liu XW, et al. Differences in immune responses between children and adults with COVID-19. *Curr Med Sci*. 2021;41:58–61. <https://doi.org/10.1007/s11596-021-2318-1>
58. Bunyavanich S, Do A, Vicencio A. Nasal gene expression of angiotensin-converting enzyme 2 in children and adults. *JAMA*. 2020;323:2427–9. <https://doi.org/10.1001/jama.2020.8707>
59. Savastano A, Crincoli E, Savastano MC, Younis S, Gambini G, Rizzo S. Peripapillary retinal vascular involvement in early post-COVID-19 patients. *J Clin Med*. 2020;9:2895. <https://doi.org/10.3390/jcm9092895>
60. Burgos-Blasco B, Güemes-Villahoz N, Vidal-Villegas B, Garcia-Feijoo J, Donate-Lopez J, Martin-Sanchez FJ, et al. Optic nerve head vessel density assessment in recovered COVID-19 patients: a prospective study using optical coherence tomography angiography. *J Glaucoma*. 2021;30:711–7. <https://doi.org/10.1097/ijg.0000000000001858>
61. Savastano A, Crincoli E, Savastano M, Younis S, Gambini G, De Vico U, et al. Peripapillary retinal vascular involvement in early post-COVID-19 patients. *J Clin Med*. 2020;9:2895. <https://doi.org/10.3390/jcm9092895>
62. Jung F, Krüger-Genge A, Franke RP, Hufert F, Küpper JH. COVID-19 and the endothelium. *Clin Hemorheol Microcirc*. 2020;75:7–11. <https://doi.org/10.3233/ch-209007>
63. Loon SC, Lun K. SARS: a timely reminder. *Br J Ophthalmol*. 2013;97:1217–8. <https://doi.org/10.1136/bjophthalmol-2013-303596>
64. Jia Y, Simonett JM, Wang J, Hua X, Liu L, Hwang TS, et al. Wide-field OCT angiography investigation of the relationship between radial peripapillary capillary plexus density and nerve fiber layer thickness. *Invest Ophthalmol Vis Sci*. 2017;58:5188–94. <https://doi.org/10.1167/iovs.17-22593>
65. Mansoori T, Sivaswamy J, Gamalapati JS, Balakrishna N. Radial peripapillary capillary density

- measurement using optical coherence tomography angiography in early glaucoma. *J Glaucoma*. 2017;26:438–43. <https://doi.org/10.1097/IJG.0000000000000649>
66. Cerdá-Ibáñez M, Duch-Samper A, Clemente-Tomás R, Torrecillas-Picazo R, Del Río NR, Manfreda-Dominguez L. Correlation between ischemic retinal accidents and radial peripapillary capillaries in the optic nerve using optical coherence tomographic angiography: observations in 6 patients. *Ophthalmol Eye Dis*. 2017;9:1179172117702889. <https://doi.org/10.1177/1179172117702889>
 67. Mansoori T, Sivaswamy J, Gamalapati JS, Agraharam SG, Balakrishna N. Measurement of radial peripapillary capillary density in the normal human retina using optical coherence tomography angiography. *J Glaucoma*. 2017;26:241–6. <https://doi.org/10.1097/IJG.0000000000000594>
 68. Augstburger E, Zéboulon P, Keilani C, Baudouin C, Labbe A. Retinal and choroidal microvasculature in nonarteritic anterior ischemic optic neuropathy: an optical coherence tomography angiography study. *Invest Ophthalmol Vis Sci*. 2018;59:870–7. <https://doi.org/10.1167/iovs.17-22996>
 69. Jin Y, Yang H, Ji W, Wu W, Chen S, Zhang W, et al. Virology, epidemiology, pathogenesis, and control of COVID-19. *Viruses*. 2020;12:372. <https://doi.org/10.3390/v12040372>
 70. Romacho T, Valencia I, Ramos-González M, Vallejo S, López-Esteban M, Lorenzo O, et al. Visfatin/eNamt induces endothelial dysfunction in vivo: a role for Toll-Like Receptor 4 and NLRP3 inflammasome. *Sci Rep*. 2020;10:5386. <https://doi.org/10.1038/s41598-020-62190-w>
 71. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. *Clin Chim Acta*. 2020;506:145–8. <https://doi.org/10.1016/j.cca.2020.03.022>
 72. Liu X, Zhang R, He G. Hematological findings in coronavirus disease 2019: indications of progression of disease. *Ann Hematol*. 2020;99:1421–8. <https://doi.org/10.1007/s00277-020-04103-5>
 73. Strain WD, Chaturvedi N. The renin-angiotensin-aldosterone system and the eye in diabetes. *J Renin Angiotensin Aldosterone Syst*. 2002;3:243–6. <https://doi.org/10.3317/jraas.2002.045>
 74. Bertoli F, Veritti D, Danese C, Samassa F, Sarao V, Rassu N, et al. Ocular findings in COVID-19 patients: a review of direct manifestations and indirect effects on the eye. *J Ophthalmol*. 2020;2020:1–9. <https://doi.org/10.1155/2020/4827304>
 75. Invernizzi A, Torre A, Parrulli S. Retinal findings in patients with COVID-19: results from the SERPICO-19 study. *EClinicalMedicine*. 2020;26:100520.
 76. Pereira LA, Soares LCM, Nascimento PA, Cirillo LRN, Sakuma HT, Veiga GL da, et al. Retinal findings in hospitalised patients with severe COVID-19. *Br J Ophthalmol*. 2022;106:102–5. <https://doi.org/10.1136/bjophthalmol-2020-317576>
 77. Acharya S, Diamond M, Anwar S, Glaser A, Tyagi P. Unique case of central retinal artery occlusion secondary to COVID-19 disease. *IDCases*. 2020;21:e00867. <https://doi.org/10.1016/j.idcr.2020.e00867>
 78. Landecho MF, Yuste JR, Gándara E, Sunsundegui P, Quiroga J, Alcaide AB, et al. COVID-19 retinal microangiopathy as an in vivo biomarker of systemic vascular disease? *J Intern Med*. 2021;289:116–20. <https://doi.org/10.1111/joim.13156>
 79. Guemes-Villahoz N, Burgos-Blasco B, Vidal-Villegas B, Donate-López J, Martín-Sánchez FJ, Porta-Etessam J, et al. Reduced retinal vessel density in COVID-19 patients and elevated D-dimer levels during the acute phase of the infection. *Med Clin (Barc)*. 2021;156:541–6. <https://doi.org/10.1016/j.medcle.2020.12.020>
 80. Pascual-Prieto J, Burgos-Blasco B, Ávila Sánchez-Torija M, Fernández-Vigo JI, Arriola-Villalobos P, Barbero Pedraz MA, et al. Utility of optical coherence tomography angiography in detecting vascular retinal damage caused by arterial hypertension. *Eur J Ophthalmol*. 2020;30:579–85. <https://doi.org/10.1177/1120672119831159>
 81. Pilotto E. Retinal microvascular and neuronal changes are also present, even if differently, in adolescents with type 1 diabetes without clinical diabetic retinopathy. *J Clin Med*. 2022;11:xxx.
 82. Zhang M, Jia F, Ch S, Yang J, Wang S. Quantitative analysis of the RPC vessel density and the RNFL thickness in patients with type 2 diabetes mellitus by using OCT angiography. *Ophthalmic Res*. 2021;64:951–9.
 83. Gomez MS, Zeng N, Catagna GE, Arribas-Pardo P, Garcia-Feijoo J, Mendez-Hernandez C. Effect of hypercholesterolemia, systemic arterial hypertension and diabetes mellitus on peripapillary and macular vessel density on superficial vascular plexus in glaucoma. *J Clin Med*. 2023;12:2071. <https://doi.org/10.3390/jcm12052071>
 84. Gadde SGK, Anegondi N, Bhanushali D, Chidambar L, Yadav NK, Khurana A, et al. Author response: quantification of vessel density in retinal optical coherence tomography angiography images using local fractal dimension. *Invest Ophthalmol Vis Sci*.

- 2016;57:2263. <https://doi.org/10.1167/iovs.16-19368>
85. Rao HL, Pradhan ZS, Weinreb RN, Reddy HB, Riyazuddin M, Sachdeva S, et al. Determinants of peripapillary and macular vessel densities measured by optical coherence tomography angiography in normal eyes. *J Glaucoma*. 2017;26:491–7. <https://doi.org/10.1097/IJG.0000000000000655>