Original Article

Long-Term Intravitreal Dexamethasone Implant Monotherapy in Naïve Patients with Diabetic Macular Edema

Gamze Karataş[1], Akın Çakır[1], Öznur Aday[1], Tahsin Uzundede[1], Furkan Kırık[2], Ahmet Melih Özoğuz[1], Hakan Özdemir[2], Mustafa Nuri Elçioğlu[1]

[1]University of Health Sciences Türkiye, İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
[2]Bezmialem Vakıf University Faculty of Medicine, Department of Ophthalmology, İstanbul, Türkiye

Abstract

Objectives: To demonstrate the efficacy and safety of repeated dexamethasone (DEX) implants in eyes with naïve diabetic macular edema (DME) using real-life data over a minimum of 36 months follow-up.

Materials and Methods: This retrospective cohort study included treatment-naïve DME patients treated with intravitreal DEX monotherapy and followed for at least 36 months. Main outcomes were best corrected visual acuity (BCVA) and central macular thickness (CMT) change. Secondary outcomes were optical coherence tomography findings, including serous macular detachment, hard exudate, hyperreflective foci, cystoid degeneration, pearl necklace sign, epiretinal membrane (ERM), disorganization of the retinal inner layers (DRIL), ellipsoid zone and external limiting membrane (EZ-ELM) integrity, and intra-cystic hyperreflective material, as well as intraocular pressures and lens status.

Results: The study included 74 eyes of 52 patients. The mean follow-up period and number of injections were 49.24±13.51 months and 6.83±2.76, respectively. Both BCVA and CMT improved significantly throughout follow-up (p=0.009; p<0.001). The mean BCVA increased by 7.9±2.1 letters, and 38 patients (51.3%) gained ≥10 letters. Hyperreflective foci (p<0.001), pearl necklace sign (p=0.012), and intra-cystic hyperreflective material (p=0.042) decreased significantly, while ERM (p=0.006), DRIL (p<0.001), and EZ-ELM defects (p<0.001) increased significantly.

Conclusion: Intravitreal DEX monotherapy is a safe and effective treatment option for treatment-naïve DME patients in long-term follow-up.

Keywords: Dexamethasone, diabetic macular edema, diabetic retinopathy, steroid

Cite this article as: Karataş G, Çakır A, Aday Ö, Uzundede T, Kırık F, Özoğuz AM, Özdemir H, Elçioğlu MN. Long-Term Intravitreal Dexamethasone Implant Monotherapy in Naïve Patients with Diabetic Macular Edema.
Turk J Ophthalmol. 2026;56:24-30

Address for Correspondence: Gamze Karataş, University of Health Sciences Türkiye, İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
E-mail: madengamze14@gmail.com
ORCID-ID: orcid.org/0000-0003-4125-4819

Received: 29.08.2025
Revision Requested: 20.10.2025
Last Revision Received: 24.10.2025
Accepted: 06.12.2025
Publication Date: 18.02.2026

DOI: 10.4274/tjo.galenos.2025.77246

Introduction

Diabetic retinopathy (DRP) is one of the most prevalent microvascular complications of diabetes mellitus, and diabetic macular edema (DME) represents the leading cause of visual impairment in affected individuals.[1,2] Although substantial evidence has demonstrated the efficacy of anti-vascular endothelial growth factor (VEGF) therapy in the management of DME,[3,4] both inflammation and VEGF play key roles in DME pathogenesis.[5] Current guidelines state that anti-VEGF injections are the first-choice treatment of DME.[6,7] However, according to the EURORETINA guidelines, steroids may be a preferable first-line therapy in patients with a history of major cardiovascular events and those who do not want to travel for monthly injections (and/or monitoring) within the first 6 months of treatment.[6] The risk of cataract and glaucoma as side effects is the main reason steroids are the second choice. According to the MEAD study on the dexamethasone (DEX) implant, increases in intraocular pressure (IOP) were usually controlled with medical therapy or observation, and glaucoma surgery was necessary in only

two patients, corresponding to 0.6% of those in the 0.7-mg implant group.[8] Cataracts have also become relatively easy to manage owing to improvement of surgical instruments.

In the Protocol T study, approximately 30-40% of patients had intraretinal and/or subretinal fluid despite anti-VEGF therapy, illustrating the importance of combination therapy.[9]

There are a few case series of DME treated with only DEX implants in the literature, but they had a maximum follow-up of two years and included both resistant and naïve patients, with relatively small treatment-naïve groups.[10,11,12] Because the visual gains of non-naïve cases are lower than those of naïve cases due to chronicity, larger naïve samples are essential. Moreover, longitudinal studies are needed because the long-term side effects of intravitreal steroids remain unclear. Several multicenter studies have been conducted to evaluate anatomical and functional success with DEX implants in DME using current ancillary testing.[13,14] However, comparing results by different researchers using different devices and optical coherence tomography (OCT) modalities may lead to misinterpretations.

This study aimed to evaluate the long-term efficacy of repeated DEX implant monotherapy in treatment-naïve eyes with DME, utilizing real-world data from up to six years of follow-up.

Materials and Methods

This retrospective cohort study was performed in accordance with the ethical principles of the Declaration of Helsinki. Approval was granted by the Institutional Review Board of University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital (approval ID: 02.05.2023/3905), and all individuals provided written informed consent prior to participation.

The medical records of 1042 consecutive DME patients treated with intravitreal DEX implants in the retina department of the University of Health Sciences Türkiye, Prof. Dr. Cemil Taşcıoğlu City Hospital since 2015, when DEX implants were approved in Türkiye, were reviewed. Of these,143 were treatment-naïve at baseline, and 52 patients had at least 36 months' follow-up. For patients who received bilateral intravitreal DEX implants, both eyes were included. The final cohort comprised 74 eyes of 52 patients with DME who met these criteria.

Patients with prior grid laser or intravitreal anti-VEGF therapy were excluded. Additional exclusion criteria were vitreomacular adhesion or traction, glaucoma, retinal vascular occlusion, tractional detachment, complicated cataract surgery, ocular trauma, poor-quality OCT images, and incomplete medical documentation or consent.

Each follow-up visit included assessment of best-corrected visual acuity (BCVA), anterior segment biomicroscopy, IOP measurement with a Goldmann applanation tonometer, indirect ophthalmoscopy, and spectral-domain OCT (SD-OCT). Baseline and follow-up data also included a history of cerebrovascular or cardiovascular events and other comorbidities. Any initiation of anti-glaucoma therapy or performance of trabeculectomy during follow-up was documented. Additionally, the total follow-up duration (in months) and the cumulative number of DEX implant injections were recorded.

All patients were managed using a pro re nata (PRN) regimen. Patients were generally reassessed at intervals of approximately 45-60 days under this protocol. Criteria for retreatment included the presence of intraretinal or subretinal fluid with a central macular thickness (CMT) exceeding 300 μm, residual intra- or subretinal fluid, or a decrease in BCVA of more than 5 letters on the Early Treatment Diabetic Retinopathy Study scale, provided there was no cataract progression. Eyes with visually significant cataract development underwent surgical removal.

Patients with epiretinal membrane (ERM) causing tangential traction were included in the study, although none underwent ERM surgery. Eyes with vitreomacular interface abnormalities causing anteroposterior traction were excluded. At each follow-up visit, SD-OCT imaging was performed using the Spectralis system (Heidelberg Engineering, Heidelberg, Germany), which automatically provided CMT measurements for quantitative assessment of DME. CMT values were documented at baseline and all subsequent visits. Two independent investigators blinded to the clinical data (G.K. and A.Ç.) evaluated OCT biomarkers at baseline and the final visit. Assessed features included serous macular detachment (SMD), hard exudates, hyperreflective foci (HRF), cystoid degeneration, pearl necklace sign, ERM, disorganization of the retinal inner layers (DRIL), integrity of the ellipsoid zone and external limiting membrane (EZ-ELM), and intra-cystic hyperreflective material.

Cystoid degeneration was defined as cystoid spaces with a horizontal diameter of 600 μm or greater. SMD was considered present if the posterior retinal surface was raised above a hyporeflective cavity. EZ and ELM integrity were analyzed together; eyes showing continuous EZ-ELM within 1 mm of the foveal center were classified as intact, while any disruption was noted as a defect.[14] HRF were quantified in three ranges (1-10, 11-20, ≥21).[15] When HRF were arranged along the inner wall of cystoid cavities in a ring-like pattern, this was termed the pearl necklace sign.[16] DRIL was defined as the inability to clearly delineate the boundaries between the ganglion cell layer, inner plexiform layer, inner nuclear layer, and outer plexiform

layer.[17] Hyperreflective material present within cystoid spaces, without shadowing and distinct from HRF or hard exudates, was classified as intra-cystic hyperreflective material.[18]

The primary outcomes assessed were changes in visual acuity and anatomical parameters over the course of follow-up. Secondary outcomes included the percentage of eyes showing a change of 10 letters or more in BCVA, the evolution of OCT biomarkers and their influence on treatment efficacy, as well as the rates of cataract surgery and interventions for IOP control during the study period.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS software version 21.0. The distribution of variables was assessed both visually (histograms) and analytically using the Kolmogorov-Smirnov test. For normally distributed variables, descriptive statistics were reported as mean ± standard deviation. Comparisons between baseline and final measurements were performed using the paired Student's t-test or the Wilcoxon signed-rank test, as appropriate. Categorical variables were compared using either the chi-square test or Fisher's exact test. Correlation coefficients were calculated using Spearman's or Pearson's tests. A multiple linear regression analysis was employed to determine independent predictors of BCVA and CMT, with model fit evaluated through residual analysis and goodness-of-fit statistics. A p value less than 0.05 was considered statistically significant.

Results

A total of 74 eyes of 52 naïve patients (23 female [44.2%] and 29 male [55.8%]) treated with repeated intravitreal DEX implants and followed for at least 3 years were included. The mean age, follow-up period, and number of injections were 68.16±9.06 years, 49.24±13.51 months (median: 45, interquartile range [IQR]: 21), and 6.83±2.76, respectively. The annual mean number of injections in years 1-6 was 2.47±0.57, 2.16±0.70, 1.35±0.95, 0.82±0.84, 0.62±0.77, and 0.50±0.65, respectively (Figure 1).

The minimum and maximum follow-up times were 36 and 80 months, respectively. Thirty-four of the 74 eyes were followed up for ≥4 years, and 11 were followed up for ≥6 years. Thirteen patients (17.5%) were followed up for a mean of 28.8±21.9 months without treatment. The mean initial HbA1c value was 8.2±1.4%, and 26 (50%) patients had a diagnosis of systemic hypertension.

Mean BCVA improved significantly between baseline (0.81±0.50 logarithm of the minimum angle of resolution [logMAR] [20/125]; median: 0.7, IQR: 0.6) and the final visit (0.65±0.54 logMAR [20/80]; median: 0.6, IQR: 0.83; p=0.009). The mean change in BCVA was +7.9±2.1 letters (median: 10, IQR: 26.25), which was significant (p=0.009), and 38 patients (51.3%) gained ≥10 letters.

The change from mean baseline to final CMT was 540.05±161.27 µm to 351.78±123.49 µm, respectively, which was significant (p<0.001). Cystoid degeneration was present in 20 eyes (27%) at baseline, which was reduced to 9/20 (45%) at last follow-up.

The mean baseline and final IOP was 14.40±2.50 mmHg and 15.48±3.36 mmHg, respectively (p=0.009). Sixty-two (83.8%), 7, 4, and 1 eyes were followed up with no, one, two, and three anti-glaucomatous agents, respectively. None of the patients underwent glaucoma surgery.

There were 41 phakic eyes at baseline, 40 (97%) of which underwent phacoemulsification surgery during the follow-up period (p<0.001).

Thirty-nine eyes (52.7%) had prior panretinal photocoagulation (PRP) at baseline. During follow-up, PRP was performed in another 9 eyes (25.7%) (p=0.012).

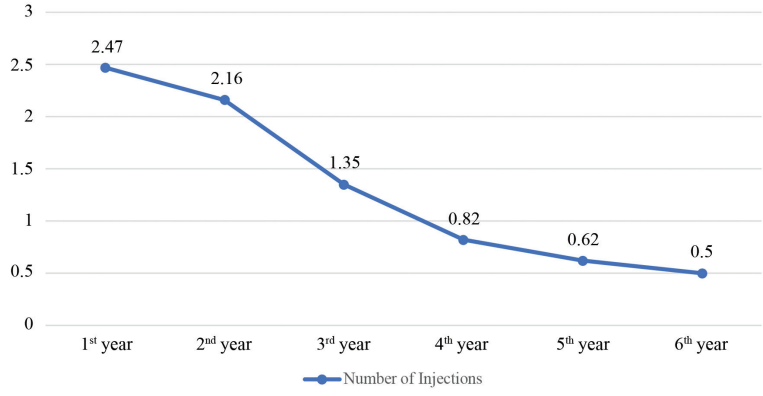

Figure 1. Number of dexamethasone implant injections per year

In those cases specifically, the mean follow-up time and injection number were 59.1±18.7 and 7.3±1.9, respectively.

Eight eyes (10.8%) were vitrectomized at baseline and 3 eyes (4.5%) underwent vitrectomy because of newly developed vitreous hemorrhage secondary to proliferative DRP during follow-up (p=0.508).

At baseline, 9 patients (17.3%) had experienced cerebrovascular or cardiovascular events within the preceding 6 months. During the treatment and follow-up periods, no new cerebrovascular or cardiovascular events were observed in any patient.

There were 27 eyes (36.5%) with SMD at baseline. At the end of follow-up, no SMD was observed in any patient (p<0.001). Initially, 52 eyes had hard exudates, which completely disappeared in 8 (15.3%) of them. However, new hard exudate formation was observed in 5 of the 22 eyes initially free of hard exudate. HRF at final follow-up was significantly decreased compared to baseline (p<0.001). From baseline to last follow-up, the prevalence of pearl necklace sign decreased from 21 eyes (28.4%) to 8 eyes (10.8%) (p=0.012), whereas the presence of ERM increased from 54 eyes (73%) to 64 eyes (86.5%) (p=0.006) and DRIL increased from 29 eyes (39.2%) to 43 eyes (58.1%) (p<0.001).

Additionally, the number of eyes with disrupted EZ-ELM increased from 14 eyes (18.9%) to 35 eyes (47.3%) (p<0.001) while intra-cystic hyperreflective material decreased from 19 eyes (25.6%) to 8 eyes (10.8%) (p=0.042) from baseline to final follow-up. The participants' baseline and final clinical characteristics are summarized in Table 1.

Multiple linear regression analysis showed a significant negative correlation between BCVA improvement and baseline BCVA in logMAR units (B=-0.524, p<0.001), the presence of EZ-ELM defects (B=-16.1 p=0.015), and the presence of HRF (B=-8.32 p=0.040). CMT improvement was positively correlated with baseline CMT (B=0.560, p<0.001), and final CMT was positively correlated with baseline CMT (B=231.5, p=0.014).

Discussion

This retrospective cohort study evaluated treatment-naïve DME patients who received intravitreal DEX implants, representing the longest single-center follow-up reported in the literature to date (36-80 months). Intravitreal DEX implant therapy alone was associated with both functional and anatomical improvements in these patients over long-term follow-up. Additionally, the study included the largest cohort of treatment-naïve eyes currently described in the literature (74 eyes). Only 9 patients (17.3%) had a prior history of cerebrovascular or cardiovascular events; therefore, intravitreal DEX implant therapy was administered to the remaining patients based on the clinician's decision.

An Australian prospective multicenter study included 200 patients from 25 ophthalmology clinics, of whom 57 (28.5%) were treatment-naïve and 41 (71.9% of 57) completed the study.[10] The IRGREL-DEX study was a retrospective, 10-center study of 71 naïve DME eyes followed up for 24 months using 4 different OCT devices (Cirrus, Spectralis, Topcon, and Optovue).[11] In contrast, the single-center and single-device nature of our study ensures standardization of results.

In the MEAD study, non-naïve patients received an average of 5 intravitreal DEX implants over 3 years.[8] In the IRGREL-DEX study, the mean number of intravitreal DEX implants was 3.5±1.0 over 24 months.[11] Adjusting for the difference in follow-up times, the number of injections in our study is consistent with these studies.

Considering that 97% of our patients underwent cataract surgery during the study period, lens status did not affect the increase in vision. Our results are in line with other studies reporting that intravitreal DEX implants provided significant long-term improvement in visual acuity in patients with naïve DME. In the IRGREL-DEX study, the BCVA gain at 24 months was 11.3±10.0 letters.[11] Kodjikian et al.[19] reported that the best response in patients with DME unresponsive to anti-VEGF treatment was in the early switch group. This supports the idea that there may be better visual improvement in cases where the retinal architecture is not impaired, such as in naïve patients. Similarly, Akıncıoğlu et al.[20] reported favorable anatomical and functional outcomes of intravitreal DEX implant therapy in patients with recalcitrant DME in a Turkish real-world setting, supporting the broader efficacy of DEX implants across different DME subgroups.

Numerous studies of DEX implants reported high IOP, which in most cases was controlled with antiglaucoma medication and rarely required surgical treatment.[8,10,11,12,21] Although we found a significant increase in IOP, only a few patients required antiglaucoma treatment, and none required surgery. If these patients had previously had glaucoma, an increase of approximately 1 mmHg would have led to a deviation from the target IOP.[22] However, this increase is not clinically significant because the patients did not have glaucoma.

Phacoemulsification surgery was performed in 40/41 (97%) eyes during the follow-up period. The IRGREL-DEX study reported that 15 of 16 phakic eyes in the treatment-

Table 1. Baseline and final clinical characteristics of patients			
	Baseline	**Final**	**p**
Age, years	68.16±9.06	-	
HbA1c, %	8.2±1.4	-	
Duration of DM, years	-	16.8±8.4	
Follow-up time, months	-	49.24±13.51	
Total DEX implants	-	6.83±2.76	
BCVA, logMAR, mean ± SD	0.81±0.50	0.65±0.54	**0.009**
CMT, µm, mean ± SD	540.05±161.27	351.78±123.49	**<0.001**
IOP, mmHg, mean ± SD	14.40±2.50	15.48±3.36	**0.009**
Lens status (pseudophakia), n (%)	33 (44.5)	73 (98.6)	**<0.001**
PRP, n (%)	39 (52.7)	48 (64.8)	**0.012**
PPV, n (%)	8 (10.8)	11 (14.8)	0.508
CVA/CVE, n (%)	9 (17.3)	9 (17.3)	1
SMD, n (%)	27 (36.4)	0	**<0.001**
Hard exudate, n (%)	52 (70.2)	49 (66.2)	0.268
Pearl necklace sign, n (%)	21 (28.3)	8 (10.8)	**0.012**
HRF, n (%) Grade 1 (1-10) Grade 2 (11-20) Grade 3 (≥21)	 48 (64.9) 13 (17.6) 8 (10.8)	 47 (63.5) 9 (12.2) 1 (1.4)	**<0.001**
ERM, n (%)	54 (72.9)	64 (86.4)	**0.006**
DRIL, n (%)	29 (39.1)	43 (58.1)	**<0.001**
EZ-ELM, n (%)	14 (18.9)	35 (47.2)	**<0.001**
Intra-cystic hyperreflective material, n (%)	19 (25.6)	8 (10.8)	**0.042**

HbA1c: Glycosylated hemoglobin, DM: Diabetes mellitus, DEX: Dexamethasone, BCVA: Best corrected visual acuity, logMAR: Logarithm of the minimum angle of resolution, SD: Standard deviation, CMT: Central macular thickness, IOP: Intraocular pressure, PRP: Panretinal photocoagulation, PPV: Pars plana vitrectomy, CVA/CVE: Cerebrovascular accident/cardiovascular event, SMD: Serous macular detachment, HRF: Hyperreflective foci, ERM: Epiretinal membrane, DRIL: Disorganization of the retinal inner layers, EZ-ELM: Ellipsoid zone-external limiting membrane

naïve DME group underwent cataract surgery by the 24-month follow-up.[11] Cataract formation is a recognized long-term complication of DEX implant therapy and occurs in the majority of patients over time.

At final follow-up, SMD had disappeared in all our patients. The number of HRF and presence of both the pearl necklace sign and intra-cystic hyperreflective material also decreased significantly. In contrast, ERM, DRIL, and EZ-ELM defects increased significantly. Similarly, Horozoglu et al.[23] reported that intravitreal DEX implant therapy provided significant short-term efficacy for SMD and HRF in patients with treatment-resistant DME but noted increases in EZ-ELM defects, ERM, and DRIL at final follow-up. DRIL is commonly observed in patients with proliferative DRP.[24] In contrast to our results, Zur et al.[25] reported that DEX implants could potentially ameliorate DRIL based on their multicenter, retrospective, 12-month study including eyes with DME. In our study, however, DRIL increased with DEX implant monotherapy in naïve DME over much longer follow-up.

We propose that the observed increase in DRIL, EZ–ELM defects, and ERM is driven by a combination of natural disease progression and real-world treatment dynamics. The literature supports an association between EZ-ELM changes and DRP severity.[26,27] Hui et al.[28] also reported a correlation between ERM and DME duration. Since proliferative and severe non-proliferative DRP predominated at baseline in our study, high initial rates of structural alterations are unsurprising. The long follow-up period of this study is also suitable for evaluating DRP progression. However, it is likely that the PRN exacerbated this process. Under a PRN regimen, patients may not always receive retreatment at optimal intervals, resulting in recurrent episodes of macular edema. These cycles of edema and resolution could induce repeated fluctuations

in retinal thickness, thereby contributing to progressive structural alterations over time. As a result of these factors, 13.5% of our naïve DME patients developed ERM, 18.9% developed DRIL, and 28.4% developed EZ-ELM defects over follow-up of 3-6 years. With DEX monotherapy, more successful results may be obtained by opting for a treat-and-extend regimen instead of PRN.

Notably, this anatomical progression did not appear to compromise overall functional gains. The final BCVA was significantly higher than at baseline.

BCVA gain was negatively correlated with baseline BCVA, whereas CMT gain was positively correlated with baseline and final CMT. In other words, patients with lower baseline BCVA had larger BCVA gains, while an increase in CMT was more common in patients with high CMT. However, even with greater increases, the final BCVA and CMT remained lower than those in patients with better baseline values. These results can be explained by the ceiling effect.[29]

A total of 13 eyes (17.5%) in the study cohort were followed without treatment for a mean duration of 28.8±21.9 months, which represents a relatively long observation period. These findings suggest that following DEX implant therapy, patients may require fewer injections over time and treatment can be discontinued in some cases. The resulting reduction in visit frequency and injection burden may substantially decrease the overall treatment load.

No serious ocular/systemic (thromboembolic events) side effects were observed in any patient during the study period.

Study Limitations

The main limitation of this study was its retrospective design. However, real-life studies can be valuable for reflecting real-life data. Our study has the following advantages: its single-center nature, long follow-up time, largest naïve cohort group studied to date, and standardization of data. Notably, as the same OCT device was used in all patients, our results contribute valuable information to the current literature.

Conclusion

In summary, intravitreal DEX monotherapy demonstrates long-term efficacy and acceptable tolerability in the management of treatment-naïve DME patients. Over extended follow-up periods without concomitant anti-VEGF therapy, both the number of injections and the frequency of visits may be reduced. With careful patient selection, DEX monotherapy could serve as a first-line option alongside current standard treatments for DME. Potential complications, such as cataract formation and elevated IOP, are generally manageable with appropriate clinical intervention. Further prospective, randomized studies are warranted to strengthen the evidence base and confirm these findings.

Ethics

Ethics Committee Approval: Approval was granted by the Institutional Review Board of University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital (approval ID: 02.05.2023/3905).

Informed Consent: All individuals provided written informed consent prior to participation.

Declarations

Authorship Contributions

Concept: G.K., A.Ç., M.N.E., Design: G.K., A.Ç., F.K., H.Ö., Data Collection or Processing: G.K., Ö.A., T.U., A.M.Ö., Analysis or Interpretation: G.K., A.Ç., M.N.E., F.K., H.Ö., Literature Search: G.K., Ö.A., T.U., A.M.Ö., Writing: G.K.

Conflict of Interest: Hakan Özdemir, MD, is an Associate Editor of the Turkish Journal of Ophthalmology. He was not involved in the peer review of this article and had no access to information regarding its peer review. The other authors has no disclosures.

Financial Disclosure: The authors declared that this study received no financial support

References

1. Wong TY, Cheung CM, Larsen M, Sharma S, Simó R. Diabetic retinopathy. Nat Rev Dis Primers. 2016;2:16012.
2. Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, Chen SJ, Dekker JM, Fletcher A, Grauslund J, Haffner S, Hamman RF, Ikram MK, Kayama T, Klein BE, Klein R, Krishnaiah S, Mayurasakorn K, O'Hare JP, Orchard TJ, Porta M, Rema M, Roy MS, Sharma T, Shaw J, Taylor H, Tielsch JM, Varma R, Wang JJ, Wang N, West S, Xu L, Yasuda M, Zhang X, Mitchell P, Wong TY; Meta-Analysis for Eye Disease (META-EYE) Study Group. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care. 2012;35:556-564.
3. Nguyen QD, Brown DM, Marcus DM, Boyer DS, Patel S, Feiner L, Gibson A, Sy J, Rundle AC, Hopkins JJ, Rubio RG, Ehrlich JS; RISE and RIDE Research Group. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology. 2012;119:789-801.
4. Heier JS, Korobelnik JF, Brown DM, Schmidt-Erfurth U, Do DV, Midena E, Boyer DS, Terasaki H, Kaiser PK, Marcus DM, Nguyen QD, Jaffe GJ, Slakter JS, Simader C, Soo Y, Schmelter T, Vitti R, Berliner AJ, Zeitz O, Metzig C, Holz FG. Intravitreal aflibercept for diabetic macular edema: 148-week results from the VISTA and VIVID studies. Ophthalmology. 2016;123:2376-2385.

5. Noma H, Yasuda K, Shimura M. Involvement of cytokines in the pathogenesis of diabetic macular edema. Int J Mol Sci. 2021;22:3427.
6. Schmidt-Erfurth U, Garcia-Arumi J, Bandello F, Berg K, Chakravarthy U, Gerendas BS, Jonas J, Larsen M, Tadayoni R, Loewenstein A. Guidelines for the management of diabetic macular edema by the European Society of Retina Specialists (EURETINA). Ophthalmologica. 2017;237:185-222.
7. Wong TY, Sun J, Kawasaki R, Ruamviboonsuk P, Gupta N, Lansingh VC, Maia M, Mathenge W, Moreker S, Muqit MMK, Resnikoff S, Verdaguer J, Zhao P, Ferris F, Aiello LP, Taylor HR. Guidelines on diabetic eye care: the International Council of Ophthalmology Recommendations for Screening, follow-up, referral, and treatment based on resource settings. Ophthalmology. 2018;125:1608-1622.
8. Boyer DS, Yoon YH, Belfort R Jr, Bandello F, Maturi RK, Augustin AJ, Li XY, Cui H, Hashad Y, Whitcup SM; Ozurdex MEAD Study Group. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. Ophthalmology. 2014;121:1904-1914.
9. Wells JA, Glassman AR, Ayala AR, Jampol LM, Bressler NM, Bressler SB, Brucker AJ, Ferris FL, Hampton GR, Jhaveri C, Melia M, Beck RW; Diabetic Retinopathy Clinical Research Network. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. Ophthalmology. 2016;123:1351-1359.
10. Fraser-Bell S, Kang HK, Mitchell P, Arnold JJ, Tainton J, Simonyi S. Dexamethasone intravitreal implant in treatment-naïve diabetic macular oedema: findings from the prospective, multicentre, AUSSIEDEX study. Br J Ophthalmol. 2023;107:72-78.
11. Iglicki M, Busch C, Zur D, Okada M, Mariussi M, Chhablani JK, Cebeci Z, Fraser-Bell S, Chaikitmongkol V, Couturier A, Giancipoli E, Lupidi M, Rodríguez-Valdés PJ, Rehak M, Fung AT, Goldstein M, Loewenstein A. Dexamethasone implant for diabetic macular edema in naive compared with refractory eyes: the International Retina Group Real-Life 24-Month Multicenter Study. The IRGREL-DEX Study. Retina. 2019;39:44-51.
12. Bux AV, Fortunato F, Barone A, Russo V, Delle Noci N, Iaculli C. Early treatment with dexamethasone intravitreal implants in diabetic macular edema: Naïve versus refractory patients. Eur J Ophthalmol. 2022;32:1619-1626.
13. Iglicki M, Busch C, Lanzetta P, Sarao V, Veritti D, Rassu N, Lupidi M, Cebeci Z, Fraser-Bell S, Bernal-Morales C, Sala-Puigdollers A, Zarranz-Ventura J, Gallego-Pinazo R, Maiti A, D'Amico Ricci G, Udaondo P, Loewenstein A, Chhablani J, Zur D. Vitrectomized vs non-vitrectomized eyes in DEX implant treatment for DMO-Is there any difference? The VITDEX study. Eye (Lond). 2023;37:280-284.
14. Arf S, Sayman Muslubas I, Hocaoglu M, Ersoz MG, Ozdemir H, Karacorlu M. Spectral domain optical coherence tomography classification of diabetic macular edema: a new proposal to clinical practice. Graefes Arch Clin Exp Ophthalmol. 2020;258:1165-1172.
15. Zur D, Iglicki M, Busch C, Invernizzi A, Mariussi M, Loewenstein A; International Retina Group. OCT biomarkers as functional outcome predictors in diabetic macular edema treated with dexamethasone implant. Ophthalmology. 2018;125:267-275.
16. Ajay K, Mason F, Gonglore B, Bhatnagar A. Pearl necklace sign in diabetic macular edema: evaluation and significance. Indian J Ophthalmol. 2016;64:829-834.
17. Sun JK, Lin MM, Lammer J, Prager S, Sarangi R, Silva PS, Aiello LP. Disorganization of the retinal inner layers as a predictor of visual acuity in eyes with center-involved diabetic macular edema. JAMA Ophthalmol. 2014;132:1309-1316.
18. Venkatesh R, Sangai S, Reddy NG, Sridharan A, Pereira A, Aseem A, Gadde SGK, Yadav NK, Chhablani J. Intracystic hyperreflective material in centre-involving diabetic macular oedema. Graefes Arch Clin Exp Ophthalmol. 2021;259:2533-2544.
19. Kodjikian L, Bellocq D, Mathis T. Pharmacological management of diabetic macular edema in real-life observational studies. Biomed Res Int. 2018;2018:8289253.
20. Akıncıoğlu D, Küçükevcilioğlu M, Durukan AH, Aykaş S, Ayyıldız Ö, Erdurman FC. Outcomes of intravitreal dexamethasone implant in the treatment of recalcitrant diabetic macular edema. Turk J Ophthalmol. 2017;47:274-278.
21. Cakir A, Erden B, Bolukbasi S, Aydin A, Yurttaser Ocak S, Maden G, Elcioglu MN. Comparison of the effect of ranibizumab and dexamethasone implant in diabetic macular edema with concurrent epiretinal membrane. J Fr Ophtalmol. 2019;42:683-689.
22. Nouri-Mahdavi K, Hoffman D, Coleman AL, Liu G, Li G, Gaasterland D, Caprioli J; Advanced Glaucoma Intervention Study. Predictive factors for glaucomatous visual field progression in the advanced glaucoma intervention study. Ophthalmology. 2004;111:1627-1635.
23. Horozoglu F, Sener H, Polat OA, Temizyurek O, Evereklioglu C. Predictive impact of optical coherence tomography biomarkers in anti-vascular endothelial growth factor resistant macular edema treated with dexamethasone implant. Photodiagnosis Photodyn Ther. 2023;42:103167.
24. Nicholson L, Ramu J, Triantafyllopoulou I, Patrao NV, Comyn O, Hykin P, Sivaprasad S. Diagnostic accuracy of disorganization of the retinal inner layers in detecting macular capillary non-perfusion in diabetic retinopathy. Clin Exp Ophthalmol. 2015;43:735-741.
25. Zur D, Iglicki M, Sala-Puigdollers A, Chhablani J, Lupidi M, Fraser-Bell S, Mendes TS, Chaikitmongkol V, Cebeci Z, Dollberg D, Busch C, Invernizzi A, Habot-Wilner Z, Loewenstein A; International Retina Group (IRG). Disorganization of retinal inner layers as a biomarker in patients with diabetic macular oedema treated with dexamethasone implant. Acta Ophthalmol. 2020;98:e217-e223.
26. Phadikar P, Saxena S, Ruia S, Lai TY, Meyer CH, Eliott D. The potential of spectral domain optical coherence tomography imaging based retinal biomarkers. Int J Retina Vitreous. 2017;3:1.
27. Jain A, Saxena S, Khanna VK, Shukla RK, Meyer CH. Status of serum VEGF and ICAM-1 and its association with external limiting membrane and inner segment-outer segment junction disruption in type 2 diabetes mellitus. Mol Vis. 2013;19:1760-1768.
28. Hui VWK, Szeto SKH, Tang F, Yang D, Chen H, Lai TYY, Rong A, Zhang S, Zhao P, Ruamviboonsuk P, Lai CC, Chang A, Das T, Ohji M, Huang SS, Sivaprasad S, Wong TY, Lam DSC, Cheung CY. Optical coherence tomography classification systems for diabetic macular edema and their associations with visual outcome and treatment responses - an updated review. Asia Pac J Ophthalmol (Phila). 2022;11:247-257.
29. Chin R, Lee BY. Principles and practice of clinical trial medicine. Burlington, MA, USA: Elsevier, Inc, 2008.