Segmentational Analysis of Retinal Thickness after Vitrectomy in Diabetic Macular Edema

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Purpose. To measure the inner and outer retinal thicknesses on spectral-domain optical coherence tomography (SD-OCT) and evaluate their association with logMAR after vitrectomy for diabetic macular edema (DME).

Methods. In this retrospective case series, there were 55 consecutive eyes with DME for which vitrectomy was performed. The total retinal thickness, the inner thickness (from the innermost of the retina to the inner nuclear layer), and the outer thickness (from the outer plexiform layer to the retinal pigment epithelium) in the parafoveal subfields were measured manually, and the association with logMAR was evaluated.

Results. The total retinal thicknesses in the central, nasal, and inferior subfields were significantly ($r = 0.37$, $P = 0.005$; $r = 0.29$, $P = 0.032$; $r = 0.33$, $P = 0.015$, respectively) associated with the baseline logMAR; no subfield thickness was correlated with the logMAR at the final visit. However, segmentational analysis showed that the outer retinal thickness of the temporal subfield was associated with disruption of the junction between the inner and outer segments at the fovea ($P = 0.021$ and $P = 0.005$) and negatively correlated with the logMAR ($r = -0.37$, $P = 0.006$ and $r = -0.28$, $P = 0.042$) at the 6-month and final visit. The inner thickness of the nasal subfield did not change after vitrectomy compared with the other subfields and the outer thickness of all subfields in the parafoveal area; the baseline nasal total thickness was correlated most significantly with the logMAR ($r = 0.40$, $P = 0.002$ and $r = 0.37$, $P = 0.006$) at the 6-month and final visits.

Conclusions. Segmentational analysis provided useful information for considering the prognosis and pathogenesis after vitrectomy for DME. (*Invest Ophthalmol Vis Sci.* 2012; 53:6668–6674) DOI:10.1167/iovs.12-9934

Diabetic retinopathy (DR) is one of leading causes of severe visual loss, which results mainly from angiogenic complications and diabetic macular edema (DME).[1] The breakdown of blood-retinal barrier (BRB) contributes to neuroglial dysfunction in the macula and concomitant visual impairment in DME.[2,3] Although several interventions, including photocoagulation, vitrectomy, steroids, and anti-VEGF agents have been applied clinically,[4–7] it remains to be determined how individual interventions provide beneficial effects for visual function, which can lead to customized medicine.

In addition to BRB breakdown, the pathological changes in the vitreomacular interface also contribute to persistent thickening or distortion of neuroglial tissue in the macula,[8,9] which was proved by peeling of the posterior hyaloid membrane during pars plana vitrectomy.[10–15] Vitrectomy removes the vitreous-containing growth factors from the ischemic retina and cytokines that modulate the inflammatory responses.[16–19] In addition, vitrectomy improves retinal oxygenation, which might ameliorate DME.[20] Despite these suggested mechanisms, it remains to be determined what neuroglial components are rescued or can recover from visual impairment after vitrectomy.

Recent advances in optical coherence tomography (OCT) have facilitated better delineation of the margins between the individual retinal layers with reduced speckle noises.[21] Because each retinal layer corresponds to a retinal function (i.e., light perception and signal transmission), disrupted photoreceptors were represented by discontinuity or absence of the external limiting membrane and the junction between the inner and outer segment (IS/OS) lines in RP and retinal vascular diseases.[22–25] Further, segmentation of the nerve fiber layers (NFLs) or ganglion cell complex might improve the objective detection of early changes or progression in eyes with glaucoma.[26–28] Quantitative analyses of the retinal layers have shown that the inner retina becomes thinner in early DR and that the thickness of outer segments is associated with visual dysfunction in DME.[29,30]

The total retinal thickening in DME seen on OCT represents edematous or degenerative changes in all the components from light perception to signal transduction in DME. Spectral-domain (SD)-OCT shows that cystoid spaces reside mainly in the inner nuclear layers (INL) and outer plexiform layer (OPL) in eyes with macular edema associated with retinal vascular diseases, as shown in previous pathohistologic studies.[31–34] However, it is unclear what factors determine where the cystoid spaces develop and how they affect the neuroglial components and concomitant visual impairment independently or collaboratively. SD-OCT defines the inner portion of the OPL,[35,36] which clearly divides the location of the cystoid spaces in the INL from those in the OPL. This encouraged us to investigate the course in the inner and outer retinal layers, which represent signal transduction and light perception, respectively, and how their thicknesses were associated with visual function after vitrectomy in eyes with DME.

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Table 1. Baseline and Surgical Characteristics

Sex, male/female	24/20
Age, y	66.5 ± 6.3 (range, 55–84)
Diabetes type	
Type 1	2
Type 2	42
HbA1c, %	7.83 ± 1.82
Prior treatment for DME, no. (%)	
Macular photocoagulation	10 (18.2)
Intravitreal or peribulbar corticosteroid	2 (3.6)
Other	0 (0)
Retinopathy severity, no. (%)	
Mild NPDR	0 (0)
Moderate NPDR	8 (14.5)
Severe NPDR	28 (50.9)
PDR	19 (34.5)
Epiretinal membranes present, no. (%)	12 (21.8)
Status of vitreous, no. (%)	
Attached	51 (92.7)
Detached	3 (5.5)
Uncertain	1 (1.8)
Epiretinal membrane peeled	12 (21.8)
Internal limiting membrane removed	39 (70.9)
Peribulbar corticosteroid used at close	17 (30.9)
Combined with cataract surgery	37 (67.3)

HbA1c, hemoglobin A1c; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Methods

Patients

We retrospectively reviewed 55 eyes of 44 patients who underwent pars plana vitrectomy for DME with or without vitreomacular traction (VMT) from July 2008 to February 2011 at the Department of Ophthalmology of Kyoto University Hospital. Eyes with clinically significant macular edema that underwent vitrectomy and were followed for more than 6 months postoperatively (mean, 13.5 ± 7.1 months) were included. The major exclusion criteria were a history of treatment for DME within 3 months, that is, macular photocoagulation, intravitreal corticosteroids or anti-VEGF agents; previous pars plana vitrectomy; a history of cataract surgery within 3 months; and a history of any other major surgery other than cataract extraction within 1 year before vitrectomy or 6 months after vitrectomy. Table 1 shows additional preoperative characteristics. All research and measurements adhered to the tenets of the Declaration of Helsinki; the ethics committee in our institution approved the study protocol.

Intervention

A standard pars plana vitrectomy was performed.[37] After a 23-gauge cannula was inserted, the vitreous gel was removed with peeling of the posterior hyaloid membrane or epiretinal membrane (ERM) if present. The inner limiting membrane (ILM) also was peeled after visualization, usually with indocyanine green staining in 39 eyes.[11,38,39] If the eyes were not pseudophakic, the standard cataract surgery (phacoemulsification, aspiration, and intraocular lens implantation) was performed in 37 eyes. Seventeen eyes received a peribulbar injection of triamcinolone (Kenakolt-A; Bristol Pharmaceuticals KK, Tokyo, Japan) at the end of surgery (Table 1).

Optical Coherence Tomography

At each preoperative and postoperative visit, the best-corrected visual acuity (VA) was measured and fundus biomicroscopy was performed, and retinal sectional images were acquired using Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany). In addition to the 30-degree cross-hair scans, raster scans also were performed. To evaluate the total retinal thickness, we analyzed the automated quantitative data in the Early Treatment Diabetic Retinopathy Study (ETDRS) grid (central 1 mm and individual quadrants [nasal, temporal, superior, inferior] in the parafoveal ring [1–3 mm]) using the manufacturer's software (Spectralis Acquisition and Viewing modules, version 4.0; Heidelberg Engineering).

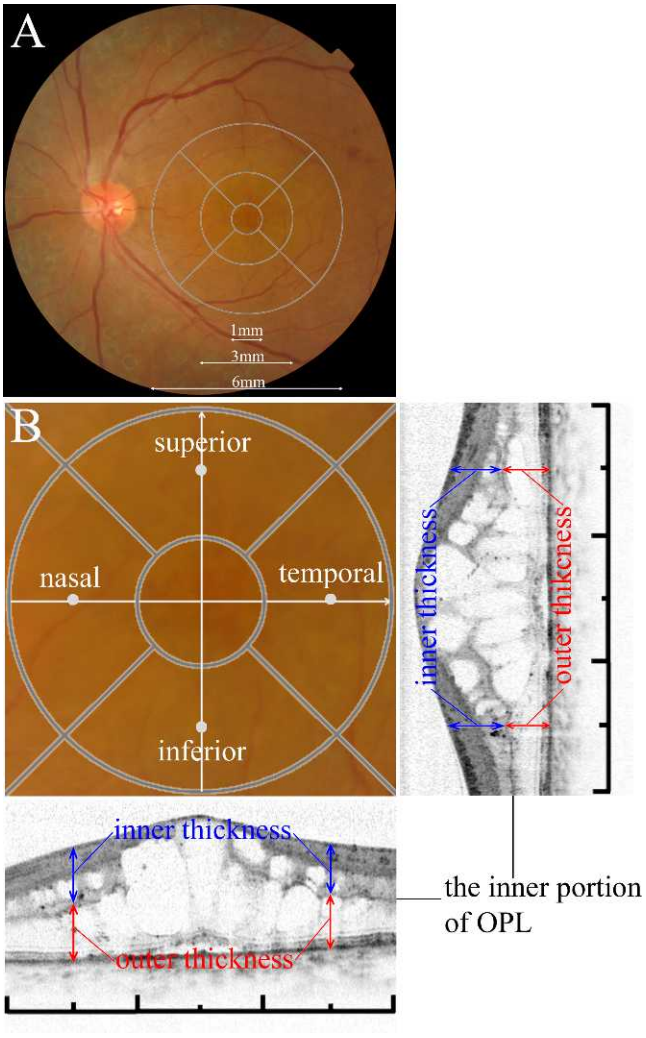

Figure 1. Measurements of inner or outer thickness in the parafoveal areas in DME. (**A**) The ETDRS grid on the color photography in a case of DME. (**B**) The magnified image of central 3 mm, and *white points* are the representative in each parafoveal subfield. The inner (*blue arrow*) and outer (*red arrow*) thicknesses at each *white point* were measured.

We further quantified the inner or outer retinal thicknesses in each subfield of the parafoveal ring. After identifying the presumed foveal center[40] on the cross-hair images, we determined the point 1 mm from the center, which might be considered representative of the each subfield of the parafoveal ring (Fig. 1). We then manually measured the distances from the innermost of the retina (ILM or NFL after ILM peeling) to the outer border of the INL as the inner thickness and from the inner border of the OPL to the retinal pigment epithelium as the outer thickness at the parafoveal points in each quadrant (Fig. 1), followed by an evaluation of the association between the retinal thickness and the logarithm of the minimum angle of resolution (logMAR) VA. There were several reasons for the choice of this procedure despite a few segmentational protocols.[27,29,30,41] Our goal was to interpret the retinal thickness with consideration of two independent functions (i.e., light perception and signal transduction).

Table 2. Course of Retinal Thickness Measured by Optical Coherence Tomography

	Pretreatment	1 mo	6 mo	Final Visit
LogMAR VA	0.63 ± 0.31	0.63 ± 0.38	0.52 ± 0.33*	0.49 ± 0.38†
Total thickness, μm				
Central	519 ± 128	413 ± 162‡	344 ± 143‡	319 ± 140‡
Nasal	469 ± 98	472 ± 116	417 ± 100*	397 ± 97‡
Temporal	501 ± 119	403 ± 92‡	341 ± 81‡	327 ± 78†
Superior	483 ± 107	428 ± 100*	378 ± 65‡	360 ± 71‡
Inferior	470 ± 109	416 ± 92*	375 ± 81‡	355 ± 87‡
Average	481 ± 96	430 ± 87†	378 ± 68‡	360 ± 70‡
Inner thickness, μm				
Nasal	231 ± 57	237 ± 76	229 ± 80	218 ± 81
Temporal	243 ± 73	203 ± 60†	172 ± 55‡	160 ± 47‡
Superior	264 ± 77	230 ± 50*	215 ± 58‡	201 ± 59‡
Inferior	250 ± 68	222 ± 55*	210 ± 57‡	196 ± 56‡
Average	247 ± 55	199 ± 82†	203 ± 58‡	194 ± 49‡
Outer thickness, μm				
Nasal	236 ± 77	222 ± 83	189 ± 58‡	178 ± 53‡
Temporal	240 ± 101	185 ± 96†	147 ± 69‡	137 ± 61‡
Superior	209 ± 62	194 ± 71	161 ± 43‡	151 ± 49‡
Inferior	200 ± 77	177 ± 66	156 ± 50‡	150 ± 44‡
Average	221 ± 67	173 ± 89‡	160 ± 45‡	154 ± 40‡

* $P < 0.05$ versus baseline.
† $P < 0.01$ versus baseline.
‡ $P < 0.001$ versus baseline.

Interestingly, both OCT and pathohistology have shown that cystoid spaces, which are a typical finding of macular edema, reside mainly in the INL and OPL in eyes with DME.[31-34] Between them, the inner portion of OPL contains the synaptic connection between photoreceptors and bipolar cells. We thus hypothesized that light perception in the photoreceptors might be affected by the cystoid spaces in the OPL, whereas those in the INL might be associated with the dysfunction in signal transduction. Based on this, we speculated that the inner and outer thicknesses, which are associated with cystoid spaces in the INL or OPL respectively, represent the pathological effects on light perception or signal transduction individually. Furthermore, Spectralis OCT provides a better view of the inner border of the OPL, which divides the INL and OPL morphologically, compared with the previous generation OCT.

We also evaluated the foveal photoreceptor status based on the status of IS/OS, as described previously.[24] Briefly, the IS/OS appearance was classified into three grades: complete, discontinuous, and absent. IS/OS (+) indicates eyes with a complete IS/OS line, and eyes with either a discontinuous or absent line were allocated to the IS/OS (–) group. The association between the foveal photoreceptor status and retinal thickness was evaluated.

Statistical Analysis

The results are expressed as the mean ± SD. The Student's *t*-test or analysis of variance was used to compare quantitative data populations with normal distributions and equal variance. The data were analyzed using the Mann-Whitney *U* test and the Kruskal-Wallis test for populations with non-normal distributions or unequal variance. Linear regression analysis was performed to test the statistical correlation. $P < 0.05$ was considered significant.

Results

Segmentational Analysis of Retinal Thickness after Vitrectomy for DME

The logMAR VA was unchanged 1 month after vitrectomy; however, the logMAR VAs at the 6-month and final visits improved significantly (Table 2). In addition, the total retinal thicknesses in all subfields decreased significantly at those two time points (Table 2 and Fig. 2). The total retinal thickness contains information derived from components of both light perception and signal transduction, which encouraged us to investigate segmentational analyses of the retinal thickness after vitrectomy for DME. The thicknesses of the outer retinal layer in all subfields decreased significantly at the 6-month and final visits, with the most significant decrease temporally. However, there was no change in the inner thickness of the nasal subfield compared with the other subfields (Table 2).

When we studied the relationship between retinal thickness and visual function, we found that the logMAR VA was associated significantly with the total retinal thickness in the central, nasal, and inferior subfields before treatment; in contrast, there was no association between the logMAR VA and the total thickness in any subfield at the final visit (Table 3). Because each retinal layer represents a function in the visual system, we investigated the association between the logMAR VA and the inner and outer thickness in each subfield. We found an interesting trend: that the inner thickness after vitrectomy was correlated positively with the logMAR VA in the superior and inferior subfields. In contrast, the outer thickness was significantly and negatively associated with the logMAR VA in two subfields at the 6-month and final visits. Especially, outer thickness in the temporal area showed positive correlation with logMAR VA preoperatively, which shifted to the negative association at both 6 months and the final visit (Table 3).

Association between Retinal Thickness and Foveal Photoreceptor Status

Paradoxical changes often occur after vitrectomy for DME, that is, deteriorated visual function with decreased retinal thickness,[14] which might be compatible with the negative correlation between the logMAR VA and the outer thickness in the temporal subfield at the final visit. We thus investigated the relationship between the IS/OS status at the fovea and the outer thickness in this parafoveal subfield. Eyes with a

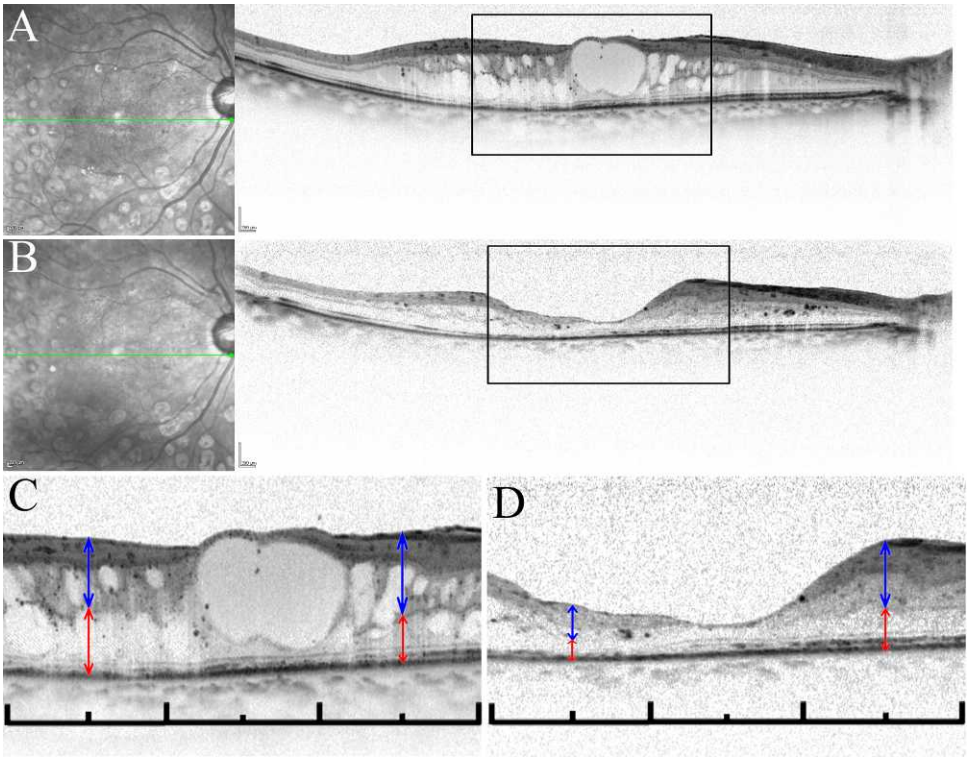

Figure 2. A representative case of DME that underwent vitrectomy. A transverse section dissecting the fovea before surgery (**A**) and 12 months after surgery (**B**), and its magnified image (**C**, **D**). Decimal VA was 0.5 and cystoid spaces were delineated at baseline (**A**). VA was not so changed 12 months after vitrectomy (decimal VA = 0.6), whereas macular edema at the fovea was resolved (**B**). Postoperative inner thickness in the nasal subfield was almost the same as preoperative one (from 340–304 μm), compared with the inner thickness (from 289–139 μm) or the outer thicknesses (from 294–84 μm) in the temporal subfield. IS/OS status at the fovea was discontinuous postoperatively.

complete IS/OS at the fovea had a thicker outer layer in the temporal subfield than those with a disrupted or absent IS/OS at the 6-month and final visits; however, there were no differences in the total retinal thickness centrally (Table 4). This suggested that the thinner outer layers in the temporal subfield better represent the foveal photoreceptor damage than the total retinal thickness at the fovea.

Optical Coherence Tomographic Prediction of Visual Prognosis

In addition to the relationship between visual function and retinal thickness at individual time points, we evaluated the relationship between the baseline retinal thickness and the logMAR VA at 6 months and the final visit. We found a

Table 3. Association between LogMAR VA and Retinal Thickness at Each Time Point

	Pretreatment	1 mo	6 mo	Final Visit
Total thickness				
Central	$r = 0.37$, $P = 0.005$	$r = -0.06$, $P = 0.675$	$r = -0.29$, $P = 0.035$	$r = -0.21$, $P = 0.130$
Nasal	$r = 0.29$, $P = 0.032$	$r = 0.25$, $P = 0.080$	$r = 0.03$, $P = 0.855$	$r = -0.02$, $P = 0.915$
Temporal	$r = 0.19$, $P = 0.221$	$r = 0.01$, $P = 0.950$	$r = -0.18$, $P = 0.183$	$r = -0.00$, $P = 0.995$
Superior	$r = 0.18$, $P = 0.185$	$r = 0.32$, $P = 0.026$	$r = 0.06$, $P = 0.647$	$r = 0.05$, $P = 0.705$
Inferior	$r = 0.33$, $P = 0.015$	$r = 0.11$, $P = 0.464$	$r = -0.08$, $P = 0.588$	$r = 0.07$, $P = 0.638$
Average	$r = 0.27$, $P = 0.047$	$r = 0.21$, $P = 0.155$	$r = -0.05$, $P = 0.703$	$r = 0.03$, $P = 0.839$
Inner thickness				
Nasal	$r = 0.13$, $P = 0.334$	$r = 0.17$, $P = 0.254$	$r = 0.18$, $P = 0.202$	$r = 0.15$, $P = 0.275$
Temporal	$r = 0.01$, $P = 0.942$	$r = 0.15$, $P = 0.316$	$r = 0.10$, $P = 0.477$	$r = 0.23$, $P = 0.095$
Superior	$r = 0.14$, $P = 0.321$	$r = 0.36$, $P = 0.012$	$r = 0.33$, $P = 0.014$	$r = 0.24$, $P = 0.073$
Inferior	$r = 0.23$, $P = 0.095$	$r = 0.24$, $P = 0.094$	$r = 0.24$, $P = 0.082$	$r = 0.35$, $P = 0.010$
Average	$r = 0.16$, $P = 0.254$	$r = 0.22$, $P = 0.100$	$r = 0.19$, $P = 0.168$	$r = 0.29$, $P = 0.032$
Outer thickness				
Nasal	$r = 0.24$, $P = 0.081$	$r = 0.24$, $P = 0.095$	$r = -0.15$, $P = 0.279$	$r = -0.36$, $P = 0.007$
Temporal	$r = 0.27$, $P = 0.050$	$r = 0.02$, $P = 0.912$	$r = -0.37$, $P = 0.006$	$r = -0.28$, $P = 0.042$
Superior	$r = 0.14$, $P = 0.303$	$r = 0.17$, $P = 0.257$	$r = -0.28$, $P = 0.042$	$r = -0.21$, $P = 0.122$
Inferior	$r = 0.24$, $P = 0.084$	$r = -0.05$, $P = 0.753$	$r = -0.23$, $P = 0.105$	$r = -0.19$, $P = 0.167$
Average	$r = 0.27$, $P = 0.047$	$r = 0.14$, $P = 0.303$	$r = -0.35$, $P = 0.009$	$r = -0.34$, $P = 0.010$

Table 4. Association between Photoreceptor Status and Retinal Thickness

	IS/OS (+)	IS/OS (–)	*P* Value
6 mo			
Total thickness of the central subfield, μm	365 ± 119	334 ± 154	0.469
Outer thickness of the temporal subfield, μm	179 ± 54	132 ± 71	0.021
Final visit			
Total thickness of the central subfield, μm	330 ± 75	313 ± 166	0.662
Outer thickness of the temporal subfield, μm	167 ± 51	120 ± 60	0.005

significant association between the postoperative logMAR VA and the total thickness in the central, nasal, and inferior subfields, with the highest correlation in the nasal subfield (Table 5). The outer thicknesses in the temporal and inferior subfields also were related to the postoperative logMAR VA, although we did not find a significant association between the postoperative logMAR VA and the pretreatment inner thickness in any subfields.

Discussion

Because vitrectomy often is combined with cataract surgery, this retrospective study seems to be more suitable for analyses of the prognosis or correlation with individual time points rather than improvements in visual function. Several studies have reported prognostic factors after vitrectomy for DME, one of which was the retinal thickness at the fovea.[42–44] We evaluated the association between logMAR and total retinal thickness in each subfield, and demonstrated for the first time that the total thickness in the nasal quadrant is the most relevant for predicting the postoperative logMAR VA. It was unexpected and interesting, although the mechanisms remain to be explained. In addition, the logMAR VA was correlated positively with the total retinal thickness in the central, nasal, and inferior subfields at baseline, which might agree with previous publications that have reported a modest correlation between VA and foveal thickness.[45] This suggested that a factor that determines the visual function was the magnitude of the baseline edematous changes. In contrast, we did not find an association between the VA and total retinal thickness in any subfield at the final visit. It might be compatible to the findings of the Diabetic Retinopathy Clinical Research Network (DRCRnet) that reported a paradoxical decrease in macular thickness with VA deterioration.[14] These data suggest that DME has pathological effects other than edematous changes on visual dysfunction after vitrectomy, which remains to be elucidated.

Because a few questions arose after the analyses of the association between visual function and total retinal thickness in each subfield, we further used segmentational analyses to search for a better system to evaluate the retinal thickness and found no improvement in the inner thickness in the nasal subfield compared with other subfields, which might be reflected by the association between the total thickness in the same subfield and visual prognosis. This suggested that a poor prognosis depends at least partly on the accumulated damage in the papillomacular bundle rather than the resultant dysfunction, because the inner thickness there was not associated with the logMAR VA at any time points. In addition, we found that the averaged thickness of the inner layer in the parafoveal area was correlated positively with the logMAR VA at the final visit, compared with a negative association between the averaged thickness of the outer layer and the logMAR VA at the same time point (Table 3). We may hypothesize that the persistent thickening of inner retinal layers contributes to visual impairments after vitrectomy, whereas degenerative or atrophic changes in outer layers have an influence on visual dysfunction.

The persistent thickening of the inner layer in the nasal subfield and concomitant visual dysfunction might depend on several pathological changes in the retinal vasculature at later time points (i.e., edema, inflammation, and ischemia), because capillary beds in the retina reside mainly in NFL/ganglion cell layer (GCL) and inner and outer borders of the INL, all of which were located in "inner retinal layers" in this study. Refractory leakage of blood components could increase the volume of retinal parenchyma and have damages on neuroglial cells, which lead to the loss of structural integrity and increased spaces for the fluid accumulation. In addition, inflammatory cells might be extravasated or resident microglia might be activated mainly in the inner retinal layers rather than in the outer retinal layers and injure the neuroglial cells, with concomitant visual impairments. Another explanation is ischemia. Considering blood supply, we hypothesized that the trend toward a positive association between the inner thickness and the logMAR VA depended partly on ischemia in the inner layers, which could be one of the main differences from the outer layers that are nourished from the choroid. Ischemia often leads to the swelling of neural parenchyma in early time points, which could contribute to the thickening in inner layers. However, all patients did not undergo fluorescein angiography (FA) in this study, and the association between ischemia in FA and inner retinal thickness on OCT images remains to be evaluated.

Table 5. Correlation between Retinal Thickness at Baseline and LogMAR VA at 6 Months or the Final Visit

Area Measured	Correlation with logMAR VA at 6 mo	Correlation with logMAR VA at Final Visit
Total thickness		
Central	$r = 0.29$, $P = 0.032$	$r = 0.29$, $P = 0.033$
Nasal	$r = 0.40$, $P = 0.002$	$r = 0.37$, $P = 0.006$
Temporal	$r = 0.11$, $P = 0.417$	$r = 0.11$, $P = 0.429$
Superior	$r = 0.18$, $P = 0.191$	$r = 0.19$, $P = 0.166$
Inferior	$r = 0.35$, $P = 0.008$	$r = 0.34$, $P = 0.012$
Average	$r = 0.29$, $P = 0.033$	$r = 0.28$, $P = 0.042$
Inner thickness		
Nasal	$r = 0.15$, $P = 0.277$	$r = 0.15$, $P = 0.278$
Temporal	$r = -0.03$, $P = 0.820$	$r = -0.06$, $P = 0.659$
Superior	$r = 0.07$, $P = 0.591$	$r = 0.13$, $P = 0.336$
Inferior	$r = 0.14$, $P = 0.294$	$r = 0.19$, $P = 0.163$
Average	$r = 0.10$, $P = 0.472$	$r = 0.12$, $P = 0.368$
Outer thickness		
Nasal	$r = 0.29$, $P = 0.030$	$r = 0.21$, $P = 0.122$
Temporal	$r = 0.30$, $P = 0.028$	$r = 0.33$, $P = 0.015$
Superior	$r = 0.23$, $P = 0.091$	$r = 0.19$, $P = 0.166$
Inferior	$r = 0.35$, $P = 0.008$	$r = 0.28$, $P = 0.040$
Average	$r = 0.35$, $P = 0.008$	$r = 0.31$, $P = 0.022$

The averaged thickness of the outer layers was negatively correlated with logMAR at the 6-months and last visits, compared with the positive association between the outer thickness and logMAR before surgery (Table 3). It suggests that the thickness of the outer layer indicated that the edematous changes shifted to degenerative or atrophic changes in the photoreceptors, possibly explaining the paradoxical changes after vitrectomy reported by the DRCRnet.[14] In addition, we found that the outer thickness in the temporal subfield especially was correlated negatively with the magnitude of the foveal photoreceptor damage and the logMAR VA at 6 months and the final visit. We often observed persistent cystoid spaces at the fovea after any treatment, which could obscure the negative association between the central thickness and degenerative or atrophic changes in the photoreceptors. This emphasizes the clinical relevance of the outer thickness of the temporal subfield for predicting damage in the foveal photoreceptors, although it was difficult to evaluate the thickness of the foveal photoreceptors per se. A recent study reported that visual function is associated with the thickness of the outer segments at the fovea, which are components of the photoreceptor cells.[30] Further documentation would elucidate the degenerative or atrophic processes in the photoreceptors by which the photoreceptors in the subfields degenerated or which components of the photoreceptor cells are damaged.

In this study, we demonstrated the association between visual dysfunction and retinal thicknesses in DME, although we could not assert that the thickness on OCT images means retinal function. Generally, SD-OCT provides better information regarding microstructure in the retinal physiology and pathology, and a few publications reported the functional information in photoreceptors using the differential reflectivity. However, there is a limitation in the application of OCT to the functional analyses of the retina, although the structural-functional correlation was demonstrated in several retinal diseases. In addition, most eyes in the current study were refractory to other interventions, suggesting that this retrospective study with a smaller number of eyes might be biased, and further study remains to be conducted.

The current study showed the differential course of the inner and outer retinal thicknesses, suggesting that mixed mechanisms exacerbate visual dysfunction after vitrectomy for DME. Segmentational analyses can refine the interpretation of the retinal thickness, especially considering the various pathological mechanisms in light perception and signal transduction. Segmentational analyses might support the debatable issues regarding the usefulness of OCT as a primary end point in the follow-up of patients with DME, because OCT parameters are not affected by media opacity, including cataract, compared with visual function.[46,47]

References

1. Klein R, Klein BE, Moss SE, Cruickshanks KJ. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XV. The long-term incidence of macular edema. *Ophthalmology*. 1995;102:7–16.
2. Gardner TW, Antonetti DA, Barber AJ, LaNoue KF, Levison SW. Diabetic retinopathy: more than meets the eye. *Surv Ophthalmol*. 2002;47:S253–262.
3. Antonetti DA, Barber AJ, Bronson SK, et al. Diabetic retinopathy: seeing beyond glucose-induced microvascular disease. *Diabetes*. 2006;55:2401–2411.
4. Mohamed Q, Gillies MC, Wong TY. Management of diabetic retinopathy: a systematic review. *JAMA*. 2007;298:902–916.
5. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. *Arch Ophthalmol*. 1985;103:1796–1806.
6. Jonas JB, Sofker A. Intraocular injection of crystalline cortisone as adjunctive treatment of diabetic macular edema. *Am J Ophthalmol*. 2001;132:425–427.
7. Haritoglou C, Kook D, Neubauer A, et al. Intravitreal bevacizumab (Avastin) therapy for persistent diffuse diabetic macular edema. *Retina*. 2006;26:999–1005.
8. Nasrallah FP, Jalkh AE, Van Coppenolle F, et al. The role of the vitreous in diabetic macular edema. *Ophthalmology*. 1988;95:1335–1339.
9. Foos RY, Kreiger AE, Forsythe AB, Zakka KA. Posterior vitreous detachment in diabetic subjects. *Ophthalmology*. 1980;87:122–128.
10. Lewis H, Abrams GW, Blumenkranz MS, Campo RV. Vitrectomy for diabetic macular traction and edema associated with posterior hyaloidal traction. *Ophthalmology*. 1992;99:753–759.
11. Gandorfer A, Messmer EM, Ulbig MW, Kampik A. Resolution of diabetic macular edema after surgical removal of the posterior hyaloid and the inner limiting membrane. *Retina*. 2000;20:126–133.
12. Harbour JW, Smiddy WE, Flynn HW Jr, Rubsamen PE. Vitrectomy for diabetic macular edema associated with a thickened and taut posterior hyaloid membrane. *Am J Ophthalmol*. 1996;121:405–413.
13. Ikeda T, Sato K, Katano T, Hayashi Y. Vitrectomy for cystoid macular oedema with attached posterior hyaloid membrane in patients with diabetes. *Br J Ophthalmol*. 1999;83:12–14.
14. Haller JA, Qin H, Apte RS, et al. Vitrectomy outcomes in eyes with diabetic macular edema and vitreomacular traction. *Ophthalmology*. 2010;117:1087–1093.e3.
15. Flaxel CJ, Edwards AR, Aiello LP, et al. Factors associated with visual acuity outcomes after vitrectomy for diabetic macular edema: diabetic retinopathy clinical research network. *Retina*. 2010;30:1488–1495.
16. Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. *N Engl J Med*. 1994;331:1480–1487.
17. Adamis AP, Miller JW, Bernal MT, et al. Increased vascular endothelial growth factor levels in the vitreous of eyes with proliferative diabetic retinopathy. *Am J Ophthalmol*. 1994;118:445–450.
18. Watanabe D, Suzuma K, Matsui S, et al. Erythropoietin as a retinal angiogenic factor in proliferative diabetic retinopathy. *N Engl J Med*. 2005;353:782–792.
19. Funatsu H, Yamashita H, Noma H, Mimura T, Yamashita T, Hori S. Increased levels of vascular endothelial growth factor and interleukin-6 in the aqueous humor of diabetics with macular edema. *Am J Ophthalmol*. 2002;133:70–77.
20. Stefansson E, Landers MB III, Wolbarsht ML. Increased retinal oxygen supply following pan-retinal photocoagulation and vitrectomy and lensectomy. *Trans Am Ophthalmol Soc*. 1981;79:307–334.
21. Wolf-Schnurrbusch UE, Enzmann V, Brinkmann CK, Wolf S. Morphologic changes in patients with geographic atrophy assessed with a novel spectral OCT-SLO combination. *Invest Ophthalmol Vis Sci*. 2008;49:3095–3099.
22. Sandberg MA, Brockhurst RJ, Gaudio AR, Berson EL. The association between visual acuity and central retinal thickness in retinitis pigmentosa. *Invest Ophthalmol Vis Sci*. 2005;46:3349–3354.
23. Murakami T, Tsujikawa A, Ohta M, et al. Photoreceptor status after resolved macular edema in branch retinal vein occlusion treated with tissue plasminogen activator. *Am J Ophthalmol*. 2007;143:171–173.

24. Sakamoto A, Nishijima K, Kita M, Oh H, Tsujikawa A, Yoshimura N. Association between foveal photoreceptor status and visual acuity after resolution of diabetic macular edema by pars plana vitrectomy. *Graefes Arch Clin Exp Ophthalmol*. 2009;247:1325–1330.
25. Murakami T, Nishijima K, Sakamoto A, Ota M, Horii T, Yoshimura N. Association of pathomorphology, photoreceptor status, and retinal thickness with visual acuity in diabetic retinopathy. *Am J Ophthalmol*. 2011;151:310–317.
26. Wollstein G, Paunescu LA, Ko TH, et al. Ultrahigh-resolution optical coherence tomography in glaucoma. *Ophthalmology*. 2005;112:229–237.
27. Ishikawa, H, Stein DM, Wollstein G, Beaton S, Fujimoto JG, Schuman JS. Macular segmentation with optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2005;46:2012–2017.
28. Tan O, Chopra V, Lu AT, et al. Detection of macular ganglion cell loss in glaucoma by Fourier-domain optical coherence tomography. *Ophthalmology*. 2009;116:2305–2314.e1-2.
29. van Dijk HW, Kok PH, Garvin M, et al. Selective loss of inner retinal layer thickness in type 1 diabetic patients with minimal diabetic retinopathy. *Invest Ophthalmol Vis Sci*. 2009;50:3404–3409.
30. Forooghian F, Stetson PF, Meyer SA, et al. Relationship between photoreceptor outer segment length and visual acuity in diabetic macular edema. *Retina*. 2010;30:63–70.
31. Otani T, Kishi S. Correlation between optical coherence tomography and fluorescein angiography findings in diabetic macular edema. *Ophthalmology*. 2007;114:104–107.
32. Bolz M, Ritter M, Schneider M, Simader C, Scholda C, Schmidt-Erfurth U. A systematic correlation of angiography and high-resolution optical coherence tomography in diabetic macular edema. *Ophthalmology*. 2009;116:66–72.
33. Tso MO. Pathology of cystoid macular edema. *Ophthalmology*. 1982;89:902–915.
34. Fine BS, Brucker AJ. Macular edema and cystoid macular edema. *Am J Ophthalmol*. 1981;92:466–481.
35. Lujan BJ, Roorda A, Knighton RW, Carroll J. Revealing Henle's fiber layer using spectral domain optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2011;52:1486–1492.
36. Otani T, Yamaguchi Y, Kishi S. Improved visualization of Henle fiber layer by changing the measurement beam angle on optical coherence tomography. *Retina*. 2011;31:497–501.
37. Eckardt C. Transconjunctival sutureless 23-gauge vitrectomy. *Retina*. 2005;25:208–211.
38. Dillinger P, Mester U. Vitrectomy with removal of the internal limiting membrane in chronic diabetic macular oedema. *Graefes Arch Clin Exp Ophthalmol*. 2004;242:630–637.
39. Kuhn F, Kiss G, Mester V, Szijarto Z, Kovacs B. Vitrectomy with internal limiting membrane removal for clinically significant macular oedema. *Graefes Arch Clin Exp Ophthalmol*. 2004;242:402–408.
40. Murakami T, Nishijima K, Sakamoto A, Ota M, Horii T, Yoshimura N. Foveal cystoid spaces are associated with enlarged foveal avascular zone and microaneurysms in diabetic macular edema. *Ophthalmology*. 2011;118:359–367.
41. Wojtkowski M, Srinivasan V, Fujimoto JG, et al. Three-dimensional retinal imaging with high-speed ultrahigh-resolution optical coherence tomography. *Ophthalmology*. 2005;112:1734–1746.
42. Otani T, Kishi S. Tomographic assessment of vitreous surgery for diabetic macular edema. *Am J Ophthalmol*. 2000;129:487–494.
43. Shah SP, Patel M, Thomas D, Aldington S, Laidlaw DA. Factors predicting outcome of vitrectomy for diabetic macular oedema: results of a prospective study. *Br J Ophthalmol*. 2006;90:33–36.
44. Kumagai K, Furukawa M, Ogino N, Larson E, Iwaki M, Tachi N. Long-term follow-up of vitrectomy for diffuse nontractional diabetic macular edema. *Retina*. 2009;29:464–472.
45. Browning DJ, Glassman AR, Aiello LP, et al. Relationship between optical coherence tomography-measured central retinal thickness and visual acuity in diabetic macular edema. *Ophthalmology*. 2007;114:525–536.
46. Al-latayfeh MM, Sun JK, Aiello LP. Ocular coherence tomography and diabetic eye disease. *Semin Ophthalmol*. 2010;25:192–197.
47. Csaky KG, Richman EA, Ferris FL III. Report from the NEI/FDA Ophthalmic Clinical Trial Design and Endpoints Symposium. *Invest Ophthalmol Vis Sci*. 2008;49:479–489.