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Dynamics and features of retinal and choroidal morphological and morphometric changes in post-COVID-19 patients with different variants of the angiotensin-converting enzyme gene

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Purpose: *To assess the dynamics of optical coherence tomography (OCT) and OCT angiography (OCTA) retinal and choroidal morphological and morphometric changes in post-COVID-19 patients depending on the angiotensin-converting enzyme (ACE) gene variant.*

Methods: *The study included 104 post-COVID-19 patients (208 eyes). We evaluated OCT and OCTA retinal and choroidal morphological and morphometric changes in patients who had recovered from COVID-19 with various courses. Patients were imaged with the RTVue XR 100 Avanti OCT. We examined the distribution of ACE (rs 4340) genotypes among 94 patients. A molecular and genetic study of ACE gene (rs4340) variants was carried out using allele-specific polymerase chain reaction. We analyzed possible correlations between retinal and choroidal morphological and morphometric changes in post-COVID-19 patients and ACE gene variants.*

Results: *In post-COVID-19 patients, we found reductions ($p < 0.001$) over time in macular retinal thickness and choroidal subfoveal thickness and increases overtime in foveal avascular zone (FAZ) area, superficial capillary plexus (SCP) vessel density, and deep capillary plexus (DCP) vessel density. II, ID and DD ACE genotypes were found in 29.6%, 50.5%, and 19.9%, respectively, of the 94 patients. There were statistically significant correlations ($p < 0.001$) of the ACE DD genotype with an increase in FAZ area, SCP vessel density, and DCP vessel density, and a reduction in choroidal subfoveal thickness at 12 months after recovery from COVID-19.*

Conclusion: *We found statistically significant correlations ($p < 0.001$) of the ACE DD genotype (but not the ACE II or ID genotype) in post-COVID-19 patients with retinal and choroidal morphological and morphometric changes; these changes indicate that the retina and choroid suffered hypoxia in the post-COVID-19 period. OCT and OCTA are non-invasive biomarkers of an early vascular dysfunction after SARS-CoV-2 infection. The risk of developing retinal and choroidal morphological and morphometric changes in post-COVID-19 patients with the ACE II or ID genotype was lower ($p = 0.001$) compared to patients with the ACE DD genotype.*

Keywords:
retina, choroid, OCT, OCTA, post-COVID-19, ACE gene variants

Introduction

Ocular manifestations of acute COVID-19 are already well known. Recently, increased attention has been given to post-COVID-19 ocular changes, particularly, posterior pole abnormalities. The posterior segment manifestations reported included cotton wool spots, retinal hemorrhages, central serous retinopathy [1, 2], papillophlebitis, optic neuritis, panuveitis, multifocal retinitis, necrotizing retinitis, central retinal artery/vein occlusion, and Purtschner like retinopathy [1].

The pathogenesis of retinal changes in acute COVID-19 involves the development of a cytokine storm syndrome [3], which is caused by endothelial dysfunction in systemic inflammation [4]. SARS-CoV-2-induced dysregulation of the renin-angiotensin system results in endothelial dysfunction and microvascular thrombosis. The retinal plexuses contain terminal vessels without anastomotic connections, making the retina especially susceptible to ischemia [5]. It is vascular endothelial lesions and coagulopathy that cause frequent thromboebolic complications of COVID-19 and potential vascular changes in post-COVID-19 period [6]. Therefore, status of the retina and vasculature during post-COVID-19 recovery is examined by optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA). Common OCT and OCTA findings include decreased vessel density in the superficial capillary plexus (SCP), increased vessel density in the deep capillary plexus (DCP) [7], and increased foveal avascular zone (FAZ) area [8].

Determining and analyzing genetic features of patients with COVID-19 is believed to be important not only for improved understanding of the pathogenetic mechanisms of the disease, but also determining the prognostic markers of disease course. We have demonstrated previously [9] that the risk of clinically significant retinal changes is higher in COVID-19 patients with angiotensin-converting

enzyme (ACE) genotype DD than in those with genotype II or ID. Consequently, further analysis of this genetic marker for potential associations with retinal morphological and morphometric changes in post-COVID-19 patients is required for early detection of retinal vascular dysfunction and prevention of retinal complications in the post-COVID-19 period.

Therefore, it is important not only to document retinal changes in the post-COVID-19 period, but also to determine their morphological and morphometric features. To the best of our knowledge, there have been no reports on correlations between changes in the retinal and choroidal morphological and morphometric parameters and ACE genotypes. This information could be used for predicting the development of retinal disorders in the post-COVID-19 period and would enable their early prevention or treatment.

The purpose of this study was to assess the dynamics of OCT and OCTA retinal and choroidal morphological and morphometric changes in post-COVID-19 patients based on the presence of ACE polymorphism.

Material and Methods

This was a prospective crossover non-controlled study. The study included 104 post-COVID-19 patients (208 eyes) who were treated at the Infection Unit and Regional Eye Center of Volyn Regional Clinical Hospital from October 2020 to December 2021. Patients with a prior history of retinal disease were excluded. Informed consent was obtained from all study subjects. The study was approved by the Bioethics Committee of Volyn Regional Clinical Hospital (Committee meeting minutes of October 29, 2020).

Characteristics of post-COVID-19 patients included in the study are presented in Table 1.

At the first phase of the study, we evaluated OCT and OCTA retinal and choroidal morphological and morphometric changes in patients who had recovered from COVID-19 with various courses. A comparison was conducted for the entire cohort of patients. Patients were imaged with the RTVue XR 100 Avanti (Optovue, Inc., Fremont, CA, USA) OCT 6 × 6 mm "Angio Retina", “Retina Line” and “Retina Radial Lines” scan protocols. Macular retinal thickness, choroidal subfoveal thickness, FAZ area, SCP vessel density (6 × 6 mm scan), and DCP vessel density (6 × 6 mm scan) were assessed at 1 month, 6 months and 12 months after recovery from COVID-19.

Retinal and choroidal morphological and morphometric measurements obtained in patients who had recovered from COVID-19 were compared with reference data of healthy individuals (Abrishami et al [10] and Bajka et al [11]).

At the second phase of the study, we examined the distribution of ACE geno-types among patients and correlations of ACE gene variants with FAZ area, cho-roidal subfoveal thickness, SCP vessel density and DCP vessel density at 12 months after recovery from COVID-19. At this phase of the study, 10 patients dropped out due to unwillingness to participate in genetic research, and the number of subjects decreased to 94. Genetic tests on patients were conducted during the acute phase of COVID-19, whereas possible correlations between the retinal and choroidal morphological and morphometric changes developed and ACE gene vari-ants were analyzed during the late post-COVID-19 period.

A molecular and genetic study of ACE gene (rs4340) variants was carried out using allele-specific polymerase chain reaction (PCR) at the Reference Centre for Molecular Diagnostic of Public Health Ministry of Ukraine. Blood samples were collected and transported to the above facility as per the guidelines on the transportation of biological materials (Decree of Public Health Ministry of Ukraine No.662 of July 30, 2013).

Statistical analysis. The normal distribution of quantitative data was tested with the Shapiro-Wilk test. Quantitative data are reported as mean plus or minus standard

Table 1. Clinical characteristics of post-COVID-19 patients (n, number of patients)

Characteristics	1 month after recovery (n = 104)	6 months after recovery (n = 104)	12 months after recovery (n = 104)
Age (mean ± SD), years	63.7 ± 10.8	63.7 ± 10.8	63.7 ± 10.8
Women (n, %)	55 (52.8)	55 (52.8)	55 (52.8)
Men (n, %)	49 (47.2)	49 (47.2)	49 (47.2)
Systolic blood pressure (median (interquartile range)), mmHg	130 (125–140)	125 (120–135)	120 (115–135)
Diastolic blood pressure (median (interquartile range)), mmHg	80 (80–90)	80 (80–90)	80 (80–90)
Heart rate (mean ± SD), beats/min	74± 17.5	69± 13.5	68± 12.5
Respiratory rate (IQR), breaths/min	16.2± 4.3	14.3± 2.3	14.1± 3.1
Comorbidity: type 1 or type 2 diabetes mellitus (n, %)	11(10.5)	11(10.5)	11(10.5)
Comorbidity: hypertensive heart disease (n, %)	29 (27.8)	29 (27.8)	29 (27.8)

Note: n, number of patients; IQR, interquartile range; SD, standard deviation

deviation (SD) when normally distributed and median (interquartile range) when not. When comparing results between groups, analysis of variance or non-parametric Kruskal-Wallis tests were used. Dunn's test was used as a post hoc test. The chi square test was used for group comparison in the presence of comorbidity. Qualitative data are reported as frequency (percentage) and 95% confidence interval (95% CI), if required. To assess quantitatively the effects of independent variables on the risk of clinically significant retinal changes, logistic regression models were developed and analyzed. A receiver operating characteristic (ROC) curve was generated using the best fit model. Area under ROC curve (AUC) and 95% CI were calculated. Odds ra-tio (OR) and 95% CI were used to assess the relationships between the risk of clini-cally significant retinal changes and independent variables. The level of significance $p \leq 0.05$ was assumed.

Results

Dynamics of OCT and OCTA retinal and choroidal morphological and morphometric changes was assessed during catamnestic observation of patients recovering from COVID-19 (Table 2).

The following significant dynamic changes in retinal and choroidal morphological and morphometric parameters were found during this observation: reductions ($p<0.001$) over time in macular retinal thickness and choroidal subfoveal thickness (Table 2, Figs. 1; 2; 3) and increases overtime in FAZ area, SCP vessel density (6 × 6 mm scan), and DCP vessel density (6 × 6 mm scan) (Table 2).

At 12 months after recovery from COVID-19, potential correlations between changes in the retinal and choroidal morphological and morphometric parameters and ACE gene variants were analyzed (Table 3).

We found statistically significant correlations ($p<0.001$) of the ACE DD genotype with an increase in FAZ area (> 0.4 mm^2) (Table 3, Fig. 4), SCP vessel density (6 × 6 mm scan) (Table 3, Fig. 5), and DCP vessel density (6 × 6 mm scan) (Table 3, Fig. 6), and a reduction in choroidal subfoveal thickness at 12 months after recovery from COVID-19, whereas correlations of other ACE genotypes with these parameters were weak and not significant ($p>0.05$).

We also assessed the risk of developing retinal and choroidal morphological and morphometric changes in patients with various ACE genotypes after recovery from COVID-19 (Table 4).

We found a reduction in the risk of developing retinal and choroidal morphological and morphometric changes in patients with the ACE II or ID genotype (OR =3.01; 95% CI, 0.99 – 9.19) compared to patients with the ACE DD genotype.

Table 2. Dynamics of retinal and choroidal morphological and morphometric changes in post-COVID-19 patients

Characteristic	1 month after recovery (n=104)	6 months after recovery (n=104)	12 months after recovery (n=104)	P-value
Macular retinal thickness, μm	252.65[2,3] (248.3–257.6)	243.8[1,3] (241.15–246.6)	236.25[1,2] (232.2–238.55)	< 0.001
Choroidal subfoveal thickness, μm	385.25[2,3] (381.35–391.25)	346.95[1,3] (339.5–354.6)	316.55[1,2] (309.5–325.9)	< 0.001
FAZ area, mm²	0.35[2,3] (0.295–0.41)	0.44[1,3] (0.39–0.51)	0.525[1,2] (0.44–0.59)	< 0.001
SCP vessel density (6 × 6 mm scan), %	14.75[2,3] (8.6–21.75)	20.45[1,3] (13.8–26.4)	25.95[1,2] (19.45–33.55)	< 0.001
DCP vessel density (6 × 6 mm scan), %	9.7[2,3] (6.3–12.8)	13.75[1,3] (10.15–16.85)	17.9[1,2] (14.65–21.4)	< 0.001

Notes: Data are reported as median (interquartile range). Friedman test was performed with subsequent pairwise comparisons using *Conover's* test (Conover WJ. Practical nonparametric statistics, 3rd edition. New York: John Wiley & Sons; 1999). [1], significant difference ($p < 0.05$) at 1 month after recovery; [2], significant difference ($p < 0.05$) at 6 months after recovery; [3], significant difference ($p < 0.05$) at 12 months after recovery; DCP, deep capillary plexus; FAZ, foveal avascular zone; SCP, superficial capillary plexus

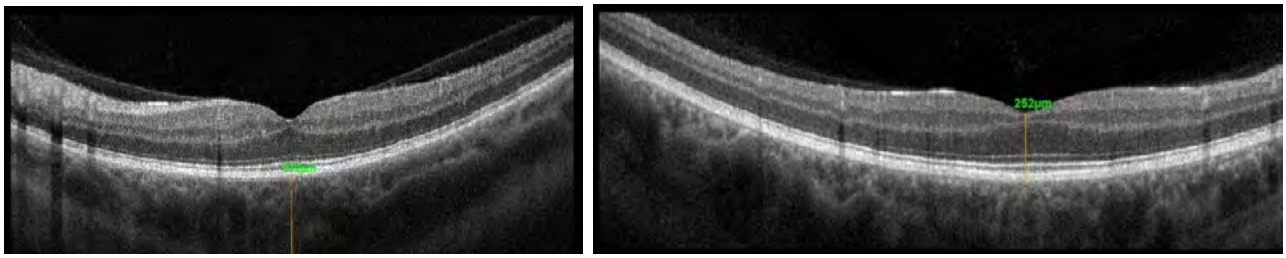

Fig. 1. Macular OCT 1 month after recovery from COVID-19. Macular retinal thickness is 252 μm. Choroidal subfoveal thickness is 379 μm.

Table 3. Spearman correlation (r) between ACE gene variants and retinal and choroidal morphological and morphometric parameters in the post-COVID-19 period

Characteristic		FAZ area at 12 months after recovery, mm²	SCP vessel density (6 × 6 mm scan) at 12 months after recovery, %	DCP vessel density (6 × 6 mm scan) at 12 months after recovery, %	Choroidal subfoveal thickness at 12 months after recovery, μm
II variant of the ACE	R	-0.09	0.12	0.01	-0.05
	P	0.34	0.24	0.95	0.59
ID variant of the ACE	R	-0.10	0.11	0.03	-0.02
	P	0.31	0.25	0.77	0.86
DD variant of the ACE	R	0.45	0.78	0.79	-0.81
	P	< 0.001	< 0.001	< 0.001	< 0.001

Notes: DCP, deep capillary plexus; SCP, superficial capillary plexus

Table 4. Association between the ACE gene variant and risk of retinal and choroidal morphological and morphometric changes in post-COVID-19 patients

Independent variable		Model coefficient, b ± m	Significance of odds ratio (OR) difference from 1, P-value	Odds ratio (OR) (95% CI)
ACE	DD	Reference		
	ID+II	1.10 ±0 ,57	0.052	3.01 (0.99 – 9.19)

Note: ACE, angiotensin-converting enzyme; CI, confidence interval

ROC curve of the model for predicting the risk of retinal and choroidal morphological and morphometric changes in post-COVID-19 patients depending on the ACE genotype is presented in Fig. 7.

An AUC of 0.72 (95% CI, 0.61–0.82) indicates a moderate correlation between the ACE DD genotype and the development of retinal and choroidal morphological and morphometric changes in post-COVID-19 patients (a sensitivity of 83.7% (95% CI, 45.6%–98.3% and specificity of 58.1% (95% CI, 73.7%–91.8%)).

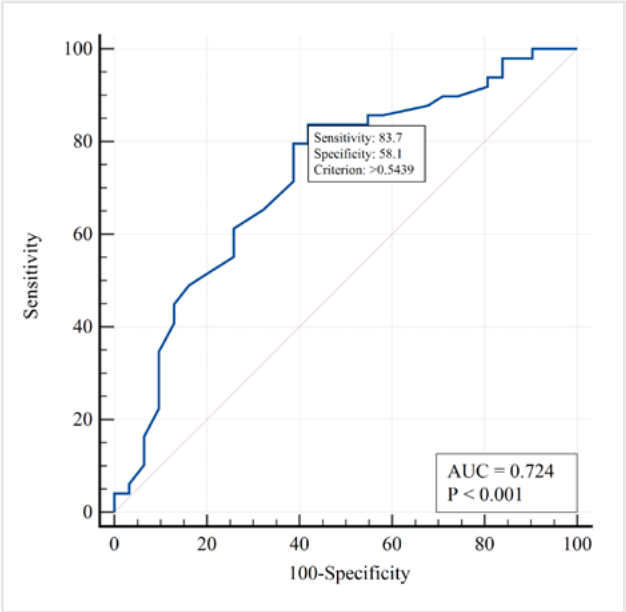

Fig. 7. Receiver Operating Characteristic (ROC) Curve for a model for predicting retinal and choroidal morphological and morphometric changes in post-COVID-19 patients with different variants of the angiotensin-converting enzyme (ACE) genetic

Discussion

A research on the development post-CIVID-19 retinal changes requires understanding how the virus gets into a retinal cell and which pathological processes are initiated after recovery from COVID-19.

ACE2 acts as the host cell receptor for SARS-CoV, and SARS-CoV-2 infects the human host by attaching to the ACE2 and CD147 (basigin) receptors in some human cells (e.g., retinal cells) [12]. It has been reported that retinal cells (e.g., Müller cells, ganglion cells, retinal pigment epithelial (RPE) cells, retinal vascular cells) have cell receptors (ACE, ACE2 receptors, prorenin receptors and renin-angiotensin receptors) for binding to various components of the renin-angiotensin system [12].

In a study by Monu and colleagues [13], intranasal exposure not only resulted in SARSCoV-2 spike (S) protein presence in different ocular tissues but also induces a hyperinflammatory immune response in the retina. Additionally, the long-term exposure to viral S-protein caused microaneurysm, retinal pigmented epithelium (RPE) mottling, retinal atrophy, and vein occlusion in mouse eyes. Notably, cells lining the blood retinal barrier (BRB), the outer barrier, RPE, and the inner barrier, retinal vascular endothelium, were highly permissive to SARS-CoV-2 replication. The cells lining the BRB showed induced expression of viral entry receptors and increased susceptibility towards SARS-CoV-2-induced cell death [13].

Kutlutürk and colleagues [14] detected a high level of structural similarity between E protein and ACE, ACE2, LAT1, and TM9SF4 endothelial proteins. This demonstrates that SARS-CoV-2 proteins may have structural similarities with vascular endothelial proteins, and therefore, as immunological target sites, the counterpart proteins on the endothelial surface of many organs may also be secondarily affected by any immune response against SARS-CoV-2 structural proteins [14].

Hernandez and colleagues [6] assessed vascular and histological alterations in two COVID-19 and three control post-mortem retinas. Analysis of the COVID-19 macular retinal tissue suggested that endothelial cells are a preferential target of SARS-CoV-2 with subsequent changes through their ACE2 receptor expression and morphology. Thus, microglial activation was hyperactive when facing an ensuing immunological challenge after SARS-CoV-2 infection [6].

In a study by Reinhold and colleagues [15], ophthalmopathologically, 8 eyes from 4 patients displayed swollen endothelial cells in congested choroidal vessels. In the 8 eyes with evidence of changes due to SARS-CoV-2, immunohistochemical staining demonstrated fibrin microthrombi, apoptotic changes of endothelial and inflammatory cells. SARS-CoV-2 RNA was detectable in both bulbi of 2/5 patients, yet in situ hybridization failed to visualize viruses. As already described in other organs of COVID-19 patients, the ophthalmological examination revealed microthrombi, that is, hypercoagulation and vasculopathy most probably due to endothelial damage [15].

It is likely that such tropism of the virus to retinal and endothelial cells explains the presence of retinal changes among COVID-19 and post-COVID-19 patients.

We compared the results of our measurements of foveal retinal thickness and subfoveal choroidal thickness in post-COVID-19 patients with measurements in normal subjects reported previously [10]. Abrishami and colleagues [10] reported that, in healthy controls, the mean ± SD values for foveal retinal thickness and subfoveal choroidal thickness were 245.7 ± 20.0 μm and 310.7±57.5 μm, respectively [10]. In the current study, the median macular retinal thickness at one month after recovery from COVID-19 was 252.65 μm (which was larger than normal), at 6 months was 243.8 μm (which was close to normal) and at 12 months was 236.25 μm (which was smaller than normal). In addition, the median submacular choroidal thickness was 385.25 μm (which was substantially larger than normal) at one month after recovery from COVID-19, but abruptly decreased to 346.9 μm at 6 months, and was 316.55 μm at 12 months (which was close to normal). These dynamic retinal and choroidal morphological and morphometric changes support the hypothesis that retinal and choroidal hypoxic lesions may develop during COVID-19 infection and result in vascular dysfunction leading to substantial changes in the parameters of the above-mentioned structures, suggesting a possible role of this dysfunction as a risk factor for eye disease.

We compared the results of our measurements of FAZ area, SCP vessel density and DCP vessel density in post-COVID-19 patients with measurements in normal subjects reported previously [11]. Bajka and colleagues [11] reported that, in normal subjects, FAZ area was 0.21 (0.04; 0.55) mm2, whereas SCP vessel density and DCP vessel density were 49.5% (43.0; 51.6) and 53.8% (46.7; 55.3), respectively. In the current study, the median FAZ area at 1 month, 6 months and 12 months after recovery from COVID-19 was 0.35 mm2, 0.44 mm2, and 0,525 mm2, respectively. That is, in our post-COVID-19 patients, median FAZ area values were larger than the average norm. Additionally, all SCP vessel density and DCP vessel density values obtained at different time points after recovery from COVID-19 in our study patients (Table 2) were significantly smaller than average norms. These morphological and morphometric measurements also support the hypothesis of the development of retinal and choroidal vascular dysfunction and its possible role as a risk factor for ocular complications in the late post-COVID-19 period.

In a study by Konuk and colleagues [16], group 1 (post-COVID-19 patients) showed a significantly thicker choroid compared to Group 2 (healthy subjects) at the subfovea, 500 μm temporal to the fovea, 500 and 1000 μm nasal to the fovea ($p = 0.011$, $p = 0.043$, $p = 0.009$, and $p = 0.019$, respectively). Although other areas measured were also thicker in Group 1, the difference was not significant ($p > 0.05$). Moreover, no significant difference in the central macular thickness and ganglion cell layer thickness were observed between the groups ($p > 0.05$). Choroidal thickness was increased in post-COVID-19 patients, which might be related to inflammation associated with the pathogenesis of COVID-19 [16]. The results of our measurements of retinal and choroidal morphological and morphometric parameters in post-COVID-19 patients are supported by findings of a study by Konuk and colleagues [16] for their group 1.

Gao and colleagues [7] reported that, compared with the pre-COVID-19 status, patients with 1- and 3-month post-COVID-19 statuses had significant thinning of ganglion cell and inner plexiform layer, thickening of inner nuclear layer, a decrease in the vessel density (VD) of superficial vascular complex, and an increase in the VD of deep vascular complex. Meanwhile, alteration in parameters of foveal avascular zone (all $p < 0.05$) and hyper-reflective dots in the vitreous of 27 patients (54 eyes) (71.1% vs pre-COVID-19, 34.2%, $p = 0.006$) were observed. These findings suggest significantly retinal and vitreal alterations occurred in patients after COVID-19 infection, possibly due to direct or indirect virus-induced injuries [7].

González-Zamora and colleagues [17] evaluated the presence of retinal and microvascular alterations in COVID-19 patients with bilateral pneumonia due to SARS-COV-2 that required hospital admission and compared this with a cohort of age- and sex-matched controls. In both SCP and DCP, COVID-19 patients presented lower VD in

the foveal region ($p < 0.001$) and a greater FAZ area than controls ($p = 0.007$).

Cennamo and colleagues [18] reported that post-COVID-19 patients showed a significant reduction in VD of the SCP in whole images and in the DCP in all sectors compared to those in healthy subjects ($P < 0.05$).

Abrishami and colleagues [19] found that the VD of the foveal and parafoveal SCP and DCP in patients were lower than in healthy controls. Similarly to a study by González-Zamora and colleagues [17], they found that the FAZ area was larger in post-COVID-19 patients than in controls, but the difference was not statistically significant. Our findings are also in agreement with the above reports.

Aydemir and colleagues [20] reported that, compared to the control group, the non-flow area and the FAZ area in the whole retina was greater in the COVID-19 group; however no statistically significant difference was observed ($p > 0.05$ respectively). As for vessel densities, all superficial parafoveal VD parameters were considerably higher in the COVID-19 group compared to the control group ($p < 0.05$ respectively). Despite the fact that the vessel densities in the remaining zones were lower in the COVID-19 group, those differences were not statistically significant ($p > 0.05$ respectively) [20].

A study by Noor and colleagues [21], however, revealed no significant differences between the post-COVID-19 syndrome (PCS) and control groups in the OCTA parameters or the macular retinal nerve fiber layer and ganglion cell layer thickness, indicating that no long-term damage ensued in the vascular bed or retinal layers within their cohort, providing a degree of reassurance for PCS patients.

Szkodny and colleagues [22] reported that OCT examination did not detect any significant changes in morphology or morphometry of the optic nerve, retina, or the retina vessels due to COVID-19.

Savastano and colleagues [23] concluded that macular and perimacular vessel density and perfusion resulted unaltered in mild post-COVID-19 patients at 1-month hospital discharge, suggesting no or minimal retinal vascular involvement by SARS-CoV-2.

To the best of our knowledge, the current study is the first to consider ACE gene variants in the context of their relationships with the features in retinal and choroidal morphological and morphometric parameters. We believe that these correlations are reasonable and of a cause-and-effect nature, given that the ACE2 receptors are prevalent in the parenchyma of lungs and kidneys and vascular endothelium [3, 4]. Additionally, our previous studies demonstrated a statistically significant relationship between the severity of COVID-19 and the severity and diversity of retinal changes [24], and a relationship between the ACE gene variants and the presence of retinal changes in patients with COVID-19 [9]. This prompted us to search for the relationships between the ACE gene variants and the features in retinal and choroidal morphological and morphometric parameters in post-COVID-19 patients, and the search was successful. We considered possible effects of the ACE gene variants on the probability of retinal changes in the post-COVID-19 period.

Kumari and colleagues [25] reported that the D allele has been identified as being linked to cardiovascular disease since the discovery of an insertion/deletion (I/D) polymorphism in the ACE gene, this polymorphism has been found to have significant associations with a variety of cardiovascular risk factors. The frequency of the DD genotype was found to be significantly higher among individuals with high total cholesterol, high triglyceride, and low low-density lipoprotein cholesterol levels (p value < 0.05) [25]. In total, findings of the study [25] are consistent with the hypothesis on the correlation between the DD genotype of ACE polymorphism and cardiovascular disease risk factors in this population. A study by Melake and Berhane [26] found that the ACE-DD genotype (OR = 3.71, 95% CI = 1.02–13.5; $P < 0.05$) and D allele (OR = 2.07, 95% CI = 1.06–4.03; $P < 0.05$) were significantly more common in patients with ischemic stroke than in controls, indicating that it is a risk factor for the development of ischemic stroke in hypertensive individuals. Birhan and colleagues [27] conducted a case-control study with a small sample size (64 patients with essential hypertension), and found the DD genotype of the ACE gene polymorphism to have a significant association with high blood pressure and blood glucose levels in the study population. They noted that advanced studies with a considerable sample size may be needed to utilize the ACE genotype as a biomarker for the early detection of hypertension-related complications. The DD and ID genotypes were found more frequently among hypertensive subjects, whereas the II genotype was found more frequently among normotensive subjects [28].

The above findings suggest that the ACE DD variant correlates with increased vasoconstriction and blood pressure, causing tissue hypoxia in the body, with the retina being no exception. From a pathogenetic point of view, retinal damage under these conditions occurs as follows: vessel narrowing causes retinal hypoxia and edema, which contribute to retinal damage, leading to functional decline [29].

The above mechanism is one of the potential pathways through which retinal and choroidal morphological and morphometric changes may develop in a patient who had recovered from COVID-19. Therefore, we believe that the above may explain (1) the diversity of morphological and morphometric changes developing in the retina and choroid, and (2) their dynamics in the post-COVID-19 period and relationships with the DD variant of the ACE gene.

To conclude, retinal and choroidal morphological and morphometric changes (1) indicated that the retina and choroid suffered from hypoxia in the post-COVID-19 period and (2) have some features in their dynamics over time. OCT and OCTA are non-invasive biomarkers of an early vascular dysfunction after SARS-CoV-2 infection, which indicates the impact of COVID-19 on retinal microcirculation vasculature and its possible role as a risk factor for

eye disease. We found statistically significant correlations ($p < 0.001$) of the ACE DD genotype (but not the ACE II or ID genotype) in post-COVID-19 patients with retinal and choroidal morphological and morphometric changes. The risk of developing retinal and choroidal morphological and morphometric changes in post-COVID-19 patients with the ACE II or ID genotype was lower (OR =3.01; 95% CI, 0.99 – 9.19) compared to patients with the ACE DD genotype.

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Appropriate informed consent was obtained from all subjects.

This study included human participants, was approved by the local bioethics committee and adhered to the tenets of the Declaration of Helsinki. This study did not include animal experiments.

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Abbreviations: *ACE, angiotensin converting enzyme; CRV, central retinal vein; DBP, diastolic blood pressure; FAZ, foveal avascular zone; HR, heart rate; OCT, optical coherence tomography; OCTA, optical coherence tomography angiography; PCR, polymerase chain reaction; RR, respiratory rate; SBP, systolic blood pressure*

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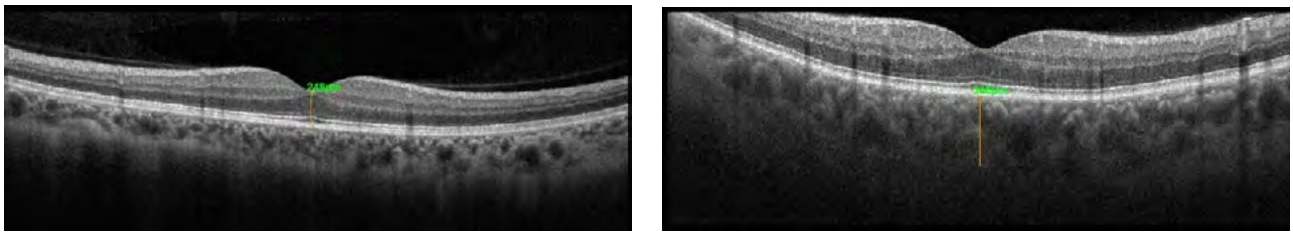

Fig. 2. Macular OCT 6 months after recovery from COVID-19. Macular retinal thickness is 248 μm. Choroidal subfoveal thickness is 346 μm.

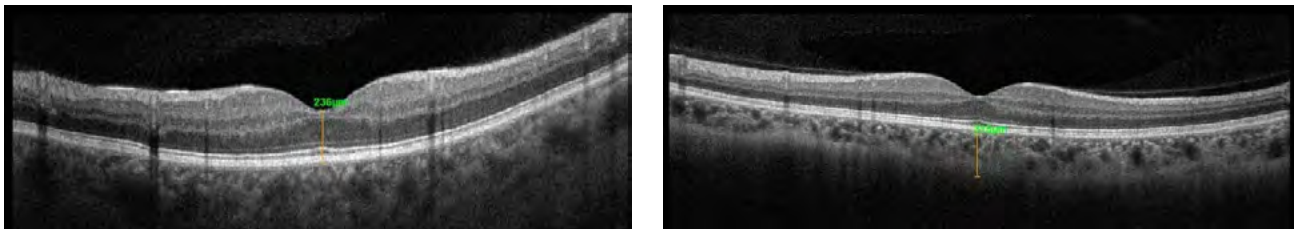

Fig. 3. Macular OCT 12 months after recovery from COVID-19. Macular retinal thickness is 236 μm. Choroidal subfoveal thickness is 315 μm.

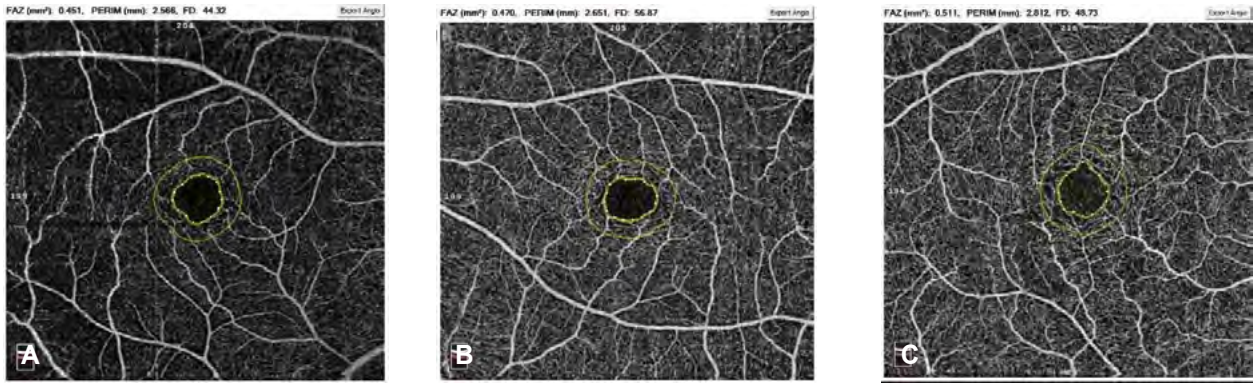

Fig. 4. Retinal OCTA with foveal avascular zone (FAZ) area measurements 1 month after recovery from COVID-19. FAZ area is 0.451 mm^2 (A), 0.470 mm^2 (B), and 0.511 mm^2 (C).

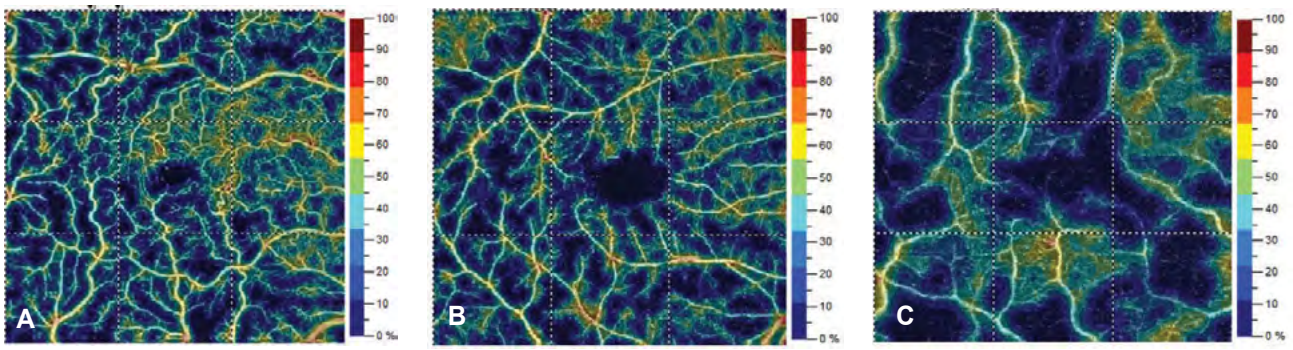

Fig. 5. Macular OCTA with superficial capillary plexus (SCP) vessel density measurements 12 months after recovery from COVID-19. SCP vessel density is 31.9% (A), 34.9% (B), and 23.1% mm^2 (C).

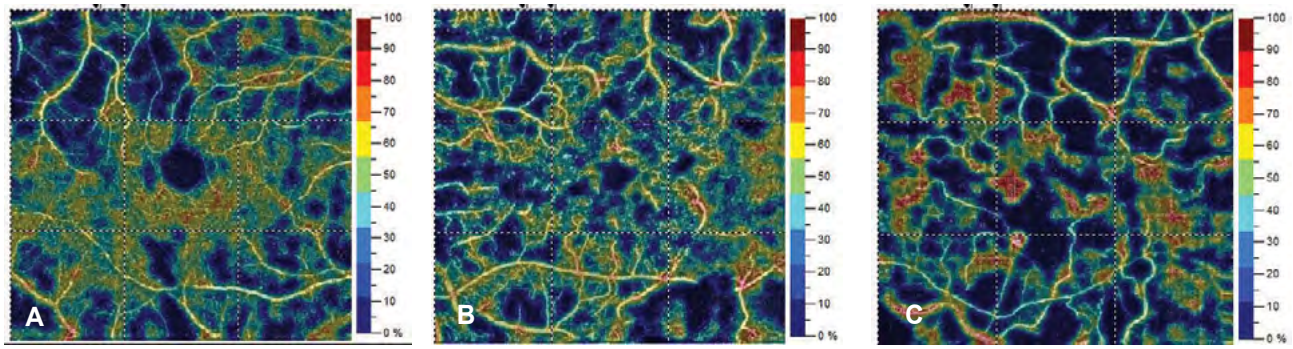

Fig. 6. Macular OCTA with deep capillary plexus (DCP) vessel density measurements 12 months after recovery from COVID-19. DCP vessel density is 21.1% (A), 19.8% (B), and 17.3% mm^2 (C)