Original Article

Ocular hemodynamics in multisystem inflammatory syndrome in children: A cross-sectional study

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Purpose: To evaluate retinal vascular changes by optical coherence tomography angiography (OCTA) in multisystem inflammatory syndrome in children (MIS-C). **Methods:** This cross-sectional study included 21 patients who were diagnosed with MIS-C and had a history of hospitalization, 20 pediatric outpatients with a coronavirus disease 2019 (COVID-19) diagnosis, and 26 healthy children. All patients underwent a detailed ophthalmologic examination and OCTA. In the MIS-C and pediatric COVID-19 groups, these evaluations were made 6 months after diagnosis. The vascular density values of the superficial, deep, and radial peripapillary capillary plexuses (SCP, DCP, and RPCP, respectively), foveal avascular zone (FAZ) parameters (area, perimeter, acircularity index, and foveal density), and outer retinal and choriocapillaris flow area values were recorded using OCTA. **Results:** No pathology was detected in the ophthalmologic examinations of the three groups with similar age and gender distributions. Although the vascular density values of SCP, DCP, and RPCP were found to be higher in most quadrants in the MIS-C group, there was no statistically significant difference among the three groups ($P > 0.05$ for all). FAZ parameters and flow area measurements were similar in all three groups ($P > 0.05$ for all). **Conclusion:** This is the first study to evaluate relatively long-term outcomes in patients with MIS-C and pediatric COVID-19 together. This study shows no changes in the SCP and DCP parameters in pediatric age group, which shows that ocular hemodynamic changes may not be reflected on OCTA after 6 months.

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Coronavirus disease 19 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged and soon affected the whole world.[1] While COVID-19 initially presented as pneumonia alone, it was later reported to affect the extrapulmonary systems as well.[2] In terms of ocular involvement, although conjunctivitis was reported most frequently at the beginning, it was also found to cause significant pathologies in the anterior and posterior segments.[3-5] Ocular findings that have been associated with COVID-19 are pathologies that affect the retina and may lead to a decrease in visual acuity, including retinal hemorrhage, cotton wool spot, panuveitis, central retinal artery occlusion, retinal vein occlusion, and acute macular neuroretinopathy.[6]

It is known that COVID-19 affects people of all ages, but the pediatric group is mostly asymptomatic and has a less severe course than adults.[7] In April 2020, Kawasaki-like diseases associated with COVID-19 were reported in children.[8] Kawasaki disease, a pediatric systemic vasculitis that can affect the coronary arteries, is often seen in children under five and presents with a skin rash, conjunctivitis, and changes in the oral mucosa.[9] Although the cases reported in April 2020 were similar to Kawasaki disease, they were considered to represent a different disease. Based on the reported cases, the Centers for Disease Control and Prevention (CDC) defined this disease as COVID-19–associated multisystem inflammatory syndrome in children (MIS-C). MIS-C patients present with fever and gastrointestinal, dermatological, cardiovascular, and pulmonary findings. Although the most common ocular finding is conjunctivitis, there is no sufficient information concerning ocular changes in these patients.[10]

In the evaluation of ocular hemodynamics in the posterior segment, the retina and the choroid are two important tissues. Optical coherence tomography angiography (OCTA) is a noninvasive imaging method that has been frequently used in the diagnosis and follow-up of ocular diseases in recent years and provides quantitative data on retinal and choroidal microvascular structures.[11] Ischemia, which is involved in the pathogenesis of many diseases, is characterized by a decrease in ocular perfusion. Ischemia has also been shown in different tissues in MIS-C disease.[10]

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Early OCTA (first- and second-month) findings have been reported in patients with MIS-C.[12,13] The limited number of OCTA studies evaluating late ocular hemodynamics in MIS-C cases led us to conduct this study. In the current study, we aimed to compare OCTA measurements 6 months after the diagnosis of MIS-C with the findings of a pediatric COVID-19 patient group and a healthy control group to contribute more objective results to the literature.

Methods

This cross-sectional, observational study was conducted in the pediatric infection clinic and ophthalmology clinic of Ankara Bilkent City Hospital. All participants and parents were informed about the study in detail and their informed consent was obtained. Approval was obtained from Ankara Bilkent City Hospital Ethics Committee No. 1, and the study was carried out according to the principles of the Declaration of Helsinki.

The study included 21 patients diagnosed with MIS-C who were followed up and treated in inpatient wards or the intensive care unit, 20 pediatric patients diagnosed with COVID-19 who were treated as outpatients, and 26 healthy participants. The ocular examinations and OCTA scans of the MIS-C and pediatric COVID-19 groups were performed 6 months after diagnosis. The diagnosis of MIS-C was made based on the CDC criteria given below:[10]

- <21 years of age
- COVID-19 positivity confirmed by the polymerase chain reaction (PCR) test or blood tests, or exposure to a patient with a diagnosis of COVID-19 within the last 1 month
- A body temperature of >38.0°C for >24 h or the presence of subjective fever
- The presence of one or more of the following parameters: increased C-reactive protein, erythrocyte sedimentation rate, procalcitonin, fibrinogen, ferritin, D-dimer, lactic acid dehydrogenase, interleukin (IL)-6, and/or neutrophil count, and/or a decrease in lymphocyte or albumin
- Involvement of two systems from among the cardiac, renal, pulmonary, hematologic, gastrointestinal, dermatological, and neurologic systems, requiring hospitalization

Patients with MIS-C were followed up in inpatient wards or the intensive care unit. According to the severity of the disease and organ involvement, intravenous immunoglobulin, steroids, anticoagulants, positive inotropics, and immunomodulatory drugs were administered. Patients who had a positive COVID-19 PCR test and mild symptoms (headache, cough, myalgia, fatigue, runny nose, etc.), did not require hospitalization, and had a negative PCR test after quarantine were included in the COVID-19 patient group. The healthy control group consisted of participants who did not have any systemic or ocular disease and had no history of COVID-19 PCR positivity or exposure to COVID-19.

The exclusion criteria were as follows: presence of systemic or ocular diseases other than MIS-C or COVID-19, presence of a known systemic disease or any medication use before the diagnosis of MIS-C and COVID-19, presence of trauma, best-corrected visual acuity <6/6 on the Snellen chart, amblyopia, congenital or juvenile glaucoma, congenital or pediatric cataract, retinal dystrophy/pathology, spherical/cylindrical refractive error >±2.00 D, any pathology detected in ocular examination, OCTA scan with quality lower than 8/10, and consanguineous marriage in parents.

In all participants included in the study, visual acuity, intraocular pressure, and axial length measurements were performed, as were detailed biomicroscopic examinations. Patients with normal ophthalmologic findings in these examinations were evaluated. Intraocular pressure was measured by applanation tonometry, and 20 mmHg was accepted as the upper limit. Axial length measurements were made using the IolMaster 500 device (Carl Zeiss Meditec, Jena, Germany) and 24.5 mm was accepted as the upper limit.

OCTA scans were obtained using the XR Avanti AngioVue OCTA device (Optovue, Fremont, CA, USA) (version 2017.1.0.151) based on the split-spectrum amplitude decorrelation angiography system. OCTA volumes consisting of 70,000 A-scans and 400 × 400 B-scans per second were obtained. Retinal capillary plexuses were evaluated with a 6 × 6 mm macular scan. Images with a signal strength index of <80 were not evaluated. Circles of 1, 3, and 6 mm diameters were placed on the retinal areas scanned at 6 × 6 mm, representing the foveal, parafoveal, and perifoveal regions, respectively. Each region was automatically divided into superior, inferior, nasal, and temporal quadrants and two equal hemispheres, namely superior and inferior. The vessel densities of the superficial capillary plexus (SCP) and deep capillary plexus (DCP), foveal avascular zone (FAZ) area, and flow area values were automatically measured in all quadrants [Fig. 1]. For the optic disc, 4.5 × 4.5 mm rectangular scans were used. The vessel density of the radial peripapillary capillary plexus (RPCP) was evaluated in different quadrants (whole, inside, peripapillary-total, superior-hemi, and inferior-hemi). The OCTA measurements of the right and left eyes were examined. Since there was a correlation between the two eyes, only the measurements of the right eye were evaluated.

Data were analyzed using the Statistical Package for the Social Sciences (version 22.0, IBM Corp., Chicago, IL, USA) software. Quantitative values were expressed as mean ± standard deviation. The conformity of the data to the normal distribution was evaluated visually with histograms and statistically with the Kolmogorov–Smirnov test. Due to the presence of three independent groups, the one-way analysis of variance and Kruskal–Wallis analysis of variance tests were used. A P value of < 0.05 was considered statistically significant.

Results

This cross-sectional study included 21 patients with a diagnosis of MIS-C, 20 pediatric patients with a diagnosis of COVID-19, and 26 healthy children. The age and gender distributions of the groups

Table 1: Demographic characteristics and ophthalmologic findings of the study groups

Parameter	MIS-C group (n=21)	COVID-19 group (n=20)	Control group (n=26)	P[a]
Age (years)	11.3±2.9	12.3±2.3	12.3±3.6	0.45
Gender (F/M)	11/10	12/8	14/12	-
Intraocular pressure (mmHg)	11.2±2.4	11.8±2.6	12.2±2.1	0.35
Axial length (mm)	23.4±1.5	23.1±1.2	23.6±1.6	0.51

COVID-19=coronavirus disease 2019, MIS-C=multisystem inflammatory syndrome in children. Age is presented as mean±standard deviation.
[a]One-way analysis of variance test

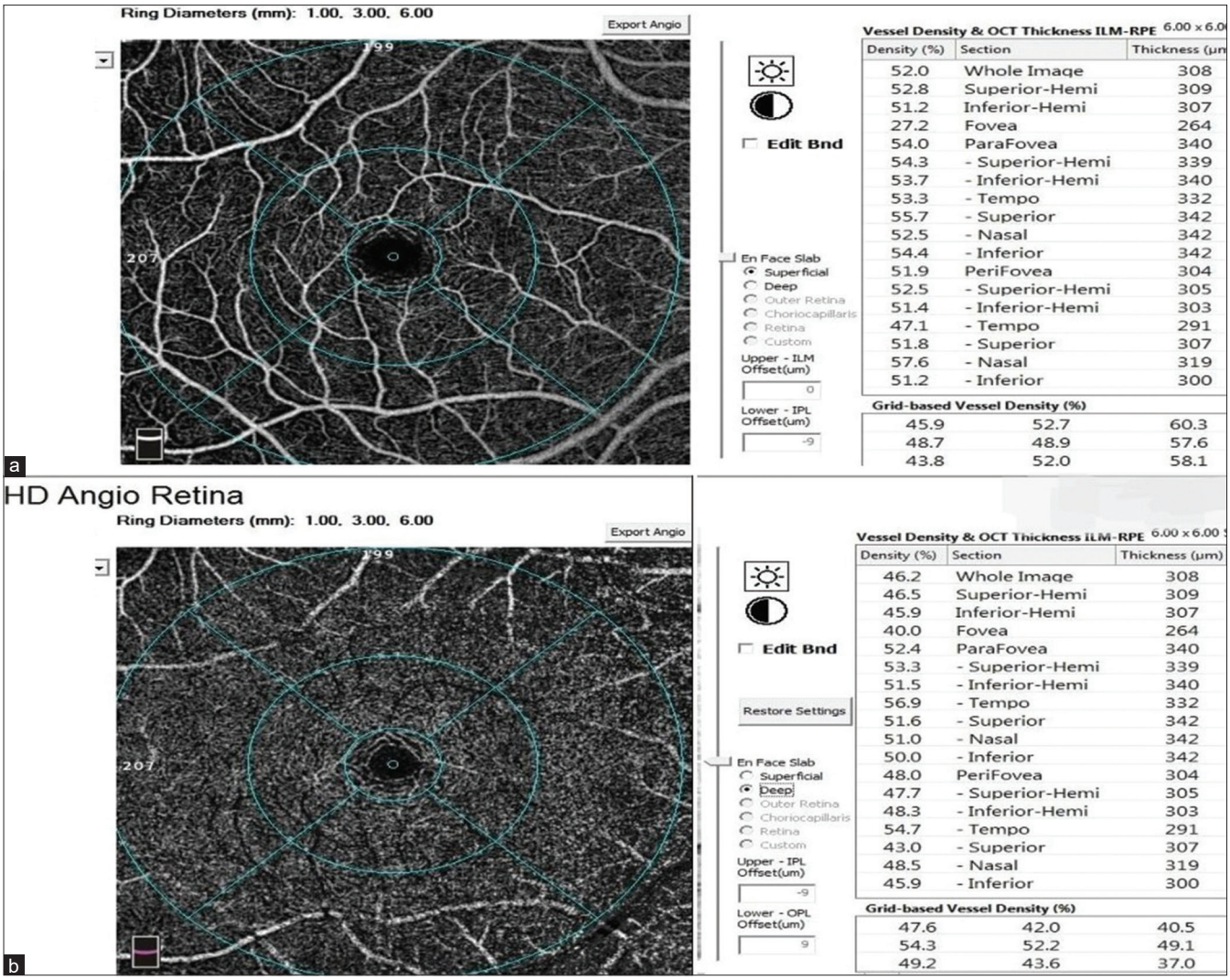

Figure 1: All quadrants of vascular density measurements of plexuses in different layers providing information about retinal microvasculature in a patient with MIS-C: (a) superficial capillary plexus; (b) deep capillary plexus. MIS-C = multisystem inflammatory syndrome in children

were similar ($P > 0.05$). Demographic data and ophthalmologic findings are shown in Table 1. While 11 (52%) of the MIS-C patients were treated in intensive care, 10 (48%) were followed up in the inpatient ward. While fever was observed in all patients, gastrointestinal involvement was detected in nine (42%) patients, renal involvement in four (19%) patients, cardiopulmonary involvement in three (14%) patients, neurologic involvement in two (10%) patients, both gastrointestinal and renal involvement in two (10%) patients, and both cardiopulmonary and neurologic involvement in one (5%) patient. The C-reactive protein value of MIS-C patients was 148 ± 90 mg/dL at the time of diagnosis and 9 ± 4 mg/dL at 6 months, while procalcitonin level was 9 ± 12 µg/L at the time of diagnosis and 0.9 ± 0.8 µg/L at 6 months. Albumin was 42 ± 14 g/L at the time of diagnosis and 5 ± 4 g/L at the sixth month, and IL-6 value was 202 ± 186 pg/mL at the time of diagnosis and 2 ± 3 pg/mL at the sixth month. A statistically significant difference was found between the time of diagnosis and sixth-month visit in terms of all these parameters ($P < 0.05$ in all values). No active or healed uveitis, glaucoma, corneal opacity, cataract, optic disc, or retinal pathology was detected in both MIS-C and pediatric COVID-19 patients.

The vessel densities of SCP and DCP were measured in the whole and superior-hemi, inferior-hemi, foveal, parafoveal, and perifoveal quadrants. The values obtained are given in Table 2. There was no statistically significant difference between the three groups in relation to SCP and DCP vessel density values in any of the quadrants ($P > 0.05$ for all).

RPCP vascular density measurements were evaluated for the whole and inside disc and peripapillary, superior-hemi, and inferior-hemi quadrants and found to be similar in all three groups ($P > 0.05$ for all) [Table 3].

Table 4 presents the FAZ area, perimeter, foveal density, acircularity index, outer retinal flow area, and choriocapillaris flow area values. There was no statistically significant difference between the groups in relation to FAZ and flow area parameters ($P > 0.05$ for all).

Discussion

Although at the onset of the pandemic, it was believed that only adults were susceptible to COVID-19, pediatric

COVID-19 cases were later identified. Furthermore, COVID-19 was initially reported to progress with milder symptoms and require less hospitalization in children than in adults.[14] However, in April 2020, Kawasaki-like diseases were detected in pediatric patients.[8] These patients were evaluated by the CDC, and the disease was defined as MIS-C, which is characterized by intense inflammation associated with COVID-19 affecting the pediatric group. This disease is known to affect different systems and most frequently presents with conjunctivitis among ocular findings.[10] However, there is still no sufficient information concerning the ocular effects of MIS-C due to the limited number of studies in the literature in which anterior and posterior segment structures have been evaluated by ocular imaging methods in this patient group.

Table 2: Comparison of SCP and DCP vessel densities between the groups

Vessel density (%)	MIS-C group (*n*=21)	COVID-19 group (*n*=20)	Control group (*n*=26)	*P*[a]
SCP				
Whole	50.1±2.6	48.3±3.5	49.4±3.0	0.19
Superior-hemi	49.8±2.6	48.2±3.5	49.3±3.2	0.24
Inferior-hemi	50.3±2.6	48.5±3.5	49.6±3.0	0.17
Fovea	19.8±8.0	23.6±7.5	20.8±9.0	0.31
Parafovea	51.7±3.8	50.4±4.4	50.9±4.8	0.62
Perifovea	50.9±4.9	49.9±5.1	50.2±2.8	0.75
DCP				
Whole	48.9±5.7	47.3±5.6	48.1±4.5	0.62
Superior-hemi	49.7±6.4	47.5±5.9	48.9±4.9	0.48
Inferior-hemi	48.4±5.2	47.1±5.4	47.2±4.3	0.65
Fovea	36.6±9.7	40.8±8.8	37.1±9.8	0.31
Parafovea	55.3±5.4	53.8±3.8	54.2±3.3	0.48
Perifovea	52.8±6.3	51.3±4.6	49.0±5.1	0.06

COVID-19=coronavirus disease 2019, DCP=deep capillary plexus, MIS-C=multisystem inflammatory syndrome in children, SCP=superficial capillary plexus. [a]One-way analysis of variance test, mean±standard deviation

Table 3: Distribution of RPCP vascular density values between the groups

Vessel density (%)	MIS-C group (*n*=21)	COVID-19 group (*n*=20)	Control group (*n*=26)	*P*[a]
RPCP				
Whole	51.01±2.2	49.6±2.6	49.9±2.3	0.15
Inside	50.97±5.0	50.7±5.4	48.8±4.5	0.29
Peripapillary	53.8±3.1	52.2±3.3	52.4±2.9	0.20
Superior-hemi	54.0±3.5	51.6±3.5	52.3±3.1	0.06
Inferior-hemi	53.5±2.8	52.8±3.4	52.5±3.0	0.49

COVID-19=coronavirus disease 2019, MIS-C=multisystem inflammatory syndrome in children, RPCP=radial peripapillary capillary plexus. [a]One-way analysis of variance test, mean±standard deviation

Studies examining retinal and choroidal microvascular structures in patients with MIS-C have examined early OCTA findings.[12,13] In the current study, the sixth-month OCTA findings of patients with MIS-C were evaluated in comparison to a pediatric COVID-19 group and a healthy control group. In addition to being the first study to evaluate long-term ocular perfusion findings in patients with MIS-C, this study is considered to make significant contributions to the literature by revealing the ocular effects of MIS-C by including pediatric patients with COVID-19 in the sample.

In a study in which OCTA findings were evaluated at the first month after the diagnosis of MIS-C, the findings of 34 patients were compared to those of a healthy control group, and while SCP vascular density was found to be lower in the MIS-C group in all quadrants, DCP and RPCP vascular density parameters were similar between the groups. Among the FAZ parameters, only foveal density was lower in the MIS-C group. In addition, the flow areas of the outer retina and choriocapillaris were lower in this group.[12] In another study that included 19 patients, OCTA findings that provided information about ocular perfusion were assessed at the time of the MIS-C diagnosis and in the second-month follow-up. The authors reported that among the SCP vascular density parameters, there was a significant increase only in the parafoveal temporal quadrant, and the remaining quadrant findings were similar. Among the DCP vascular density parameters, significant increases were reported in the parafoveal and parafoveal temporal/superior/nasal quadrants. The mean FAZ area value was 0.30 mm^2 at the time of diagnosis and 0.28 mm^2 in the second-month follow-up, indicating a statistically significant difference. RPCP vascular density parameters were similar in all quadrants at both visits.[13] These two studies also evaluated early ocular perfusion findings after MIS-C diagnosis and reported differences in vascular density parameters in some quadrants.[12,13] In the current study, OCTA findings evaluated 6 months after MIS-C diagnosis showed similar values for SCP, DCP, and RPCP vascular density measurements and FAZ and flow area parameters between the MIS-C group and the healthy control and pediatric COVID-19 groups.

Table 4: Distribution of FAZ and flow area evaluation parameters between the groups

Parameter	MIS-C group (*n*=21)	COVID-19 group (*n*=20)	Control group (*n*=26)	*P*
FAZ area (mm^2)	0.30±0.1	0.22±0.1	0.26±0.1	0.15
FAZ perimeter (mm)	2.0±0.4	1.7±0.4	1.9±0.5	0.36
Foveal density	54.5±4.3	54.1±4.2	52.4±6.8	0.35
Acircularity index	1.0±0.04	1.0±0.01	1.1±0.05	0.24
Flow area, outer retina (mm^2)	0.99±0.35	1.0±0.35	1.01±0.58	0.98
Flow area, choriocapillaris (mm^2)	2.2±0.1	2.2±0,07	2.2±0.09	0.81

COVID-19=coronavirus disease 2019, FAZ=foveal avascular zone, MIS-C=multisystem inflammatory syndrome in children

The spike protein plays a role in the entry of the SARS-CoV-2 virus into the cell. The spike protein uses the angiotensin-converting enzyme (ACE) receptor to bind to the cell membrane. This receptor is found in the endothelium, lung, kidney, myocardium, arterial smooth muscle cells, etc.[15,16] Among ocular structures, it is present in the retina and choroid.[17] With stimulation of the inflammatory process by the entry of the virus into the cell, endothelial damage occurs, thrombotic–antithrombotic balance is impaired, and the coagulation cascade is affected, resulting in thrombotic microangiopathy and eventually leading to the development of ischemia.[18] However, MIS-C is a pathology that occurs with an intense cytokine storm and is seen 4–6 weeks after the active COVID-19 infection.[13] Fraser *et al*.[19] showed the presence of mediators such as Matrix metalloproteinase (MMP), IL-3, and resistin that caused hyperinflammation in patients with MIS-C. These mediators are known to cause endothelial damage. Possible changes that can be detected in the retina and choroid, which both contain ACE receptors and have a rich structure in terms of vascularization, necessitate further addressing this issue.

Consistent with our findings, in a study in which early-stage and sixth-month OCTA findings of adult patients with COVID-19 were evaluated, no significant difference was found in the vascular densities of the SCP or DCP and FAZ area parameters.[20] Although the pathogenesis of COVID-19 is not yet clearly understood, a new term, long COVID-19, has been introduced to refer to the long duration of some COVID-19 symptoms. In a study including a large number of patients, the majority of patients hospitalized due to COVID-19 infection were evaluated on average 2 months after discharge, and at least one symptom was reported to persist in 87.4% of these patients.[21] Cardiac imaging has also shown that cardiac involvement due to COVID-19 may be seen in the late period.[22] These studies demonstrate the need for the long-term follow-up of patients with COVID-19. However, the long-term follow-up of a disease such as MIS-C that presents with intense inflammation is also very important. In a previous study evaluating the cardiac findings of 51 patients with MIS-C 3 months after active disease using cardiac magnetic resonance imaging, the authors reported that they did not observe any of the diagnostic criteria for acute myocarditis in these patients.[23]

In this study, late changes in ocular perfusion in patients with MIS-C were evaluated using OCTA, which is a noninvasive imaging method that provides quantitative results. In a study conducted with adult patients with COVID-19 with a design similar to our study, among the sixth-month post-COVID-19°CTA findings, the SCP and RPCP plexus vascular density values in the whole image and DCP vascular density in all quadrants were found to be significantly lower in the patient group than in the healthy control group. However, no significant difference was noted in the FAZ area value.[24] The reason for these late changes observed in SCP and DCP vascular densities may be that the patients included in the study were followed up with a diagnosis of COVID-19 pneumonia that required hospitalization. In addition, the late-stage immune responses to inflammation in adult and pediatric patients may differ.[25] The importance of the ACE receptor in SARS-CoV-2 is known. This receptor declines with age.[26,27] If there are no sufficient ACE receptors, angiotensin degradation cannot occur. As is known, angiotensin has vasoconstrictive, fibrotic, and proinflammatory effects.[28] The effect of angiotensin increases with the decrease in destruction in the production–destruction balance. In the pediatric group, the high level of ACE receptors, the lower destructive effects of angiotensin, and the healthier endothelial structure support our late findings.

In a study evaluating third-month OCTA measurements in pediatric patients with COVID-19, the SCP, DCP, outer retinal, and choriocapillaris parafoveal, nasal, and foveal central vascular density values were found to be lower in the pediatric COVID-19 group. The patients included in the study consisted of those with a history of hospitalization due to COVID-19 and moderate pneumonia detected on computed tomography.[29] In another study in which OCTA measurements were evaluated on average on the 37th day after the diagnosis of pediatric COVID-19, the inner ring, outer ring, and full area macular perfusion vascular density values were found to be higher in the pediatric COVID-19 group than in the healthy control group; however, unlike other studies, there was no significant difference in FAZ area and perimeter values.[30] Although the reason for this paradox is not yet clearly understood, it can be considered that the SARS-CoV-2 virus may affect adult and pediatric groups differently in terms of anatomy and structure, and even the immune system response may differ within the pediatric group depending on age and other factors. Yuan *et al*.[31] evaluated the immune responses of adult and pediatric patients who had mild pneumonia and were diagnosed with COVID-19 and found that leukopenia and IL-2, IL-4, and IL-6 levels were higher in the adult group. The more severe course of COVID-19 and more aggressive lung involvement in adults may be due to this immunologic difference. In a study evaluating the early OCTA findings of pediatric patients with COVID-19, while the SCP vessel density and FAZ parameter values were similar, the DCP vessel density values were lower in the COVID-19 group in most quadrants compared to the healthy control group.[32] These early changes may be due to the vasoconstrictive effect of angiotensin and other mediators in the arterial and venule systems, as well as obstruction in the vessel lumen.[24,30,33] Other possible causes are inflammation-induced endothelial damage and apoptosis.[34] Although these effects can be seen in the early period, the current study showed that ocular perfusion was not affected in the relatively long term in MIS-C and COVID-19 groups. In the literature, the longest-term OCTA evaluation of ocular perfusion was 2 months for patients with MIS-C and 3 months for patients with COVID-19.[13,29]

One of the strengths of this study is that it is the first in the literature to evaluate late findings in both MIS-C and pediatric COVID-19 patient groups. We consider that the comparison of patients with MIS-C to not only a control group but also a pediatric COVID-19 patient group, unlike previous studies in the literature, provided more objective results. Nevertheless, the most important limitations of the study are that the number of patients was small and it was conducted in a single center. Due to the small number of patients, we were not able to make subgroup evaluations in terms of factors such as diagnosis, treatment, and organ involvement in patients with MIS-C. Another limitation of this study includes the absence of measurements at baseline (before the onset of COVID-19) or at the time of acute phase illness

and diagnosis. OCTA is a frequently used modality for the diagnosis and follow-up of systemic vascular and inflammatory diseases.[35,36] Although it presents quantitative data concerning capillary plexus structures and provides information on ocular perfusion, the latter was not evaluated using Doppler ultrasonography or similar imaging methods. We hope to gain a deeper understanding of the ocular effects of MIS-C through multicenter studies conducted with a larger number of patients.

In conclusion, this study shows no changes in the SCP and DCP parameters in pediatric age group, which shows that ocular hemodynamic changes may not be reflected on OCTA after 6 months. However, this study does not answer whether ocular hemodynamic changes never occur or they recover with time. In addition, pediatric patients with COVID-19 had similar results to the healthy control group 6 months after diagnosis.

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