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Optical coherence tomography angiography features in post COVID-19 pneumonia patients: a pilot study

Short title: OCTA and Covid-19

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ABSTRACT

Purpose: To investigate retinal vessel density changes in macular and papillary regions in post SARS-CoV-2 pneumonia patients by means of optical coherence tomography angiography (OCTA).

Design: Prospective, observational, cohort study.

Methods: Forty eyes of 40 patients (mean age 49.7 ± 12.6) post SARS-CoV-2 infection and 40 healthy subjects were enrolled in this study. Covid-19 patients had to be fully

recovered from Covid-19 pneumonia and were evaluated 6 months after Covid-19 infection. The primary outcome was the results of the OCTA study of the following vascular structures: vessel density (VD) in the retinal superficial capillary plexus (SCP), deep capillary plexus (DCP), radial peripapillary capillaries (RPC), compared to those of controls. We also evaluated the structural spectral domain (SD)-OCT parameters: ganglion cell complex (GCC) and retinal nerve fiber layer (RNFL).

Results: The patients showed a significant reduction in VD of the SCP in whole image and in the DCP in all sectors compared to healthy subjects ($p<0.05$). Covid-19 patients featured a reduced VD of the RPC compared to controls ($p<0.001$). No difference was found in the GCC, while the RNFL was reduced in the COVID-19 group compared to controls ($p=0.012$). Significant correlations were found between the RNFL and VD of the SCP, DCP, RPC and FAZ area in the Covid-19 group ($p<0.05$).

Conclusion: OCTA showed retinal vascular changes in subjects fully recovered from Covid-19 pneumonia. These findings could be a consequence of a thrombotic microangiopathy that affected retinal structures as well as other systemic organs. OCTA could represent a valid, non-invasive biomarker of early vascular dysfunction after SARS-CoV-2 infection.

Keywords: OCTA, vessel density, Covid-19, SARS-CoV-2, thrombotic microangiopathy

INTRODUCTION

Since December 2019, the SARS-CoV-2 outbreak has been a dramatic issue all over the world. On March the 11th 2020, the WHO declared a pandemic.[1] All countries have been tremendously affected and all healthcare systems have been overwhelmed by this calamity. To date, no effective therapy has been developed and there is no clue as to whether a future vaccine will be able to stop it.[2]

This infection can be completely asymptomatic, or it can involve several organs and tissues, eyes included. A hypercoagulable state, leading to thromboembolic events and disseminated intravascular coagulation, has been observed in many critical patients.[3,4] Recent research demonstrated diffuse endothelial damage that causes ischemic injury to different body districts. Such an impairment of the microcirculatory system may lead to functional disorders in multiple organs.[5,6]

Ocular implications have not been fully studied. Non-specific retinal signs, such as micro-hemorrhages, vein dilatation, cotton-wool spots, and flame-shaped hemorrhages, have been reported in many recent studies. However, it was not possible to clearly establish whether these signs were secondary to COVID-19 or just incidental findings, given the high presence of comorbidities in the general population.[7–9] Optical coherence tomography angiography (OCTA), a new non-invasive imaging technique, may provide qualitative and quantitative features of retinal and choroidal vascularization and could monitor the changes of vascular perfusion in patients with Covid-19.[10,11]

The aim of this pilot study was to evaluate retinal vessel density (VD) in patients who fully recovered from Covid-19 pneumonia, and to compare these findings with healthy controls.

METHODS

The present study was a prospective, observational, cohort study. The study protocol was registered on clinicaltrial.gov (NCT04601012). The study adhered to the tenets of the Declaration of Helsinki and was approved by the local Institutional Review Board. Written informed consent was obtained from all subjects enrolled in the study.

Consecutive patients who had been admitted to Hospital with Covid-19 pneumonia and had fully recovered from the infection were referred after 6 months from discharge to the Eye Clinic of the University of Naples "Federico II" in October 2020, and were assessed for eligibility. The following inclusion criteria had to be satisfied to be enrolled: a) history of hospital admission for Covid-19 pneumonia, classified as moderate illness, not requiring supplemental oxygen; b) full recovery; c) 2 consecutive upper respiratory tract samples negative for viral nucleid acid. Moderate illness was defined as evidence of disease affecting the lower respiratory tract with an SpO2 ≥ 94%, not requiring administration of supplemental oxygen.[12] Exclusion criteria were congenital eye disease, high myopia and high hyperopia (greater than 6 diopters), retinal vascular diseases, macular diseases, previous ocular surgery except uneventful cataract surgery, history of other ocular disorders, or significant lens opacity to avoid low-quality OCT-A images. All subjects with a history of stroke, blood disorders, diabetes, uncontrolled hypertension and neurodegenerative disease were also excluded. Each patient enrolled in the Covid-19 group was age- and gender-matched with a healthy control. Each subject underwent a complete ocular assessment including best corrected visual acuity measurement (BCVA), slit-lamp biomicroscopy, Goldmann applanation tonometry, dilated fundus examination. Snellen BCVA measurement was based on the Early Treatment Diabetic Retinopathy Study (ETDRS) charts (converted into logMAR for statistical analysis). Spectral domain-optical coherence tomography (SD-OCT) and OCTA were performed by two independent observers (GC, DM) that carefully reviewed the OCTA and SD-OCT scans to confirm accurate retinal layer segmentation.

Only one eye for each participant was randomly selected and included in the analysis.

The primary outcome of this study was the vessel density of macular and papillary regions on OCTA in the Covid-19 group, compared with the control group. Foveal avascular zone, sd-OCT parameters, such as ganglion cell complex (GCC) and retinal nerve fiber layer (RNFL), were considered as secondary outcome measures, as well as clinical variables, including BCVA and retinal findings.

Spectral Domain Optical Coherence Tomography

All the patients were examined using spectral domain-OCT (SD-OCT) (software RTVue XR version 2017.1.0.151, Optovue Inc., Fremont, CA, USA). The optic nerve head (ONH) analysis measures the disc area, the rim area, and the cup-to-disc ratio and was used to assess the RNFL thickness, calculated along a 3.45-mm diameter circle around the optic disc. The GCC thickness was obtained from a 7 × 7 mm grid of the macula centered 1-mm temporal to the fovea. The GCC thickness is the distance from the internal limiting membrane to the outer boundary of the inner plexiform layer.[13]

Optical Coherence Tomography Angiography

All the subjects underwent OCTA (Optovue Angiovue System, software ReVue XR version 2017.1.0.151, Optovue Inc., Fremont, CA, USA). It is based on a split-spectrum amplitude decorrelation algorithm (SSADA).[14] The OCTA analysis divided the macular region into whole image, fovea and parafovea in each vascular network of the retina, according to the ETDRS classification of diabetic retinopathy.[15] The software (AngioAnalytic™) automatically calculated the vessel density in different retinal vascular networks: Superficial Capillary Plexus (SCP) and Deep Capillary Plexus (DCP) in a 6x6 mm quadrat scan centered on the fovea. Moreover, the software automatically calculated the Foveal Avascular Zone (FAZ) area in the full retinal plexus.[16] The VD of the Radial Peripapillary Capillary plexus (RPC), analyzing the whole papillary region, inside the disc and peripapillary region with an area scan of 4.5 x 4.5 mm, was automatically calculated by the Angio Vue disc mode.[17]
The OCTA device included the 3D Projection Artifact Removal (PAR) algorithm to remove projection artifacts, for improving depth resolution on OCTA signal and then distinguishing vascular plexus-specific features.[18-20] Each OCTA scan underwent Automatic Scan Quality (1~10), values >=6 were accepted.
OCTA images with a Signal Strength Index (SSI) less than 80 and residual motion artifacts were excluded from the analysis.

Statistical Analysis

Statistical analysis was performed with the Statistical Package for Social Sciences (Version 25 for Windows; SPSS Inc, Chicago, Ill, USA). The Chi-squared test was used to determine differences in terms of sex. Student's t-test analysis for independent samples was used to compare structural SD-OCT and OCTA parameters between patients and controls. The multiple linear regression model was used to evaluate the relationship between OCT and OCTA parameters in the post Covid-19 group. The agreement between two observers in the measurement of SD-OCT and OCTA parameters was assessed using the intraclass correlation coefficient. A p value of < 0.05 was considered statistically significant.

RESULTS

A total of 40 eyes of 40 patients were included in the Covid-19 group (mean age 49.7 ± 12.6; 11 females and 29 males) and a total of 40 eyes of 40 age- and gender-matched healthy subjects in the control group (mean age 48.6 ± 12.2). Demographic and ocular characteristics of enrolled patients are reported in Table 1. Mean BCVA was 0.06 ± 0.06 logMAR (Snellen 20/23) and 0.05 ± 0.05 logMAR (Snellen 20/22) in the Covid-19 group and the control group, respectively. All patients included in the Covid-19 group presented unremarkable ocular examination on the slit lamp as well as normal fundus examination. None of them complained of eye symptoms at the time of enrollment and no participant had a history of previous eye symptoms during hospital admission for Covid-19 pneumonia. All patients were phakic in both the Covid-19 and the control group. Recovery time from SARS-CoV-2 infection, confirmed by two consecutive negative oropharyngeal swabs, was 4.1 ± 1.3 months. There is no significant correlation between OCTA parameters and recovery time after SARS-CoV-2 infection (p=0.732).

On OCTA imaging, SSI value was comparable between the two groups (p=0.921). SCP vascular density was decreased in the COVID-19 group compared to the control group

only in the whole image (p=0.038). DCP vascular density showed a significant reduction in all macular sectors in the COVID-19 group compared to the control group (p=0.029, p=0.016 and p=0.027 in whole image, parafovea and fovea, respectively). A significant reduction of RCP vessel density in the whole image was found in the COVID-19 group compared to the control group (p<0.001) (Table 2, Figure 1). The FAZ area did not show any significant change between the two study groups (p>0.05) (Table 2, Figure 1). The structural SD-OCT showed no significant difference in GCC average (p=0.309), while RNFL average was decreased (p=0.012) in the COVID-19 group compared to the control group (Table 2, Figure 1).

The agreement between two observers for measuring the SD-OCT and OCTA parameters was excellent, with an intraclass correlation coefficient >0.8 (Table 3)

Multiple regression analysis revealed in all Covid-19 patients a significant relationship between reduced RNFL average thickness and impaired OCTA parameters (r=0.818, p=0.001), in particular with SCP parafovea (p=0.004), DPC whole image (p=0.006), DCP parafovea (p=0.002), RPC whole image (p=0.001), RPC inside (p=0.012) and FAZ area (p=0.008). No significant relationship was found between GCC average thickness and OCTA parameters (r=0.712, p=0.057) (Table 4).

DISCUSSION

To the best of our knowledge, this is the first report that investigated macular and peripapillary vessel density changes using OCTA in subjects after the Covid-19 infection. Our results show a significantly altered retinal vascular density in post Covid-19 subjects compared with healthy controls: DCP vessel density was reduced in all macular regions, while SCP and RCP vessel density was reduced only in the whole image. These findings could be explained by the multiple pathogenic mechanisms linked to the SARS-CoV-2 infection, including thrombo-inflammatory microangiopathy and angiotensin-converting enzyme (ACE) 2 disruption.[6,21]

Complement-mediated thrombotic microangiopathy (TMA) has been assumed to be one of the main factors involved in Covid-19 related microvascular damage.[22] Complement activation plays a central role in the pathophysiology of TMA determining platelet activation, leukocyte recruitment, endothelial cell dysfunction and coagulation.[23,24] Complement cascade activation is, in turn, a response to an endothelial injury secondary to local renin-angiotensin system disruption.[6,21] Endothelial cells express high levels of angiotensin-converting enzyme 2 (ACE 2) receptors, which are used by SARS-CoV-2 to gain entry into the cell that is then disrupted.[25] Endothelial damage and subsequent thrombo-inflammatory microangiopathy lead to a hypercoagulative state that may explain the microvascular occlusion and the consequent multi-organ failure that characterizes advanced disease.[21,26]

Although severe respiratory complications are the main clinical features, Covid-19-associated coagulopathy predisposes to a very wide spectrum of thromboembolic events, including pulmonary embolism, large-vessel ischemic strokes, venous thrombosis, renal failure, and cardiomyopathy, which can culminate in multiple organ dysfunction.[21,27,28]

It should be noted that immunohistochemical studies conducted on the human eye reported that also the ciliary body, choroid, retina and retinal pigment epithelium showed significant levels of ACE 2 receptors.[29] Therefore, SARS-CoV-2 could cause microvascular damage to retinal and choroidal vessels.[9]

Several retinal findings have been reported in Covid-19 patients, such as cotton-wool exudates, retinal flame-shaped hemorrhages, central retinal artery occlusion, and sectorial retinal pallor. All these could be considered signs of retinal vascular impairment following thrombotic complications.[7–9,30,31] Hitherto, only one report conducted by Savastano et al. used OCTA imaging in Covid-19 patients.[32] The authors demonstrated a reduction of perfusion density of the radial peripapillary capillary plexus in Covid-19 patients compared to healthy controls after one month from infection. Our results on RCP are in line with those of Savastano et al.[32] However, OCTA imaging focused mainly on the study of RCP, with no information on other regions or plexuses. Furthermore, the present study has shed light on vascular changes affecting capillary plexuses of the macula area as well. Our analysis also revealed a significant relationship between RNFL and OCTA parameters, which could be explained by the anatomical localization of the RCP in the peripapillary RNFL.[33] Covid-19 related thrombotic microangiopathy could have caused vascular perfusion damage to the SCP and RPC, leading to interference in axoplasmic flow and subsequent retinal structural loss. The anastomosis that interconnect the SCP with the DCP may explain the possible correlation between this plexus and the RNFL.

Interestingly, our findings showed no significant change in GCC thickness. Ganglion cell layer is expected to get reduced when there is a thinning of RNFL, since the latter one consists mainly of the ganglion cell axons. Probably, the vessel density of SCP was not compromised enough to cause such a reduction of metabolic support to GCC that would have determined an anatomic thinning of this layer.

OCTA highlighted a much more significant impairment of the DCP than the SCP in Covid-19 patients compared to controls, as also occurs in diabetic retinopathy and other systemic vasculopathies.[34,35] The vascular structure of the deep plexus is characterized by a fine capillary network that makes it more vulnerable to thrombotic events compared to the greater vascular calibre of the SCP.[36] Of note, our OCTA findings showed that the perfusion loss was diffuse, with no specific pattern. Similarly, no specific pattern was demonstrated in RNFL thinning, which was a diffuse reduction of the whole area. There is no sectorial co-localization but a significantly correlation between damages in OCT and OCTA parameters.

There was no pattern of retinal structural and perfusion loss and no sectorial co-localization of damages in OCT and OCTA parameters

All patients enrolled in the Covid-19 group of this study had no visual acuity reduction, no visual symptoms and their ocular examination proved unremarkable. They also had no history of any eye symptoms during their admission. The presence of retinal microvascular changes on OCTA imaging in otherwise healthy and asymptomatic eyes has a great scientific relevance. This might support the hypothesis of widespread microvascular damage that could be clinically silent. Idilman et al. found lung and kidney perfusion deficits in patients affected by mild to moderate Covid-19.[37] Dual-energy computed tomography angiography showed lung perfusion deficits in 26% of cases, most of which had no detectable emboli in pulmonary arteries and did not overlap with areas of consolidation or ground glass opacity. Kidney perfusion deficits were demonstrated in 50% of cases, in the absence of major kidney dysfunction.[37] Similarly, retinal microvascular changes did not cause clinical symptoms. It would be useful to know whether these microvascular deficits are associated with alterations on microperimetry and electrodiagnostic testing. On the other hand, a study conducted by Bussani et al. reported a persistence of virus-infected cells in lung pneumocytes and endothelial cells several weeks from COVID-19 diagnosis.[38] These findings could explain the retinal vascular changes as long-term consequences of SARS-CoV-2 infection. More importantly, long-

term follow-up is needed to see whether this subclinical microvascular impairment could be responsible for the development of ischemic diseases or a choroidal neovascular membrane. Further studies are warranted for such purposes.

The present trial has some limitations. First, the sample size was relatively small. Second, no data on vascular changes at the time of acute infection were available. There is no information on long-term follow-up. However, this is a novel coronavirus disease and more time is needed to get longer follow-ups. No fluorescein angiogram was performed to investigate the retinal periphery. However, the purpose of the study was to analyze macular and peripapillary regions by using a dyeless methodology. Further longitudinal studies are needed to evaluate the correlation between the OCTA parameters and both the onset and the duration of SARS-CoV-2 infection.

In conclusion, OCTA detected retinal microvascular changes following SARS-CoV-2 infection, helping to highlight the presence of microvascular damage in clinically asymptomatic eyes. In this clinical scenario, where physicians and scientists have been puzzled as to how deal with an utterly new viral infection, new insights in pathogenetic mechanisms could be meaningfully appreciated. This non-invasive imaging technique could represent a valid biomarker of systemic vascular dysfunction as well. Longitudinal studies on larger cohorts are needed to detect the possible progression of retinal vascular alterations on long-term follow-up.

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Table of Contents Statement

The patients post COVID-19 show a significant decrease in vessel density in macular and papillary regions at optical coherence tomography angiography (OCTA) and an impairment of RNFL thickness respect to healthy subjects. Statistically significant correlations were found between structural spectral domain OCT and OCTA parameters. OCTA allows to detect the signs of retinal thrombotic microangiopathy that could reflect the systemic vascular impairment occuring in multiorgan dysfunction. OCTA could represent a valid biomarker of systemic vascular disfunction after SARS-CoV-2 infection.

REFERENCES

1. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. *Acta Biomed*. 2020;91(1):157-160. doi:10.23750/abm.v91i1.9397
2. Peiris M, Leung GM. What can we expect from first-generation COVID-19 vaccines? *Lancet*. 2020. doi:10.1016/S0140-6736(20)31976-0
3. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation.

Blood. 2020;135(23):2033-2040. doi:10.1182/BLOOD.2020006000

4. Levi M, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. *Lancet Haematol*. 2020;7(6):e438-e440. doi:10.1016/S2352-3026(20)30145-9

5. Giannis D, Ziogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. *J Clin Virol*. 2020;127. doi:10.1016/j.jcv.2020.104362

6. Vinci R, Pedicino D, Andreotti F, et al. From angiotensin-converting enzyme 2 disruption to thromboinflammatory microvascular disease: A paradigm drawn from COVID-19. *Int J Cardiol*. 2020. doi:10.1016/j.ijcard.2020.11.016

7. Invernizzi A, Torre A, Parrulli S, et al. Retinal findings in patients with COVID-19: Results from the SERPICO-19 study. *EClinicalMedicine*. 2020;27. doi:10.1016/j.eclinm.2020.100550

8. Pereira LA, Mansano Soares LC, Nascimento PA, et al. Retinal findings in hospitalised patients with severe COVID-19. *Br J Ophthalmol*. 2020. doi:10.1136/bjophthalmol-2020-317576

9. Bertoli F, Veritti D, Danese C, et al. Ocular Findings in COVID-19 Patients: A Review of Direct Manifestations and Indirect Effects on the Eye. *J Ophthalmol*. 2020;2020. doi:10.1155/2020/4827304

10. Rocholz R, Corvi F, Weichsel J, Schmidt S, Staurenghi G. OCT Angiography (OCTA) in Retinal Diagnostics. In: *High Resolution Imaging in Microscopy and Ophthalmology*. ; 2019:135-160. doi:10.1007/978-3-030-16638-0_6

11. Wang J, Jiang J, Zhang Y, Qian YW, Zhang JF, Wang ZL. Retinal and choroidal vascular changes in coronary heart disease: an optical coherence tomography angiography study. *Biomed Opt Express*. 2019;10(4):1532. doi:10.1364/boe.10.001532

12. NIH. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Available on: https://covid19treatmentguidelines.nih.gov/. July 2020.

13. Cennamo G, Montorio D, Velotti N, Sparnelli F, Reibaldi M, Cennamo G. Optical coherence tomography angiography in pre-perimetric open-angle glaucoma. *Graefe's Arch Clin Exp Ophthalmol*. 2017;255(9):1787-1793. doi:10.1007/s00417-017-3709-7

14. Jia Y, Tan O, Tokayer J, et al. Split-spectrum amplitude-decorrelation angiography with optical coherence tomography. *Opt Express*. 2012;20(4):4710. doi:10.1364/oe.20.004710

15. Huang D, Jia Y, Gao SS, Lumbroso B, Rispoli M. Optical Coherence Tomography Angiography Using the Optovue Device. *Dev Ophthalmol*. 2016;56:6-12. doi:10.1159/000442770

16. Moein HR, Novais EA, Rebhun CB, et al. OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY to DETECT MACULAR CAPILLARY ISCHEMIA in PATIENTS with INNER RETINAL CHANGES after RESOLVED DIABETIC MACULAR EDEMA. *Retina*. 2018;38(12):2277-2284. doi:10.1097/IAE.0000000000001902

17. Rao HL, Pradhan ZS, Weinreb RN, et al. Regional Comparisons of Optical Coherence Tomography Angiography Vessel Density in Primary Open-Angle Glaucoma. *Am J Ophthalmol*. 2016;171:75-83. doi:10.1016/j.ajo.2016.08.030

18. Zhang M, Hwang TS, Campbell JP, Bailey ST, Wilson DJ, Huang D, Jia Y. Projection-resolved optical coherence tomographic angiography. *Biomed Opt Express*. 2016;7(3):816-28. doi: 10.1364/BOE.7.000816.

19. Wang J, Zhang M, Hwang TS, Bailey ST, Huang D, Wilson DJ, Jia Y. Reflectance-based projection-resolved optical coherence tomography angiography [Invited]. *Biomed Opt*

Express. 2017;8(3):1536-1548. doi: 10.1364/BOE.8.001536.

20. Patel RC, Wang J, Hwang TS, Zhang M, Gao SS, Pennesi ME, Bailey ST, Lujan BJ, Wang X, Wilson DJ, Huang D, Jia Y. Plexus-Specific Detection of Retinal Vascular Pathologic Conditions with Projection-Resolved OCT Angiography. *Ophthalmol Retina*. 2018; 2(8): 816–826. doi: 10.1016/j.oret.2017.11.010

21. Gencer S, Lacy M, Atzler D, van der Vorst EPC, Döring Y, Weber C. Immunoinflammatory, Thrombohaemostatic, and Cardiovascular Mechanisms in COVID-19. *Thromb Haemost*. 2020. doi:10.1055/s-0040-1718735

22. Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19. *N Engl J Med*. 2020;382(17):e38. doi:10.1056/nejmc2007575

23. Gavriilaki E, Brodsky RA. Severe COVID-19 infection and thrombotic microangiopathy: success does not come easily. *Br J Haematol*. 2020;189(6):e227-e230. doi:10.1111/bjh.16783

24. Bellinvia S, Edwards CJ, Schisano M, Banfi P, Fallico M, Murabito P. The unleashing of the immune system in COVID-19 and sepsis: the calm before the storm? *Inflamm Res*. 2020;69(8):757-763. doi:10.1007/s00011-020-01366-6

25. Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. *Intensive Care Med*. 2020;46(4):586-590. doi:10.1007/s00134-020-05985-9

26. Llitjos JF, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *J Thromb Haemost*. 2020;18(7):1743-1746. doi:10.1111/jth.14869

27. Helms J, Kremer S, Merdji H, et al. Neurologic Features in Severe SARS-CoV-2 Infection. *N Engl J Med*. 2020;382(23):2268-2270. doi:10.1056/nejmc2008597

28. Guan W, Ni Z, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020. doi:10.1056/nejmoa2002032

29. Strain WD, Chaturvedi N. The renin-angiotensin-aldosterone system and the eye in diabetes. *JRAAS - J Renin-Angiotensin-Aldosterone Syst*. 2002;3(4):243-246. doi:10.3317/jraas.2002.045

30. 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. doi:10.1016/j.idcr.2020.e00867

31. Landecho MF, Yuste JR, Gándara E, et al. COVID-19 retinal microangiopathy as an in vivo biomarker of systemic vascular disease? *J Intern Med*. 2020. doi:10.1111/joim.13156

32. Savastano A, Crincoli E, Savastano M, et al. Peripapillary Retinal Vascular Involvement in Early Post-COVID-19 Patients. *J Clin Med*. 2020;9(9):2895. doi:10.3390/jcm9092895

33. Campbell JP, Zhang M, Hwang TS, et al. Detailed Vascular Anatomy of the Human Retina by Projection-Resolved Optical Coherence Tomography Angiography. *Sci Rep*. 2017;7. doi:10.1038/srep42201

34. Ashraf M, Sampani K, Clermont A, et al. Vascular Density of Deep, Intermediate and Superficial Vascular Plexuses Are Differentially Affected by Diabetic Retinopathy Severity. *Invest Ophthalmol Vis Sci.* 2020;61:53. doi: 10.1167/iovs.61.10.53.

35. Coscas F, Glacet-Bernard A, Miere A, et al. Optical Coherence Tomography Angiography in Retinal Vein Occlusion: Evaluation of Superficial and Deep Capillary Plexa. Am J Ophthalmol. 2016 Jan;161:160-71.e1-2. doi: 10.1016/j.ajo.2015.10.008.

36. Lavia C, Bonnin S, Maule M, Erginay A, Tadayoni R, Gaudric A. Vessel density of superficial, intermediate, and deep capillary plexuses using optical coherence tomography angiography. Retina. 2019;39(2):247-258. doi: 10.1097/IAE.0000000000002413.

37. Idilman IS, Telli Dizman G, Ardali Duzgun S, et al. Lung and kidney perfusion deficits diagnosed by dual-energy computed tomography in patients with COVID-19-related systemic microangiopathy. *Eur Radiol*. 2020. doi:10.1007/s00330-020-07155-3

38. Bussani R, Schneider E, Zentilin L, et al. Persistence of viral RNA, pneumocyte syncytia and thrombosis are hallmarks of advanced COVID-19 pathology. EBioMedicine. 2020;103104.

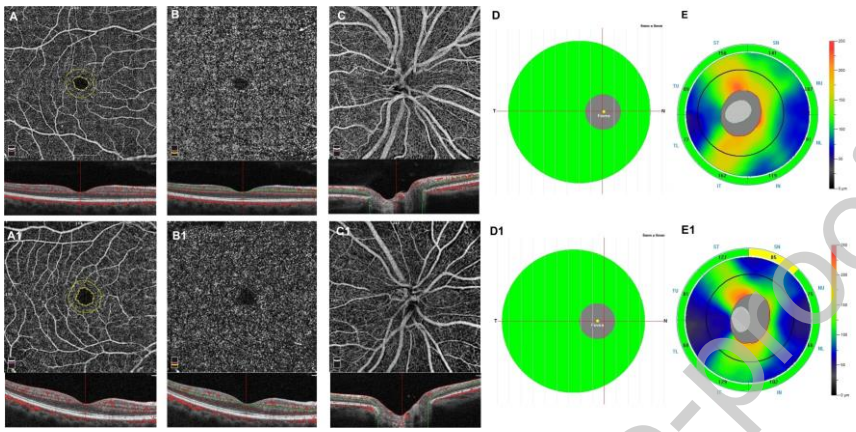

Figure 1: Right eye of a healthy subject (44 years-old female) shows on Optical Coherence Tomography Angiography (OCTA) (SSI: 83) a normal vascular texture of the superficial capillary plexus (SCP), foveal avascular zone (FAZ) area (A), deep capillary plexus (DCP) (B) and radial peripapillary capillary (RPC) (C). Spectral domain (SD) OCT shows a normal ganglion cell complex (D) and retinal nerve fiber layer thicknesses (E).
Right eye of a post Covid-19 patient (45 years-old female) reveals on OCTA (SSI:82) a focal reduction of SCP with normal FAZ area (A1), a diffuse rarefaction of the vascular texture in DCP (B1) and some alterations in RPC (C1). SD-OCT shows normal GCC (D1) and a focal reduction in RNFL thicknesses (E1).

Table 1. Demographic and ocular characteristics of COVID-19 group and controls

	COVID-19 group	**Control group**
Eyes (n.)	40	40
Gender (male/female)	29/11	29/11
Age (years)	49.7 ± 12.6	48.6 ± 12.2
BCVA, logMAR (Snellen)	0.06 ± 0.06 (20/23)	0.05 ± 0.05 (20/22)
Axial length (mm)	23.3 ± 0.3	23.2 ± 0.5
IOP (mmHg)	13.9 ± 2.2	13.6 ± 2.3
SSI	83.5 ± 2.2	84.1 ± 2.1
Recovery time from SARS-CoV-2 (months)	4.1 ± 1.3	-

Data are expressed as mean ± SD
BCVA: best-corrected visual acuity; logMAR: logarithm of the minimum angle of resolution; IOP: intraocular pressure; SSI: signal strength index.

Table 2. Differences in OCT angiography and SD-OCT parameters between COVID-19 group and healthy subjects.

	Post COVID-19 group	Healthy subjects	P value
OCTA parameters			
SCP (%)			
Whole image	48.86 ± 4.32	50.94 ± 4.49	0.038
Parafovea	52.34 ± 5.29	52.59 ± 6.72	0.858
Fovea	25.21 ± 5.28	25.30 ± 4.22	0.929
DCP (%)			
Whole image	52.42 ± 7.18	55.79 ± 6.35	0.029
Parafovea	56.27 ± 6.31	59.72 ± 6.20	0.016
Fovea	44.08 ± 7.16	47.80 ± 7.57	0.027
RPC (%)			
Whole image	46.43 ± 4.01	50.44 ± 4.67	<0.001
Inside disc	52.40 ± 3.42	53.61 ± 4.34	0.171
Peripapillary	48.02 ± 4.80	50.02 ± 5.03	0.073
FAZ area (mm^2)	0.225 ± 0.07	0.223 ± 0.07	0.883
SD-OCT parameters			
GCC average (µm)	99.17 ± 6.81	100.77 ± 7.15	0.309
RNFL average (µm)	98.27 ± 6.64	101.92 ± 6.06	0.012

Data are expressed as mean ± SD
SCP: superficial capillary plexus; DCP: deep capillary plexus; RPC: radial peripapillary capillary plexus; FAZ: foveal avascular zone; GCC: ganglion cell complex; RNFL: retinal nerve fiber layer.
Student's t-test for independent samples
Statistical significance P value <0.05

Table 3. Intraclass correlation coefficients of OCT Angiography and SD-OCT parameters in COVID-19 group and healthy subjects.

	Post COVID-19 group	Healthy subjects
	ICC (95% IC)	ICC (95% IC)
OCTA parameters		
SCP (%)		
Whole image	0.759 (0.711-0.852)	0.841 (0.804-0.945)
Parafovea	0.814 (0.795-0.908)	0.816 (0.792-0.916)
Fovea	0.825 (0.783-0.913)	0.822 (0.780-0.919)
DCP (%)		
Whole image	0.797 (0.781-0.806)	0.844 (0.781-0.933)

Parafovea	0.772 (0.744-0.811)	0.881 (0.851-0.914)
Fovea	0.783 (0.752-0.837)	0.856 (0.795-0.907)
RPC (%)		
Whole image	0.755 (0.721-0.811)	0.885 (0.794-0.943)
Inside disc	0.874 (0.830-0.954)	0.873 (0.826-0.950)
Peripapillary	0.802 (0.773-0.930)	0.804 (0.780-0.915)
FAZ area (mm^2)	0.823 (0.700-0.901)	0.822 (0.714-0.892)
SD-OCT parameters		
GCC average (µm)	0.840 (0.731-0.912)	0.843 (0.727-0.925)
RNFL average (µm)	0.764 (0.728-0.910)	0.883 (0.756-0.934)

ICC: intraclass correlation coefficient; IC: confidence interval; SCP: superficial capillary plexus; DCP: deep capillary plexus; RPC: radial peripapillary capillary plexus; FAZ: foveal avascular zone; GCC: ganglion cell complex; RNFL: retinal nerve fiber layer.
Statistical significance P value <0.05

Table 4. Multiple linear regression model between SD-OCT and OCTA parameters in COVID- 19 group.

	r	ANOVA p value	β	p value
GCC average	0.712	0.057		
SCP whole image			0.178	0.830
SCP parafovea			-0.771	0.378
SCP fovea			-0.165	0.550
DCP whole image			2.166	0.028
DPC parafovea			-1.911	0.012
DCP fovea			-0.479	0.269
RPC whole image			1.232	0.154
RPC inside			0.545	0.097
RPC peripapillary			-0.421	0.644
FAZ area				
RNFL average	0.818	0.001		
SCP whole image			0.851	0.217
SCP parafovea			-2.259	0.004
SCP fovea			0.200	0.377
DCP whole image			2.255	0.006
DPC parafovea			-2.023	0.002
DCP fovea			0.091	0.796
RPC whole image			2.584	0.001
RPC inside			0.702	0.012
RPC peripapillary			-1.442	0.061

FAZ area	0.924	0.008

SCP: superficial capillary plexus; DCP: deep capillary plexus; RPC: radial peripapillary capillary plexus; FAZ: foveal avascular zone; GCC: ganglion cell comples; RNFL: retinal nerve fiber layer.
Multiple linear regression model; statistical significance P <0.05