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Original Article

# Pupillographic Analysis of COVID-19 Patients: Early and Late Results After Recovery

**Gamze Ucan Gunduz,[1] Aysegul Mavi Yildiz,[2] Ozgur Yalcinbayir,[1] Mehmet Baykara,[1] Esin Sogutlu Sari,[1] Sevde Isleker,[1] Nilufer Aylin Acet Ozturk[3]**

[1]Department of Ophthalmology, Bursa Uludag University, Bursa, Türkiye
[2]Retina Eye Hospital, Bursa, Türkiye
[3]Department of Pulmonology, Bursa Uludag University, Bursa, Türkiye

## Abstract

**Objectives:** We aimed to investigate the short- and long-term static and dynamic pupillary responses of patients recovered from coronavirus disease-19 (COVID-19) using quantitative infrared pupillography.

**Methods:** This study included patients who recovered from COVID-19 (Group 1) and age- and gender-matched controls (Group 2). A detailed ophthalmic examination was performed at 1 month and 6 months after the diagnosis of COVID-19. Photopic, mesopic, and scotopic pupil diameters (PDs) were measured using a quantitative infrared pupillography which was integrated into Scheimpflug/Placido photography-based topography system. PDs at 0, 2nd, 4th, and 6th seconds, and average pupil dilation speeds at 2nd, 4th, 6th, and 8th seconds were recorded.

**Results:** Eighty-six eyes of 86 patients (Group 1: n=42; Group 2: n=44) were included. While the mean photopic, mesopic, and scotopic PDs were significantly larger in the COVID-19 group than the control group in the 1st month (p=0.035, p=0.017, p=0.018, respectively), no statistically significant difference was found in the 6th month. Besides, average pupil dilation speeds and PDs at the 0, 2nd, 4th, and 6th seconds were not statistically significantly different between the two groups in the 1st month and 6th month.

**Conclusion:** PDs were significantly larger in COVID-19 patients in all light intensities in the 1st month after COVID-19. However, pupillary dilation was transient, and no significant difference was found in the 6th month. We suggest that the transient pupillary dilation may be secondary to the autonomic nervous system dysfunction and/or optic nerve and visual pathways alterations following COVID-19.

**Keywords:** COVID-19, parasympathetic inhibition, pupil diameter, pupillography, sympathetic hyperactivity

## Introduction

Severe acute respiratory syndrome (SARS) coronavirus-2 (SARS-CoV-2) was first identified at the end of 2019 as the cause of Coronavirus disease-2019 (COVID-19) and reached the size of a global pandemic in March 2020 (1,2). Current evidence shows that COVID-19 has the potential to affect various organs and systems in the body. Although the respiratory system is primarily affected by COVID-19, increasing data on individual or combined involvement of cardiovascular, neurological, and ocular systems are emerging (3-8). Moreover, new patterns and syndromes, such as "long COVID", caused by autonomic instability, are being added to the literature (9,10).

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**Address for correspondence:** Gamze Ucan Gunduz, MD. Department of Ophthalmology, Bursa Uludag University, Bursa, Türkiye
**Phone:** +90 506 234 20 70 **E-mail:** gamzeug@uludag.edu.tr

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SARS-CoV-2 infection has been associated with a variety of findings, including conjunctivitis, uveitis, retinitis, and neuro-ophthalmologic manifestations such as Adie's tonic pupil, cranial nerve palsies, optic neuritis, and Guillain–Barré syndrome (11-17). Although no correlation has been documented between the overall prognosis and ocular tissue involvement, it has been shown that in-hospital mortality rates increase with neurological involvement (18). Still, it is undeniable that the eye is a gateway to the nervous system. In this context, it may be useful to focus on retinal findings and/or the ocular reflexes that connect the peripheral nervous system to the central nervous system to predict prognosis using ocular findings.

Assessment of the pupils has been used as a diagnostic tool for a wide range of clinical conditions (8,19). The most common method for the evaluation of the pupil light reflex and pupil diameters (PDs) utilizes a penlight. However, infrared pupillography can be used especially for PDs under different light intensities (20,21). Infrared pupillography is a non-invasive method that provides a quantitative assessment of the pupils and has been used before in several neuro-ophthalmological disorders (Horner's syndrome, oculomotor nerve palsy, tonic pupil, etc.), neuro-psychiatric conditions (Parkinson's disease, Alzheimer's disease, schizophrenia, traumatic brain injury, etc.), and for the assessment of autonomic function in different disorders (22-27). The tendency to adopt infrared pupillography as a routine part of the neuro-ophthalmologic examination is increasing.

In this study, we aimed to investigate possible changes in pupillary function caused by COVID-19 in cases at different time points of the recovery period. Accordingly, we compared the static and dynamic pupillographic values of those patients using quantitative infrared pupillography with healthy individuals and discussed the plausible underlying pathophysiology.

## Methods

This case–control study was carried out between June 2020 and December 2021 at Uludag University. A total of 86 participants were included in the study. Patients who were diagnosed with COVID-19 and referred for ophthalmic examination by the pulmonology department comprised Group 1. Group 2 consisted of age- and gender-matched, otherwise healthy individuals who were examined in the ophthalmology department for routine refractive errors.

In the study group (Group 1), the diagnosis of COVID-19 was based on a positive SARS-CoV-2 real-time, reverse transcription-polymerase chain reaction (RT-PCR) of the nasopharyngeal swab sample. Oral administration of favipiravir with a loading dose of 2 × 1600 mg and a 5-day maintenance dose of 2 × 600 mg was used for all the patients. All patients showed a negative RT-PCR test at the end of the 2$^{nd}$ week. The ophthalmological examination was performed 2 times for each individual, in the 1$^{st}$ month and 6$^{th}$ month after RT-PCR negativity. Participants in the control group (Group 2) were questioned about the presence of potential symptoms of COVID-19 and suspicious contacts. Participants with potential signs and symptoms of COVID-19 were excluded from the control group.

Individuals with diabetes mellitus, systemic hypertension or any other systemic diseases, high myopia (axial length ≥26.5 mm) and hyperopia (axial length ≤21.5 mm), glaucoma, uveitis, retinal or corneal disease, optic neuropathy or atrophy, and previous ocular surgery (including phacoemulsification and corneal refractive surgery) were excluded from the study. Cases using topical or systemic medications that could affect pupillary functions other than the treatment of COVID-19 were not included.

All participants underwent comprehensive ophthalmic examinations, including refraction, assessment of best corrected visual acuity (BCVA) with Snellen chart, and anterior and posterior segment examination. An automatic refractometer (RF10, Canon Inc., Tokyo, Japan) was used for measuring the manifest refraction. The spherical equivalent was calculated by adding half of the cylindrical power to the sum of the spherical power used for statistical analysis. The axial length was measured using the Lenstar 900 (version 2.1.1, Haag-Streit AG, Switzerland).

Pupillary reflexes, including light and near responses, were evaluated in all patients. In order to avoid any possible bias, only one eye of each patient was selected with simple random sampling. PDs were measured with Scheimpflug/Placido photography-based topography system (Sirius, CSO, Costruzione Oftalmici, Florence, Italy). This device includes Placido disc properties and a 3D rotating Scheimpflug camera. The pupillography is integrated into this topography system and captures PDs either dynamically or statically based on the lighting conditions. All the pupillographic measurements were performed by the same technician under similar lighting conditions in the room. No topical anesthetic, cycloplegic, and/or mydriatic eye drops were applied to the participants before pupillographic measurements. Before the pupillographic measurements were started, the lights of the room were switched off except for the illumination of the device. The Sirius device provided a certain amount of illumination for photopic (40 lux), mesopic (4 lux), and scotopic (0.04 lux) conditions. Subsequently, scotopic, mesopic, and photopic PDs were measured, and the Sirius topographer recorded a video of the pupillary response. Dynamic pupillography began with 500 lux illumination, and after the capture has started, the illumination was turned off. In this way, from the photopic to the scotopic condition, PDs and average pupil dilation speeds could be measured every 2 s.

This study adhered to the tenets of the Declaration of Helsinki and was approved by the Ministry of Health (May 11, 2020) and Institutional Review Board of Uludag University (April 29, 2020) with the number of 2020-7/13.

### Statistical Analysis

All statistical analyses were performed with IBM SPSS version 23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, version 23.0. Armonk, NY: IBM Corp.), and p<0.05 was considered statistically significant. The results are presented as mean±standard deviation or frequency and percentage. The Shapiro–Wilk test was used as the test for normality. Student's t-test was used for the comparison of the two groups. Categorical variables were compared using Pearson's Chi-square test between groups. Dependent variables were compared using paired samples t-test. Simple random sampling was used for the randomization of the eye for assessments.

## Results

A total of 86 eyes of 86 participants (52 females, 34 males) with a mean age of 40.6±10.6 years were enrolled in the study. Group 1 included 42 eyes of 42 patients diagnosed with COVID-19. Group 2 included 44 eyes of 44 healthy controls. There were no statistically significant differences in terms of age and gender between groups (p=0.649, p=0.291, respectively). All participants were phakic and had a BCVA value equal to 20/20. Except for refractive errors, none of the participants had any coexisting ocular or systemic disease. No statistically significant difference was detected between groups in terms of refractive status (p=0.956) and axial length (p=0.864). The patients were questioned in terms of neurological symptoms during the PCR-positive period. None of them had neurological symptoms during acute infection. Furthermore, during the ophthalmic examination, none of the patients had neurological and ocular symptoms or visual loss. Demographic characteristics and ophthalmological features are provided in Table 1.

Pupillary light and near responses were normal in all patients. The mean values of PDs (photopic, mesopic, and scotopic) in the 1st month and 6th month after COVID-19 are summarized in Table 2. In the 1st month, the mean PDs were 3.37±0.56 mm in photopic, 4.28±0.81 mm in mesopic,

**Table 1.** Demographic characteristics and ophthalmologic features of participants in Group 1 (recovered from COVID-19) and Group 2 (controls)

| | Group 1 (n=42 pts, 42 eyes) | Group 2 (n=44 pts, 44 eyes) | p |
|---|---|---|---|
| Age (years) | 40.05±9.3 | 41.09±11.7 | 0.649* |
| Gender (female/male) | 23/19 | 29/15 | 0.291† |
| Spherical equivalent (D) | 0.05±0.6 | 0.03±1.4 | 0.956* |
| Axial length (mm) | 23.47±0.8 | 23.50±0.9 | 0.864* |
| BCVA (Snellen) | 1.0 | 1.0 | - |

COVID-19: Coronavirus disease 19; pts: Patients; BCVA: Best corrected visual acuity; D: Diopters. P<0.05 was considered the significance level. *Student's t-test, †Pearson's Chi-square test.

**Table 2.** Comparison of pupil diameters between Group 1 (recovered from COVID-19) and Group 2 (controls)

| | Group 1 (COVID-19) | Group 2 (Controls) | p* |
|---|---|---|---|
| Static PDs in the 1st month | | | |
| Photopic PD (mm) | 3.37±0.56 | 3.10±0.53 | 0.035 |
| Mesopic PD (mm) | 4.28±0.81 | 3.87±0.70 | 0.017 |
| Scotopic PD (mm) | 5.71±0.84 | 5.24±0.93 | 0.018 |
| Static PDs in the 6th month | | | |
| Photopic PD (mm) | 3.27±0.63 | 3.33±0.81 | 0.787 |
| Mesopic PD (mm) | 4.11±0.88 | 4.09±0.92 | 0.931 |
| Scotopic PD (mm) | 5.33±0.70 | 5.47±1.01 | 0.627 |

COVID-19: Coronavirus disease 19; pts: Patients; PD: Pupil diameters. P<0.05 was considered the significance level, and bold characters were used for the statistically significant values, *Student's t-test.

and 5.71±0.84 mm in scotopic conditions in Group 1. However, in Group 2, the mean PDs were 3.10±0.53 mm, 3.87±0.70 mm, and 5.24±0.93 mm in photopic, mesopic, and scotopic conditions, respectively. PDs in all light intensities were significantly higher in patients recovering from COVID-19 than controls in the 1st month (p=0.035, p=0.017, p=0.018, respectively) (Table 2 and Fig. 1). However, in the 6th month, there were no statistically significant differences in terms of mean photopic, mesopic, and scotopic PD between the COVID-19 group and control group (p=0.787, p=0.931, p=0.627, respectively) (Table 2). In addition, a slight reduction in the photopic, mesopic, and scotopic PDs was detected in the COVID-19 group between the 1st month (3.37±0.56 mm, 4.28±0.81 mm, 5.71±0.84 mm) and the 6th month (3.27±0.63 mm, 4.11±0.88 mm, 5.33±0.70 mm) (Table 3). However, the difference in PD did not reach a statistically significant level (p=0.282 for photopic PD, p=0.140 for mesopic PD) except for the scotopic PD (p=0.017).

Dynamic pupillography analysis is shown in Figure 2. In the COVID-19 group, PDs at 0, 2nd, 4th, and 6th s were higher than the control group in the 1st month. However, the difference between groups was not statistically significant (p=0.390, p=0.110, p=0.257, p=0.403, respectively). PDs at 0, 2nd, 4th, and 6th s were similar between two groups at 6th month (p=0.542, p=0.622, p=0.706, p=0.642, respectively). The average pupil dilation speed values at the 2nd, 4th, 6th, and 8th s were also similar in both groups at the 1st month and 6th month (p=0.488, p=0.520, p=0.482, p=0.610, the 1st month, respectively; p=0.862, p=0.685, p=0.622, p=0.977, the 6th month, respectively).

## Discussion

The pathophysiological pathways in ocular involvement of COVID-19 are not yet well-defined (11-13). It is not known when, why, how, and to what extent SARS-CoV-2 would affect ocular tissues. Herein, we examined the impact of COVID-19 on pupillary functions at two different visits (1st

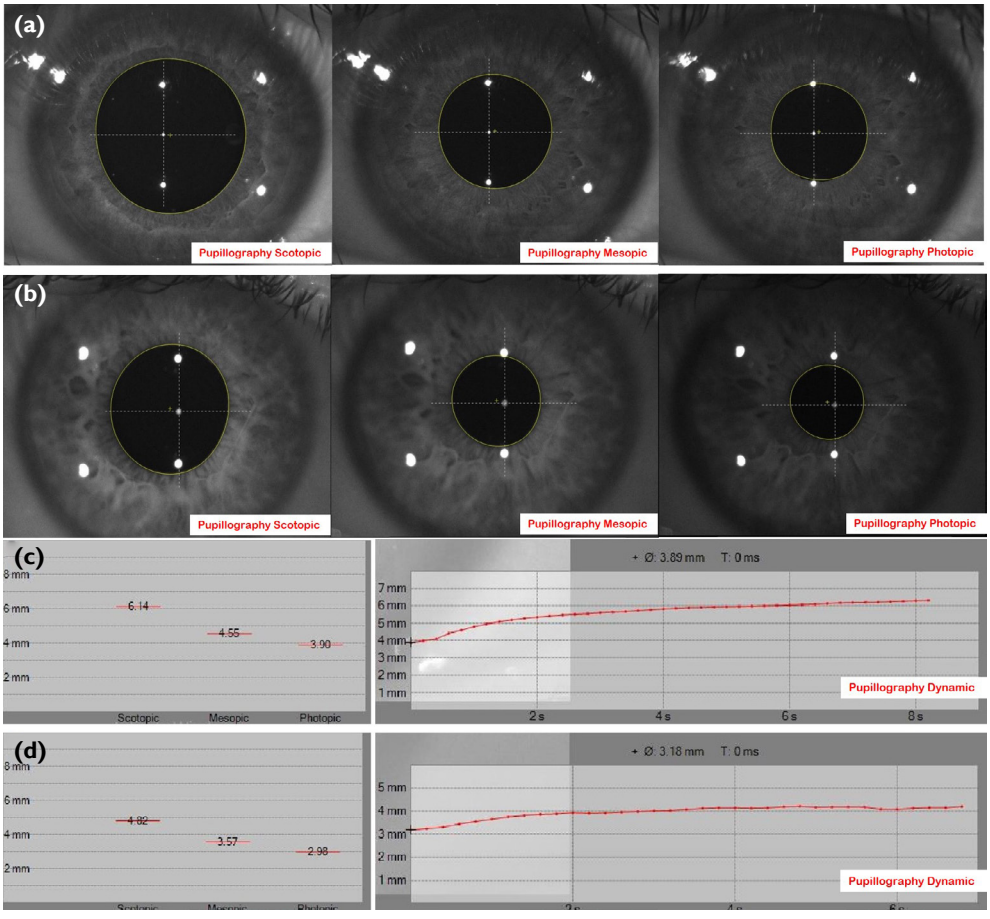


**Figure 1.** Scotopic, mesopic, and photopic pupillographic images of a patient who recovered from COVID-19 **(a)** versus a normal control **(b)** note the larger pupils under all light intensities in the post-COVID-19 case. The diagram of dynamic pupillography and static pupil diameters of post-COVID-19 patient **(c)** and that of the normal control **(d)** were also given.

**Table 3.** Pupil diameters of patients in Group 1 (recovered from COVID-19) and Group 2 (controls) were measured in the 1st and 6th months

| | 1st month | 6th month | p* |
|---|---|---|---|
| Group 1 (COVID-19) | | | |
| Photopic PD (mm) | 3.37±0.56 | 3.27±0.63 | 0.282 |
| Mesopic PD (mm) | 4.28±0.81 | 4.11±0.88 | 0.140 |
| Scotopic PD (mm) | 5.71±0.84 | 5.33±0.70 | 0.017 |
| Group 2 (Controls) | | | |
| Photopic PD (mm) | 3.09±0.59 | 3.33±0.81 | 0.093 |
| Mesopic PD (mm) | 3.83±0.84 | 4.09±0.92 | 0.155 |
| Scotopic PD (mm) | 5.18±1.06 | 5.47±1.01 | 0.228 |

COVID-19: Coronavirus disease 19; pts: Patients; PD: Pupil diameters. P<0.05 was considered the significance level, and bold characters were used for the statistically significant values. *Paired samples t-test.

and 6th months) in cases who recovered from the disease. The results of our study showed that the photopic, mesopic, and scotopic PDs become larger in the early convalescence (1st-month post-infection) and returned to normal within 6 months. Several mechanisms, such as subclinical structural and/or inflammatory neuropathy, post-infectious immune-mediated neuropathy, and autonomic instability, may be contributing to the pathophysiology.

Recently, Lecler et al. (27) showed that 13% of patients had abnormal magnetic resonance imaging (MRI) findings in the orbit and visual pathways, whereas 35% of these patients had an abnormal signal of at least one of the visual pathway structures on fluid-attenuated inversion recovery-weighted imaging. Marsiglia et al. (28) suggested that COVID-19 could affect both the afferent and efferent components of the visual axis. In addition, changes in peripapillary retinal nerve fiber layer thicknesses have been reported in patients recovering from COVID-19 (29-31). Burgos–Blasco et al. (31) suggested that the optic nerve may get affected while the infection resolves. Based on the MRI and OCT studies mentioned above, one may suggest that post-infectious and subclinical structural and/or inflammatory changes within the optic nerve and visual pathways may have led to pupillary dilation, as in our cases.

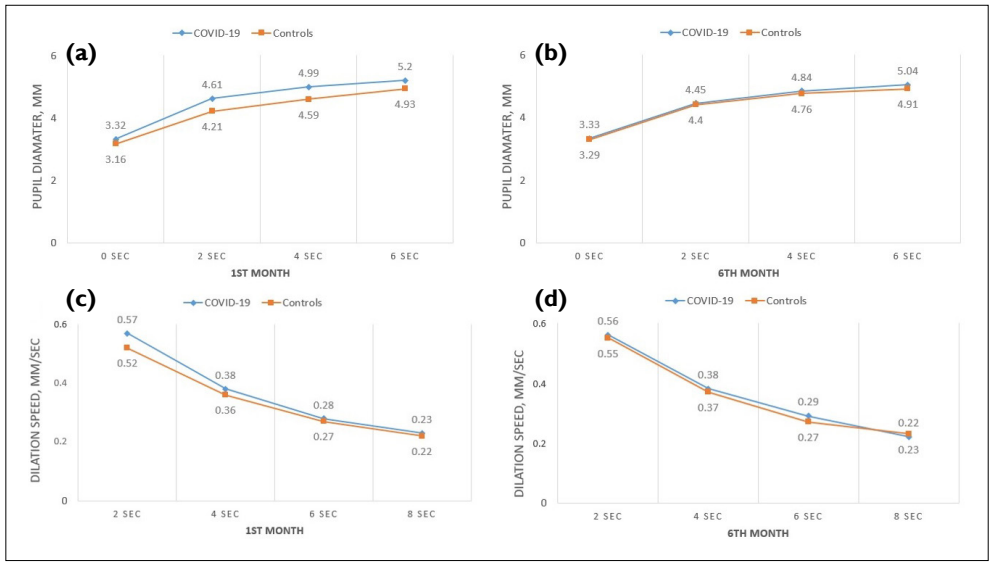


**Figure 2.** Dynamic pupillography values were given. Pupil diameters at 0, 2nd, 4th, and 6th s in the 1st **(a)** and the 6th **(b)** months after COVID-19 infection were shown graphically. Note the larger pupils at all-time points in the post-COVID 1st month, although there was no statistically significant difference. The average pupil dilation speed values in the post-COVID 1st month **(c)** and 6th month **(d)** were similar in both groups. In all graphics (A, B, C, and D), all p>0.05 between the two groups. *Student's t-test.

Another possible mechanism for pupil dilation in COVID-19 cases could be "dysautonomia," which develops in the post-infectious period. It is a neurological disorder caused by dysfunction of the autonomic nervous system (ANS) that affects the functions of the heart, bladder, sweat gland, intestines, and pupils (32). Thus, pupillometric tests have previously been used to assess autonomic functions and are suggested to have diagnostic value in differentiating underlying conditions (14,27,33). It is well-known that pupillary autonomic dysfunction may precede a more generalized involvement of the ANS in various systemic disorders (15,33,34). In concordance with this notion, in the 1st month following COVID-19, pupillary functions were impaired in our study, whereas none of these patients had ocular (i.e., photophobia and blurred vision) or systemic symptoms indicating an autonomic dysfunction.

The major clinical characteristics of dysautonomia in COVID-19 patients are fatigue, labile blood pressure, orthostatic hypotension, and damage in bowel and bladder functions (32,35). However, it could cause light-threatening complications in patients with comorbid diseases such as diabetes and hypertension (32). The fact that our patients were asymptomatic in terms of ANS dysfunction, other than pupillary dilation, might be attributed to the absence of comorbid systemic diseases. While Barizien et al. (35) reported the duration of dysautonomia as 7.0–7.5 months from the first symptoms of COVID-19, Shouman et al. (36) suggested that patients had developed dysautonomia between 0 and 122 days. In our study, the pupillary dilation that was observed in the 1st month following COVID-19 returned to normal in the 6th month. Based on these results, we suggest that pupillary dilation observed in the current study may be a sign of dysautonomia associated with COVID-19.

Recently, Stute et al. (37) have reported that resting sympathetic activity is elevated in otherwise healthy young adults recovering from COVID-19. The authors have demonstrated that survivors of SARS-CoV-2 had similar heart rates and blood pressure to that of the control participants while the perception of pain decreases (37). Pupillary dilation may be an overlooked component of this spectrum. The presence of larger pupils in our cases may be a mild and subclinical sign of a form of sympathetic hyperactivity associated with COVID-19.

On the other hand, pupillary dilation following COVID-19 may have been caused by parasympathetic inhibition. Adie's tonic pupil has been recently reported in several COVID-19 cases (13,16,38). Adie's tonic pupil is defined as a dilated pupil with poor light reaction despite preserved near response and is due to abnormal regeneration of parasympathetic nerve fibers after ciliary ganglion injury (38). Although Adie's tonic pupil is usually idiopathic, it has been related to autoimmune diseases, paraneoplastic syndromes, and post-infectious conditions such as syphilis, Lyme disease, or herpesviridae (39). In this respect, one may hypothesize that post-infectious immune-mediated parasympathetic system damage may have caused the presence of pupillary dilation in our study cases.

In the literature, there are two pupillometric studies, including acute COVID-19 patients. Vrettou et al. (40) found no significant differences in the pupil parameters between COVID-19-positive and COVID-19-negative intensive care unit patients. Yurttaser Ocak et al. (41) analyzed the PDs during acute infection and 3 months later in COVID-19 patients. Contrary to our study, they reported that PDs were significantly lower during acute infection compared to the 3rd month's results. However, our study included COVID-19 patients in the recovery period, and pupil responses during acute infection were not included.

Dynamic and static pupillary responses in post-COVID-19 patients were evaluated in three recent studies (42,43). In two studies, the pupillographic analysis was performed in the 1st or 2nd months after acute COVID-19. Both studies reported significantly higher static PDs in post-COVID-19 patients and similar dynamic pupillography values between post-COVID-19 patients and controls. Bitirgen et al. (44) performed dynamic pupillography and long-COVID questionnaires in 35 post-COVID-19 patients and healthy controls. They reported no significant differences in the initial PD. However, there were significant alterations in contractile pupillary light responses. The results of three studies (42-44) could indicate the parasympathetic dysfunction following COVID-19 and were comparable to the current study. However, we performed repetitive pupillographic measurements on each participant following the acute phase and found that early pupil dilation detected in the 1st month resolved within 6 months. Accordingly, this is the first study providing information about the duration and improvement of pupillary dilation associated with COVID-19.

The current study has some limitations. The relatively small number of cases, lack of measurements during acute COVID-19, and lack of information about long-COVID symptoms can be listed among the drawbacks of this study. However, this study may be considered noteworthy for it may help to gain insight into an open field where little information is present.

## Conclusion

The spectrum of ocular involvement in COVID-19 is expanding. The results of our study demonstrated that transient higher PDs were present under all light intensities in post-COVID-19 patients compared to healthy controls. Pupillographic analysis might be a biomarker of dysautonomia-related sympathetic excitation and/or parasympathetic inhibition in post-COVID-19 cases. Improvement of pupil dilation within 6 months might give us information about the duration of dysautonomia in COVID-19.

**Disclosures**

**Ethics Committee Approval:** This study adhered to the tenets of the Declaration of Helsinki and was approved by the Ministry of Health (May 11, 2020) and Institutional Review Board of Uludag University (April 29, 2020) with the number of 2020-7/13.

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**Conflict of Interest:** None declared.

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