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Macular vessel density in patients recovered from COVID 19

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ABSTRACT

Purpose: The purpose is to evaluate macular vascular densities (VDs) using optical coherence tomography angiography (OCTA) in patients effected by coronavirus disease-2019 (COVID-19).
Methods: The superficial (SF) and deep macular VD of 50 patients with SARS CoV2 pneumonia who had positive polymerase chain reaction (PCR) tests and who recovered after receiving treatment and 55 healthy age- and gender-matched controls were compared using OCTA. Blood inflammation parameters were also recorded.
Results: There was no statistically significant difference between the two groups in terms of age and gender ($p = 0.147$ and $p = 0.504$, respectively). Nor was there a difference with respect to smokers between the two groups ($p = 0.231$). In COVID-19 patients, the VDs in superior hemi quadrant, superior quadrant and inferior quadrant, were significantly lower ($p = 0.033$, $p = 0.029$ and $p = 0.042$, respectively) in superficial plexus. It was also significantly lower in parafovea, superior hemi and superior quadrants ($p = 0.026$, $p < 0.001$ and $p = 0.004$, respectively) in deep plexus. In addition, white blood cell and neutrophil counts were significantly negatively correlated with the VD of the deep parafovea, deep superior quadrant and deep superior hemi quadrant ($p < 0.05$). There was no difference between the patient and control groups in both superficial and deep foveal avascular zone (FAZ) ($p = 0.101$ and $p = 0.691$ respectively).
Conclusion: In COVID-19 disease, VD is low in some sectors in both SF and deep layers, but no change in FAZ. The effect of COVID 19 disease on the retina and whether it makes the retina sensitive to damage can only be understood with long-term follow-up.

1. Introduction

In December 2019, a new strain of coronavirus appeared in Wuhan, China and spread rapidly around the world, resulting in a global pandemic. Coronavirus disease 2019 (COVID-19, designated by the World Health Organization) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a newly discovered CoV. COVID-19 is transmitted mainly through respiratory droplets and physical contact, causing pneumonia, including multi-organ failure, which can be fatal in severe cases [1–4].

In addition, the virus has been detected in the tears of symptomatic and asymptomatic patients using the polymerase chain reaction (PCR) method [5]. The presence of the SARS CoV-2 virus in the human retina has been demonstrated by real-time PCR in cadavers [6]. Previously, the SARS-CoV2 entry receptor angiotensin-converting enzyme (ACE) 2 was detected in vitreous body and in different cell types of the retina, including Müller cells, retinal vascular endothelial cells and photoreceptor cells [7,8].

Since the beginning of the pandemic, it has been reported that COVID-19 can cause retinal vascular pathologies [9–11]. The necessity of evaluating the retinal vascular effects of COVID-19, which has gained attention with its morbidity and mortality, has arisen. We believe more research must be done to understand the ocular effects of COVID-19 disease.

It is possible to visualize the macula and peripapillary vascular densities (VDs) and non-flow area non-invasively using optical coherence tomography angiography (OCTA). Some studies have shown that OCTA can successfully display retinal microvascular properties. The ability of OCTA to provide vascular mapping of separate layers is also an important advantage [12,13]. In this study, we aimed to investigate macular VDs and the foveal avascular zone (FAZ) in patients recovered from COVID-19 disease.

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2. Methods

The study included 50 staff working at the Dicle University Medical School who were affected by COVID-19 and a control group comprised of 55 healthy age- and gender-matched individuals. The study was conducted in accordance with the Helsinki Declaration. All subjects participated in the study voluntarily and gave written informed consent. Approval for the study was obtained from the Ministry of Health and Dicle University's ethics committee (26.11.2020/49).

The study included patients who had a positive PCR test upon experiencing COVID-19 symptoms and pneumonic infiltration and who recovered after treatment. PCR tests, blood tests, computed tomography, and treatment were performed in the same hospital. All patients had symptoms such as fever, muscle pain, a cough, sore throat, respiratory rate <30 breaths per minute, SpO2 level >90 % on room air, and mild to moderate pneumonia based on tomography findings was recorded. Of the patients, those with signs of high inflammation indicated by blood tests (such as a low lymphocyte count and high CRP, ferritin and D-dimer levels) were hospitalized, treated and followed up. It was learned that all patients were given an oral loading dose (2 * 1600 mg) and a 5-day maintenance dose (2 * 600 mg) of favipiravir and nonsteroidal anti-inflammatory drugs as treatment [14]. The white blood cell (WBC), neutrophil, lymphocyte, CRP, D-dimer and ferritin levels of all COVID-19 patients at the onset of disease were recorded from hospital archive. The smoking status of all patients and of the control group was also recorded. A complete ophthalmologic examination was performed one month after the patients were discharged with recovery, and PCR negativity was confirmed. A visual acuity test with a Snellen chart, intraocular pressure measured with an air puff tonometer and a fundus examination was performed for all participants. Those with severe COVID-19 requiring intensive care, participants with additional systemic diseases (diabetes, hypertension or rheumatic disease), eye diseases (glaucoma, retinal disease or eye trauma) and media opacities affecting the imaging quality were excluded from the study. Participants with refractive errors of more than three diopters were also excluded.

3. Optical coherence tomography angiography measurements

In this study, an AngioVue OCTA device (Optovue, Fremont, CA; software version 2016.2.0.35) with split spectrum amplitude-unrelated angiography was used to examine the microvascular structure of the retina. The A-scan rate of this device is 70,000 scans per second using a

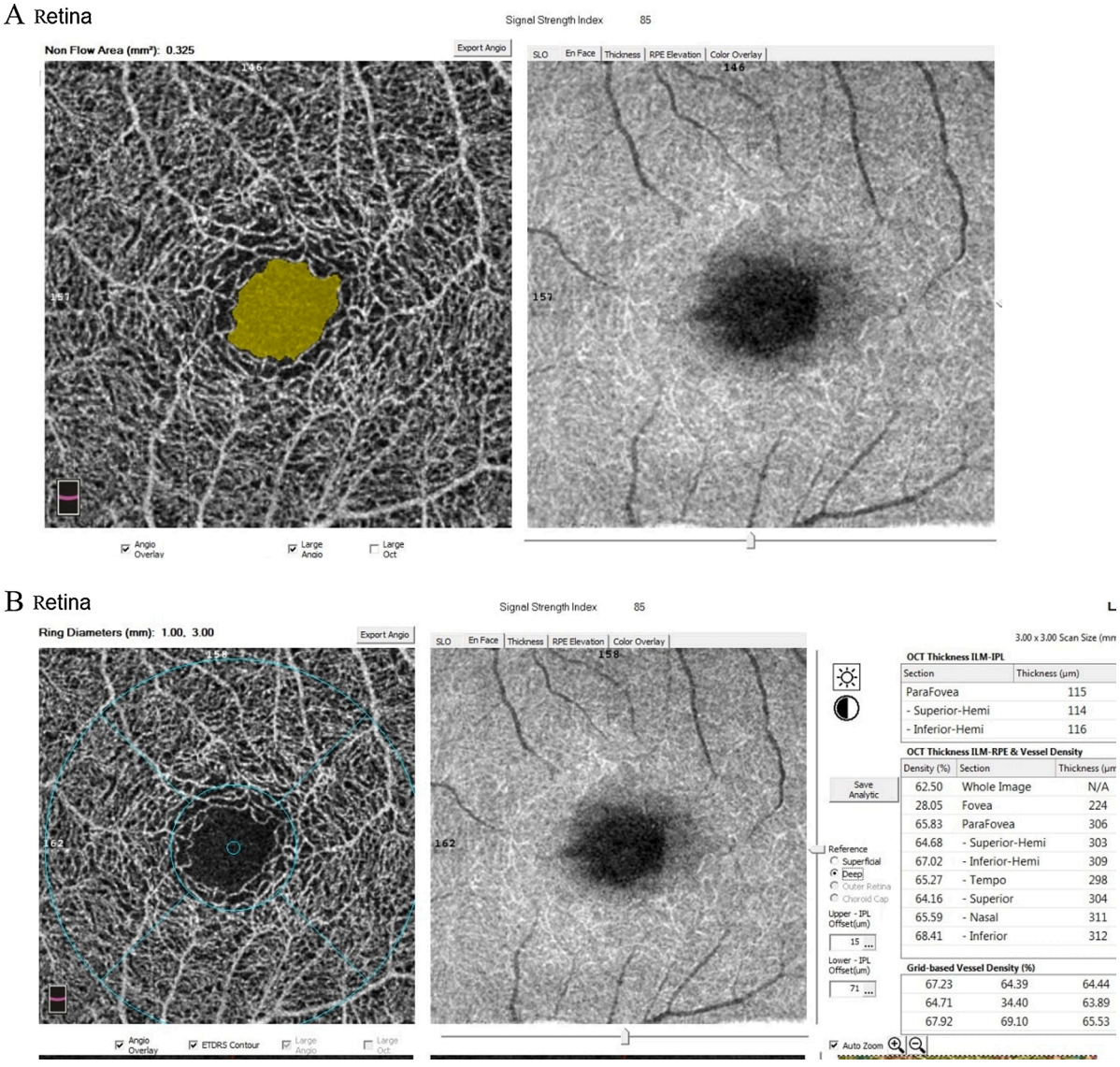

Fig. 1. Representative images of OCTA analysis: Scanning is performed in a 3 × 3 mm area and centered on the fovea. Vascular density of deep macula was shown different quadrant of parafoveal area between 1 and 3 mm rings. (Fig. 1A). Non-flow area (FAZ) measurement boundaries are shown in yellow (Fig. 1B).

light source centred on 840 nm and a bandwidth of 50 nm. The macula was examined with a 3 × 3 mm screening protocol. VD was calculated as the percentage of the area occupied by blood vessels, and the non-flow area was used to calculate the area of the FAZ with function of the OCTA software.

Subtraction and analysis of the VD values (%) of the superficial (SF) and deep parafoveal retina were performed. To perform SF and deep macula scans, the VDs of all four sectors (nasal, inferior, temporal and superior) of the parafoveal area and the average VDs of the parafoveal, superior and inferior hemi zones were computed (Fig. 1). Based on the default settings, the boundaries of the SF capillary network extended from 3 μm below the internal limiting membrane to 15 μm below the inner plexiform layer. The retinal imaging system defines the deep capillary network as 15–70 μm below the inner plexiform layer.

All OCTA scans were performed by the same technician, and the pupils of the patients were not dilated. All scans were reviewed independently by two ophthalmologists (LH and MK) to ensure correct segmentation. Images showing signal strengths >50 without segmentation errors were used in the study.

4. Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 21.0 for Windows (SPSS Inc., Chicago, IL, USA). The normality of the data was analysed using the Shapiro–Wilk test. Descriptive statistics were expressed as mean ± standard deviation. Comparisons between the two groups were analysed using an independent *t*-test for normally distributed data and a Mann–Whitney *U* test for data that did not show a normal distribution. A chi-square test was used to analyse categorical variables between the two groups, and Pearson correlation was used to examine the relationships between variables. A p-value <5% was considered to be statistically significant.

5. Results

There was no statistically significant difference between the two groups in terms of age or gender (p = 0.147 and p = 0.504, respectively). Nor was there a difference between the smokers in the two groups (p = 0.231; see Table 1). The signal strength index (SSI), which reflects the macula imaging quality, was 78.54 ± 7.62 in the patient group and 77.58 ± 7.97 in the control group (p = 0.540). The laboratory parameters of the COVID-19 patients are given in Table 1. SF and deep capillary VD values in the macular region are given in Table 2. In patients affected by COVID-19 disease, VDs were significantly lower in the SF superior hemi quadrant, superior quadrant and inferior quadrant (p = 0.033, p = 0.029, p = 0.042, respectively), and VDs in the deep parafovea, superior hemi quadrant and superior quadrant were significantly lower (p = 0.026, p = 0.003 and p = 0.004, respectively). In addition, WBC and neutrophil levels were significantly negatively correlated with the VDs of the deep parafovea, deep superior quadrant and deep superior hemi quadrant (p < 0.05; Table 3). However, there was no significant correlation between WBC and neutrophil values with SF VD in any quadrant (p > 0.05). In addition, there was no significant correlation between lymphocyte values and deep VD and SF VD in any quadrant (p > 0.05).

The mean FAZ value in the superficial layer was 0.24 ± 0.09 in COVID 19 patients, while it was 0.26 ± 0.07 in the control group (p = 0.101). In COVID 19 patients, the mean FAZ value in the deep layer was 0.31 ± 0.13 while it was 0.30 ± 0.08 in the control group (p = 0.691).

Table 1
Demographic characteristics of the participants in the two groups and laboratory characteristics of Group 1 (COVID 19) patients.

	Group 1 (COVID 19) mean ± SD, (min-max)	Group 2 (Healthy controls) mean ± SD	p value
Age (year)	37.00 ± 5.93	35.14 ± 6.95	†0.147
Gender			
Female/Male	20/30	23/32	*0.504
Smoker /non-smoker	15/35	12/43	*0.231
WBC (10e3/uL)	7.05 ± 3.22 (3.66–21.93)		
Neutrophil (10e3/uL)	4.36 ± 2.99 (1.84–19.99)		
Lymphocyte (10e3/uL)	2.28 ± 2.21 (0.32–13.80)		
CRP (mg/dl)	0.85 ± 1.03 (0.09–7.48)		
D Dimer (mg/l)	0.33 ± 0.23 (0.08–0.96)		
Ferritin (μg/l)	98.98 ± 114.30 (3.70–552)		

† Independent *t*-test.
* Chi-square, p < 0.05 is statistically significant.

Table 2
Comparison of superficial and deep macular vessel density (VD) between the two groups.

	SF VD			Deep VD		
	COVID 19 (Group 1)	Healty Control (Group 2)	*p value	COVID 19 (Group 1)	Healty Control (Group 2)	p value
Whole Image	53.87 ± 2.34	54.03 ± 2.00	*0.702*	60.25 ± 1.83	60.65 ± 1.73	*0.245*
Parafovea	55.63 ± 2.55	56.46 ± 1.98	*0.073*	**62.69 ± 2.08**	**63.53 ± 1.72**	***0.026***
Superior hemi	**55.38 ± 2.60**	**56.36 ± 1.88**	***0.033***	**62.28 ± 2.32**	**63.52 ± 1.79**	***0.003***
Inferior hemi	55.89 ± 2.66	56.55 ± 2.25	*0.183*	63.10 ± 2.17	63.52 ± 1.82	*0.281*
Temporal	54.90 ± 2.32	55.14 ± 2.07	*0.594*	61.78 ± 2.18	62.31 ± 1.84	§0.182
Superior	**55.63 ± 3.23**	**56.94 ± 2.66**	***0.029***	**63.09 ± 3.05**	**64.61 ± 2.13**	***0.004***
Nasal	55.36 ± 2.63	55.87 ± 2.14	*0.289*	61.97 ± 2.82	62.81 ± 1.98	§0.078
Inferior	**56.66 ± 2.95**	**57.76 ± 2.37**	***0.042***	63.80 ± 2.28	64.40 ± 1.88	*0.146

Significant p values are denoted in bold.
* Independent *t*-test.
§ Mann Whitney *U* test, **p < 0.05** is statistically significant.

6. Discussion

Our study showed that VDs were significantly lower in the superior quadrant and superior hemi quadrant in both the SF and deep layers. SF inferior quadrant and deep parafovea VDs were also significantly affected. Lower VDs were found to be significantly correlated with the baseline WBC and neutrophil values of the COVID-19 patients. However, it was observed that the SF FAZ and the deep FAZ did not have any differences when compared with healthy controls.

It has been reported that SARS-CoV-2 infection of endothelial cells and the accumulation of inflammatory cells induces endothelitis in multiple organs, which may contribute to the systemic impaired microcirculatory function during COVID-19 [15,16]. The vascular

Table 3
Correlation between blood inflamation parameters and macular vessel densities.

Pearson correlation	r value	p value
WBC& Deep Superior	−0.424	**0.010**
Deep Superiorhemi	−0.386	**0.020**
Deep parafovea	−0.344	**0.040**
Neutrophil & Deep Superior	−0.340	**0.043**
Deep Superiorhemi	−0.349	**0.037**
Deep parafovea	−0.340	**0.042**

p < 0.05 is statistically significant.
Significant p values are denoted in bold.

endothelium has an active paracrine, endocrine and autocrine function that is essential for the regulation of vascular tone and the maintenance of vascular homoeostasis [17]. Endothelial dysfunction causes vasoconstriction and a pro-coagulant state consequent microvascular dysfunction with subsequent organ ischaemia [18]. Thromboembolic complications have also been reported in particularly severe cases of COVID-19, which is thought to lead to perfusion deficit and retinal vascular pathologies [19,20].

Some studies have reported that severe COVID-19 is associated with acute vascular lesions of the inner retina, including flame-shaped haemorrhages and cotton wool spots [9–11]. Marinho et al. reported hyper-reflective lesions at the level of ganglion cells and more prominent inner plexiform layers in the papillomacular bundle in both eyes of all 12 patients in their study [10]. Cotton wool exudates are a marker of vascular disease severity in diabetic retinopathy and hypertensive retinopathy and are associated with an increased risk for acute vascular events. It is thought that cotton wool spots are the result of the occlusion of precapillary retinal arterioles in the nerve fibres cell layer, with consequent retinal ischaemia named as' inner retinal ischemic spot', possibly caused by branch arterial occlusion secondary to thromboembolic phenomena [21].

Measuring vascular area density and FAZ parameters using OCTA helps in objective quantification of macular perfusion and accurate FAZ area measurement in retinal diseases. This is especially advantageous when there are no findings during preclinical examination. In previous studies, OCTA has shown that retinal pathologies, such as retinal vein occlusion, diabetic retinopathy, sickle cell retinopathy and Behcet vasculitis, decreased in areas with vascular density [22–26].

To date, few studies have been published on retinal vascular density without signs of disease in COVID 19.

Savastano et al. suggested that the perfusion density of the radial peripapillary capillary plexus decreased in patients, especially the elderly and hypertensive patients, who recovered from COVID-19 [27]. Furthermore, Abrishami et al. reported lower VD in the SF and deep capillary plexus in patients who recovered from the disease.

They concluded that direct coronavirus infection of the retina and secondary effects of inflammation should be considered [28]. In our study, young adults without comorbidity were evaluated and baseline blood inflammation parameters analysed. The significantly negative correlation between the patients' blood inflammatory parameters and vascular density suggests that inflammation may be the cause in mild to moderate COVID-19 patients. While significantly lower absolute leukocyte or neutrophil counts have been observed in the early stages of the disease compared to non-COVID-19 infections, it has been reported that both leukocyte and neutrophil counts are significantly higher with the progression of COVID-19 disease [29–31]. Because the mobilization of those with severe COVID-19 may take a long time, we could not take in this study, but vasculitis-like clinical findings have already been reported in COVID-19 in the studies mentioned above [9–11].

The SF capillary plexus is located in the inner retina and provides blood to the inner layers, including the ganglion cell layer and the inner plexiform layer. The deep capillary plexus occupies the outer plexiform layer that is adjacent to the outer nuclear layer and is composed of the high oxygen-dependent synapses of photoreceptors, bipolar cells and horizontal cells [32]. Anatomically, it has been shown that the parallel organization between the SF and deep capillary plexus, also called the "hammock", may affect both SF and deep VDs [23,33,34]. In our study, both SF and deep capillary plexus VDs were lower in the patient group than in the healthy controls. This parallel organization may also explain why both the SF and deep similar regions are affected in our study.

An important limitation of the study is the relatively small scanning area of OCTA (3 × 3 mm) and the inability to evaluate retinal microvascularity outside the macula. We took images with high SSI values in the study and excluded those with artifacts [35]. However, we could not completely eliminate the projection artifact. Projection artifact-resolved (PAR) software provides clearer visualization and more reliable VD calculation within each capillary plexus, especially deep layers [36].

In those with COVID-19 disease, VD is low in some sectors in both the SF and deep layers, but this does not cause changes in FAZ, a finding that is compatible with the absence of visual impairment. The effect the reduction in VD found in our study will have on the retina and whether it makes the retina sensitive to damage can only be understood with long-term follow-up.

Declaration of Competing Interest

The authors report no conflict of interest.

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