Ocular Immunology and Inflammation

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ioii20

Retinal Vessel Diameter Changes in COVID-19 Infected Patients

Nazife Aşıkgarip, Emine Temel, Lokman Hızmalı, Kemal Örnek & Fikriye Milletli Sezgin

To cite this article: Nazife Aşıkgarip, Emine Temel, Lokman Hızmalı, Kemal Örnek & Fikriye Milletli Sezgin (2021) Retinal Vessel Diameter Changes in COVID-19 Infected Patients, Ocular Immunology and Inflammation, 29:4, 645-651, DOI: 10.1080/09273948.2020.1853783

To link to this article: https://doi.org/10.1080/09273948.2020.1853783

Published online: 26 Jan 2021.

OCULAR IMMUNOLOGY AND INFLAMMATION
2021, VOL. 29, NO. 4, 645–651
https://doi.org/10.1080/09273948.2020.1853783

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Retinal Vessel Diameter Changes in COVID-19 Infected Patients

Nazife Aşıkgarip MD[a], Emine Temel MD[a], Lokman Hızmalı MD[b], Kemal Örnek MD[c], and Fikriye Milletli Sezgin MD[d]

[a]Department of Opthalmology, Kırşehir Ahi Evran Training and Research Hospital, Kırşehir, Turkey; [b]Department of Infectious Disease and Clinical Microbiology, Kırşehir Ahi Evran University School of Medicine, Kırşehir, Turkey; [c]Department of Opthalmology, Kırşehir Ahi Evran University School of Medicine, Kırşehir, Turkey; [d]Department of Medical Microbiology, Amasya University School of Medicine, Amasya, Turkey

ABSTRACT

Purpose: To evaluate the longitudinal changes in retinal vessel diameters in patients with coronavirus disease 2019 (COVID-19).

Methods: This study included 25 patients with COVID-19 (Group 1) and 25 healthy subjects (Group 2). The diameters of peripapillary temporal and nasal retinal arteries and veins were measured at baseline and at 4 months after remission.

Results: The baseline diameters of the inferior temporal vein and the artery were increased in group 1 compared to controls ($p = .007$ and $p = .041$, respectively). There was also an increase in the diameters of the inferior and superior nasal veins and arteries in group 1 at baseline ($p = .001$, $p = .019$, $p = .037$, and $p = .008$, respectively). Retinal vessel diameters decreased after remission in all quadrants in comparison to baseline measurements (all $p < .05$).

Conclusion: Increased retinal vessel diameters were measured in COVID-19 patients during the disease. Measurement of retinal vessel diameters may be a noninvasive method of estimating the vascular risk.

ARTICLE HISTORY
Received 31 July 2020
Revised 30 October 2020
Accepted 16 November 2020

KEYWORDS
COVID-19; coronavirus; optical coherence tomography; retinal vessel diameter

Since first identified in December 2019 at Wuhan, China, the COVID-19 pandemic has become a major public health challenge around the world.[1] As of September 4, 2020, more than 26 million COVID-19 infected cases, including 869.600 deaths, were reported in 216 countries.[2,3]

COVID-19 is caused by SARS-CoV-2, a beta coronavirus and most acutely and severely affects the lungs. However other organs and systems, including the heart, kidneys, liver, and gastrointestinal tract may also be involved. Although COVID-19 may be asymptomatic or cause only mild symptoms in the majority of the cases, it may progress to interstitial pneumonia and acute respiratory distress syndrome, especially in those having older age and comorbid disease.[4] The exact pathophysiologic mechanism of severe COVID-19 infection remains stil largely unknown. It has been suggested that during the disease course, rapidly progressing systemic immune-mediated inflammation, vascular damage, and thrombosis play an important role in the pathogenesis of severe COVID-19 and death.[5]

Recently, pulmonary vascular changes on chest computerized tomography associated with COVID-19 have been reported. Li et al.[6] and Caruso et al.[7] have found vascular enlargement in 82.4% and 89% of cases with COVID-19 pneumonia, respectively. Pulmonary vascular metrics were evaluated using chest computerized tomography in COVID-19 patients.[8] COVID-19 patients showed a higher median pulmonary artery maximum diameter compared to values measured on the previous chest computerized tomography performed for any reason.[6]

The retina is one of the most metabolically active tissues in the human body. The retinal vasculature is considered a unique window to assess vascular health and to detect early structural changes and pathological characteristics of the human microcirculation.[9,10] Evaluating retinal vascular changes provide information regarding the presence and severity of many systemic diseases like hypertension, diabetes, or various systemic inflammatory or infectious diseases. Since COVID-19 has been shown to cause systemic vascular dysfunction and hyperinflammation, we hypothesized that retinal vessel diameter changes may be shown during the acute phase of the disease.

Therefore, the aim of our study was to assess longitudinal changes of retinal vessel diameters measured by optical coherence tomography (OCT) in patients with COVID-19 and to determine the possible association of inflammation markers with these data. As far as we know this is the first study to evaluate the retinal vessel calibers in patients infected with COVID-19.

Methods

This prospective study included patients who were hospitalized for confirmed COVID-19 between April 2020 and June 2020 at the University Training and Research Hospital. Twenty-five patients with COVID-19 (Group 1) and 25 healthy subjects (Group 2) were included in the study. All patients (100%) in group 1 were positive for COVID-19 on real-time reverse transcriptase-polymerase chain reaction (RT-PCR) from nasopharyngeal swabs.

The study was performed in adherence to the tenets of the Declaration of Helsinki and was approved by the institutional review board. Each patient was informed about the aims and methods of the study and informed consent was obtained from all patients.

CONTACT Emine Temel emine912@hotmail.com Department of Ophthalmology, Kırşehir Ahi Evran Training and Research Hospital, Kırşehir, Turkey.

Patients with previous ocular surgery, retinal vein occlusion, retinal artery occlusion, optic neuropathy, glaucoma, macular degeneration, an intraocular inflammatory disorder, hypertensive retinopathy, and coronary artery disease were excluded from the study.

Slit-lamp biomicroscopy including dilated fundus examination and OCT (Spectralis®, Heidelberg Engineering Inc., Heidelberg, Germany) measurements were performed by the ophthalmologists at baseline and at four months after remission in patients with COVID-19. The same measurements were repeated for the eyes in the control group. Only the right eyes of the patients were included in the study. All measurements were taken at the same time of day (between 10:00 a.m. and 12:00 p.m.) to avoid the effects of diurnal variation in retinal vessel diameters.

After dilating each eye with 2.5% phenylephrine hydrochloride and 0.5% tropicamide, OCT recordings (Spectralis®, Heidelberg Engineering Inc., Heidelberg, Germany) were made. Peripapillary temporal and nasal retinal vessel diameter measurements were focused on the optic disc center and obtained using a circular scanning area of 3.46 mm (Figure 1).[11] Retinal vessel diameters were measured from the cross-sections of these circular scans surrounding the optic disc.[12] The scanning light from OCT reflects vertically on the vessel walls and lumen, creating the innermost and outer most hyperreflective lines seen in cross-sections.[11] These lines are the upper and lower point of the vessel wall (Figure 2).[13] Normal vessels have an oval-shaped heterogeneous reflectivity. When the image dimensions are changed to 1:1 by adjusting the horizontal-vertical ratio, the cross-sections of the vessels are rounded (Figure 3). For each eye, the location of the upper and lower temporal arteries, the superior and inferior temporal veins were determined from the infrared image and were marked in cross-sections (Figure 3). The vertical diameters of the vessels were determined by measuring the distance between the upper and lower boundaries of the two hyperreflective lines (Figure 4).

All comparisons between groups were statistically analyzed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). The normality of all data was tested by the Kolmogorov–Smirnov test. The mean standard deviation value was given for numerical variables with a normal distribution. For numerical variables with normal distribution, the difference between the two groups was determined by t-test in independent groups. The Pearson

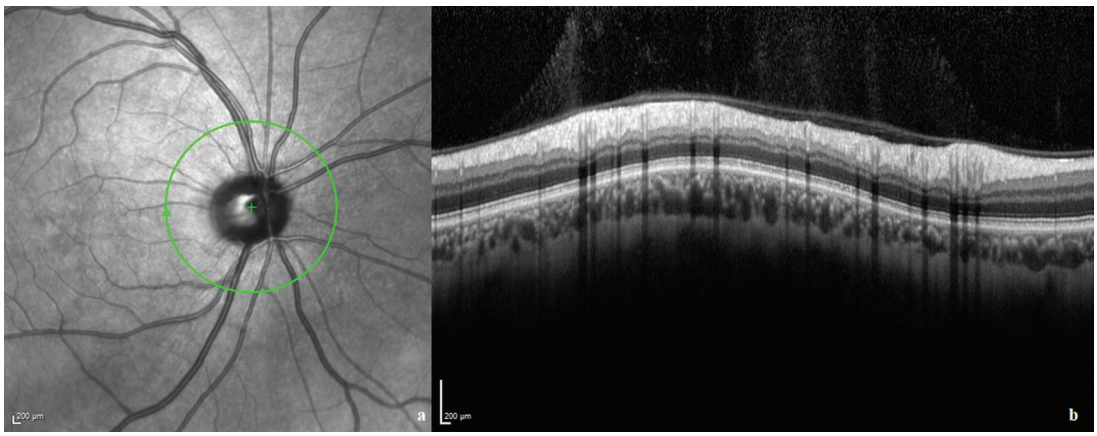

Figure 1. (a): Scanning area of 3.46 mm diameter (circular gren arrow). (b): Cross-sectional OCT image of the retina corresponding to the green circular arrow.

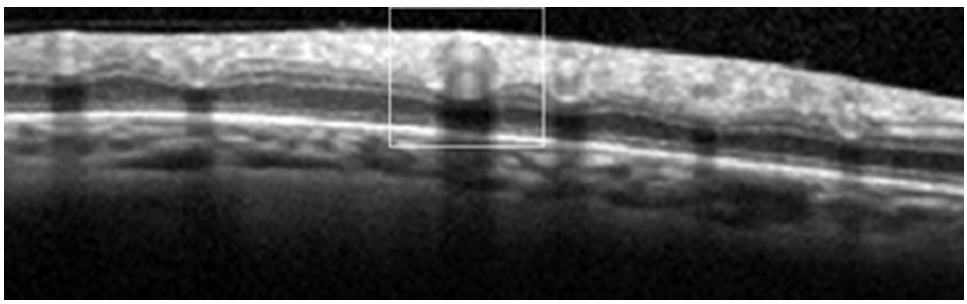

Figure 2. Circular view of the vein (inner most and outer most hyperreflective points are the upper and lower point of the vessel wall).

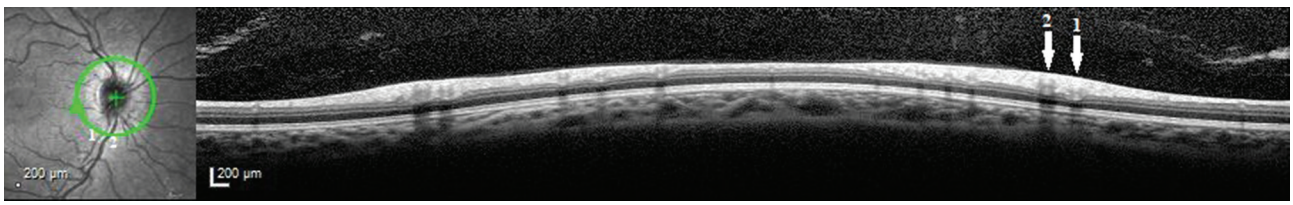

Figure 3. Circular view of the vein when the vertical-horizontal ratio of OCT image is made 1:1, marked vessels (1 and 2).

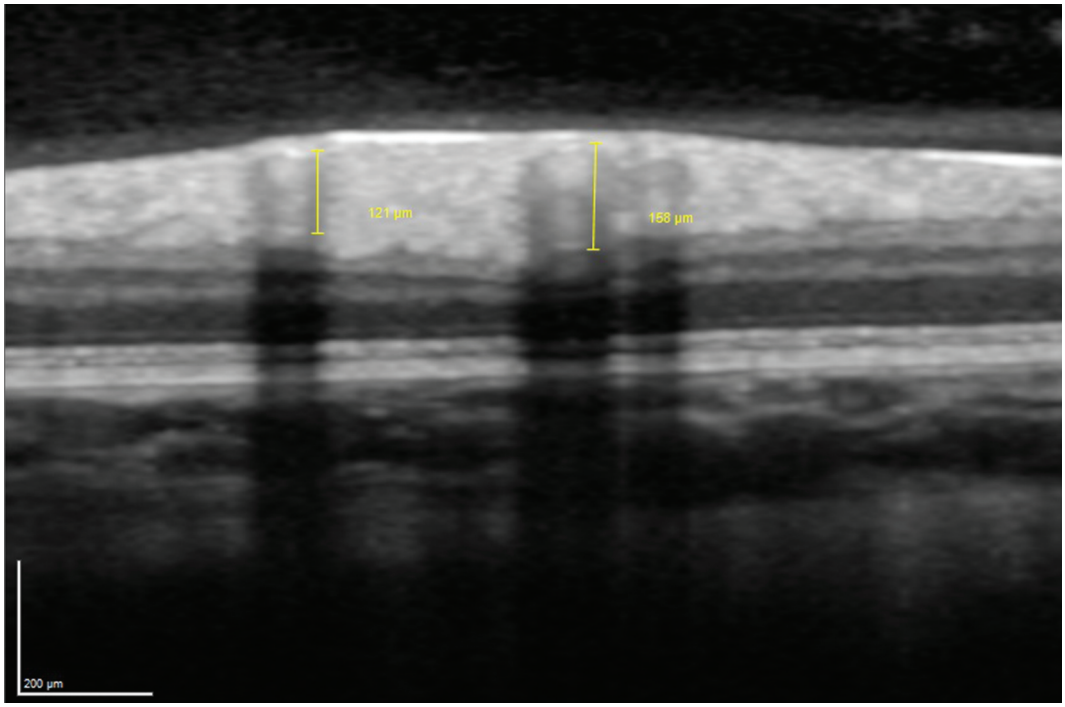

Figure 4. Measurement of vertical vessel diameter.

correlation coefficient used to measure the strength of a linear association between two variables, where the value r = 1 means a perfect positive correlation, and the value r = −1 means a perfect negative correlation. Statistical significance was defined at a level of 5% ($p < .05$).

Results

There were 25 patients (25 eyes) with moderate clinical COVID-19 type and 25 healthy controls (25 eyes) in the study. There were 16 (64%) females and 9 (36%) males in group 1 with a mean age of 34 ± 20.6 years (range: 9–76). There were 11 (44%) females and 14 (56%) males in group 2 with a mean age of 35.4 ± 18.8 years (range: 10–78). There was no statistically significant difference between the two groups in terms of age and gender ($p = .442$ and $p = .262$, respectively). The demographic data of the participants are given in Table 1.

Nasopharyngeal swab test results of all patients (100%) were found positive by RT-PCR. None of the patients, both symptomatic/asymptomatic had coexisting ocular symptoms or ocular changes. There were no abnormalities of the ocular surface, anterior chamber or posterior segment at slit-lamp examination.

At baseline, except for superior temporal retinal artery and vein ($p > .05$), the diameters of the temporal and nasal retinal arteries and veins were significantly increased in COVID-19 patients compared to controls (all $p < .05$). At four months after remission, retinal vessel diameters showed a significant decrease in all quadrants in comparison to baseline measurements (all $p < .005$). Retinal vessel diameters of COVID-19 patients at baseline and after remission are shown in Tables 2 and 3.

There was no statistically significant difference between the follow-up measurements of COVID-19 patients after remission and those of the control group (all $p > .05$). Retinal vessel diameters of COVID-19 patients at remission period and comparison with the control group are shown in Table 4. The distribution of retinal vessel diameter measurements by groups is shown in Figure 5.

Table 1. Demographic data of the participants.

	Group 1 (Patients)	Group 2 (Controls)
Participants		
n	25	25
Eyes		
n	25	25
Female n (%)	16 (64)	11 (44)
Male n (%)	9 (36)	14 (56)
Mean age (years) ± SD	34 ± 20.6	35.4 ± 18.8
(Range)	(9–76)	(10–78)

SD: Standart deviation.

Table 2. Comparison of baseline retinal vessel diameters in COVID-19 patients with the controls.

	Diameter of retinal vessels (µm) Mean±SD		
	Group 1 (Patients)	Group 2 (Controls)	p-value
Inferior temporal vein	185.92 ± 21.53	170.80 ± 1.34	0.007*
Superior temporal vein	178.60 ± 29.33	166.80 ± 15.50	0.082
Inferior temporal artery	142.96 ± 17.59	133.80 ± 12.82	0.041*
Superior temporal artery	138.12 ± 14.64	133.12 ± 16.21	0.258
Inferior nasal vein	141.28 ± 16.86	126 ± 13.25	0.001*
Superior nasal vein	141.68 ± 16.99	132.04 ± 14.73	0.037*
Inferior nasal artery	116.40 ± 17.60	105.32 ± 14.65	0.019*
Superior nasal artery	117.28 ± 16.21	106.80 ± 9.53	0.008*

SD: Standart deviation; *: Statistically significant *p*-value.

Table 3. Comparison of retinal vessel diameters at baseline and after remission period in COVID-19 patients.

	Diameters of retinal vessels (µm) Mean±SD		
	Baseline	Remission	p-value
Inferior temporal vein	185.92 ± 21.53	170.08 ± 15.9	0.005*
Superior temporal vein	178.60 ± 29.33	165.5 ± 23.3	0.088
Inferior temporal artery	142.96 ± 17.59	133.08 ± 14.4	0.035*
Superior temporal artery	138.12 ± 14.64	131.6 ± 14.5	0.123
Inferior nasal vein	141.28 ± 16.86	126.7 ± 14.7	0.002*
Superior nasal vein	141.68 ± 16.99	131.7 ± 14.8	0.032*
Inferior nasal artery	116.40 ± 17.60	104.7 ± 12.9	0.010*
Superior nasal artery	117.28 ± 16.21	106.4 ± 13.2	0.012*

SD: Standart deviation; *: Statistically significant *p*-value.

Table 4. Comparison of retinal vessel diameters in COVID-19 patients after remission period with the control group.

	Diameter of retinal vessels (µm) Mean±SD		
	Patients (Remission)	Controls	p-value
Inferior temporal vein	170.08 ± 15.9	170.80 ± 1.34	0.875
Superior temporal vein	165.5 ± 23.3	166.80 ± 15.50	0.826
Inferior temporal artery	133.08 ± 14.4	133.80 ± 12.82	0.853
Superior temporal artery	131.6 ± 14.5	133.12 ± 16.21	0.735
Inferior nasal vein	126.7 ± 14.7	126 ± 13.25	0.857
Superior nasal vein	131.7 ± 14.8	132.04 ± 14.73	0.939
Inferior nasal artery	104.7 ± 12.9	105.32 ± 14.65	0.887
Superior nasal artery	106.4 ± 13.2	106.80 ± 9.53	0.903

SD: Standart deviation.

The mean neutrophil to lymphocyte ratio was 2.06 ± 1.34, mean platelet to lymphocyte ratio was 146.66 ± 75.75, and mean C-reactive protein level was measured as 7.17 ± 11.11 mg/L in COVID-19 patients. There was a moderately significant positive correlation between the neutrophil-lymphocyte ratio (NLR) and the diameter of the inferior nasal retinal vein (r = 0.504, $p = .039$) (Figure 6). Correlation analysis between the platelet-to-lymphocyte ratio (PLR), C-reactive protein (CRP)], and retinal vessel diameter measurements did not reveal a statistically significant difference (for all, $p > .05$).

Discusison

COVID-19 is known to affect primarily the respiratory system. However, the virus involves not only the lungs but also the eye, heart, nerves, brain, vessels, kidneys, and skin. Although clinical studies on COVID-19 patients are limited, they are mostly focused on pulmonary findings. The pathophysiology of disease and the extent of multiorgan involvement has not been fully understood yet. It has been shown that hyperinflammation and vascular damage contribute to disease severity and death in COVID-19 patients.[14]

The role of the human vascular system is to control tissue homeostasis in different organs and systems. Under normal circumstances, the vessels maintain the transport of blood supplies and nutrients to the tissues. The vascular endothelium plays a critical role in the normal functioning of the blood vessels. However, in patients with increased inflammation, as in COVID-19, properties of vascular endothelium may be changed and pathological processes get started.

Zhao et al. investigated the relationship between chest computerized tomography findings and the clinical condition in patients with COVID-19 pneumonia.[15] The Authors found that most patients (71.3%) had vascular enlargement in the lesions that might have been caused by an acute inflammatory reaction.[15] In other studies, pulmonary vascular changes associated with COVID-19 have also been shown on chest

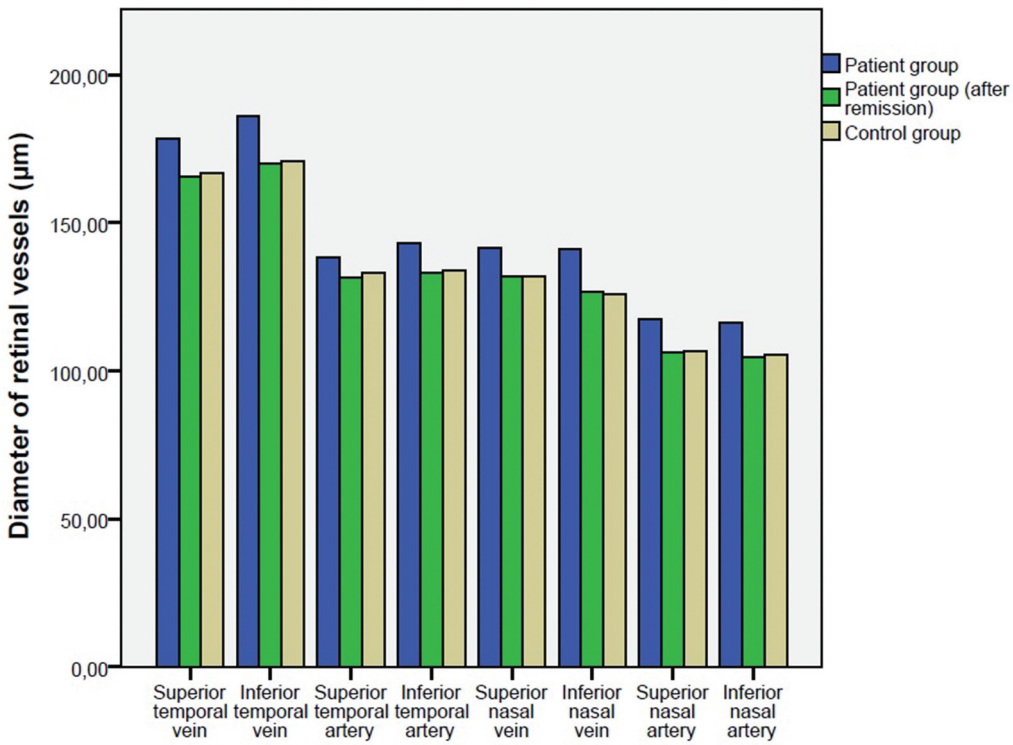

Figure 5. Bar graph showing the changes in retinal vessel diameters in each group.

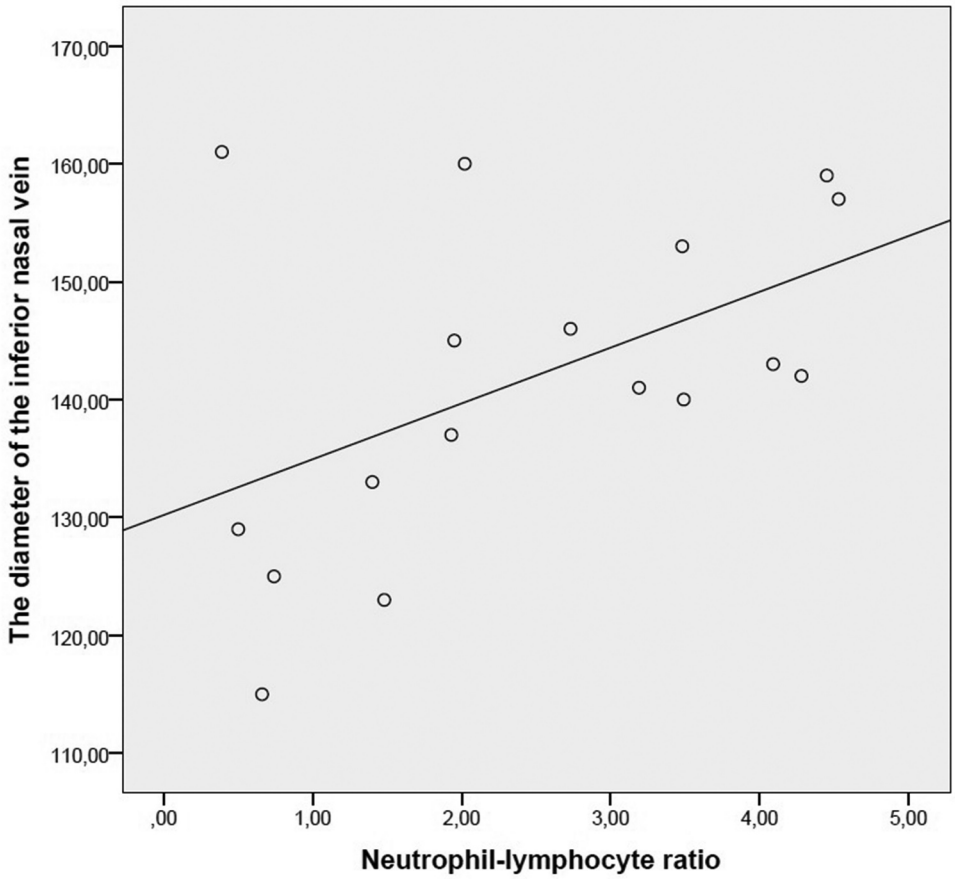

Figure 6. Correlation graph of neutrophil-lymphocyte ratio (NLR) and the diameter of the inferior nasal retinal vein.

computerized tomography.[6,7] Li et al.[6] and Caruso et al.[7] reported vascular enlargement in 82.4% and 89% of patients with COVID-19, respectively. Li et al. measured an increased median pulmonary artery maximum diameter in COVID-19 patients compared to the previous chest computerized tomography results performed for any reason.[6] Spagnolo et al.[8] observed that pulmonary artery diameter showed a significant difference between patients with favorable and unfavorable outcomes in COVID-19.

Ocular involvement of COVID-19 has been limited to the conjunctiva and tear film layer in recent studies in the literature.[16] It has been shown that viral ribonucleic acid might be detected in the retina of infected patients.[17] Seah et al. reported that coronaviruses were capable of producing various ocular inflammatory conditions from anterior segment pathologies like conjunctivitis and anterior uveitis to vision-threatening circumstances like retinitis and optic neuritis.[18]

In the current study, we measured the peripapillary retinal vessel diameters by OCT in hospitalized COVID-19 patients. We found that the diameters of the inferior temporal retinal vein, the inferior temporal retinal artery, and nasal retinal arteries and veins were significantly increased in the patients compared to healthy controls. The diameters of the superior temporal retinal vein and superior temporal retinal artery were also increased in the COVID-19 group, but the difference was not statistically significant. Retinal vessel diameters were found to be significantly decreased at 4 months after remission in all quadrants compared to baseline.

SARS-CoV-2 uses the angiotensin-converting enzyme-related carboxypeptidase (ACE2) receptor to enter the cells.[19] ACE2 receptor is widely found in multiple tissues, including the retina.[20,21] The ACE2 receptor is involved in the pathogenesis of systemic vascular diseases that produce ocular manifestations, like diabetic retinopathy and hypertensive retinopathy. There are at least two major possible ways of vascular damage in COVID-19 patients: disseminated intravascular coagulation like a hypercoagulable state and a vasculitis like process, due to direct viral infection of the endothelial cell and diffuse endothelial inflammation.[22,23] Endothelial dysfunction together with a generalized inflammatory state may contribute to the overall pro-coagulative state described in COVID-19 patients, leading to the occlusions of veins and arteries.[24] Due to this phenomenon, COVID-19 has been shown to cause rare clinical events like thromboses of renal veins, mesenteric vessels, etc. and myocardial thrombotic vessels.

Retinal vascular diameter changes have been shown to predict a range of systemic vascular diseases such as coronary heart disease, diabetes, hypertension, renal disease, and stroke in population-based studies.[25–28] Endothelial dysfunction is associated with increased retinal vein diameter independent of traditional cardiovascular risk factors.[29] Data from a study by Klein et al. showed an association of inflammatory markers with increased retinal vein diameter, suggesting that retinal venular caliber might be a marker of systemic inflammation.[30] Yang et al. evaluated the diagnostic and predictive role of neutrophil to lymphocyte ratio and platelet to

lymphocyte ratio in COVID-19 patients and reported that elevated neutrophil to lymphocyte ratio may be considered as an independent biomarker for indicating poor clinical outcomes in patients with COVID-19.[31]

We propose that COVID-19 with high viral load and inflammatory cytokines may manifest as endothelial damage and retinal vessel dilation. There was a moderately significant positive correlation only between the neutrophil-lymphocyte ratio and the diameter of the inferior nasal vein in our study. This may be attributed to the limited number of patients in the study group including only the moderate clinical COVID-19 type. Whether retinal vessel changes due to COVID-19 is a direct viral effect or shares the mechanism of coexisting systemic vascular damage needs further investigation.

Measurement of retinal vessel diameter is a validated, non-invasive method and can be easily performed by experienced non-clinical staff. Our findings support the hypothesis that retinal vascular diameter changes occur in COVID-19 patients, reflecting systemic vascular involvement.

Therefore, the occurrence of retinal vessel changes may be a relevant ocular manifestation of COVID-19 and these changes may help to detect patients with endothelial damage that are prone to acute vascular events and to start appropriate medications that can play an important role on the clinical outcome. Patients with a low increase in retinal vessel diameter can be less affected by endothelial damage and thrombosis. Changes in retinal vessel diameters can also be a marker of the treatment effect and reflect the response. There are studies demonstrating retinal vessel diameter changes in response to the treatment of patients with diabetic macular edema.[32,33] Diabetic retinopathy also results from endothelial dysfunction leading to increased permeability and incompetence of retinal vasculature.

Limitations of the study may include a relatively small sample size and absence of detailed retinal vascular findings as in fluorescein and/or OCT angiography because of the logistical challenges of managing the patients with COVID-19. Measurement of retinal vessel diameter was performed only in the right eye of each participant, therefore inter-eye differences might have an effect on the results. Another limitation was the administration of topical phenylephrine as pupil dilation, which might have caused vasoconstriction in the retinal vessels. The drop was applied to all participants. Therefore, possible vasoconstriction can be considered as a constant effect for all participants.

In conclusion, depending on the findings, we suggest that measuring retinal vessel diameter changes may help to identify patients with signs of systemic vasculopathy. To the best of our knowledge, this is the first study to show changes in the retinal vessel diameters in patients with COVID-19. Further studies with a larger sample size are needed to clarify that quantitative assessment of retinal vascular diameter changes may be useful in the treatment and follow up of patients with systemic diseases associated with inflammation like COVID-19.

Declarations of interest

The Authors declare no competing interests.

References

1. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med*. 2020;382(13):1199–1207.
2. CSSE J. https://coronavirus.jhu.edu/map.html. Published 2020. Accessed August 17, 2020.
3. WHO. https://www.who.int/emergencies/diseases/novel-coronavirus-2019. Published 2020
4. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497–506. doi:10.1016/S0140-6736(20)30183-5.
5. Leisman DE, Deutschman CS, Facing LM. COVID-19 in the ICU: vascular dysfunction, thrombosis, and dysregulated inflammation. *Intensive Care Med*. 2020;46(6):1105–1108. doi:10.1007/s00134-020-06059-6.
6. Li Y, Xia L. Coronavirus disease 2019 (COVID-19): role of chest CT in diagnosis and management. *AJR Am J Roentgenol*. 2020;214(6):1280–1286. doi:10.2214/AJR.20.22954.
7. Caruso D, Zerunian M, Polici M, et al. Chest CT features of COVID-19 in Rome, Italy. *Radiology*. 2020;296(2):E79–E85. doi:10.1148/radiol.2020201237.
8. Spagnolo P, Cozzi A, Foà RA, et al. CT-derived pulmonary vascular metrics and clinical outcome in COVID-19 patients. *Quant Imaging Med Surg*. 2020;10(6):1325–1333. doi:10.21037/qims-20-546.
9. Ikram MK, Ong YT, Cheung CY, Wong TY. Retinal vascular caliber measurements: clinical significance, current knowledge and future perspectives. *Ophthalmologica*. 2012;229:125–136. doi:10.1159/000342158.
10. Sun C, Wang JJ, Mackey DA, Wong TY. Retinal vascular caliber: systemic, environmental, and genetic associations. *Surv Ophthalmol*. 2009;54:74–95. doi:10.1016/j.survophthal.2008.10.003.
11. Arichika S, Uji A, Ooto S, et al. Comparison of retinal vessel measurements using adaptive optics scanning laser ophthalmoscopy and optical coherence tomography. *Jpn J Ophthalmol*. 2016;60:166–171. doi:10.1007/s10384-016-0435-3.
12. Muraoka Y, Tsujikawa A, Kumagai K, et al. Age- and hypertension-dependent changes in retinal vessel diameter and wall thickness: an optical coherence tomography study. *Am J Ophthalmol*. 2013;156(4):706–714. doi:10.1016/j.ajo.2013.05.021.
13. Ouyang Y, Shao Q, Scharf D, et al. Retinal vessel diameter measurements by spectral domain optical coherence tomography. *Graefes Arch Clin Exp Ophthalmol*. 2015;253(4):499–509. doi:10.1007/s00417-014-2715-2.
14. Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. *Nat Rev Immunol*. 2020;20(6):355–362. doi:10.1038/s41577-020-0331-4.
15. Zhao W, Zhong Z, Xie X, et al. Relation between chest CT findings and clinical conditions of coronavirus disease (COVID-19) pneumonia: a multicenter study. *AJR Am J Roentgenol*. 2020;214(5):1072–1077. doi:10.2214/AJR.20.22976.
16. Wu P, Duan F, Luo C, et al. Characteristics of ocular findings of patients with coronavirus disease 2019 (COVID-19) in Hubei Province, China. *JAMA Ophthalmol*. 2020;138(5):575–578. doi:10.1001/jamaophthalmol.2020.1291.
17. Casagrande M, Fitzek A, Püschel K, et al. Detection of SARS-CoV-2 in human retinal biopsies of deceased COVID-19 patients. *Ocul Immunol Inflamm*. 2020;1–5.
18. 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(3):391–395. doi:10.1080/09273948.2020.1738501.
19. 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;46:586–590. doi:10.1007/s00134-020-05985-9.

20. Verma A, Shan Z, Lei B, et al. ACE2 and Ang-(1–7) confer protection against development of diabetic retinopathy. *Mol Ther*. 2012;20:28–36. doi:10.1038/mt.2011.155.
21. Duan Y, Beli E, Li Calzi S, et al. Loss of angiotensin-converting enzyme 2 exacerbates diabetic retinopathy by promoting bone marrow dysfunction. *Stem Cells*. 2018;36:1430–1440. doi:10.1002/stem.2848.
22. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18:844–847. doi:10.1111/jth.14768.
23. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet*. 2020;395:1417–1418. doi:10.1016/S0140-6736(20)30937-5.
24. Jung F, Krüger-Genge A, Franke R, Hufert F, Küpper JHCOVID-19. and the endothelium. *Clin Hemorheol Microcirc*. 2020;75(1):7–11.
25. Wong TY, Klein R, Sharrett AR, et al. Retinal arteriolar narrowing and risk of coronary heart disease in men and women: the Atherosclerosis Risk in Communities Study. *JAMA*. 2002;287:1153–1159. doi:10.1001/jama.287.9.1153.
26. Wong TY, Klein R, Sharrett AR, et al. Retinal arteriolar narrowing and risk of diabetes mellitus in middle-aged persons. *JAMA*. 2002;287:2528–2533. doi:10.1001/jama.287.19.2528.
27. Wong TY, Shankar A, Klein R, Klein BE, Hubbard LD. Prospective cohort study of retinal vessel diameters and risk of hypertension. *BMJ*. 2004;329:79–82. doi:10.1136/bmj.38124.682523.55.
28. Wong TY, Klein R, Couper DJ, et al. Retinal microvascular abnormalities and incident stroke: the atherosclerosis risk in communities study. *Lancet*. 2001;358:1134–1140. doi:10.1016/S0140-6736(01)06253-5.
29. Nguyen TT, Islam FMA, Farouque HMO, et al. Retinal vascular caliber and brachial flow-mediated dilation: the multi-ethnic study of atherosclerosis. *Stroke*. 2010;41:1343–1348. doi:10.1161/STROKEAHA.110.581017.
30. Klein R, Klein BEK, Knudtson MD, et al. Are inflammatory factors related to retinal vessel caliber? The Beaver dam eye study. *Arch Ophthalmol*. 2006;124:87–94. doi:10.1001/archopht.124.1.87.
31. Yang AP, Liu JP, Tao WQ, et al. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. *Int Immunopharmacol*. 2020;84:106504. doi:10.1016/j.intimp.2020.106504.
32. Consigli A, Papanastasiou A, Roquelaure D, et al. Changes in retinal vascular caliber after intravitreal aflibercept treatment for diabetic macular oedema. *Klin Monbl Augenheilkd*. 2019;236:1318–1324.
33. Lundberg K, Kawasaki R, Sjølie AK, Wong TY, Grauslund J. Localized changes in retinal vessel caliber after focal/grid laser treatment in patients with diabetic macular edema: a measure of treatment response? *Retina*. 2013;33(10):2089–2095. doi:10.1097/IAE.0b013e3182891dda.