

Treatment Approaches in Patients with Advanced Diabetic Eye Disease

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ABSTRACT

Purpose: To report our treatment approaches and results in patients whose retinopathy progressed to advanced diabetic eye disease during the pandemic period.

Materials and Methods: In this single-centered, retrospective case series, medical records were reviewed for patients who could not come to the controls and not receive treatment, and whose retinopathy progressed to advanced diabetic eye disease during the pandemic period. Anatomical and functional results, and complications after treatments were evaluated. We recorded the data from the initial visit to last follow-up 3rd month visit after treatments.

Results: Seventeen eyes of 16 patients were included in the study. Before the pandemic, 4 (23.5%) eyes had severe NPDR and 13 (76.5%) eyes had mild, moderate or high risk PDR. These patients did not want to come to the hospital and have their treatments because of the danger of COVID-19, although we called them by phone. In post-pandemic visit nine eyes (52.9%) had grade 3-4 vitreous hemorrhage, 5 (29.4%) had neovascular glaucoma, 1 (5.8%) eye had neovascularization iris without glaucoma. Two (11.7%) eyes had macular tractional retinal detachment. Visual acuity increased significantly in eyes with vitreous hemorrhage, but in eyes with neovascular glaucoma and tractional retinal detachment, visual acuity did not increase significantly in the 3rd month when compared to before the pandemic ($p = 0.001$, $p = 0.65$, $p=0.052$).

Conclusion: In some of the patients with diabetic retinopathy who could not have their controls and treatments due to pandemic, permanent vision loss developed. Patients with diabetic retinopathy should be adequately informed about the complications of diabetes and should be encouraged to have their treatments during the pandemic period.

Keywords: Tractional retinal detachment, vitreous hemorrhage, neovascular glaucoma

INTRODUCTION

Proliferative diabetic retinopathy occurs with the formation of fibrovascular proliferations and membranes as a result of increased vascular endothelial growth factor (VEGF) and cytokines due to retinal ischemia.¹ If these membranes and fibrovascular proliferations are not treated, extensive vitreous hemorrhage, tractional retinal detachment and neovascular glaucoma may occur, which is called advanced diabetic eye disease.²

Vitreous hemorrhages can clear spontaneously by applying the head elevation and hydration. Thus, panretinal coagulation can be done after hemorrhage has been removed. In the Diabetic Retinopathy Vitrectomy Study

(DRVS), PPV was recommended for vitreous hemorrhages that was not cleared within 1-4 months.³

Neovascular glaucoma occurs when the fibrovascular membranes formed at the iridocorneal angle.⁴ The first treatment to be done is panretinal laser photocoagulation. Intravitreal or anterior segment anti-VEGFs can be used as an adjunct to panretinal laser photocoagulation. Pars plana vitrectomy can be performed in patients with small pupils and media opacity for whom panretinal laser photocoagulation can not be performed. Seton implantation surgery is performed in medically resistant neovascular glaucoma.⁵

Neovascular membranes can form tight vitreoretinal adhesions and subsequently contract over time, causing

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tractional retinal detachment.⁶ If the tractional retinal detachment involves the macula, the treatment is peeling the membranes with PPV.⁷

In this study, we reported the treatment approaches applied to patients who could not come to the controls and who could not receive treatment during the pandemic period, and whose retinopathy progressed to advanced diabetic eye disease.

MATERIALS AND METHODS

The protocol of the present study conformed to the Declaration of Helsinki. Written informed consent was obtained from each patient after the risks, benefits and alternatives of the treatment were explained to the patients. The study protocol approved from Umraniye Training and Research Hospital Ethics Committee. The study protocol approval number was 23863(12/10/2020).

Study Design

In this single-centered, retrospective and case series; the medical records and retinal imagings were reviewed for 16 patients 17 eyes between 23 March 2020 and 29 August 2020. Patients who has severe non-proliferative, mild, moderate or high risk proliferative diabetic retinopathy without advanced diabetic eye disease and patients who could not have treatments (panretinal laser photocoagulation and intravitreal anti-VEGF) because of the onset of the pandemic and whose retinopathy progressed and, developed vitreous hemorrhage, neovascular glaucoma and tractional retinal detachment during the pandemic period were included in the study.

Patients who could come their controls and take treatments during the pandemic period, patients whose retinopathy did not progressed, patients with retinal vein occlusions, age-related macular degeneration, glaucoma and incomplete imaging or clinical data were not included in the study.

Demographic information, age, sex, best corrected visual acuity (BCVA) on Snellen charts, slitlamp and dilated fundus examination, Intra Ocular Pressure (IOP) measurement, fundus imaging, Central Macular Thickness (CMT) on spectral-domain OCT (Optovue, RTVue 100, CA, USA), treatments after the pandemic, intraoperative and postoperative complications were documented from patients medical records. We recorded the data from the initial visit to last follow-up 3rd month visit after treatments.

To classify vitreous hemorrhage Early Treatment of Diabetic Retinopathy Study (ETDRS) classification system was used.⁸

Surgical Techniques

Pars plana vitrectomy: Three eyes (17.6%) were operated under regional anesthesia and 14 (82.4%) under general

anesthesia. All surgeries were performed by 2 surgeons. Pars plana vitrectomy surgery performed by U.L. and AGV implantation surgery was performed by B.I.S.A. Constellation Vitreoretinal Surgical System (Alcon, USA) was used for PPV with Resight (Carl Zeiss Meditec AG) wide-angle viewing system and, 23 and 25 gauge instrumentation. In patients with vitreous hemorrhage, the hemorrhage was cleared by complete vitrectomy and vitreous base shaving was performed in all patients. Endo-PRP was applied up to ora serrata with indentation. Approximate 45-90 degrees endocryphotocoagulation treatment was applied to inferior part of the ciliary body with indentation in patients with neovascular glaucoma. In patients with tractional retinal detachment removal of the diabetic membrane was performed bimanually with a cutter, curved microscissors and forceps. At the end of the surgery, tamponade was not used if it was not necessary, and air, gas or silicone oil tamponade was used in patients who needed it. 7/0 vicryl suture was applied to all sclerotomies at the end of surgery.

Ahmed Glaucoma Valve (AGV) Implantation: A limbal-based conjunctival incision was made and the implant body was placed between 2 rectus muscles in the superotemporal quadrant 8-10 mm from the limbus. Vicryl suture (6.0) was used to suture the implant to the sclera. After viscoelastic injection into the anterior chamber, the anterior chamber was entered using a 22-23G needle 1-3 mm behind the limbus. Then, the tube tip was cut to remain 2-3 mm in the anterior chamber and placed in the anterior chamber through the needle entrance.

Pars plana vitrectomy combined with phacoemulsification: Crystalline lenses of patients with cataracts were removed using phacoemulsification techniques before PPV and a posterior chamber intraocular lens was inserted.

Statistical Methods

The decimal BCVA was converted to logMAR for statistical analysis. The changes in preoperative, in pandemic and postoperative results were evaluated by ANOVA test. SPSS software 20.0 for Windows (SPSS Inc., Chicago, IL, USA.) was used for analysis and a p-value <0.05 was considered statistically significant.

RESULTS

Seventeen eyes of 16 patients were included in the study. All patients have type-2 diabetes mellitus. The mean age of the patients were 54.76 ± 12 (30-76). Eleven (68.75%) of the patients were male and 5 (31.25%) were female. Patients mean glycated haemoglobin (HbA1c) level was 12.7% (7.4%-14.3%) Patients mean systolic and diastolic blood pressures were 150mmHg (140-190 mmHg) and 95

mmHg (80-110 mmHg). Before the pandemic, 4 (23.5%) eyes had severe NPDR and 13 (76,5%) eyes had mild, moderate or high risk PDR. One of these patients had COVID-19 during the pandemic period and was treated in another hospital for COVID-19. These patients did not want to come to the hospital and have their treatments because of the danger of COVID-19, although we called

them by phone. The mean exact time interval while the patients could not follow their visits was 4.2 ± 1.2 months. The demographic characteristics of the patients and their treatments before the pandemic are given in table 1.

Nine eyes (52.9%) had grade 3-4 vitreous hemorrhage, 5 (29.4%) had neovascular glaucoma, 1 (5.8%) eye had

Table 1: Demographic and clinical data for patients with advanced diabetic eye disease

Patients eyes	Age (Gender)	Prior treatments	Lens	The ETDRS stage of diabetic retinopathy in the last control before the pandemic	Pre-treatment IOP, (mmHg)	IOP at last follow-up, (mmHg)	Snellen BCVA at the last control before the pandemic(logMAR)	Pre-Treatment snellen BCVA (logMAR),	Snellen BCVA at last follow-up (logMAR)	Intraoperative and postoperative complications
Grade 3-4 vitreous hemorrhage (9)										
1	49(M)	Scattered retinal laser+IVA×4	Pseudophakic	Mild PDR+CME	12	14	20/50, (0.4)	Counting fingers, (2.0)	20/32, (0.2)	None
2	63(F)	IVA×7	Pseudophakic	High risk PDR	14	14	20/40, (0.3)	Hand movements, (2.3)	20/25, (0.1)	None
3	62(M)	IVA×5	Phakic	Mild PDR+CME	18	19	20/25, (0.1)	Hand movements, (2.3)	20/32, (0.2)	None
4	51(M)	IVA×6	Pseudophakic	Severe NPDR	13	14	20/50, (0.4)	Counting fingers, (2.0)	20/32, (0.2)	None
5	30(F)	None	Phakic	Severe NPDR	13	12	20/32, (0.6)	Counting fingers, (2.0)	20/25, (0.1)	None
6	70(M)	IVA×7	Phakic	Mild PDR+CME	16	14	20/25, (0.1)	Counting fingers, (2.0)	20/25, (0.1)	None
7	55(M)	IVA×8	Pseudophakic	Moderate PDR	12	13	20/40, (0.3)	Hand movements, (2.3)	20/25, (0.1)	None
8	50(M)	IVA×6	Phakic	Severe NPDR	16	15	20/50, (0.4)	Counting fingers, (2.0)	20/40, (0.3)	None
9	66(M)	IVA×7	Pseudophakic	Severe NPDR+CME	14	17	20/400, (1.3)	Counting fingers, (2.0)	20/32, (0.2)	None
Neovascular glaucoma (5)										
10	76(M)	Scattered retinal laser	Pseudophakic	Mild PDR	51	16	20/40, (0.3)	Counting fingers, (2.0)	Counting fingers, (2.0)	Posterior capsule rupture
11	76(M)	Scattered retinal laser	Pseudophakic	Mild PDR	48	17	20/40, (0.3)	Counting fingers, (2.0)	Counting fingers, (2.0)	HypHEMA
12	67(M)	None	Pseudophakic	High risk PDR	36	15	20/50, (0.4)	Hand movements, (2.3)	20/400, (1.3)	None
13	64(F)	PRP	Pseudophakic	High risk PDR	39	14	20/32, (0.2)	Hand movements, (2.3)	Hand movements, (2.3)	None
14	63(M)	PRP+IVA×9	Pseudophakic	Moderate PDR+CME	48	46	20/32, (0.2)	Light sensation negative	Light sensation negative	None
Rubeosis iridis without glaucoma with grade 4 vitreous hemorrhage (1)										
14	43(F)	None	Phakic	Moderate PDR	16	17	20/25, (0.1)	Hand movements, (2.3)	20/25, (0.1)	None
Tractional retinal detachment with macular involvement with grade 1-2 vitreous hemorrhage (2)										
15	57(M)	IVA×5+IVL×2	Pseudophakic	Moderate PDR	14	13	20/50, (0.4)	Counting fingers, (2.0)	20/200, (1.0)	Iatrogenic rupture
16	52(F)	None	Phakic	High risk PDR	15	15	20/25, (0.1)	Hand movements, (2.3)	Counting fingers, (2.0)	None

neovascularization iris without glaucoma and grade 4 vitreous hemorrhage. Two (11.7%) eyes had macular tractional retinal detachment and grade 1-2 vitreous hemorrhage.

Retinal detachment was not detected in all of the patients with vitreous hemorrhage on ocular ultrasonographic examination. Vitreous hemorrhage started to clear in 6 (66.6%) of 9 eyes with head elevation (45 degrees of head elevation) and hydration between 2 and 3 weeks. Then panretinal laser photocoagulation (PRP) was applied gradually to areas where hemorrhage was cleared. Pars plana vitrectomy (PPV) and PRP was performed after bevacizumab (Altuzan, Roche, Switzerland) injection 2 days before the surgery in the other 3 eyes (33.4%) whose vitreous hemorrhage did not clear within 2 or 3 weeks. Intraocular tamponade was not used in 2 of the eyes, and air tamponade was used in 1 of the eyes. Combined cataract surgery was performed in 1 eye. Other 2 eyes were pseudophakic. The mean BCVA at the last control before the pandemic in patients with vitreous hemorrhage was 0.43 logMAR. In eyes with vitreous hemorrhage mean BCVA was 2.1 logMAR at the initial visit after pandemic and increased to 0.16 logMAR at the 3rd month visit ($p = 0.001$). Anatomical improvement was achieved in all eyes. There were no complications intraoperative or postoperative in these eyes.

Ahmed Glaucoma Valve (AGV) was inserted in 2 eyes (40%) with neovascular glaucoma after anterior and posterior segment bevacizumab injection 1 day before the surgery, and PRP was applied. Adequate PRP could not be performed in 2 eyes (40%) with neovascular glaucoma because sufficient pupil dilation could not be achieved. In these 2 eyes PPV, endo-PRP and approximate 45-90 degrees endocytphotocoagulation treatments were applied after anterior and posterior segment bevacizumab injection 1 day before the surgery. Intraocular tamponade was not used in these two eyes. All patients were pseudophakic. One (20%) eye with neovascular glaucoma, which had no light sensation for the last 1 month, was not treated with surgery. Only topical antiglaucomatous drugs were given. The mean BCVA at the last control before the pandemic in patients with neovascular glaucoma was 0.28 logMAR. In eyes with neovascular glaucoma BCVA was 2.18 logMAR at the initial visit after pandemic and 1.98 logMAR at the 3rd month visit ($p = 0.65$). In the postoperative period intraocular pressure was 16 and 15 mmHg, respectively in 2 eyes with vitrectomy, with 2 topical anti glaucomatous drops. In the postoperative period intraocular pressure was 17 and 14 mmHg, respectively in 2 eyes with AGV, without anti glaucomatous drops. In one of the eyes with AGV, 1mm hyphema was developed in the anterior chamber in first postoperative day. The hyphema cleared spontaneously

within 1 week. In one of our patients who underwent PPV, a small tear occurred in the posterior capsule with laser probe during endocytphotocoagulation.

In one eye with grade 4 vitreous hemorrhage with rubeosis iridis without glaucoma and without retinal detachment on ocular ultrasonographic examination was treated with anterior segment and intravitreal bevacizumab, and PRP after clearing of the hemorrhage. The mean BCVA at the last control before the pandemic in this eye was 0.1 logMAR. In this eye BCVA was 2.3 logMAR at the initial visit after pandemic and 0.1 logMAR at the 3rd month visit ($p = 0.001$).

Tractional retinal detachment was detected in two patients on fundus and ultrasonographic examination with grade 1-2 vitreous hemorrhage. Pars plana vitrectomy, membranectomy and endolaser therapies were applied to 2 eyes with macular tractional retinal detachment after intravitreal bevacizumab injection 2 days before the surgery. In one eye 1000cst silicon oil tamponade and in the other eye with iatrogenic rupture that close to the main vessel arches perfluoropropane (C3F8) tamponade was used. Combined cataract surgery was performed in 1 eye. Other eye was pseudophakic. The mean BCVA at the last control before the pandemic in patients with tractional retinal detachment was 0.25 logMAR. In these eyes mean BCVA was 2.15 logMAR at the initial visit and 1.5 logMAR at the 3rd month visit ($p = 0.052$). Anatomical improvement was achieved in both of the eyes. There were not any postoperative complications in these eyes.

Examples of cases are given in figures 1, 2, 3 and 4.

DISCUSSION

When diabetic retinopathy is not treated, it can progress to advanced diabetic eye disease and as a result, severe vision loss may develop.⁹ In this study, we presented the treatment methods and the results of our patients who developed advanced diabetic eye disease because they could not receive treatment during the pandemic period.

Vitreous hemorrhage was the most common diabetic eye disease in our study. Our PPV ratio shows (33.4%) that most patients with vitreous hemorrhage can be managed with non-surgical methods as head elevation and hydration similar to the literature.¹⁰⁻¹¹ It has been reported that anti-VEGFs accelerate the clearing of vitreous hemorrhage.¹² Although we did not apply anti-VEGF treatment to any of our patients who did not undergo PPV, vitreous hemorrhage started to clear within 1-2 weeks and laser treatment was gradually applied to the areas where the hemorrhage was cleared. However, we applied anti-VEGF treatment 2-3 days before the surgery to reduce possible intraoperative

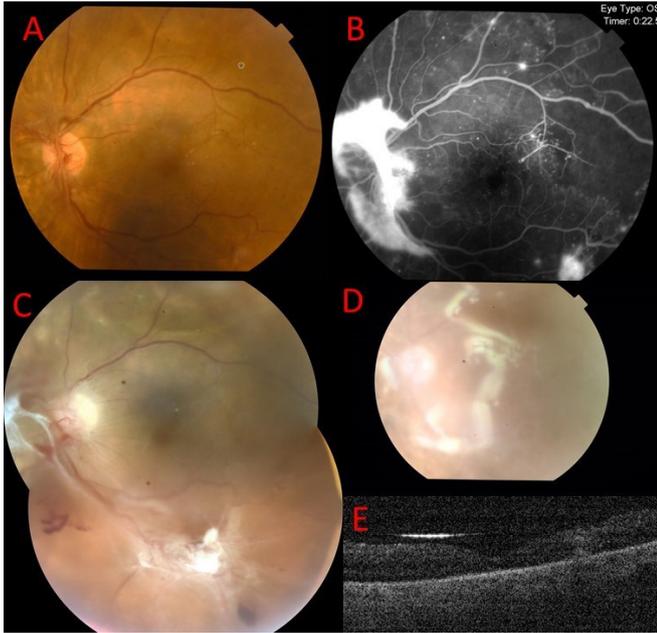


Figure 1: (A) A 52 year-old woman with type-2 diabetes (Patient 16 in the table-1). Her BCVA was 20/25 in the left eye, neovascularization and mild fibrovascular proliferation at the optic disk are observed in the colored fundus image at the last control before the pandemic. (B) In the early phase of fundus fluorescein angiography before the pandemic, there are leakages relative to the neovascularization in the optic disc and inferior quadrant of the retina. Large ischemic area is seen in the temporal of the macula. The fovea looks normal. (C) Montage color fundus picture of the patient who did not have the recommended panretinal photocoagulation (PRP) treatment because of the pandemic and came for a control approximately 5 months after the last examination. Extensive fibrovascular traction starting from the optic disc nasal to the inferior temporal retina has lifted the macula. Her BCVA was hand movements. (D) Color fundus picture 3 months after PPV, membranectomy, PRP and 1000 cst silicone oil injection. Her BCVA was counting fingers from 2 meters. (E) At postoperative 3rd month OCT, the retina is attached and the bright reflex created by silicone oil is seen.

hemorrhage in our patients with vitreous hemorrhage who will undergo PPV.

In this study the advanced diabetic eye disease with the most severe vision loss is neovascular glaucoma. It is not easy to perform PRP in eyes with neovascular glaucoma.¹³ Resistant corneal edema and small pupil in patients with neovascular glaucoma can prevent effective PRP. Since adequate fundus imaging could not be achieved in 2 of our pseudophakic patients, endocytphotocoagulation to the lower part of the ciliary bodies between 45-90 degrees and endo-PRP were applied by performing PPV.



Figure 2: (A) A 30 year-old woman with type-2 diabetes (Patient 5 in the table-1). Her BCVA was 20/32 in the right eye at the last control before the pandemic. The optic disc is edematous and there are extensive hemorrhages and soft exudates in the retina in the colored fundus image. Fundus fluorescein angiography was recommended to the patient, but the patient could not come to control due to the onset of the pandemic. (B) Colored fundus image of the patient approximately 4 months after the last examination. Grade-3 vitreous hemorrhage is seen. Her BCVA was counting fingers. (C) Colored fundus image of the patient 3 weeks after PRP started. Hemorrhages have begun to clear. Her BCVA was 20/200 (D) Colored fundus image of the patient 1.5 months after panretinal photocoagulation finished. Hemorrhages cleared completely. Her BCVA was 20/25.

Although Ahmed Glaucoma Valve can effectively reduce intraocular pressure¹⁴; PPV and endocytphotocoagulation may be the first choice in the treatment of neovascular glaucoma in patients whose fundus imaging cannot be achieved.¹⁵ However, it can not be predicted how much endocytphotocoagulation will decrease IOP.

The intraocular lens makes endocytphotocoagulation process difficult in both phakic and pseudophakic patients, and the laser probe may damage the posterior capsule during the procedure. A small tear which does not impair the stabilization of the intraocular lens developed in the posterior capsule during the procedure in one of our patients. In our study, in 2 patients who underwent PPV and endocytphotocoagulation, IOP could only be kept under 20 mmHg with 2 topical anti-glaucomatous drops. This may be because endocytphotocoagulation is not sufficiently broad.

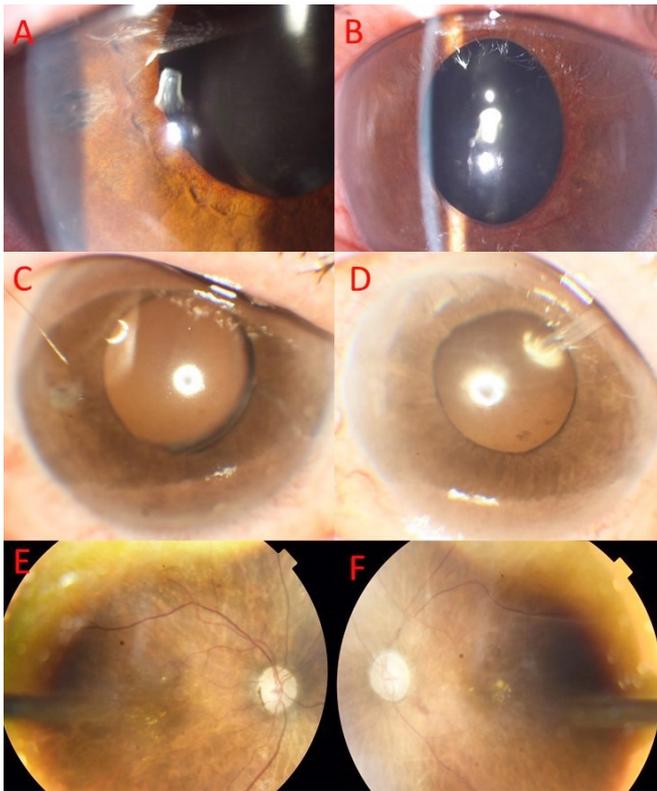


Figure 3: (A) A 76 year-old man with type-2 diabetes (Patient 10 in the table-1). His BCVA was 20/40 in both eyes at the last control before the pandemic. Anterior segment image of the right eye 5 months after the last control. There is neovascularization at the edge of the pupil and the eye pressure is 51 mmHg. His BCVA was counting fingers (B) Anterior segment image of the left eye 5 months after the last control. There is neovascularization at the edge of the pupil and the eye pressure is 48 mmHg. His BCVA was counting fingers. (C) Anterior segment image of the right eye. Neovascularizations at the edge of the pupil regressed after the preoperative anterior and posterior segment bevacizumab, PPV, endo-panretinal photocoagulation and approximate 45-90 degrees endocytphotocoagulation treatments on the right eye. (D) Anterior segment image of the left eye. Neovascularizations at the edge of the pupil regressed after the preoperative anterior and posterior segment bevacizumab, and Ahmed Glaucoma Valve (AGV) implantation on the left eye. (E) Fundus image of the right eye. Proliferative retinopathy is stabilized. (F) Fundus image of the left eye. Proliferative retinopathy is stabilized.

Tractional retinal detachment is also one of the most devastating complications of diabetic retinopathy. Surgical treatment is required when tractional retinal detachment involves or threatens the macula or is accompanied vitreous hemorrhage.¹⁶ The use of preoperative anti-VEGFs decreases vascular permeability, reduces the possibility of bleeding in the intraoperative and postoperative period,

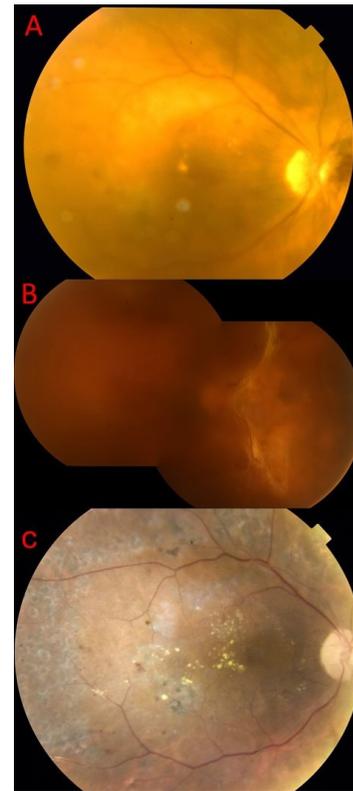


Figure 4: (A) A 63 year-old woman with type-2 diabetes (Patient 2 in the table-1). Her BCVA was 20/40 in the right eye at the last control before the pandemic. In fundus image there are neovascularizations in the optic disc. Patient did not have the recommended panretinal photocoagulation (PRP) treatment. (B) Fundus image of the patient 3 months after the last control. She has grade 3 vitreous hemorrhage and fibrovascular proliferation in the optic disk. Her BCVA was hand movements. (C) Fundus image of the patient 3 months after preoperative bevacizumab, PPV and endo-panretinal photocoagulation treatments. Her BCVA was 20/25.

facilitates peeling of membranes during surgery and shorten the surgical time.¹⁷ We administered intravitreal bevacizumab injection to our patients 2 days before surgery. After removing all membranes, we applied PRP to all retinal areas under the perfluorodecaline and stabilized the retinopathy in the postoperative period in both patients.

Using telemedicine to get information about the health status of patients with diabetic retinopathy who cannot go to the hospital due to the pandemic may prevent the disconnection of the patient and the doctor. Galiero et. al.¹⁸ mentioned the importance of telemedicine in their study. However, it will not be easy for our patient population to access the devices and digital applications required for telemedicine due to their socioeconomic status.

The major limitations of our study are small sample size,

having a small number of different disease groups, its retrospective nature, and lack of control group.

CONCLUSION

In some of the patients with diabetic retinopathy who could not have their controls and treatments due to pandemic, permanent vision loss developed because of the diabetic retinopathy complications. Patients with diabetic retinopathy should be adequately informed about the complications of diabetes and should be encouraged to have their treatments during the pandemic period.

Acknowledgements: No

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