RETROSPECTIVE ANALYSIS OF THE IMPACTS OF TREATMENT REGIMENS ON THE PROGRESSION AND PROGNOSIS OF DIABETIC RETINOPATHY AND VISUAL ACUITY IN TRAKYA UNIVERSITY SCHOOL OF MEDICINE

Mustafa Ömer İzzettinoğlu[1], Rüveyde Garip[2]

[1]Trakya University School of Medicine, Edirne, TURKEY
[2]Department of Ophthalmology, Trakya University School of Medicine, Edirne, TURKEY

ABSTRACT

Aims: To retrospectively analyze the impacts of treatment regimens on progression and prognosis of diabetic retinopathy and visual acuity in Trakya University Hospital. ***Methods:*** This retrospective cross-sectional study was conducted with patients who were diagnosed with diabetic retinopathy in the Ophthalmology Department of Trakya University Hospital between January 2006 and January 2020. ***Results:*** Initially, 798 eyes from 399 patients diagnosed with diabetic retinopathy met the inclusion criteria. Non-proliferative diabetic retinopathy was present on 202 (50.6%) patients, and 197 (49.4%) patients had proliferative diabetic retinopathy. Twenty-five patients (6.2%) had proliferative diabetic retinopathy progression. Patients with proliferative diabetic retinopathy progression had no difference in terms of cataract surgery, gender, and hypertension existence than the ones who did not experience proliferative diabetic retinopathy progression. There was no relation between stability, increase or decrease of visual acuity, the type of diabetes, retinal laser photocoagulation treatment, and the type of intravitreal injection. ***Conclusion:*** Our study showed that retinal laser photocoagulation treatment and cataract surgery had no significant impact on visual acuity prognosis, unlike the initial examination visual acuity values. Additionally, it was also shown that the different types of intravitreal injections made no dissimilar results on visual acuities. In addition, in our study, it was revealed that gender, presence of hypertension, and cataract surgery may not have a significant relation with proliferative diabetic retinopathy progression. Further studies are needed to thoroughly reveal the relation between the treatment regimens, progression, and prognosis of the disease. ***Keywords:*** Diabetes mellitus, diabetic retinopathy, epidemiology, macular edema

INTRODUCTION

Diabetic retinopathy (DR) is the most common cause of preventable blindness in the working-age population in developing countries (1). DR is a specific microvascular complication of diabetes at early stages (1). Presently, the global prevalence of DR goes up to 34.6%, meaning that it could occur in a third of the people with diabetes and is associated with an increased risk of life-threatening systemic complications including coronary heart disease, heart failure, nephropathy, and stroke (2). The prevalence hits even higher ratios, around 40.3%, in developed countries (2). Thus, 3.6% of patients with type 1 diabetes mellitus (DM) and 1.6% of patients with type 2 DM are estimated to become blind at further stages (2).

Diabetic retinopathy is graded clinically in most of the ophthalmology centers and the grading remains to be based on the original Early Treatment Diabetic Retinopathy Study (ETDRS) grading scheme, including mild and moderate non-proliferative diabetic retinopathy (NPDR), severe NPDR (pre-proliferative diabetic retinopathy), non-high-risk proliferative diabetic retinopathy (PDR), and high-risk PDR (3). The presence of diabetes for 20 years causes retinopathy in about 80% of the patients (4). DR causes microaneurysms, appearing as tiny red dots which represent small capillary aneurysms and bulges. These aneurysms are abnormally permeable but not harmful by themselves. Permeability increase leads to yellow-white discrete patches called hard exudates to form on the retina in a ring around the leaking capillaries. The progression of hard exudates on the macula gradually causes vision loss and eventually leads to blindness. In PDR, ischemia of the retina predisposes to the development of new vessels with dangerous formation. New peripheral vessels are less likely to cause vitreous hemorrhage than the ones on the disc, which are commonly known to bleed and cause preretinal hemorrhages resulting in blindness due to vitreous hemorrhage (3).

Routine fundus examination should be performed on all diabetic patients (4). A screening modality for DR is recommended to be performed with dilated slit-lamp biomicroscopy with a lens or dilated fundoscopy containing a stereoscopic examination of the posterior pole. New technologies such as digital cameras and teleophthalmology provide improved results in screening (5). Optimal control of blood glucose, blood lipids, and blood pressure plays a humongous role in the risk reduction of retinopathy development and progression (1). Intravitreal injections, panretinal photocoagulation (PRP) and vitrectomy are the interventional approaches in order to manage the complications of DR. Anti-VEGF therapy are recommended as a stand-alone treatment or in combination with PRP. While studies of anti-intravitreal anti-VEGF injections in the

Address for Correspondence: Mustafa Ömer İzzettinoğlu, Trakya University School of Medicine, Edirne, TURKEY
e-mail: omer.iz@icloud.com
Recieved: 03.01.2021 Accepted: 17.01.2021 • DOI: 10.4274/tmsj.galenos.2021.08.01.05

Available at https://tmsj.trakya.edu.tr/

ORCID iDs of the authors: MÖİ: 0000-0001-6736-7294; RG: 0000-0003-2235-9017

Cite this article as:
İzzettinoğlu MÖ, Garip R. Retrospective analysis of the impacts of treatment regimens on the progression and prognosis of diabetic retinopathy and visual acuity in Trakya University School of Medicine. Turkish Med Stud J 2021;8(1):17-21.

treatment of DR are promising, this approach is not yet considered standard. In addition, the difference in effects between different types of intravitreal anti-VEGF injections is still under debate and being studied (4). Recognizing the patients with DR at the early stages provides better visual acuity results. Therefore, it is quite important to check up on patients regularly for DR and know the potential complications of the disease for better patient management.

The aim of this study is to retrospectively analyze the impacts of treatment regimens on prognosis and progression of diabetic retinopathy and visual acuity in a tertiary clinic in the Thrace region in Turkey.

MATERIAL AND METHODS

This study was approved by the Scientific Research Ethics Committee of Trakya University School of Medicine (Protocol Code: TUTF-BAEK 2020/426). This retrospective cross-sectional study analyzed patients who were diagnosed with DR in the Ophthalmology Department of Trakya University Hospital between January 2006 and January 2020. The study was carried out in accordance with the tenets of the Declaration of Helsinki. Written informed consent for the use of medical information of patients was received from all of the participants.

Demographic data such as age and gender, accompanying systemic comorbidities (such as hypertension, diabetic nephropathy), the type of diabetes mellitus (type 1 or type 2), the usage of oral anti-diabetic agents or insulin injection, and initial and following clinical findings were obtained from the medical records of the patients. All patients underwent a complete ophthalmologic examination at each visit including best-corrected visual acuity (BCVA) determined by Snellen chart, anterior segment biomicroscopic examination, intraocular pressure (IOP) measurement with Goldmann applanation tonometer, and detailed fundus examination obtained with 78-diopters non-contact lens.

The following findings were documented at the initial visit: type of DR (non-proliferative or proliferative), lens status (phakic, pseudophakic, or aphakic), presence of macular edema, and presence of glaucoma. DR classification was made based on the criteria determined by the ETDRS (4).

The following findings were documented at the follow-up visits: the presence of intravitreal injection, number of injections, the progression of DR from non-proliferative to proliferative, the presence of PRP, and the presence of surgical interventions (cataract surgery or vitreoretinal surgery).

Patients who were diagnosed with DR are included. DR patients who have poorer visual acuity than positive light perception, on-set corneal pathologies, ocular-vascular diseases, and macular pathologies that could be unreliable for fundi examination were excluded from this retrospective study.

In this retrospective study, treatment data such as the presence of cataract or/and vitrectomy surgeries, appliance, and the type of intravitreal anti-VEGF injections, medical treatment regimens for diabetes mellitus; and examinational findings such as BCVA, IOP, examinational fundi findings such as the presence of macular edema, intravitreal hemorrhage, type of on-set DR during follow-ups were statistically tested to reveal the clinical impacts on progression and prognosis of diabetic retinopathy and visual acuity.

Statistical Analysis

The collected data were analyzed statistically by using the SPSS version 20 for Windows. Mean and standard deviation values were calculated using descriptive statistical measures. The frequency distribution of qualitative data was quantified in percentages. The Chi-square test was used for qualitative comparison. The normality distribution of the data was evaluated with the One-sample Kolmogorov-Smirnov test. Quantitative data were compared with the Independent Sample t-test. P-value of <0.05 was considered to be statistically significant.

RESULTS

Initially, 798 eyes from 399 patients with the diagnosis of DR met the inclusion criteria of having visual acuity results greater than positive light perception and above, absence of corneal pathologies, ocular-vascular diseases (central retinal artery occlusion, retinal venous occlusion), accompanying macular pathologies like macular hole and macular degeneration. Two hundred and thirty-two (58.4%) patients were female, and 166 (41.6%) patients were male. The summary of patients' characteristics (age, mean duration of follow-up, gender, type of DM, comorbidity, and DM treatment) is presented in Table 1. Six (1.5%) patients had diabetic nephropathy at the first admission to the clinic.

Table 1: Patients' characteristics.

	Number of Patients [n (%)]
Age (years)*	63.5 ± 9.1 (31-85)
Duration of follow-up (years)*	5.7 ± 3.5 (1-14)
Gender	
Female	232 (58.4)
Male	167 (41.6)
Type of DM	
Type 1	12 (3)
Type 2	387 (96.5)
Comorbidity	
Hypertension	213 (53.4)
Hyperlipidemia	6 (1.5)
Renal disease	3 (0.7)
Cardiac disease	65 (16.2)
Pulmonary disease	5 (1.2)
None	107 (26.8)
Treatment of DM	
OAD	130 (32.6)
Insulin	129 (32.3)
OAD + Insulin	109 (27.3)
None	31 (7.8)

DM: *Diabetes Mellitus,* ***OAD:*** *Oral anti-diabetic*
*Data were expressed as mean ± SD (min-max).

Initial visual acuities were 0.32 ± 0.37 LogMAR units (range; from 3 to 0 LogMAR units) in the right eyes and 0.32 ± 0.36 LogMAR units (range; from 3 to 0 LogMAR units) in the left eyes. Three hundred and nine (77.4%) patients were phakic, 90 (22.6%) patients were pseudophakic, and 238 (59.6%) patients had cataracts. Twenty-one (5.3%) patients had rubeosis iridis. The mean intraocular pressure was 16.1 ± 4.3 mmHg (range; from 7 to 56 mmHg) in the right eyes and 16.2 ± 4.1 mmHg (range; from 8 to 50 mmHg) in the left eyes. Forty-two (12.5%) patients had glaucoma at the initial examination. First ophthalmologic examinational

Table 2: Outcomes of patients.

	Initial		*Final*	
	Right Eye	***Left Eye***	***Right Eye***	***Eye***
BCVA (LogMAR Unit)	0.32± 0.37	0.32 ± 0.36	0.41 ± 0.39	0.4 ± 0.38
IOP (mmHg)*	16.1 ± 4.3 (7 - 56)	16.2 ± 4.1 (8 - 50)	-	-
CMT (µm)	323 ± 117.5 (18 - 748)	336.5 ± 131.4 (23 - 763)	290.1 ± 121.3 (17 - 801)	291.1 ± 128.1 (8 - 921)
Stage of Retinopathy [n (%)]				
NPDR	202 (50.6)			
PDR	197 (49.4)			
Macular Edema* [n (%)]				
Present	182 (45.6)			
Absent	217 (54.4)			
Lens Statement [n (%)]				
Phakic	309 (77.4)			
Pseudophakic	90 (22.6)			
Intravitreal Hemorrhage* [n (%)]				
Present	93 (23.3)			
Absent	306 (76.7)			

Mean ± SD (min – max); n (%)
***BCVA:** Best corrected visual acuity, **IOP:** Intraocular pressure, **CMT:** Central macular thickness*
**The data presented here were obtained only from the initial examinations.*

data (BCVA values, intraocular pressures (IOPs), mean macular thickness, number of patients with NPDR or PDR, macular edema presence, lens statement, and intravitreal hemorrhage presence) are presented in Table 2.

Phacoemulsification cataract surgery was performed on 136 (34.1%) patients and vitrectomy on 63 (15.8%) patients due to tractional retinal detachment, resistant macular edema, and intravitreous hemorrhage. PRP was performed on 278 (69.7%) patients in order to treat PDR and ischemic pathologies. Sixty-seven (16.8%) patients had intravitreal aflibercept injection, 117 (29.3%) patients had intravitreal ranibizumab injection, 66 (16.5%) patients had intravitreal dexamethasone implant, and 71 (17.8%) patients had intravitreal bevacizumab injection by the reason of diabetic macular edema. Twenty-five (6.2%) patients had a progression from NPDR to PDR. The mean progression duration was 37.6 ± 43.1 months (range; from 3 months to 168 months). Patients with PDR progression had no statistically significant difference in terms of cataract surgery, gender, and hypertension existence than the ones who did not experience PDR progression (p=0.146, p=0.802, p=0.272, respectively). On the latest examination, the mean visual acuity value was 0.41 ± 0.39 LogMAR units (range; from 3 to 0 LogMAR units) in the right eyes and 0.4 ± 0.38 LogMAR units (range; from 3 to 0 LogMAR units) in the left eyes. One hundred and sixty-five (20.7%) eyes were stable on visual acuity. Two hundred and fifty-two (31.6%) eyes had an increase in visual acuity by time whereas 381 (47.7%) eyes were observed to have a decrease. There was a strong positive correlation in visual acuity between the latest and initial examinations (r= 0.445, p < 0.001). Eventually, we concluded that there was no statistically significant relationship between stability, increase or decrease of visual acuity and the type of diabetes, retinal laser photocoagulation treatment, and the type of intravitreal injection (p= 0.967, p= 0.333, p= 0.132, respectively) (Table 2 and 3).

Table 3: Outcomes of patients.

	Number of Patients [n (%)]
PRP	
Yes	278 (69.7)
No	121 (30.3)
Type of Intravitreal Injection	
Aflibercept	67 (16.8)
Bevacizumab	71 (17.8)
Ranibizumab	117 (29.3)
Dexamethasone	66 (16.5)
None	78 (19.5)
Surgery	
Phacoemulsification	136 (34.1)
Vitrectomy	63 (15.8)
None	200 (50.1)

***PRP:** Panretinal Photocoagulation*

DISCUSSION

Diabetic retinopathy has been known to be a microvascular disease for a long time. Earlier population-based studies have revealed that almost all individuals who have type 1 diabetes and more than 60% of the ones with type 2 diabetes come across the development of DR in the first 2 decades of the disease (6, 7). Type 2 diabetes is expected to increase in prevalence since sedentary lifestyles and obesity have become more common, which would result in more individuals with DR (6, 8).

Diabetic retinopathy more commonly occurs in elderly individuals with diabetes. In our study, it was revealed that the mean

age of patients with type 1 diabetes was 51.3 years and the mean age of patients with type 2 diabetes was 63.8 years, which are quite similar to other studies (9, 10). Regarding gender, the number of female patients (58.4%) was slightly more than males in our study. However, in most studies, the number of male and female patients was similar (9, 11-15). These demographic data are important for the different clinical approaches in daily practice.

Previous studies have shown that DR is asymptomatic at early stages, and visual impairments only develop due to PDR or advanced macular disease. Therefore, patients with DR should regularly undergo complete ophthalmologic examinations including BCVA, anterior segment biomicroscopic examination, IOP measurement, and detailed fundus examination for better management of the disease (3, 16). In the present study, patients had visual impairments at the initial examination, whereas in other studies patients at the early stages had decent visual acuities (17, 18). IOPs were found to be in the normal range. The number of patients with NPDR was greater than the ones with PDR. According to other studies, approximately 27.5% of the individuals with DR have diabetic macular edema (19, 20). It has been seen that 45.6% of patients had diabetic macular edema at the first admission. The difference between the results of initial visual acuities could be attributed to the poor attendance of patients to ophthalmological appointments alongside the differences of genetic and environmental factors.

The stage of DR severity primarily affects the tendency of pr gression to vision-threatening PDR. The ETDRS has shown that the possibility of progression to PDR from severe NPDR is approximately 52% in 1 year (21). Recent studies have revealed various rates of PDR progression from baseline DR, ranging from 5.3% to 11.0% (22, 23). Our results of PDR progression from NPDR (6.2%) align our findings with most of the recent studies. The primary cause of chronic renal disease has been known to be diabetic nephropathy, accounting for 40% of total annual new cases of end-stage renal disease development. Albuminuria, progressive glomerular filtration rate decline, and blood pressure elevation are the complications of diabetic nephropathy. These complications of diabetic nephropathy have been revealed to be important independent predictors of PDR progression. As for DR, the major risk factors for diabetic nephropathy were identified to be prolonged duration of diabetes, hypertension, and poor glycemic control. In addition, proteinuria or being on dialysis increase the risk of vision-threatening PDR. In the present study, there were not enough patients with nephropathy to evaluate the relationship between nephropathy and PDR progression. We have found that cataract surgery, gender, and the presence of hypertension had no statistically significant impact on PDR progression, which is supported by other studies (21, 24).

Diabetic retinopathy can cause changes in blood vessels, microaneurysms, hemorrhages, exudates, and retinal thickening. Any advanced pathologies of DR on the macula can lead to visual loss. Peripheral retinal laser photocoagulation is performed to reduce the risk of advanced vision impairments. It is still unknown if any type of laser treatment is superior to another. Focal macular laser photocoagulation is performed in order to reduce the risk of moderate visual impairment in patients with clinically severe macular edema and mild to moderate NPDR. Grid photocoagulation performed to the zones of the thickened retina can improve visual acuity. However, studies have shown that the photocoagulation treatment is unlikely to remain beneficial on patients with maculopathy but is helpful on clinically significant macular edema. Intravitreal triamcinolone acetonide was applied to patients with macular edema who were resistant to the previous macular laser photocoagulation treatments. This was done to provide improved visual acuity and reduced macular thickness; however, repeated injections were required to maintain beneficial features. Common complications of intravitreal triamcinolone are the progression of cataract and secondary ocular hypertension; infectious endophthalmitis complication is rare. Intravitreal anti-VEGF injections are performed to reduce the macular thickness and improve visual acuities. Repeated injections are also needed to maintain beneficial features (25). In our clinic, patients with PDR and ischemic pathologies had panretinal laser photocoagulation treatment and had intravitreal injections with the purpose of macular edema medication. According to the results of the study of Baker et al. (26), aflibercept is superior to bevacizumab and ranibizumab in eyes with moderate to severe visual impairments but neither panretinal laser photocoagulation nor any kind of anti-VEGF injection has a statistically significant difference in eyes with mild visual impairments. The prognosis of visual acuities is associated with various factors like the severity of retinopathy and HbA1c management. In the study of Bressler et al. (27), it was revealed that panretinal laser photocoagulation had less impact on the improvement in visual acuities in eyes with severe retinopathy or higher HbA1c, compared with the eyes with less severe retinopathy or lower HbA1c. Our results have shown that the type of diabetes, retinal laser photocoagulation, and the type of intravitreal injection have no significant impact on visual acuity. Vitrectomy can help to reduce visual loss if performed early in patients with intravitreal hemorrhage, especially in ones with PDR (27). Patients with DR in our clinic underwent cataract surgery and vitrectomy for the reason of tractional retinal detachment, resistant macular edema, and intravitreal hemorrhage.

The main limitations in our study were the lack of data in HbA1c values of the patients throughout follow-ups and the poor number of DR patients with nephropathy to investigate further impacts on the prognosis of the disease. Diabetic nephropathy and HbA1c values are known to be considerably related to PDR progression from NPDR, have a strong impact on the prognosis of visual acuity and, highly important in managing the complications of DR (21-23).

In conclusion, DR happens to be a common and feared vision-threatening microvascular disease despite the increased treatment availability for the disease. With the global rise in the number of diabetic individuals, the number of people at the risk of DR is likely to increase considerably. Early diagnosis, check-ups, and proper treatment are the crucial points of DR management. Retinal laser photocoagulation treatment and intravitreal anti-VEGF injections are significantly useful for neovascularization, ischemic pathology, and macular edema treatment. As our study showed, retinal laser photocoagulation treatment and cataract surgery had no significant impact on visual acuity prognosis unlike the initial examination visual acuity values. In addition, the results have also revealed that the difference between the types of intravitreal injections made no dissimilar end-results on the prognosis of visual acuities. Furthermore, it was revealed that gender, hypertension presence, and cataract surgery may not have a significant relationship with PDR progression. Further studies are needed to thoroughly reveal the relationship between treatment regimens and the progression and prognosis of the disease.

Ethics Committee Approval: This retrospective study was approved by the Scientific Research Ethics Committee of Trakya University School of Medicine (Protocol Code: TUTF-BAEK2020/339). ***Informed Consent:*** Informed consent was obtained from all subjects. ***Conflict of Interest:*** The authors declared no conflict of interest. ***Author contributions:*** Concept: MÖİ, RG. Supervision: MÖİ, RG. Resources: MÖİ, RG. Materials: MÖİ, RG. Data collection and/or processing: MÖİ, RG. Analysis and/or Interpretation: MÖİ, RG. Literature Search: MÖİ, RG. Writing Manuscript: MÖİ, RG. Critical Review: MÖİ, RG. ***Financial disclosure:*** The authors declared that this study received no financial support.

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