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Diabetic retinopathy treatment and management during the COVID-19 pandemic

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Ethics Committee Approval
This study was approved by the University of Health Sciences, Gazi Yaşargil Education Research Hospital, 16.10.2020 / 598.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Diabetic macular edema (DME) is a common retinal disease and is the most common cause of vision loss due to diabetic retinopathy. During the COVID-19 pandemic, there has been a serious decrease in hospital visits due to both the measures taken by governments and the anxiety of patients fearful of contracting COVID-19. The aim of this study is to determine the problems occurring during the COVID-19 pandemic period in patients treated with intravitreal (IV) injection for diabetic retinopathy, and to provide recommendations for treatment management in these patients.

Methods: Twenty-nine eyes of 17 patients who were diagnosed with DME were included. The frequency of hospital visits, treatments performed, and detailed ophthalmological examination findings, including optical coherence tomography findings and glycated haemoglobin (HbA1c) values, were recorded in the period before the COVID-19 pandemic. During the COVID-19 pandemic period, the detailed ophthalmological examination findings and HbA1c values were noted after the patients who had delayed their routine control time (>90 days) applied to the hospital. New treatments were planned according to the current situation.

Results: Seventeen patients were included in the study; 10 were female (58.8%) and seven were male (41.2%). The mean time interval between following visits was 45.5 (5.9) days during the pre-pandemic period, but it increased to 110.4 (13.5) days during the COVID-19 pandemic period (P<0.001). Visual acuity (LogMAR) was 0.4 (0.4) in the pre-pandemic period and 0.8 (0.5) during the COVID-19 pandemic period (P=0.003). Central macular thickness was 300.1 (85.6) µm in the pre-pandemic period and it increased to 387.1 (144.5) µm during the COVID-19 pandemic period (P=0.007). In three patients, complications of diabetic retinopathy that could not be cured by medical treatment developed and surgical treatment was recommended.

Conclusions: Delays in the treatment of diabetic retinopathy may cause permanent impairment in visual functions. The COVID-19 pandemic has caused an increase in the hospital visit intervals of patients, and this situation has resulted in disruptions in the follow-up and treatment of patients with diabetic retinopathy. Alternative diagnosis and treatment practices are needed in order to manage these and similar processes smoothly.

Keywords: COVID-19, Diabetic retinopathy, Intravitreal injection, Optical coherence tomography

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Introduction

Diabetic macular edema (DME) is a common retinal disease and is the most common cause of vision loss due to diabetic retinopathy [1]. The prognosis of DME depends on various factors, such as age, glucose regulation and other systemic diseases (e.g. hypertension, renal disorders) [2]. Direct fundus examination and fundus fluorescein angiography are used for the diagnosis of DME. Furthermore, there have been important advances in the diagnosis and treatment of DME following the development of optical coherence tomography (OCT) technology, which plays an important role in the diagnosis and follow-up of, and treatment planning for diabetic patients [1].

The most important step in DME treatment is metabolic regulation, and while laser photocoagulation is often the first treatment option, anti–vascular endothelial growth factor (VEGF) agents have also entered the ophthalmology practice, resulting in changes in treatment algorithms. VEGF is an important mediator that causes abnormal vascular permeability in DME [3]. There are different anti-VEGF agents used as an intravitreal (IV) injection in the treatment of DME to supress rising VEGF levels [4-6]. In addition to anti-VEGF agents, long-acting IV steroid injections are also used in the treatment of DME [7, 8]. Routine ophthalmological controls are performed in certain periods in patients with a diagnosis of diabetic retinopathy, and IV injections are applied according to various treatment protocols.

The coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus was first identified in Wuhan, China, by the ophthalmologist, Dr Wenliang Li, at the end of 2019 [9]. The disease spread worldwide in a short period of time, and the World Health Organization declared COVID-19 as a pandemic on March 11, 2020 [10]. The transmission of the disease through droplets caused many countries to take local precautions, and routine examinations and practices in healthcare facilities became limited except for in the cases of emergencies and semi-emergencies [11]. With the spread of cases in March 2020 in Turkey, the government implemented some restrictive measures in order to control the distribution rate of the virus, similar to other countries.

During the COVID-19 pandemic, there has been a serious decrease in hospital visits due to both the measures taken by governments and the anxiety of patients fearful of contracting COVID-19, which has led to morbidity and mortality due to delays in treatment of some acute and chronic diseases. The aim of this study is to examine the anatomical and functional results of diabetic macular edema in diabetes mellitus (DM) patients due to the prolongation of routine periodic examination intervals during the COVID-19 pandemic, and to provide recommendations for treatment management in these patients during the pandemic.

Materials and methods

This was a prospective, observational study conducted in Diyarbakır Gazi Yaşargil Training and Research Hospital. Ethics Committee approval was obtained for the study (University of Health Scıences Gazi Yaşargil Education Research Hospital, 16.10.2020 / 598), written informed consent form was obtained from all participants and the principles in the Helsinki Declaration were followed.

29 eyes of 17 patients who were followed-up with and treated for DME in one or both eyes in the ophthalmology clinic were examined in this prospective cohort study. Patients were selected from those who were previously diagnosed with type 2 DM, had developed DM-related posterior segment complications in one or both eyes during the follow-up period, and applied IV anti-VEGF injection and/or panretinal laser photocoagulation. Patients who underwent a long-acting IV steroid injections were excluded from the study due to its longer potency. In addition, patients with visual impairment due to anterior or posterior segment complications, such as age-related macular degeneration or cataracts, were also excluded.

The patients were selected from those who were followed-up with and treated at regular intervals due to diabetic retinopathy, but were unable to attend for routine controls for at least 90 days due to the COVID-19 pandemic. The time that the patient was absent from the hospital was calculated by subtracting the time they last came to the hospital in the pre-pandemic period from the time of their visit to the hospital during the COVID-19 pandemic period. Patients who developed visual impairments due to complications such as cataract and glaucoma during the period when they could not come to the hospital for routine controls were excluded from the study. Ophthalmological examination findings and OCT measurements during the last examination before and during the pandemic period were noted. Treatments performed during the follow-up period were also noted. In addition, the glycated haemoglobin (HbA1c) values of the patients were recorded at the last examination during their controls in COVID-19 pandemic period.

After the pupil was dilated (with 1% cyclopentolate hydrochloride and 2.5% phenylephrine hydrochloride), spectral domain OCT (SD-OCT) was performed by the same experienced physician at the same time interval (2.00-4.00 pm) using Heidelberg's Spectralis OCT (Spectralis HRA + OCT; Heidelberg Engineering, Heidelberg, Germany). Real-time eye tracking using the TruTrack Active Eye Tracking function was used, and automatic real-time image averaging was set at 100 images. After the stabilization of the eye, six radial macular scans with equal angular orientation and 200 μm spacing were performed with an infrared camera in the centre of the fovea. The value at the centre of the scan was determined and recorded as central macular thickness (CMT). Patients with poor image quality due to anterior or posterior segment complications, and those who could not comply with SD-OCT imaging were excluded from the study. Fundus fluorescein angiography (TRC-50DX, Topcon) was performed in patients as deemed necessary. Based on these results, new treatment plans (IV injection and/or panretinal laser photocoagulation) were determined.

Statistical analysis

All of the data were recorded using the Statistical Package for the Social Sciences for Windows (version 20; SPSS Inc., Chicago, IL, USA). The categorical variables were presented as mean (standard deviation). An independent t test was used for comparisons between two groups of numerical

variables. A *P*-value of <0.05 was considered to be statistically significant.

Results

Seventeen patients who were treated for DME were included to the study; 10 were female (58.8%) and seven were male (41.2%). The mean age of the patients was 63.0 (5.5) years (range 56-74 years). Twelve (70.6%) patients presented with bilateral DME and five (29.4%) patients presented with unilateral DME. The mean time interval between follow-up visits was 45.5 (5.9) days in the pre-pandemic period, but it increased to 110.4 (13.5) days during the COVID-19 pandemic period (*P*<0.001). HbA1c values were 8.0 (1.2%) in the pre-pandemic period, it increased to 8.6 (1.6%) during the COVID-19 pandemic period (*P*=0.245). Visual acuity was 0.4 (0.4) LogMAR in the pre-pandemic period and 0.8 (0.5) LogMAR during the COVID-19 pandemic period (*P*=0.003). CMT was 300.1 (85.6) µm in the pre-pandemic period and it increased to 387.1 (144.5) µm during the COVID-19 pandemic period (*P*=0.007) (Table 1).

Table 1: Demographic characteristics of the patients, and visual acuity (logMAR) and central macular thickness values at different visits

	Before the COVID-19 pandemic	During the COVID-19 pandemic	*P*-value *
Gender (M/F) n, %	10 (58.8%) / 7 (41.2%)		
Age (years)	63.0 (5.5		
Unilateral/Bilateral, n, %	5 (29.4%) / 12 (70.6%)		
HbA1c (%)	8.0 (1.2)	8.6 (1.6)	0.245
Days of visits (days)	45.5 (5.9)	110.4 (13.5)	<0.001
BCVA (logMAR)	0.4 (0.4)	0.8 (0.5)	0.003
CMT (µm)	300.1 (85.6)	387.1 (144.5)	0.007

Results are denoted as mean (standard deviation), M: Male F: Female Hb A1c: Hemoglobin A1c BCVA: Best-corrected visual acuity, CMT: Central macular thickness µm: micron meter, *: Independent t test (*P*<0.05 statistically significant)

Demographic findings of all patients, HbA1c values, findings of the last pre-pandemic ophthalmologic examination, visit intervals and applied treatments were noted. The duration of delay in days, current ocular examination findings and planned treatments during the visits in pandemic period were recorded and are detailed in Table 2. The OCT images of the first two patients taken in the pre-pandemic and during pandemic periods are shown in Figure 1a, 1b, 2a, and 2b.

Figure 1a: OCT images of the first patient taken at the last hospital visit before the pandemic, 1b: OCT images of the first patient taken at the hospital visit during the pandemic period. (* OCT: Optical coherence tomography)

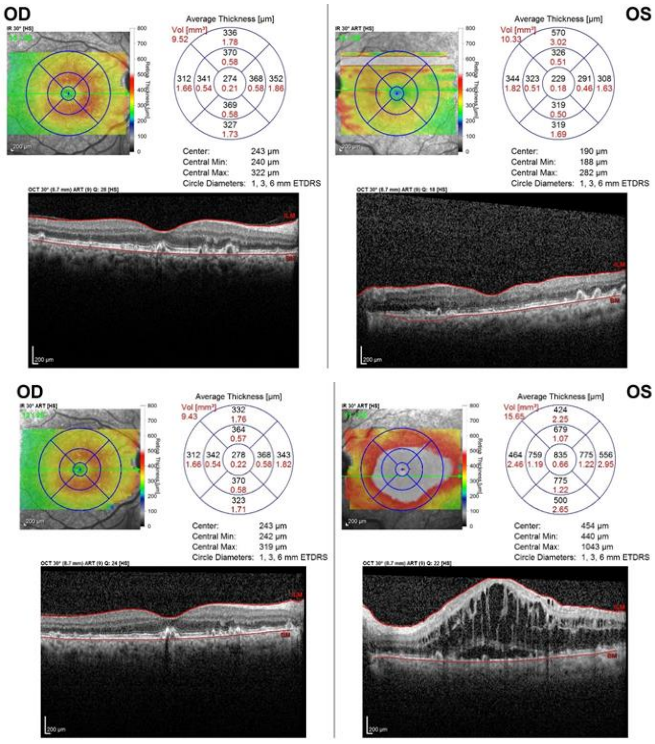

Figure 2a: The OCT images of the second patient taken at the last hospital visit before the pandemic, 2b: The OCT images of the second patient taken at the hospital visit during the pandemic period (* OCT: Optical coherence tomography)

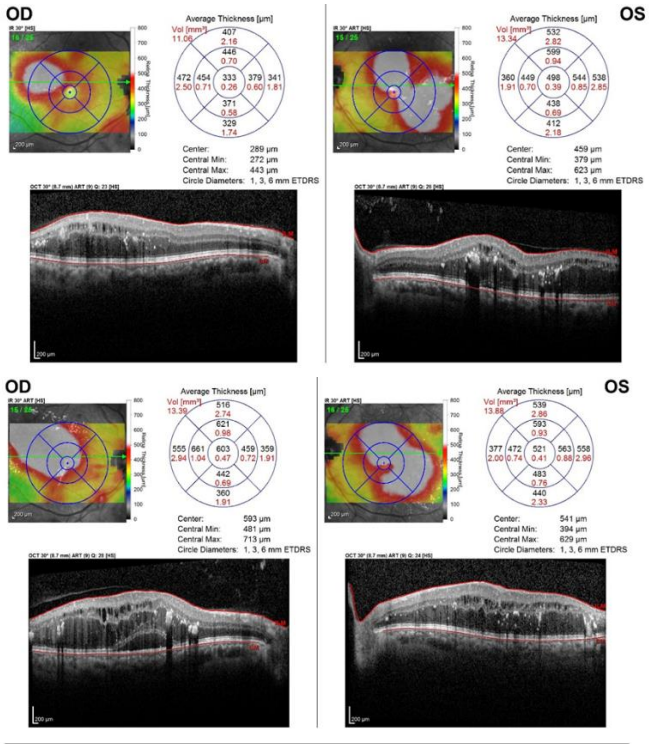

Table 2: Detailed information about the demographic, clinical features, ocular examination findings, and treatment plans of patients with diabetic retinopathy whose treatment is delayed due to the Covid 19 pandemic.

No, Gender, Age (years)	Last HbA1c* (%)	Current HbA1c** (%)	Laterality	Previous treatments (number of IV injections)	Pre-pandemic visit frequency (days), total number of visits	Elapsed time after last visit (days)	Last BCVA at pre-pandemic examination (RE/LE) (logMar) CMT (µm) (RE/LE)	Current BCVA (RE/LE) (logMar) CMT (µm) (RE/LE)	Current ocular examination results	Planned treatment
1, F, 67	6.2	6.7	Bilateral	RE: IV injection (4) LE: IV injection (5)	38.6 (7)	126	0.2 / 0.3 274 / 229	0.3 / 1.3 278 / 835	LE: DME	LE: IV injection
2, M, 56	7.2	7.8	Bilateral	RE: IV injection (3)+ Panretinal Laser LE: IV injection (2)+ Panretinal Laser	42.4 (5)	97	0.4 / 0.5 333 / 498	1.3 / 0.7 603 / 521	Bilateral: DME	Bilateral: IV injection + Panretinal Laser
3, F, 58	6.7	8.8	Unilateral	LE: IV injection (5)	41.1 (7)	104	0.1 / 0.3 251 / 339	0.1 / 0.7 265 / 454	LE: DME	LE: IV injection
4, M, 61	8.7	8.4	Bilateral (RE: NVG)	RE: IV injection (9)+ Panretinal Laser LE: IV injection (7)+ Panretinal Laser	34.3 (13)	92	- / 0.5 -/ 288	- / 1.0 -/ 346	LE: DME	LE: IV injection
5, F, 60	8.6	7.7	Bilateral	RE: IV injection (3)+ Panretinal Laser LE: IV injection (4)+ Panretinal Laser	39.7 (6)	128	0.5 / 0.5 545 / 549	1.0 / 1.0 652 / 668	Bilateral: DME	Bilateral: IV injection
6, F, 64	10.4	8.3	Bilateral	RE: IV injection (5)+ Panretinal Laser LE: IV injection (4)+ Panretinal Laser	52.3 (7)	135	1.3 / 1.3 345 / 306	1.6 / 1.5 - / 486	RE: VH LE: DME	RE: PPV LE: IV injection
7, M, 57	8.7	7.8	Bilateral	RE: IV injection (2)+ Panretinal Laser LE: IV injection (3)+ Panretinal Laser	44.3 (4)	103	0.2 / 0.5 254 / 296	0.3 / 1.3 304 / 442	Bilateral: DME	RE: IV injection+ Panretinal Laser LE: IV injection
8, M, 71	6.3	6.7	Bilateral	RE: IV injection (7)+ Panretinal Laser LE: IV injection (5)+ Panretinal Laser	48.6 (10)	112	0.2 / 0.2 242 / 238	0.4 / 0.2 314 / 248	RE: DME	RE: IV injection
9, F, 63	9.4	7.2	Unilateral	LE: IV injection (1)	48.5 (2)	129	0.2 / 0.4 236 / 276	0.3 / 0.4 334 / 298	Bilateral: DME	Bilateral: IV injection
10, F, 67	8.1	11.7	Bilateral	RE: IV injection (5)+ Panretinal Laser LE: IV injection (6)+ Panretinal Laser	56.7 (9)	132	1.5 / 1.3 -/ 312	1.6 / 1.3 -/ 352	RE: VH LE: DME	RE: PPV LE: IV injection
11, M, 74	7.2	6.9	Unilateral	RE: IV injection (2)	46.7 (3)	95	0.3 / 0.2 262 / 254	0.5 / 0.2 336 / 248	RE: DME	RE: IV injection
12, F, 60	8.8	8.0	Unilateral	LE: IV injection (2)	38.5 (4)	117	0.1 / 0.4 232 / 287	0.2 / 0.7 268 / 298	Bilateral: DME	Bilateral: IV injection LE: Panretinal laser
13, M, 72	7.5	6.9	Bilateral	RE: IV injection (4) LE: IV injection (3)	45.3 (6)	99	0.3 / 0.2 246 / 234	0.5 / 0.3 354 / 246	RE: DME	RE: IV injection
14, F, 60	10.2	7.8	Bilateral	RE: IV injection (3) LE: IV injection (2)	50.3 (4)	92	0.3 / 0.5 284 / 322	0.7 / 0.7 414 / 406	Bilateral: DME	Bilateral IV enjeksiyon
15, M, 57	8.8	8.1	Unilateral	LE: IV injection (6)	46.1 (8)	124	0.2 / 0.3 238 / 226	0.2 / 0.7 234 / 306	LE: DME	LE: IV injection
16, F, 64	12.1	9.4	Bilateral	RE: IV injection (4)+ Panretinal Laser LE: IV injection (3)+ Panretinal Laser	49.8 (5)	128	0.4 / 0.4 304 / 264	1.6 / 1.3 - / 457	RE: VH LE: DME	RE: PPV LE: IV injection
17, F, 60	10.4	7.2	Bilateral	RE: IV injection (2) LE: IV injection (2)	50.7 (3)	106	0.2 / 0.3 281 / 296	0.7 / 0.5 344 / 302	Bilateral: DME	Bilateral: IV injection

F: Female M: Male Hb A1c: Hemoglobin A1c IV: Intravitreal, BCVA: Best-corrected visual acuity RE: Right Eye LE: Left Eye, CMT: Central macular thickness µm: micron meter NVG: Neovascular glaucoma, DME: Diabetic macular edema VH: Vitreous hemorrhage PPV: Pars plana vitrectomy, *: HbA1c values before the pandemic period, **: HbA1c values during the pandemic period

Discussion

The COVID-19 outbreak that emerged at the end of 2019 has led to numerous cases of severe respiratory distress that have led to death, and has affected the whole world in a short period of time. The fact that COVID-19 is transmitted especially by the respiratory tract has led to the implementation of serious isolation practices [10]. In the fight against the pandemic, governments have applied restrictive measures, including restrictions on attendance to public places, curfews, travel restrictions and quarantines in order to prevent the uncontrolled spread of the virus. While the COVID-19 pandemic continued, other diseases unfortunately did not stop their progression, especially chronic diseases such as diabetic retinopathy. The pandemic has revealed a side effect resulting from the disruption of follow-up and treatment protocols and the cancellation of surgical services, in addition to the public health effects of the disease itself: Hospital admissions have decreased significantly, and many patients have been unable to attend their routine examinations and, thus, their treatments have been delayed [12, 13]. Unfortunately, the negative consequences of pandemic have emerged and still continue to emerge. In this study, we

demonstrated that the COVID-19 pandemic significantly delayed the in-person visits and subsequent possible IV procedures in diabetic retinopathy follow-up. More importantly, we proved that this deferral was significantly associated with worsened short-term outcomes in patients with diabetic retinopathy.

Some vascular diseases of the retina that require IV injection are on the list of emergencies that need to be treated during the pandemic period [12, 13]. Diabetic retinopathy is the most common among them. After DME—which is the most common cause of vision loss due to DM—develops, the most important treatment is to achieve glycaemic control [1]. However, researchers have revealed that there have been problems related to achieving glycaemic control in patients with DM during the pandemic period. Zhou et al. [14] observed that 56.6% of 881 diabetic patients who were hospitalized for COVID-19 had abnormal blood glucose levels. However, poorly controlled levels of hyperglycaemia in diabetic patients are also known to increase the severity of COVID-19 and thus mortality [15]. It is necessary to raise the awareness of diabetic patients about glycaemic control, nutrition and physical exercise, and to reduce the number and duration of hospital admissions as much as possible. To this end, diabetic patients should be encouraged to use telemedicine and teleconference-like applications. The COVID-19 pandemic should be turned into opportunities to develop innovative management strategies for DM and other chronic diseases.

Periodic routine controls performed in the ophthalmology department on diabetic patients are of great importance in maintaining and improving visual acuity. However, the risk of close contact and contamination in the examination room during patient examinations poses a risk for both the doctor and the patient, since tears can contain the virus [16]. Therefore the need to close, face-to-face ophthalmologic examinations have increased the postponement of patient examinations. In this respect, many preventive measures have been taken instead. In some retina clinics in Europe and America, biomicroscopic examinations were not considered appropriate for the routine follow-up of retina patients; instead, it was deemed appropriate to evaluate the patients' visual acuity and macular evaluation using OCT [17, 18]. With the developing technology, it will be possible to evaluate patients in terms of diabetic retinopathy without applying to the hospital in the future. For this purpose, deep learning algorithms and systems can help patients to have an idea about the presence and progression of their diabetic retinopathy without applying to the hospital [19, 20]. The integration of these systems with smartphones can make life easier for DM patients in the current and similar times of crisis [21].

Delays and cutbacks in IV injection therapy have been associated with reduced efficacy and decreased visual acuity, as well as increased retinal thickness [22-24]. However, the fact that the patients who most need IV injections are generally elderly and those with comorbid diseases is worrisome. Borrelli et al. [25] reported a 59.6% decrease in the number of patients who were applied to a tertiary eye centre who received IV injections due to DM, and they found a decrease in the average age of the patients who applied. However, in two prospective studies in which more than 100 IV injections were made during the pandemic period, no complications were found in patients or healthcare workers, as long as the anti-sepsis rules were followed [26].

The duration of treatment and its applications show changes during the pandemic period. The main goal is to keep the number of visits to a minimum, but not to hinder treatment. It is recommended that it would be more appropriate to choose a 'treat-and-extend' regimen for patients who will be newly starting treatment during the pandemic period, and that patients following up with this protocol should be monitored for the longest and safest intervals possible [27]. Antaki et al. [28] stated that 'treat-and-plan', which is a combination of the 'treat-and-extend' and 'observe-and-plan' strategies, may be more effective in patients who have started treatment, and thus the number of hospital visits required to monitor the disease may be fewer. In addition, in crisis periods such as during the COVID-19 pandemic, choosing long-acting anti-VEGFs and extending treatment regimens should be considered as an alternative treatment option.

Borelli et al. [25] examined cases of patients who applied to retina clinics due to age-related macular degeneration during the COVID-19 pandemic quarantine in Italy. They examined the cases who applied to the retina unit in March and May 2020 and those who applied to the retina unit in the same period of 2019, and they found a significant decrease in the number of patients who applied to the hospital in pandemic period. Researchers found that a worse visual acuity at a visit during a real-life emergency setting may indicate that a longer time interval between visits may be causing a reduction in visual acuity in age-related macular degeneration patients. Salah et al. [26] reported that diabetic patients in need of IV injection presented to the hospital with a delay of 6.4 weeks. In these patients, it was observed that visual acuity decreased from 20/55 to 20/70, and mean CMT values increased from 344 µm to 381 µm. The authors also reported progress in diabetic retinopathy staging in these patients.

Limitations

There are some factors limiting our study, most importantly, a larger case series is needed. A second important data is that studies comparing patients treated with long-acting anti-VEGF and patients treated with anti-VEGF agents are needed.

Delays in the treatment of diabetic retinopathy may cause permanent impairments in visual functions and a decrease in quality of life. The most important step in preventing complications due to DM is blood glucose regulation. For this purpose, new threshold levels should be determined in these patients and methods such as teleconsultation and telemedicine should be developed. In addition, in order to eliminate the gaps in diagnosis, digital technology should be integrated more into our lives and home-based OCT applications should be brought into our daily practices as soon as possible. In this way, only patients in severe need will be directed to hospitals, and the potential viral load of patients and ophthalmologists will be reduced. However, in the current and similar pandemic periods, the use of long-acting anti-VEGFs, should be evaluated as an alternative treatment method in suitable patients who need IV injection.

Conclusions

In this study, we evaluated 17 patients with diabetic retinopathy who came to their routine controls before March 2020, but could not come to their routine controls due to the pandemic in the post-March 2020 period, which resulted in anatomical and functional losses in their ocular structures. We observed that these patients had a mean delay of 8.6 weeks in their hospital visits. We found that this delay caused the development of DME, the progression of diabetic retinopathy and a severe decrease in visual acuity. In addition, posterior segment diabetic retinopathy complications, such as vitreous haemorrhage, occurred in three patients that could not be treated medically, so a surgical course of treatment was recommended instead. These results are important in terms of drawing attention to the negative consequences of the failure to provide timely and effective treatment to patients with diabetic retinopathy during the epidemic period.

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