ORIGINAL ARTICLE

Does SarsCoV-2 infection really cause damage to retinal microcirculation in mild cases of COVID-19?

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ABSTRACT

Aim To evaluate changes of retinal microcirculation in mild cases of recovered COVID-19 patients at least three months after the infection by optical coherence tomography angiography (OCTA) non-invasive method.

Methods In this prospective cross-sectional study, 50 right eyes of 50 recovered COVID-19 patients were compared with 50 right eyes of age and gender-matched healthy controls. After the complete ophthalmological examination, all participants underwent OCTA measurements (RTVue XR Avanti, Optovue, Fremont, CA, USA).

Results The time between the initial onset of symptoms, and ophthalmologic examination was 479.20 ±197.10 (126-754) days. Findings of ophthalmic examination of all eyes of the recovered COVID-19 patients were within normal range. Significantly reduced superficial (p=0.046) and deep (p=0.044) macular vessel density (VD) in foveal region in the eyes of the recovered COVID-19 patients was found compared with healthy controls. Significantly enlarged foveal avascular zone (FAZ) area and perimeter in the eyes of the recovered COVID-19 patients (p<0.001) were found too.

Conclusion Recovered COVID-19 patients have impaired retinal microcirculation, which can be a cause of the development of retinal vascular diseases.

Key words: coronavirus, OCT angiography, retina, vascular density

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INTRODUCTION

The SARS-CoV-2 virus utilizes the angiotensin converting enzyme 2 (ACE2) receptor on the surface of host cells for invasion and cellular entry through the interaction of its spike protein with the entry receptor angiotensin-converting enzyme (ACE)-2, in the presence of transmembrane serine protease (TMPRSS), and cells that are infected express ACE2, while cells that are not infected do not express ACE2 (1,2). ACE-II receptor has been found in the retinal ganglion cell layer, inner plexiform layer, inner nuclear layer, and photoreceptor outer segments, while TMPRSS is found in multiple retinal neuronal cells, vascular and perivascular cells, and in retinal Müller glial cells, and these may suggest possible viral entry in the retinal cells (2).

As a part of the renin-angiotensin system (RAS), ACE 2 converts angiotensin II (Ang II) to angiotensin (Ang)-1-7 and has roles in protecting endothelial cells by inhibiting inflammation (3).

A local or tissue RAS also present in the retina is very important for homeostasis and the regulation of inflammation (4). Although the role of local RAS on ocular diseases and the connection with systemic RAS is still unclear, there is an assumption that the reduced expression of ACE2 receptors in SARS-CoV-2 infection due to the utilization of the receptors results in the local accumulation of Ang II, which manifests its inflammatory effects (1).

Hyperinflammatory response and thromboembolic events lead to endothelial damage in the retinal deep capillary plexus or choroidal capillary (2).

As known, RAS activity and inflammation can be associated with various ocular diseases (4).

Previous studies have found contradictory results on retinal microcirculation damage after SARS-CoV-2 infection (5-11, 15,23). By establishing the existence of retinal microcirculation damage caused by the SARS-CoV-2 virus, it can be a biomarker of subsequent retinal and systemic vascular diseases (12,15).

The aim of our study was to investigate a long-term effect of SARS-CoV-2 virus on retinal microcirculation in mild cases of recovered COVID-19 patients with OCTA non-invasive method at least three months after a positive PCR test for SARS-CoV-2 virus.

PATIENTS AND METHODS

Patients and study design

Prospective cross-sectional study was conducted at the Eye Clinic University Clinical Centre in Tuzla, Bosnia and Herzegovina between 1st March 2022 and 1st March 2023. Consecutive 50 recovered COVID-19 patients and 50 healthy controls who reported the ophthalmology department for any health complaints and were invited to voluntarily participate in the study were included. All recovered COVID-19 patients were isolated at home during the acute infection and can be considered mild cases as they did not need hospital treatment and they did not establish any complication of COVID-19 disease. Two patient groups were age and gender matched. Only one eye per patient was included in the analysis. The right eye was randomly chosen for the assessment.

The inclusion for post-COVID-19 group was a positive real time polymerase chain reaction (RT PCR) test from nasopharyngeal swab for SARS-CoV-2 performed at least three months before. On the other hand, the control group included subjects who had never had a positive RT PCR test from nasopharyngeal swab for SARS-CoV-2 or the symptoms compatible with COVID-19 disease.

Exclusion criteria to both groups were: history of eye surgery, diabetes mellitus, glaucoma, migraine, retinal disease, hypertension, auto-immune diseases, and patients with a spherical refractive error greater than 5 dioptres and a cylindrical refractive error of more than 2 dioptres. OCTA scan quality less than 7/10 and the best corrected visual acuity less than 20/20 were also excluded from the analysis.

All the patients underwent a complete ophthalmological examination including best-corrected Snellen visual acuity (BCVA), a slit lamp examination of the anterior segment, a measurement of intraocular pressure (IOP), a fundus examination and OCTA (not less than three months after a positive PCR test).

The study was performed based on the tenets of the Declaration of Helsinki. Accordingly, a written informed consent was obtained from all the participants before enrolment, and the study was also approved by the Regional Committee on Medical Ethics at University Clinical Centre in Tuzla.

Methods

All the OCTA scans were performed with the AngioVue system (RTVue XR Avanti, Optovue, Fremont, CA, USA). The centration of the fovea was checked for all images. All measurements were performed using the automated default segmentation with the preset settings for the superficial retinal capillary plexus (SCP) and the deep retinal capillary plexus (DCP), and it is to be highlighted that all segmentations were checked manually. The Angio Retina protocols of 3×3-mm scan were used, and the macular vessel density (VD) of the fovea and parafovea at the level of the SCP and DCP and the foveal avascular zone (FAZ) (namely FAZ area and FAZ perimeter circumference of the FAZ-FAZ PERIM, and foveal vessel density (FD) were measured.

All the images were centred on the fovea and displayed a quality scan index of at least 8/10 and they were carefully reviewed by experienced ophthalmologists to ensure their adequate quality and resolution and to check for possible segmentation errors. The VDs in perifoveal regions were extracted from the 3×3 mm AngioAnalytic report. A circle with an inner diameter of 1 mm and an outer diameter of 3 mm was considered the parafoveal area.

Statistical analysis

To present the data, descriptive statistics was used, including mean, median, standard deviation (SD), and range. Differences in age and sex between the post-COVID-19 group and the control group were compared using the Mann-Whitney U test and the $\chi 2$ test. The OCTA data of both groups were represented as means and standard deviation. Normal distribution of the variables was checked using the Shapiro-Wilk test. To analyse the differences in the OCTA parameters between the post-COVID-19 group and the control group, a t test for independent samples was performed for quantitative variables that followed a normal distribution and a Mann-Whitney U test was performed for quantitative variables not normally distributed. A $p<0.05$ was considered statistically significant.

RESULTS

The study included 50 right eyes of recovered COVID-19 patients (mean age 30.86±8.45 years, 34 females and 16 males) and 50 right eyes of healthy controls (mean age 30.08±7.69 years, 34 females and16 males). The groups were age and gender matched and there was no difference between the groups.

Means (range) of scan quality indices were 9.30±0.58 (8-10) in post-COVID-19 group, and 9.24±0.55 (8-10) in the control group; segmentation errors were found in none of the images included in the final analysis.

Superficial foveal vessel density (SFVD) and deep foveal vessel density (DFVD) were significantly lower in the post COVID-19 group versus normal controls respectively (p=0.046; p=0.044).

There was no significant difference between the groups in VD of whole image macular area and also in parafoveal area (Table 1).

Table 1. Comparison of superficial and deep macular vessel density between post-COVID-19 and control groups

Variable (%)	Mean±SD		p
	Post-COVID-19 group (n=50)	Control group (n=50)	
Whole-image SCP VD	48.06±3.75	47.47±2,78	0.836
Fovea SCP VD	18.28±4.34	19.94±5,36	0.046
Parafovea SCP VD	50.77±2.20	50.38±3,12	0.901
Parafoveal temporal SCP VD	49.14±2.34	48.92±3,26	0.593
Parafoveal superior SCP VD	51.82±2.70	51.46±3,65	0.931
Parafoveal nasal SCP VD	50.04±2.42	49.60±2,99	0.858
Parafoveal inferior SCP VD	52.08±2.27	51.72±3,55	0.956
Whole-image DCP VD	53.62±2.48	53.82±2,58	0.353
Fovea DCP VD	35.19±5.59	37.36±6,87	0.044
Parafovea DCP VD	55.17±3.13	55.75±2,51	0.656
Parafoveal temporal. DCP VD	55.87±2.49	55.85±2,69	0.997
Parafoveal superior DCP VD	55.41±2.64	55.43±2,88	0.679
Parafoveal nasal DCP VD	55.94±2.74	56.08±2,49	0.989
Parafoveal inferior DCP VD	55.07±2.89	55.64±2,84	0.448

SD, standard deviation; SCP, superficial capillary plexus; DCP, deep capillary plexus; VD, vessel density

Fovea avascular zone area (FAZ area) and perimeter circumference of the fovea avascular zone (FAZ PERIM) were significantly greater in the post COVID-19 group versus normal controls, respectively ($p<0.001$; $p<0.001$). There was no significant difference between the groups in foveal vessel density (FD) (Table 2).

Table 2.Comparison of optical coherence tomography angiography fovea measurements between the post-COVID-19 and control groups

Variable	Mean±SD		p
	Post-COVID-19 group (n=50)	Control group (n=50)	
FAZ (mm^2)	0.26±0.08	0.23±0.09	<0.001
PERIM (mm)	2.03±0.32	1.92±0.40	<0.001
FD (%)	51.90±3.26	50.94±3.54	0.202

FAZ, fovea avascular zone; PERIM, perimeter circumference of the fovea avascular zone; FD, foveal vessel density

DISCUSSION

Our study analysed the OCTA retinal changes of the patients who recovered from COVID-19 after at least three months of SARS-CoV-2 infection and those patients who belonged to the healthy control group. The main findings in our study were the reduction of foveal VD of both layers, superficial and deep, as well as an enlargement of the FAZ area and FAZ perimeter in recovered COVID-19 patients. These findings suggest an impairment in the blood supply only to the sub-foveal area of the SCP and DCP, but not to the para-foveal area in recovered COVID-19 patients (13).

In addition, in our study there was no difference in the VD of the whole image macular area and para-foveal area of the superficial and deep layers between the groups. Previous studies found macular VD reduction and tried to explain possible reasons for such reduction (14,15). Banderas Garcia et al. (14) concluded that some of the reasons for the reduction in macular VD and an enlargement of the FAZ area were the direct effect of the virus through the ACE-2 receptor on the retinal endothelium, as well as metabolic changes in serum interleukin 6 (IL-6) that led to disruption of the blood-retinal barrier.

There is evidence that vasculitis and thromboembolism are the reasons for retinal microcirculation damage (15). The virus causes systemic inflammatory microvascular endotheliopathy (16), and leads to disruption of the RAS, which together with excessive production of cytokines leads to endothelial dysfunction (11).

Our study showed no visible retinal changes in recovered COVID-19 patients, which is contradictory to some previous studies where a significant reduction of the VD in whole macular area in the SCP and in the DCP in recovered COVID-19 patients, and also in the foveal and parafoveal area of DCP was found (17,18).

Our findings of significant reduction of VD in the foveal area of the SCP and DCP in COVID-19 patients and also FAZ enlargement are similar to some previous studies (19,20).

It was shown that macular VD correlates with the severity of the COVID-19 (21,22). Our study was conducted on recovered COVID-19 patients who were not hospitalized after SARS-CoV-2 infection, but were isolated at home; they did not have any history of COVID-19 related complications, and it could be considered that patients had a mild form of COVID-19 disease. Reportedly, VD reduction in whole macular area in mild forms of recovered COVID-19 patients was found, but FAZ area enlargement was not (21). However, there were numerous studies showing no reduction in the macular VD of recovered COVID-19 patients (11,15,23).

As our study excluded patients with comorbidities that may affect retinal microcirculation, the results should be considered to be highly reliable.

Limitations of this study are a relatively small sample taken for the analysis, only mild cases of the disease analysed, and the need for a longer follow-up of COVID-19 patients.

In conclusion, our study showed a significantly altered retinal microcirculation, including reduced VD in the superficial and in the deep foveal areas, as well as an enlargement of FAZ area and perimeter in mild cases of recovered COVID-19 patients.

A long-term follow-up of recovered COVID-19 patients will allow a better insight into the state of retinal microcirculation after SARS-CoV-2 infection, as well as possible development of retinal vascular diseases.

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TRANSPARENCY DECLARATION

Competing interests: None to declare.

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