Changes in subfoveal choroidal thickness following intravitreal dexamethasone implant therapy for diabetic macular edema

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Abbreviated Title: Choroidal thickness after DEX for DME

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Summary Statement: After intravitreal dexamethasone implant injection for diabetic macular edema, we observed a significant decrease in SFCT and major improvements in central macular thickness and visual acuity by weeks 7 and 14. SFCT reduction was significantly correlated with CMT reduction, morphological features on optical coherence tomography, and vision improvement.

Abstract

Purpose: To investigate changes in subfoveal choroidal thickness (SFCT) and their relationship with best-corrected visual acuity (BCVA) and optical coherence tomography (OCT) parameters after intravitreal dexamethasone implant (DEX) injection for diabetic macular edema (DME)

Methods: Eighty-one eyes treated with DEX injection for DME were evaluated for BCVA, central macular thickness (CMT), SFCT, and OCT parameters at baseline and weeks 7 and 14.

Results: The mean baseline SFCT significantly decreased at weeks 7 ($P<0.001$) and 14 ($P<0.001$). At week 7, each 1-µm reduction in CMT and 5 Early Treatment Diabetic Retinopathy Study letters (-0.1 logMAR) improvement were associated with SFCT reductions of 0.09 ($P=0.002$) and 3.91 ($P=0.044$) · m, respectively. At week 14, each 1-µm reduction in CMT was associated with a 0.14-µm reduction in SFCT ($P<0.001$). Eyes with good functional and anatomical responses exhibited significantly greater SFCT reductions. Subretinal fluid resulted in greater SFCT changes ($P=0.039$) and better BCVA ($P=0.033$) at week 7. A continuous ellipsoid zone/interdigitation zone layer was associated with a smaller mean SFCT at week 7 ($P=0.002$) and better BCVA at weeks 7 and 14 (both, $P<0.001$).

Conclusion: Changes in SFCT after DEX injection therapy for DME may predict anatomical and functional outcomes and correlate with OCT features that are known as predictors of treatment response.

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Key Words: diabetic macular edema, intravitreal dexamethasone implant, spectral-domain optical coherence tomography, subfoveal choroidal thickness,

INTRODUCTION

Diabetic macular edema (DME) is the leading cause of visual impairment in patients with diabetic retinopathy.\(^1\) For the treatment of DME, anti-vascular endothelial growth factor (VEGF) agents are generally considered as the gold-standard first-line therapy. However, not all patients with DME respond satisfactorily to anti-VEGF agents, and some authors have raised concerns regarding the neurotoxic effects associated with chronic VEGF suppression.\(^2\)

Corticosteroids, which are strong anti-inflammatory drugs, have been introduced as possible therapeutic agents, targeting pathways in the pathogenesis of DME that are different from those targeted by anti-VEGF treatments. Among steroids, 0.7 mg intravitreal dexamethasone implant (DEX) (Ozurdex, Allergan; Irvine, CA) has shown efficacy in DME treatment, specifically in improving visual acuity and decreasing retinal thickness in difficult-to-treat eyes, i.e., vitrectomized eyes, and even in eyes with anti-VEGF-resistant DME.\(^3\)\(^-\)\(^5\)

Although alterations of the blood retinal barrier (BRB) are primarily responsible for DME development, the choroid, which nourishes the central foveal structures, has been shown to participate in DME pathophysiology in several studies using angiography.\(^6\)\(^-\)\(^7\) Enhanced depth imaging (EDI) with optical coherence tomography (OCT), which enables accessible measurement of choroidal thickness, has also enabled a more precise investigation of choroidal anatomy and has broadened our understanding of various retinal diseases, including DME.\(^8\)\(^-\)\(^10\) In addition to its association with the mechanism of diabetic retinopathy or DME, choroidal thickness reportedly shows changes after treatments such as laser therapy, photodynamic therapy, intravitreal anti-VEGF injection, and even DEX injection.\(^11\)
To predict treatment response in DME treated with anti-VEGF, several specific morphological features observed on OCT, such as the presence of subretinal fluid (SRF), vitreomacular adhesion (VMA), the integrity of the inner/outer segment junction, the existence of hyperreflective foci (HRF), and disorganization of retinal inner layers (DRIL), have been proposed as potential predictors of treatment outcomes. A recent study also proposed specific morphological OCT features such as the presence of SRF, lack of HRF, and a continuous inner segment-outer segment (IS/OS) layer as potential predictors of the functional response to DEX injection for DME.\(^{12}\)

Evaluation of the relationship between choroidal changes in DME after DEX injection and treatment response from a multifaceted view is useful and may help clinicians make better treatment decisions and monitor the therapeutic responses more effectively.

The purpose of this study was to evaluate subfoveal choroidal thickness (SFCT) changes after DEX injection therapy for DME and investigate their relationship with functional and anatomical treatment responses and OCT parameters.

**METHODS**

This retrospective review was approved by the Institutional Review Board of Ajou University Hospital (Suwon, Republic of Korea) and adhered to the tenets of the Declaration of Helsinki. The requirement for informed consent was waived because of the retrospective nature of the study.

**Study Subjects**

In this retrospective study, patients had to satisfy the following inclusion criteria: 1) type 1 or 2 diabetes mellitus; 2) DME (both naïve and refractory) identified clinically and by a retinal thickness >300 \(\mu\)m in the central subfield on OCT; and 3) first treatment with DEX.
injection. Both eyes were included for patients who received bilateral treatment with DEX. Refractory DME was defined as central macular thickness (CMT) >300 µm with persistent and increased intraretinal fluid or no morphological improvement in DME on OCT despite at least three anti-VEGF injections administered at monthly intervals. Exclusion criteria were as follows: 1) other ocular diseases that cause macular edema (i.e., retinal vein occlusion, neovascular age-related macular degeneration, uveitis, and mechanical traction to the fovea); and 2) previous intraocular surgery, i.e., vitrectomy, cataract surgery, and intraocular or periocular corticosteroid injection, within the 6 months before treatment with the DEX injection.

All patient medical records were reviewed for demographic and laboratory data, the severity of diabetic retinopathy (non-proliferative or proliferative), previous treatments for DME, and OCT data for measurement of CMT and SFCT at baseline and at 7 and 14 weeks after DEX injection therapy. During the follow-up period, no other treatments were performed in any of the eyes.

OCT Analysis

All OCT scans were obtained using spectral domain (SD)-OCT (Spectralis OCT, Heidelberg Engineering; Heidelberg, Germany). A standardized imaging protocol with EDI was used: a 31-line horizontal and vertical raster scan (30° × 25°, 9.2 mm × 7.6 mm) that was fovea-centered. Each OCT B-scan had 25–35 frames averaged to improve image quality. Quantitative assessments included CMT, which was calculated automatically on a 1-mm circle centered on the fovea by the instrument, and SFCT, which was measured manually using digital calipers provided by Heidelberg Eye Explorer software (Heidelberg Engineering, Heidelberg, Germany) at baseline and at 7 and 14 weeks after the DEX injection. EDI-OCT scans were analyzed. SFCT was defined as the distance from the outer border of the
A hyperreflective line corresponding to the retinal pigment epithelium (RPE) perpendicular to the choriocapillary interface and was measured manually using the caliper tool in the Heidelberg Eye Explorer software (Fig 1). OCT images of poor quality that were difficult to analyze were excluded from the study. Two experienced physicians (MKY and CSY), who were blinded to patient clinical data, performed measurements independently. Qualitative evaluations of SD-OCT images were performed at baseline and at weeks 7 and 14 to assess the presence and changes of OCT morphologic features (Fig 1), including (1) SRF; (2) presence of intraretinal cystoid changes; (3) continuity of the ellipsoid zone/interdigitation zone (EZ/IZ) layer (continuous and disrupted); and (4) presence of an epiretinal membrane.

Main Outcome Measures

We analyzed changes in SFCT from baseline depending on the anatomical and functional responses to DEX treatment. A good anatomical response was defined as the mean change in CMT from baseline, i.e., its categorical reduction from baseline (≥50 or <50 µm). A good functional response was defined as the mean change in BCVA from baseline, i.e., its categorical improvement from baseline (≥10 or <10; Early Treatment Diabetic Retinopathy Study (ETDRS) letters). We also analyzed changes in SFCT according to OCT morphological features at baseline.

Statistical Analyses

SPSS software version 23.0 (IBM; Armonk, NY) was used for statistical analyses. Qualitative variables were presented as percentages, and quantitative measures were presented as means ± standard deviations. BCVA, CMT, and SFCT from baseline were evaluated using the paired t-test and Wilcoxon-signed rank test after performing a Kolmogorov–Smirnov normality test. To evaluate categorical variables, we used the chi-
squared test and Fisher’s exact test. To quantify the association of the mean changes in BCVA and CMT with each unit of SFCT, we used linear regression. To evaluate significant factors related to treatment outcomes, we used logistic regression. The cut-off values for SFCT changes to estimate good functional and anatomical treatment responses were evaluated using receiver operating characteristic curve analysis. Statistical significance for all tests was considered to be \( P < 0.05 \). For statistical analysis, BCVA was converted to logMAR units. To assess the reliability of the two raters’ measurements, we used intra-class correlation (ICC). The ICC reliability was equal to 0.99 (95% CI: 0.98–0.99), indicating good reliability.

**RESULTS**

**Study Population and Baseline Characteristics**

A total of 81 eyes from 70 patients (39 [48.1%] men, 42 [51.9%] women; mean age 58.19 ± 10.13 years) were initially included in this study according to the inclusion and exclusion criteria (Table 1). Among 81 eyes, 79 eyes were followed for more than 7 weeks and 75 eyes for up to 14 weeks. For data assessment at weeks 7 and 14, only available cases were analyzed. Demographic data and general characteristics of the study population are presented in Table 1. Thirty eyes (37.0%) with DME were treatment-naïve, and 51 eyes (63.0%) were refractory to previous anti-VEGF injections. The mean number of previous anti-VEGF injections was 3.66 ± 1.17 before switching to DEX treatment. Thirty-seven eyes (45.7%) were diagnosed with proliferative diabetic retinopathy (PDR). Among them, 31 eyes (83.8%) were treated with panretinal photocoagulation, and 23 eyes (62.2%) had undergone previous anti-VEGF treatment. Nine eyes (24.3%) from PDR patients received macular laser treatment. There were no significant differences in baseline SFCT, CMT, or BCVA between the treatment-naïve and refractory groups (Table 2). PDR and non-proliferative diabetic retinopathy (NPDR) groups, and eyes with and without previous PRP or macular laser
Changes in CMT, SFCT, and BCVA

The mean preoperative CMT at baseline was $473.35 \pm 163.73 \, \mu m$, and it significantly decreased to $298.40 \pm 53.55 \, \mu m$ at week 7 ($P<0.001$) and $386.49 \pm 128.48 \, \mu m$ at week 14 ($P<0.001$; Fig 2A). Similarly, the mean preoperative SFCT significantly decreased from $299.81 \pm 116.60 \, \mu m$ at baseline to $269.30 \pm 104.32 \, \mu m$ at week 7 ($P<0.001$) and $278.10 \pm 112.07 \, \mu m$ at week 14 after DEX injection ($P<0.001$) (Fig 2B). The mean logMAR BCVA significantly improved from 0.61 (Snellen equivalent [SE], 20/81) $\pm 0.36$ at baseline to 0.51 (SE, 20/65) $\pm 0.33$ at week 7 ($P=0.002$) and 0.54 (SE, 20/69) $\pm 0.32$ at week 14 ($P=0.028$; Fig 2C).

Subgroup analysis showed no significant difference in SFCT, CMT, BCVA, or their changes at weeks 7 and 14 between the naïve and refractory groups (Table 2). All outcome measures at weeks 7 and 14 did not differ significantly between the PDR and NPDR groups, and eyes with and without previous PRP or macular laser treatment groups.

There was a statistically significant linear correlation between SFCT changes and CMT or BCVA changes. At week 7, regression coefficients for CMT change and BCVA change were 0.09 and 39.14, respectively, which means that each 1-µm reduction in CMT was associated with a 0.09-µm decrease in SFCT ($P=0.002$) when BCVA was the same, and each 5 letters (-0.1 logMAR) BCVA improvement was associated with a 3.91-µm decrease in SFCT ($P=0.044$) when CMT was the same (Table 3). Similarly, at week 14, each 1-µm reduction in CMT was associated with a 0.14-µm decrease in SFCT ($P<0.001$; Table 3). However, BCVA changes at week 14 did not significantly correlate with SFCT changes ($P=0.988$).

Correlation of SFCT with Functional and Anatomical Outcomes

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At 7 weeks after DEX injection, 25 eyes (31.6%) showed good functional responses (≥10 letters [-0.2 logMAR] improvement in BCVA) and 51 eyes (75%) demonstrated good anatomical responses (CMT reduction ≥ 50 µm). At 14 weeks, 22 eyes (29.3%) exhibited a ≥10 letters [-0.2 logMAR] improvement in BCVA, and 28 eyes (47.5%) showed a CMT reduction ≥ 50 µm.

Eyes with a good functional response at week 7 or 14 showed greater SFCT reduction at week 7 compared to eyes without a good functional response at the same stage (P=0.047 and P=0.021, respectively) (Table 4). Eyes with a good anatomical response at weeks 7 and 14 also showed a greater reduction of SFCT at week 7 and week 14, respectively, compared to eyes without a good anatomical response (P=0.025 and P=0.018, respectively) (Table 5).

After evaluation of factors contributing to good treatment responses during the follow-up period, changes in SFCT at week 7 were found to be a significant contributing factor in good functional and anatomical responses at week 7 (OR, 1.01; 95% CI, 1.00–1.03; P=0.039 and OR, 1.02; 95% CI, 1.00–1.04; P=0.035) and good functional responses at week 14 (OR, 1.03; 95% CI, 1.00–1.05; P=0.022). The cut-off value for the SFCT changes at week 7 to predict good functional response at week 14 was 22 µm (P=0.021) (see Figure in Supplemental Digital Content 1, which illustrates the ROC curve of SFCT changes, http://links.lww.com/IAE/B346). On the other hand, the cut-off value for the SFCT changes at week 7 to predict good anatomical response at week 14 was 20.5 µm, but it was not statistically significant (P=0.173).

**OCT Parameters and SFCT**

Eyes with SRF at baseline showed a significantly greater reduction in SFCT at week 7 (P=0.039), and a significantly higher proportion of eyes with baseline SRF resulted in good functional response at week 7 than eyes without SRF (P=0.033) (Table 6). Moreover, eyes...
with a continuous EZ/IZ layer had significantly lower SFCT at week 7 \((P=0.002)\) and better BCVA at baseline, and weeks 7 and 14 compared to eyes with a disrupted EZ/IZ layer \((P=0.001, P<0.001, \text{and} P<0.001, \text{respectively})\) (Table 6).

**DISCUSSION**

We demonstrated that greater SFCT reduction after DEX injection for DME may be associated with better anatomical and functional treatment outcomes and specific OCT features such as SRF and the integrity of the EZ/IZ layer, which have been proposed as predictors of the response to DEX injection.\(^{12}\) Moreover, we found a significant correlation of SFCT changes with CMT and BCVA changes by measuring the mean changes in BCVA and CMT with each unit change in SFCT.

The choroid is a highly vascularized structure that provides oxygen and nutrients to the outer retinal layers, especially the central avascular fovea and the prelaminar portion of the optic nerve.\(^{13}\) It has been implicated in the pathophysiology of many retinal diseases. Diabetic retinopathy is also reported to be accompanied by alterations in the choroidal vasculature. Previous studies using EDI OCT have described an abnormal (decreased or increased) choroidal thickness in patients with diabetic retinopathy. These studies mostly suggested choroidal thinning at various stages of diabetic retinopathy and DME.\(^{14,15}\) These changes may be related to ischemia in the RPE and outer retina that results in increased VEGF expression in the RPE, breakdown of the BRB, and, ultimately, DME.\(^{16,17}\) However, Kim et al. reported greater choroidal thickness in eyes with PDR than in those with non-PDR (NPDR) or healthy eyes, with choroidal thinning seen in eyes treated with PRP.\(^{18}\) The same authors also showed a thicker choroid in eyes with DME than in those without.

Concerning changes after anti-VEGF treatment and treatment responses in terms of SFCT, a previous study revealed a significant reduction in SFCT 3 months after anti-VEGF
treatment and hypothesized that increased VEGF production results in choroidal thickening; therefore, blockade of these VEGF effects on the choroid decreases choroidal permeability and choroidal thickening.\textsuperscript{16} Nourinia et al. examined 20 patients with DME treated with intravitreal bevacizumab and found a significant correlation between SFCT reduction and CMT reduction or BCVA improvement.\textsuperscript{19} However, they did not find any correlations between baseline SFCT and CMT reduction or BCVA improvement after treatment. Concerning baseline SFCT, we found no correlation with CMT or BCVA changes after DEX injection.

Steroids have been reported to downregulate the expression of \textit{VEGF} gene and VEGF-mediated responses, not only by decreasing inflammatory cytokines and downregulating the release of prostaglandin through strong anti-inflammatory effects but also by inhibiting the synthesis of endothelial nitric oxide synthase.\textsuperscript{20} Hence, the effects of steroids on the choroid are expected to decrease vasodilation, vascular leakage, tissue edema, and choroidal thickness. A previous study of 35 eyes with refractory DME treated with DEX injection reported significant reductions in SFCT and CMT at 3 months after treatment, with no significant improvement in BCVA.\textsuperscript{11} Moreover, they reported a significant correlation between SFCT changes and CMT changes at 3 and 6 months after treatment. Similar results were seen in our study, i.e., chronological reductions in mean SFCT and CMT were noted, and SFCT reduction was correlated with CMT changes at week 14. However, our study has some important advantages over these previous reports. First, we included a large number of study eyes comprising both treatment-naïve and refractory patients and performed subgroup analyses in various ways. We also found 1) a significant correlation between SFCT changes and CMT changes at week 7, when the treatment effect of DEX injection was supposed to be at its maximum, and 2) a significant correlation between SFCT changes and BCVA improvement. The differences between the results of the two studies could be attributed to the
different study designs and populations included, which were limited to refractory DME in the previous study. Moreover, this study also found 3) cut-off SFCT values measured at 7 weeks following DEX injection that may be predictive of a good functional response at the 14-week time point.

The cut-off value for SFCT changes at week 7 was not statistically significant for the prediction of better anatomical outcomes at week 14. This might have been because there were various types of DME, which are known to have different concentrations of inflammatory cytokines. Although all types of DME respond to DEX injection, accompanied by BCVA improvements and SFCT changes, the edema decreases in thickness to various degrees depending on its shape. Diffuse-type DME would have changed much less in thickness than cystoid edema or serous detachment types. Therefore, the statistical power of the ROC analysis may not have been enough to represent these differences in CMT improvement and SFCT changes at week 7 were not statistically significant for the prediction of good anatomical outcome at week 14.

We also examined whether OCT biomarkers that are known to predict treatment responses in DME were related to the SFCT or its changes. A recent study demonstrated that the presence of SRF, absence of HRF, and integrity of the EZ-IZ layer were predictors of better visual outcomes after DEX injection therapy. However, the authors did not evaluate SFCT or anatomical outcomes related to the specific OCT features evaluated in this study. To the best of our knowledge, this is the first study to demonstrate that SFCT or its changes after DEX injection are related to known OCT biomarkers and better functional and anatomical outcomes. We found that eyes with SRF showed greater SFCT reduction and good functional outcomes at 7 weeks after DEX injection than did eyes without SRF. Although the pathogenesis is not fully understood, the development of submacular fluid in diabetic eyes has been postulated to be in relation with choroidal inflammation and macular ischemia.
which disturb the outer BRB, increase the hyperpermeability of the chorioretinal capillaries, and result in DME with SRF.\(^7,21\) Our finding of greater SFCT reduction and better functional outcomes in eyes with SRF after DEX injection might be explained by previous findings regarding interleukin-6. Interleukin-6 is a well-known cytokine that induces acute inflammatory reactions and increased vascular permeability, and it appears at significantly higher levels in eyes with submacular detachment than in eyes with other DME patterns.\(^22,23\) Thus, the anti-inflammatory effect of DEX might facilitate better treatment responses in eyes with SRF.\(^12\) Moreover, we noted that eyes with an intact EZ-IZ layer showed significantly lower SFCT at week 7 and significantly better BCVA throughout the 14 weeks of follow up than did eyes with EZ/IZ layer disruption.

Thirty eyes (37.0\%) included in this study were treatment-naïve. We considered using DEX preferably in pseudophakic eyes or eyes with advanced cataracts that needed to be operated soon, especially if the patient had already had a chronic pattern of DME at presentation or submacular detachment on OCT.\(^4,12,24\) Vitrectomized eyes and DME with extensive hard exudates are other conditions where we tried early DEX treatment in DME.\(^25\) We are also considering DEX as a first-line therapy for DME patients with a recent history of cardiovascular or cerebrovascular accident and in pregnant women.\(^26\)

This study has some limitations, mostly attributed to its retrospective nature. First, patients received OCT scans at week 7 and week 14, not at monthly timepoints; therefore, our data should be interpreted cautiously compared to other studies that are based on 3-month or 6-month timepoints. Moreover, 14 weeks may be too short period to assess the efficacy of DEX injection therapy. However, we saw DME recurrence within 4 months after treatment in most cases and had to retreat those patients. Previous studies have also reported that mean CMT peaks again at 4 months after DEX injection therapy; the same authors have argued against the belief that the therapeutic effects of DEX injection last about 6 months, suggesting that...
further studies in which DEX is administered for only 6 months should be avoided.\textsuperscript{24} Therefore, we usually follow our patients for 7 and 14 weeks after DEX injection to assess treatment efficacy and DME recurrence. Second, we included a heterogeneous population comprising both treatment-naïve and refractory patients. However, we found no significant differences in baseline or changes from SFCT, CMT, and BCVA values between these two groups. Third, OCT images were taken at various times of the day; therefore, diurnal variation seen in SFCT could have affected study results. However, OCT images in this study were taken usually from 9 AM to 4 PM, and the amount of diurnal change in SFCT was reported to be relatively small during these hours, in contrast with early in the morning or late in the evening.\textsuperscript{27} Furthermore, a large sample size could compensate for the possibility of such errors.

In summary, this multifaceted and diverse analysis of SFCT demonstrates the predictive value of SFCT after DEX injection therapy in eyes with DME. Greater SFCT reductions, especially in the early stages after DEX injection therapy, may predict better anatomical and functional treatment responses and correlate with OCT features known as predictors of treatment responses. Further studies with larger sample sizes and better control of possible confounders are warranted in order to determine whether changes in SFCT and their association with key OCT features are valuable predictors of treatment outcomes in patients with DME.
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Figure Legends

Figure 1 Enhanced depth imaging optical coherent tomography (OCT) findings for a representative eye with diabetic macular edema (DME) treated with dexamethasone implant (DEX) injection

A. Baseline OCT images show cystoid DME with a giant outer nuclear layer cyst, small inner nuclear layer cysts, and a disrupted ellipsoid zone/interdigitation zone layer.

B. OCT images at 7 weeks after DEX injection

C. OCT images at 14 weeks after DEX injection

The subfoveal choroidal thickness (double-headed arrow) was measured from the outer border of the hyperreflective line of the retinal pigment epithelium perpendicular to the chorioclaeral interface (arrowheads) under the center of the fovea using the caliper program of the Heidelberg Eye Explorer software of OCT.

Figure 2 Changes in the mean central macular thickness (A), subfoveal choroidal thickness (B), and best-corrected visual acuity (C) at 7 and 14 weeks after dexamethasone implant injection, relative to baseline, in eyes with diabetic macular edema.
Table 1. Characteristics of 81 eyes (70 patients) with diabetic macular edema treated by intravitreal dexamethasone implant therapy

| Characteristic                                      | Total, N = 81                                      |
|----------------------------------------------------|---------------------------------------------------|
| **Age (years), mean ± SD**                         | 58.19 ± 10.13                                     |
| **Sex, n (%)**                                     |                                                   |
| Male                                               | 39 (48.1)                                         |
| Female                                             | 42 (51.9)                                         |
| **Direction, n (%)**                               |                                                   |
| Right eye                                          | 41 (50.6)                                         |
| Left eye                                           | 40 (49.4)                                         |
| **Diabetic retinopathy, n (%)**                    |                                                   |
| NPDR                                               | 44 (54.3)                                         |
| PDR                                                | 37 (45.7)                                         |
| **Previous treatment for diabetic macular edema, n (%)** |                                               |
| Naïve                                              | 30 (37.0)                                         |
| Refractory                                         | 51 (63.0)                                         |
| **Vitrectomy before >6 months**                    | 10 (12.3)                                         |
| **OCT features at baseline, n (%)**                |                                                   |
| Subretinal fluid                                   | 25 (30.9)                                         |
| ONL cyst                                           | 78 (96.3)                                         |
| INL cyst                                           | 58 (71.6)                                         |
| IZ-EZ integrity                                    |                                                   |
| Continuous                                         | 28 (34.6)                                         |
| Disrupted                                          | 53 (65.4)                                         |

INL, inner nuclear layer; IZ-EZ, interdigitation zone-ellipsoid zone; NPDR, non-proliferative diabetic retinopathy.
retinopathy; OCT, optical coherence tomography; ONL, outer nuclear layer; PDR, proliferative diabetic retinopathy; SD, standard deviation
Table 2. OCT measures and its changes in naïve and refractory groups at weeks 7 and 14

|                          | Naive         | Refractory   | \( P \) value |
|--------------------------|---------------|--------------|---------------|
| **SFCT (µm), mean ± SD** |               |              |               |
| Baseline                 | 285.83 ± 122.21 | 308.04 ± 111.59 | 0.411\(^*\) |
| Week 7                   | 244.08 ± 93.80  | 285.29 ± 108.54 | 0.116\(^*\) |
| Week 14                  | 239.53 ± 114.00 | 291.25 ± 109.61 | 0.052\(^*\) |
| Reduction at week 7 from baseline | 35.50 ± 50.03   | 22.07 ± 39.63   | 0.429\(^*\) |
| Reduction at week 14 from baseline | 47.93 ± 68.51   | 19.30 ± 42.46   | 0.145\(^*\) |
| **CMT (µm), mean ± SD**  |               |              |               |
| Baseline                 | 523.50 ± 217.74 | 443.84 ± 114.00 | 0.071\(^*\) |
| Week 7                   | 291.92 ± 55.07  | 302.40 ± 52.85  | 0.437\(^*\) |
| Week 14                  | 393.00 ± 146.61 | 384.27 ± 127.47 | 0.754\(^*\) |
| Reduction at week 7 from baseline | 225.92 ± 226.75  | 135.21 ± 125.21 | 0.136\(^*\) |
| Reduction at week 14 from baseline | 103.73 ± 216.11  | 68.70 ± 152.12  | 0.494\(^*\) |
| **Log MAR BCVA (Snellen), mean ± SD** | | | |
| Baseline                 | 0.66 (20/91) ± 0.47  | 0.58 (20/76) ± 0.28 | 0.317\(^*\) |
| Week 7                   | 0.52 (20/66) ± 0.42  | 0.50 (20/63) ± 0.27 | 0.661\(^*\) |
| Week 14                  | 0.57 (20/74) ± 0.41  | 0.52 (20/66) ± 0.27 | 0.853\(^*\) |
| Reduction at week 7 from baseline | 0.13 ± 0.34       | 0.08 ± 0.23      | 0.903\(^*\) |
| Reduction at week 14 from baseline | 0.11 ± 0.34       | 0.05 ± 0.21      | 0.850\(^*\) |

BCVA, best-corrected visual acuity; logMAR, logarithm of the minimal angle of resolution; SD, standard deviation; SFCT, subfoveal choroidal thickness

\(^*\) Student’s T-test

\(^\dagger\) Mann-Whitney test
**Table 3.** Correlation of changes in subfoveal choroidal thickness with changes in central macular thickness and best-corrected visual acuity after intravitreal dexamethasone implant therapy for diabetic macular edema

| Independent variable for SFCT change | Coefficient of SFCT change | 95% CI | \( P \)-value* |
|-------------------------------------|-----------------------------|--------|---------------|
|                                     | \( r \) | \( B \) | Lower | Upper |
| Week 7                              |       |        |        |       |
| CMT changes (\( \mu \)m)            | 0.38  | 0.09   | 0.04  | 0.147 | **0.002** |
| BCVA changes (logMAR)               | 0.25  | 39.14  | 1.05  | 77.23 | **0.044** |
| Week 14                             |       |        |        |       |
| CMT changes (\( \mu \)m)            | 0.50  | 0.14   | 0.075 | 0.211 | <**0.001** |
| BCVA changes (logMAR)               | 0.002 | 0.31   | -41.18| 41.81 | 0.988   |

*Linear regression analysis

**B, regression coefficient based on a linear mixed model:** BCVA, best-corrected visual acuity; CI, confidence interval; CMT, central macular thickness; logMAR, logarithm of the minimum angle of resolution; \( r \), partial correlation coefficient; SFCT, subfoveal choroidal thickness
Table 4. Subfoveal choroidal thickness and its changes in eyes with a good functional response at weeks 7 and 14 after intravitreal dexamethasone implant therapy for diabetic macular edema

| Functional response at week 7 | P-value | Functional response at week 14 | P-value |
|------------------------------|---------|-------------------------------|---------|
| BCVA gain ≥ 10 Letters       |         | BCVA gain ≥ 10 Letters        |         |
| N = 25                       |         | BCVA gain < 10 Letters        |         |
| N = 54                       |         | BCVA gain < 10 Letters        |         |
| N = 22                       |         |                               |         |
| SFCT (µm), mean ± SD         |         |                               |         |
| Baseline                     |         |                               |         |
| 299.08 ± 135.52              | 0.916†  | 309.32 ± 134.08               | 0.637†  |
| 302.07 ± 107.23              |         | 295.42 ± 107.42               |         |
| 297.20 ± 102.11              | 0.729†  | 272.20 ± 104.78               | 0.736†  |
| 262.21 ± 112.26              |         |                               |         |
| Week 7                       |         |                               |         |
| 273.00 ± 114.32              | 0.759†  | 274.21 ± 113.45               | 0.718†  |
| 282.82 ± 110.97              |         |                               |         |
| Week 14                      |         |                               |         |
| 47.05 ± 58.69                | 0.047†  | 41.33 ± 39.47                 | 0.021†  |
| 20.00 ± 34.75                |         | 17.44 ± 36.21                 |         |
| 34.44 ± 67.56                |         |                               |         |
| Reduction at week 7 from baseline | 0.385† | Reduction at week 14 from baseline |        |
| 34.44 ± 67.56                |         |                               |         |
| Student’s t-test             |         |                               |         |
| †Mann–Whitney test           |         |                               |         |

BCVA, best-corrected visual acuity; logMAR, logarithm of the minimal angle of resolution; SD, standard deviation; SFCT, subfoveal choroidal thickness.
Table 5. Subfoveal choroidal thickness and its changes in eyes with a good anatomical response at weeks 7 and 14 after intravitreal dexamethasone implant therapy for diabetic macular edema

|                          | CMT reduction ≥ 50 µm | CMT reduction < 50 µm | CMT reduction ≥ 50 µm | CMT reduction < 50 µm |
|--------------------------|-----------------------|-----------------------|-----------------------|-----------------------|
|                          | N = 50                | N = 17                | N = 28                | N = 31                |
| **SFCT (µm), mean ± SD** |                       |                       |                       |                       |
| Baseline                 | 303.31 ± 129.12       | 284.00 ± 85.19        | 298.96 ± 138.44       | 290.94 ± 115.44       | 0.744
| Week 7                   | 266.74 ± 107.00       | 276.82 ± 98.72        | 263.59 ± 126.69       | 281.83 ± 105.82       | 0.602
| Week 14                  | 281.33 ± 124.41       | 272.23 ± 97.51        | 261.18 ± 120.37       | 293.39 ± 103.60       | 0.274
| Reduction at week 7 from baseline | 34.64 ± 44.44 | 7.18 ± 37.40 | 33.36 ± 35.42 | 24.91 ± 60.07 | 0.025†
| Reduction at week 14 from baseline | 29.42 ± 57.82 | 14.92 ± 42.82 | 37.79 ± 45.49 | 16.45 ± 54.72 | 0.018†

† Student’s t-test

†† Mann–Whitney test

CMT, central macular thickness; SD, standard deviation; SFCT, subfoveal choroidal thickness
Table 6. SFCT and functional outcomes in groups with and without baseline OCT features

|                      | SRF at baseline | $P$ value | IZ/EZ integrity at baseline | $P$ value |
|----------------------|-----------------|-----------|-----------------------------|-----------|
|                      | With SRF        | Without SRF | Continuous                 | Disrupted |
| **SFCT (µm), mean ± SD** |
| Baseline             | 326.36 ± 140.91 | 287.96 ± 103.18 | 0.172*                     | 278.39 ± 120.80 | 311.13 ± 113.84 | 0.123†|
| Week 7               | 282.38 ± 119.06 | 263.33 ± 97.70   | 0.492*                     | 222.91 ± 98.417 | 291.98 ± 100.49 | 0.002†|
| Week 14              | 286.47 ± 115.84 | 274.13 ± 111.51 | 0.696*                     | 255.05 ± 114.72 | 290.84 ± 110.03 | 0.268†|
| Reduction at week 7  | 47.05 ± 55.18   | 18.26 ± 35.38    | **0.039†**                  | 35.64 ± 36.14  | 23.78 ± 47.48  | 0.125†|
| Reduction at week 14 | 40.16 ± 60.69   | 20.13 ± 45.56    | 0.181†                     | 39.57 ± 55.66  | 19.40 ± 47.92  | 0.159†|
| **Log MAR BCVA (Snellen), mean ± SD** |
| Baseline             | 0.72 (20/105) ± 0.41 | 0.56 (20/73) ± 0.33 | 0.058†                     | 0.45 (20/56) ± 0.30 | 0.70 (20/100) ± 0.37 | 0.001†|
| Week 7               | 0.49 (20/62 ± 0.26) | 0.52 (20/66) ± 0.36 | 0.970†                     | 0.33 (20/43) ± 0.27 | 0.61 (20/81) ± 0.32 | <0.001†|
| Week 14              | 0.57 (20/74) ± 0.24 | 0.52 (20/66) ± 0.35 | 0.174†                     | 0.37 (20/47) ± 0.27 | 0.63 (20/85) ± 0.32 | <0.001†|
| **Functional Response at week 7, n (%)** |
| BCVA gain ≥ 10 Letters | 12 (48.0)      | 13 (24.1)       | 9 (33.3)                   | 16 (30.8) |
| BCVA gain < 10 Letters | 13 (52.0)      | 41 (75.9)       | 18 (66.7)                  | 36 (69.2) |
| Total                | 25 (100)       | 54 (100)        | **0.033†**                 | 27 (100)  | 52 (100)       | 0.816†|
| **Functional Response at week 14, n (%)** |
| BCVA gain ≥ 10 Letters | 9 (39.1)       | 13 (25)         | 10 (38.5)                  | 12 (24.5) |
| BCVA gain < 10 Letters | 14 (60.9)      | 39 (75)         | 16 (61.5)                  | 37 (75.5) |
| Total                | 23 (100)       | 52 (100)        | 0.215†                    | 26 (100)  | 49 (100)       | 0.206†|

* Student’s T-test
† Mann-Whitney test
‡ Chi-square test
** BCVA, best-corrected visual acuity; CMT, central macular thickness; IZ/EZ interdigitation zone/ellipsoid zone; logMAR, logarithm of the minimal angle of resolution; SD, standard deviation; SFCT, subfoveal choroidal thickness; SRF, subretinal fluid.
**A**

|             | Baseline     | Week 7   | Week 14   |
|-------------|--------------|----------|-----------|
| CMT (µm),  | 473.35 ± 163.73 | 298.40 ± 53.55 | 386.49 ± 128.48 |
| mean ± SD   |              |          |           |
| *P Value*   |              | < 0.001  | < 0.001   |

* Paired t-test

† CMT, Central macular thickness

**B**

|             | Baseline     | Week 7   | Week 14   |
|-------------|--------------|----------|-----------|
| SFCT (µm),  | 299.81 ± 116.60 | 269.30 ± 104.32 | 278.10 ± 112.07 |
| mean ± SD   |              |          |           |
| *P Value*   |              | < 0.001  | < 0.001   |

* Paired t-test

† SFCT, Subfoveal choroidal thickness

**C**

|             | Baseline     | Week 7   | Week 14   |
|-------------|--------------|----------|-----------|
| BCVA (LogMAR)| 0.61 ± 0.36  | 0.51 ± 0.33 | 0.54 ± 0.32 |
| mean ± SD   |              |          |           |
| *P Value*   |              | 0.002    | 0.03      |

* Paired t-test

† BCVA, Best-corrected visual acuity