■ REVIEW ■

Optical Coherence Tomography in the Diagnosis and Management of Diabetic Macular Edema: Time-Domain Versus Spectral-Domain

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ABSTRACT

Optical coherence tomography (OCT) is an important imaging modality in the setting of diabetic macular edema (DME). Its use allows more precise evaluation of retinal pathology in DME, including retinal thickness and edema, vitreomacular interface abnormalities, subretinal fluid, and foveal microstructural changes. Additional advantages include its ability to quantitatively monitor response to treatment of DME by laser, intravitreal pharmacotherapies, and vitreoretinal surgery. OCT measurements are now used in all major clinical studies of DME treatment as critical endpoints. This article presents a review of both time-domain and spectral-domain OCT in the diagnosis and management of DME. The authors discuss the various parameters evaluated by the OCT systems and provide an evidence-based evaluation of their accuracy, significance, reliability, and limitations. As the capability of OCT continues to advance, it appears that its use will play an increasingly important role in the understanding, evaluation, and treatment of DME. **[Ophthalmic Surg Lasers Imaging 2011;42:S41-S55.]**

INTRODUCTION

Imaging modalities of the ocular fundus have vastly improved over the past 40 years with successive use of angiography (fluorescein and indocyanine green), scanning laser ophthalmoscopy, and, more recently, optical coherence tomography (OCT). OCT was introduced in 1991 as a non-invasive in vivo ophthalmic imaging technique with the initial purpose of allowing retinal thickness measurement.[1,2] Similar to other "time of flight" distance measuring devices (pulse-echo ultrasonography), OCT provides cross-sectional images derived from rapidly acquired A-scans using low-coherence infrared light and interferometry. Light backscatter provides distance and intensity information. Early images were novel with modest resolution. Over time, improvements in hardware and software improved cross-sectional image quality. Comparison to histological and pathological cross-sections is compelling and care must be taken to avoid over-interpretation of these reflectance images. Although many normal and abnormal structures appear visible, understanding of the images continues to evolve with clinicopathological comparison and experience.

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Time-Domain OCT (TD-OCT)

Time-domain OCT 3000 (Stratus OCT; Carl Zeiss Meditec, Dublin, CA) became commercially available in 2002, and rapidly became a standard for posterior segment retinal tomography. TD-OCT functions by splitting a superluminescent diode light source (843 nm) into two perpendicular beams. One is directed to a known reference arm while the other enters the patient's eye. Backscatter from the layers of the retina and superficial choroid are co-mingled with those from the reference arm. The interference pattern is then detected and displayed as a B-scan image. In TD-OCT, a movable mirror is required for data collection and this movement represents a limiting obstacle to faster acquisition times. With longer acquisition time, patient movement can become a problem, resulting in poorer images. Axial resolution with TD-OCT systems is approximately 10 µm, whereas lateral resolution is in the range of 20 µm when imaging is performed on the retina. Scan velocity is approximately 400 axial scans per second.[3,4]

Spectral-Domain OCT (SD-OCT)

The next generation of OCT devices involved a switch to frequency analysis. These devices, called SD-OCT, provide more rapid data acquisition speeds along with significantly higher axial image resolutions of 5 to 6 µm, whereas lateral resolution remains unchanged. SD-OCT imaging is more than 50 times faster than TD-OCT, acquiring A-scan signals at a rate of up to 40,000 per second.[5] The source beam is split in a similar fashion to TD-OCT, but no moving mirror is required in data capture. A spectrometer is employed to analyze light frequency changes that occur from reference arm and subject beam interactions.[6,7]

The field of OCT continues to evolve. Improvements in hardware and software have greatly enhanced a host of parameters, including image quality, resolution (including axial and lateral), three-dimensional display, and image depth. These changes make comparisons difficult. Attention to the type of display and recognition of image capability with each device permits a broader understanding of the disease process and an appreciation of instrument improvements.

OCT clinical research in diabetes incorporated time-domain technology as soon as instruments became available. In fact, most ongoing studies are still mandated to collect TD-OCT data. More recently, focus has changed to SD-OCT analysis. However, no large, prospective, multicenter clinical trials have been published using SD-OCT at this time. For the purpose of this report, both formats will be reviewed, with the majority of clinical evidence demonstrated using TD-OCT technology.

The following is a review of both TD-OCT and SD-OCT in the diagnosis and management of diabetic macular edema (DME). We have discussed the various parameters evaluated by the OCT systems and provided an evidence-based evaluation of their accuracy, significance, reliability, and limitations.

OCT IN DME

The important role of OCT in DME management involves the evaluation of retinal pathology, including retinal thickness, cystoid macular edema and intraretinal exudates, vitreomacular interface abnormalities, subretinal fluid, and photoreceptor inner segment–outer segment (IS/OS) junction abnormalities.

OCT is also important in monitoring the response to treatment of DME by laser treatment, intravitreal pharmacotherapies, and vitreoretinal surgery.

Macular edema is an important cause of visual impairment in individuals with diabetes and a frequent manifestation of diabetic retinopathy.[8,9] Intraretinal fluid develops secondary to microaneurysm formation, increased vascular permeability, and breakdown of the blood–retinal barrier. The incidence of macular edema over a 10-year period has been estimated at 20.1% of patients with type 1 diabetes, 25.4% of patients with type 2 diabetes who require insulin, and 13.9% of patients with type 2 diabetes who do not require insulin, making it the principal mechanism of vision loss in patients with non-proliferative diabetic retinopathy.[10] The ability to detect and quantify the central retinal thickness in patients with clinically diagnosed DME is important in the treatment of patients with diabetes. Prior to OCT technology, precision in central retinal thickness monitoring was not possible.

OCT Measurement Variables

A discussion of OCT and DME would not be possible without the standardization of terms used by the Diabetic Retinopathy Clinical Research (DRCR) Network for Stratus TD-OCT technology.[11]

- Retinal thickness: value in microns of the distance between the OCT layers assumed to be the retinal

pigment epithelium and the internal limiting membrane.
- Retinal thickening: calculated value equal to the thickness minus the population mean for the variable under consideration (either center point thickness or central subfield mean thickness [CSMT]).
- Center point: the intersection of the radial scans of the fast macular thickness protocol of the OCT.
- Center point thickness: average of the thickness values for the radial scans at their point of intersection.
- Central subfield: circular area of diameter 1 mm centered around the center point.
- CSMT: mean value of the thickness values obtained in the central subfield.

Clinically, it is important to recognize that TD-OCT and SD-OCT provide significantly different values for retinal thickness, with SD-OCT giving larger values ranging from 30 to 55 µm compared to TD-OCT.[12] This is based on reference points, where Cirrus SD-OCT measures the thickness of the retina from the retinal pigment epithelium to the internal limiting membrane and Stratus TD-OCT measures the thickness of the retina from the IS/OS junction of the photoreceptors to the internal limiting membrane.

Patterns of DME on OCT

DME had been characterized as focal or diffuse based on clinical examination and fluorescein angiography.[13] OCT was first used to measure the thickness of the retina in DME in 1998[14] and was quickly found to be more sensitive and specific in the detection of DME and macular edema compared to other available diagnostic modalities.

OCT-demonstrated structural macular derangements in patients with DME provide a more in-depth understanding and generally include retinal swelling or thickening, cystoid macular edema, and serous retinal detachment or subretinal fluid.[15] A fourth category of vitreomacular interface abnormalities includes the presence of epiretinal membranes, vitreomacular traction, or both.

Reproducibility of Retinal Thickness and Volume Measurements

The DRCR Network has demonstrated a highly significant correlation between center point thickness and CSMT in eyes that have DME.[16] Typically, CSMT is used to follow changes in center-involved DME because measurements of center point thickness appear to have a greater variability than measurements of CSMT.[17] Patients with DME undergo small diurnal variation in CSMT with a mean decrease of 6% between morning and late afternoon, but this diurnal variation has not been shown to be statistically significant.[18] The clinical threshold for a change in OCT thickness is generally greater than 11% because variability of OCT measurements of retinal thickness has been shown to be less than 11% in individuals with diabetes both with and without DME.[19,20]

Visual Acuity and OCT-Measured Central Retinal Thickness in DME

With the development of contemporary OCT systems, it is now possible to measure objective macular thickness and quantitatively evaluate the relationship of DME and visual acuity. To investigate the relationship between visual acuity and OCT-measured central retinal thickness, 251 eyes of 210 patients with DME were enrolled in a cross-sectional and longitudinal randomized clinical trial.[21] The DRCR Network documented a modest correlation between best-corrected visual acuity and OCT center point thickness before focal laser photocoagulation, as well as a modest correlation between change in visual acuity and change in OCT center point thickening through the first year after laser treatment. The correlation between change in visual acuity and change in OCT center point thickening 3½ months after laser treatment was 0.44, with no significant difference at other follow-up times. There was considerable variation in visual acuities for any given retinal thickness. Of note, many eyes with a thickened macula had excellent visual acuity, and many eyes with a macula of normal thickness had decreased visual acuity. The results suggest that OCT measurements, although an important clinical tool, are not an ideal surrogate for visual acuity as a primary outcome in studies of DME.

Visual Acuity and OCT-Measured Foveal Microstructural Abnormalities in DME

SD-OCT provides a significant improvement over TD-OCT with its enhanced ability to evaluate foveal microstructural abnormalities, including disruption of the photoreceptor IS/OS junction. A disruption of the hyperreflective photoreceptor IS/OS junction on OCT,

located just above the retinal pigment epithelium, may reveal damage to macular photoreceptors. There have been several retrospective studies evaluating this phenomenon in the literature. An early attempt to evaluate foveal photoreceptor status and its relationship to visual acuity was performed in patients after resolution of DME by pars plana vitrectomy.[22] In this study, TD-OCT was used to determine whether the IS/OS junction was entirely complete or not complete at final observation. Final visual acuity in patients without a complete IS/OS junction was demonstrated to be significantly worse than in those patients with a complete IS/OS junction. The authors speculated that the use of SD-OCT and its ability to average multiple scans to reduce noise might provide more insight into this phenomenon.

A more recent study retrospectively evaluated 62 eyes from 38 patients with DME using SD-OCT and found a significant correlation between percentage disruption of the IS/OS junction and visual acuity.[23] In the study, the photoreceptor IS/OS layer was evaluated 500 µm in either direction of the fovea and a percentage of junction disruption on horizontal and vertical images was averaged to generate a percentage score. A larger retrospective study was performed on 154 eyes from 116 patients with DME in Japan.[24] SD-OCT was used to evaluate external limiting membrane and the IS/OS junction in the fovea, which was graded as mildly, moderately, or severely disrupted as defined by the proportional loss of the back-reflection line. SD-OCT was determined to be an important tool in the evaluation of foveal microstructural changes, including the external limiting membrane and IS/OS junction, which were strongly correlated with visual acuity when compared to CSMT in DME.

EVALUATION OF OCT MEASUREMENTS IN DME MANAGEMENT

Prior to this decade, the most widely accepted methods to reduce the risk of vision loss from DME included intensive glycemic control,[25,26] blood pressure control,[27,28] and focal/grid photocoagulation, as demonstrated by the Early Treatment Diabetic Retinopathy Study (ETDRS).[13] The ETDRS defined clinically significant macular edema as edema on clinical examination within 500 µm of the foveal center, or edema associated with lipid within 500 µm of the foveal center, or 1 disc area of edema within 1 disc area of the foveal center as determined by stereo fundus photography. They further reported that focal/grid photocoagulation of eyes with clinically significant macular edema reduced the 3-year risk of losing 3 or more lines of visual acuity by 50%, from 30% in the control group to 15% in the laser group (Figs. 1 and 2). Pharmacotherapies are believed to be an exciting new frontier in the treatment of DME, and OCT measurements were used in all major clinical studies as critical endpoints.

Corticosteroids in the Management of DME

The treatment of DME with peribulbar triamcinolone acetonide was not shown to significantly improve OCT-measured CSMT or visual acuity.[29] The DRCR Network Protocol B further evaluated the use of corticosteroids in the treatment of DME in a multicenter, randomized clinical trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation in 840 eyes of 693 subjects (summarized in Table 1).[30] There was determined to be no long-term benefit of intravitreal triamcinolone relative to focal/grid photocoagulation in patients with DME similar to those fitting inclusion criteria in the study. Furthermore, OCT-measured CSMT was significantly improved in the focal/grid laser group at 2 years (primary outcome data point) compared to either triamcinolone group. Subjects were observed for an additional year to evaluate a more long-term response to treatment with focal/grid laser versus intravitreal triamcinolone. Although visual acuity and CSMT improved more often than worsened in all treatment groups during the third year, treatment group differences continued in the same direction, somewhat favoring the laser group. The likelihood of needing cataract surgery and having increased intraocular pressure were also significantly greater in the triamcinolone groups compared to the laser group.[31]

Anti-vascular Endothelial Growth Factor (anti-VEGF) Molecules in the Management of DME

The newest frontier in the treatment of DME involves the use of anti-VEGF agents. The rationale for using anti-VEGF agents to treat DME is based on the observation that VEGF levels, found to increase vessel permeability, are increased in the retina and vitreous of eyes with diabetic retinopathy.[32,33] Inhibition of VEGF therefore addresses the underlying pathogenesis in DME.

Pegaptanib. The initial major study using anti-VEGF agents in patients with DME involved the use

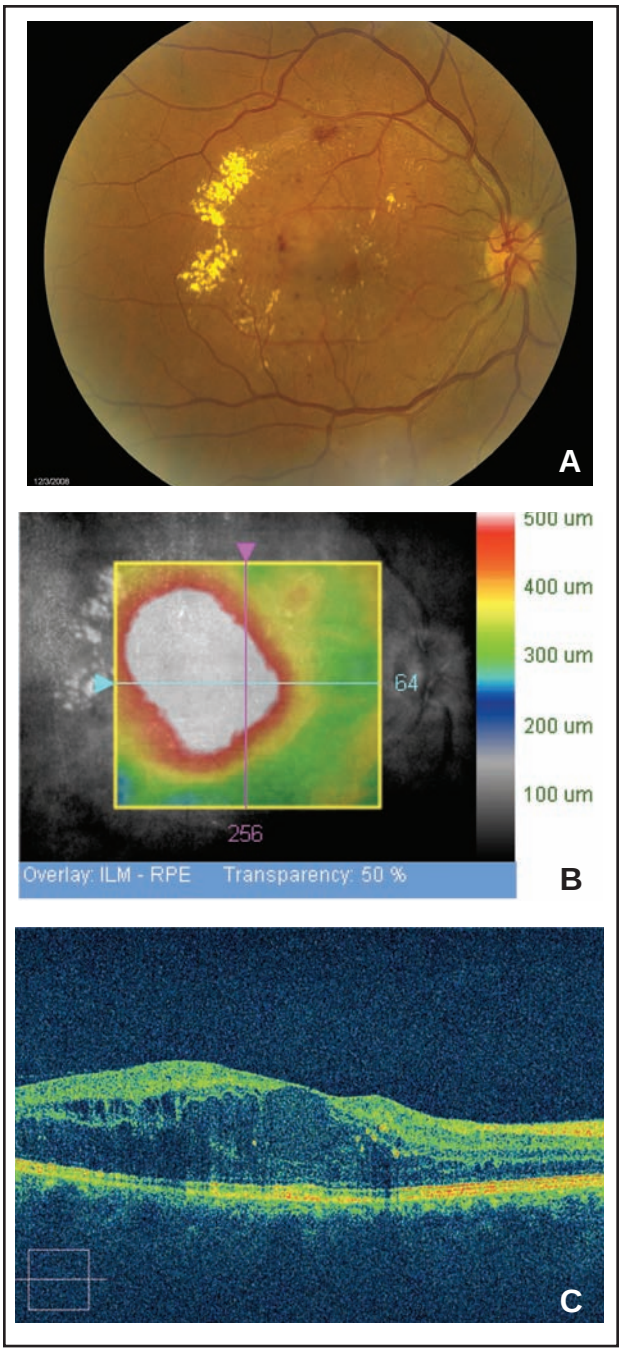

Figure 1. (A) Color fundus image of an eye with clinically significant macular edema demonstrating extensive exudative changes in a circinate ring and scattered microaneurysm throughout the macula. (B) Color macular thickness map obtained by spectral-domain optical coherence tomography (Cirrus HD-OCT; Carl Zeiss Meditec Inc., Dublin, CA) reveals diffuse macular thickening. (C) Representative horizontal optical coherence tomography scan with extensive macular edema and exudative changes. Note this is an eye of a patient with uncontrolled type II diabetes who presents with clinically significant macular edema and Snellen best-corrected visual acuity of 20/30 prior to any treatment.

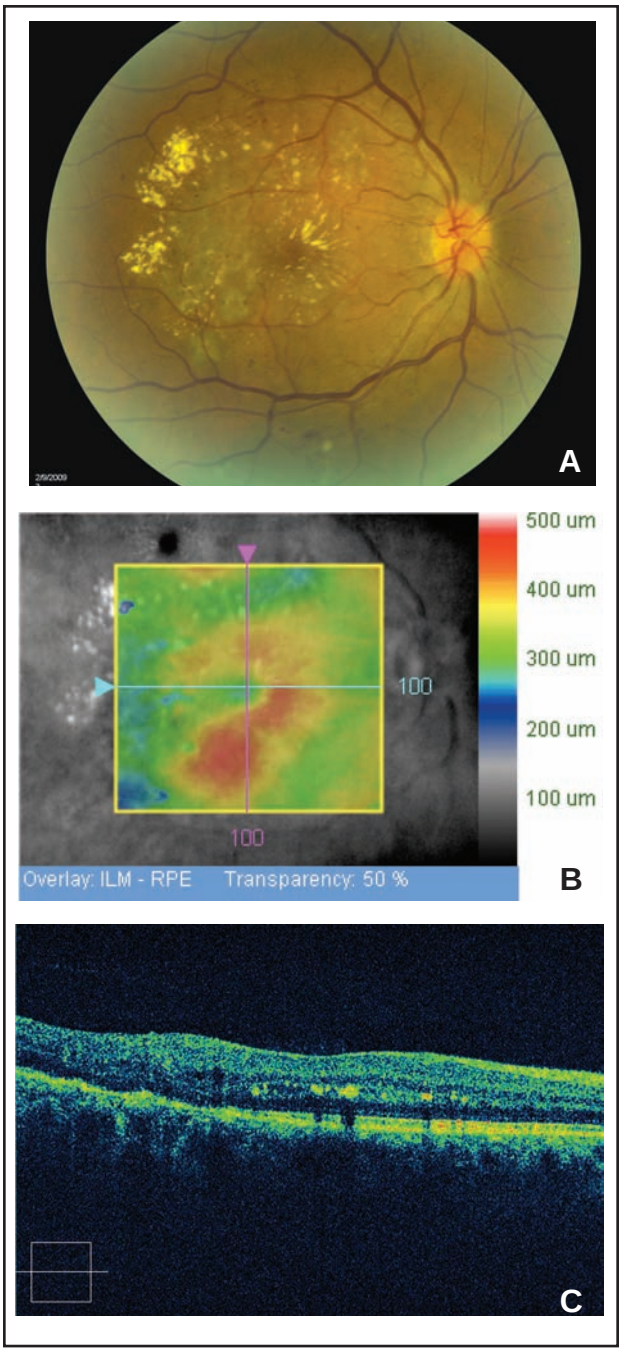

Figure 2. (A) Color fundus image of the same eye as Figure 1 after focal/grid laser treatment. (B) Color macular thickness map reveals significant improvement of macular edema and thickening. (C) Representative horizontal optical coherence tomography scan demonstrates significant improvement in macular edema. Extensive exudative changes are still noted consistent with the color fundus image. Snellen best-corrected visual acuity in this eye was 20/20.

TABLE 1
Diabetic Retinopathy Clinical Research Network Protocol B

840 eyes of 693 subjects enrolled
Entry criteria
VA 20/32 to 20/320
DME involving the foveal center
TD-OCT measured CSMT ⩾ 250 µm
Randomization
Focal/grid photocoagulation
1 mg intravitreal triamcinolone
4 mg intravitreal triamcinolone
Baseline statistics
Mean VA letter score: 59 (approximately 20/63)
Mean OCT-measured CSMT: 424 µm (Zeiss Stratus TD-OCT)
TD-OCT results
Greater benefit at 4 months in the 4-mg triamcinolone group compared with the other two groups
Greater benefit at year 2 in the laser group compared with the other two groups
No difference between the two triamcinolone groups during the second year
OCT CSMT decreased from baseline to 2 years by a mean of
139 µm in the laser group
86 µm in the 1-mg triamcinolone group ($P < .001$ compared to laser)
77 µm in the 4-mg triamcinolone group ($P < .001$ compared to laser)
Similar results comparing OCT-measured retinal volumes
VA results (generally paralleled OCT results)
Greater benefit at 4 months in the 4-mg triamcinolone group compared with the other two groups
By 1 year, there were no significant differences in visual acuity among groups
Beginning with the 16-month visit through 2 years, the laser group showed a greater beneficial effect on VA compared with both triamcinolone groups (which were similar to each other)
3-year results were consistent with 2-year results
Conclusions
No long-term benefit of intravitreal triamcinolone relative to focal/grid photocoagulation in patients with DME similar to those fitting inclusion criteria
OCT CSMT was improved by significantly more at 2 years with focal/grid laser treatment than with either triamcinolone group

VA = visual acuity; DME = diabetic macular edema; TD-OCT = time-domain optical coherence tomography; CSMT = central subfield mean thickness. Data from Diabetic Retinopathy Clinical Research Network. A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. Ophthalmology. *2008;115:1447-1449.*

of intravitreal pegaptanib, a pegylated anti-VEGF aptamer that targets the $VEGF_{165}$ isomer, for center-involving DME.[34] One-hundred seventy-two patients were enrolled in a study performed by the Macugen Diabetic Retinopathy Study Group (summarized in Table 2). Results demonstrated an overall improvement in OCT-measured retinal thickness and visual acuity in eyes with DME treated with intravitreous pegaptanib.

Ranibizumab. More recently, the anti-VEGF drug ranibizumab, a monoclonal antibody fragment with binding affinity for VEGF-A, has been evaluated in the treatment of DME. Initial small studies with short-term follow-up demonstrated promising results.[35] A multicenter, randomized, clinical trial enrolled 126 patients to evaluate the use of ranibizumab and/or focal/grid laser photocoagulation in the treatment of DME (summarized in Table 3).[36] Results demonstrated that intravitreal injections of ranibizumab provide significant benefit for patients with DME, both in terms of decreased OCT-measured retinal thickness and improved visual acuity, for at least 2 years. Optimal effects of treatment on retinal thickness and visual acuity were demonstrated with the combination of intravitreal ranibizumab and focal/grid laser treatments.

The DRCR Network performed a larger multicenter, randomized clinical trial (Protocol I) involving 854 eyes of 691 patients to evaluate the use of ranibizumab with or without prompt or deferred focal/grid laser in the treatment of DME (summarized in Table 3).[37] Results demonstrated that intravitreal ranibizumab with prompt or deferred focal/grid laser is more effective compared with prompt focal/grid laser alone for

TABLE 2

Phase II Randomized Double-Masked Trial of Pegaptanib, an Anti-vascular Endothelial Growth Factor Aptamer, for DME

172 patients enrolled
Entry criteria
Best-corrected VA between 20/50 and 20/320
DME involving the foveal center
Randomization
Intravitreous pegaptanib 0.3 mg
Intravitreous pegaptanib 1 mg
Intravitreous pegaptanib 3 mg
Sham injections
Injections at study entry, week 6, and week 12 with additional injections and/or focal photocoagulation as needed for another 18 weeks
TD-OCT results
Decrease in CSMT by 68 µm with 0.3 mg
Increase of 4 µm with sham
Larger proportions of those receiving 0.3 mg had an absolute decrease of both ⩾ 100 µm (42% vs 16%) and ⩾ 75 µm (49% vs 19%)
VA results
Better at week 36 with 0.3 mg (20/50), as compared with sham (20/63)
Larger proportion of those receiving 0.3 mg gained VAs of ⩾ 10 letters (34% vs 10%) and ⩾15 letters (18% vs 7%)
Conclusions
Subjects treated with intravitreal pegaptanib were more likely to show reduction in OCT-measured CSMT and have better VA outcomes

VA = visual acuity; DME = diabetic macular edema; TD-OCT = time-domain optical coherence tomography; CSMT = central subfield mean thickness. Data from Cunningham ET Jr, Adamis AP, Altaweel M, et al. A phase II randomized double-masked trial of pegaptanib, an anti-vascular endothelial growth factor aptamer, for diabetic macular edema. Ophthalmology. *2005;112:1747-1757.*

the treatment of DME involving the central macula for both OCT-measured retinal thickness and visual acuity improvement.

Bevacizumab. Bevacizumab is another anti-VEGF humanized monoclonal antibody fragment with binding affinity for VEGF-A. Many studies have found significant improvement in OCT-measured retinal thickness and visual acuity using intravitreal bevacizumab in the treatment of DME (Figs. 3 and 4).[38-40] A recent prospective, single-center, randomized 2-year trial enrolled 80 patients to evaluate the use of bevacizumab in the treatment of DME (summarized in Table 4). The Intravitreal Bevacizumab or Laser Therapy in the Management of Diabetic Macular Edema Study (summarized in Table 4), demonstrated that bevacizumab has a greater treatment effect on visual acuity than modified ETDRS macular laser treatments in patients with center-involving persistent clinically significant macular edema despite previous laser therapy (with OCT data trending toward significance, $P = .06$).[41]

Vitrectomy in the Management of DME

The management of DME has further been revolutionized by the ability of OCT to assess vitreomacular interface abnormalities.[42,43] Ghazi et al. evaluated the OCT characteristics of eyes with persistent clinically significant DME after focal laser treatment, with emphasis on the vitreomacular interface abnormalities characteristics in 50 eyes. Overall, 52.1% of eyes demonstrated definite vitreomacular interface abnormalities, including anomalous vitreal adhesions, epiretinal membrane, or both, and 12.5% of additional eyes had questionable vitreomacular interface abnormalities. OCT was 1.94 times more sensitive than traditional techniques including biomicroscopy, fundus photography, and fluorescein angiography combined in detecting vitreomacular interface abnormalities, demonstrating the superiority of OCT in detecting vitreomacular interface abnormalities.[44]

Vitrectomy is an important management tool for the treatment of DME in the presence of vitreomacular interface abnormalities. Determination to proceed with vitrectomy is typically made based on OCT determination of vitreomacular interface abnormalities with significant DME and poor visual acuity (Figs. 5 and 6).

The DRCR Network (Protocol D) recently performed a prospective, observational clinical trial enrolling 87 eyes to evaluate the role of vitrectomy in the treatment of DME (summarized in Table 5).[45] Vitrec-

TABLE 3A

Ranibizumab for Edema of the mAcula in Diabetes (READ-2) Study

Enrolled 126 patients
Entry criteria
Best-corrected VA between 20/40 and 20/320
VA deficit resulting from DME
TD-OCT measured CSMT ⩾ 250 µm
Randomization
Receive 0.5 mg ranibizumab at baseline and months 1, 3, and 5 (group 1)
Focal or grid laser photocoagulation at baseline and month 3 if needed (group 2)
Combination of 0.5 mg ranibizumab and focal/grid laser at baseline and month 3 (group 3)
Starting at month 6, if retreatment criteria were met, all subjects could be treated with ranibizumab
TD-OCT results at 2 years
Group 1 CSMT of 340 µm (36% ⩽ 250 µm)
Group 2 CSMT of 286 µm (47% ⩽ 250 µm)
Group 3 CSMT of 258 µm (68% ⩽ 250 µm)
VA results at 6 months
Group 1 improved 7.4 letters (21% gained ⩾ 3 lines)
Group 2 improved 0.5 letters (0% gained ⩾ 3 lines)
Group 3 improved 3.8 letters (6% gained ⩾ 3 lines)
VA results at 2 years
Group 1 improved 7.7 letters (24% gained ⩾ 3 lines)
Group 2 improved 5.1 letters (18% gained ⩾ 3 lines)
Group 3 improved 6.8 letters (26% gained ⩾ 3 lines)
Snellen equivalent of ⩾ 20/40 at 2 years
45% in group 1, 44% in group 2, and 35% in group 3
Conclusions
Intravitreal injections of ranibizumab provide significant benefit for patients with DME for at least 2 years
When combined with focal/grid laser treatments, the amount of residual edema was reduced, as were the frequency of injections needed to control edema

VA = visual acuity; DME = diabetic macular edema; TD-OCT = time-domain optical coherence tomography; CSMT = central subfield mean thickness.
Data from Nguyen QD, Shah SM, Khwaja AA, et al. Two-year outcomes of the Ranibizumab for Edema of the mAcula in diabetes (READ-2) study. Ophthalmology. *2010;117:2146-2151.*

tomy was determined to be a successful treatment in the setting of DME, vitreomacular interface abnormalities, and at least moderate vision loss in reducing OCT-measured retinal thickening in most eyes. Visual acuity results were also improved after vitrectomy in the treatment of DME.

OCT in the Diagnosis, Evaluation and Management of DME

In a systematic review of the literature comparing OCT with traditional tests including stereoscopic fundus photography or biomicroscopy, it has been concluded that OCT performs well in the diagnosis of DME.[46] The DRCR Network has unanimously adopted OCT assessment in studies involving diagnosis, treatment, and follow-up of patients with DME, with examination of OCT values in all outcome data.[47] Multiple DRCR Network Protocols further use OCT data to help determine re-treatment criteria, demonstrating the importance given to OCT assessment in the management of DME.[37] It has been argued that OCT is the single most important diagnostic and prognostic tool in the management of DME.[47]

Although most of the studies reported here used TD-OCT, SD-OCT should serve to improve the use of OCT in patients with DME. It is easier to operate, faster to perform, has a significantly higher resolution with more reliable thickness measurements, and has a reproducible spatial registration with fundus imaging.[48] SD-OCT technology has generated impressive amounts of new anatomic, physiologic, and pathologic data allowing a virtual in vivo histologic section of the retina that allows further evaluation of foveal microstructural abnormalities in DME. Although both the TD-OCT and SD-OCT demonstrate excellent reproducibility, the SD-OCT has shown a significantly better intrasession reproducibility when measuring macular thickness in healthy eyes, although not in eyes with DME.[12,49] In a recent study, the coefficient of variations of macular thickness was measured with

TABLE 3B
Diabetic Retinopathy Clinical Research (DRCR) Network Protocol I

Enrolled 854 eyes of 691 patients
Entry criteria
VA of 20/32 to 20/320
Presence of CSME
TD-OCT measured CSMT ⩾ 250 um in central macula
Baseline characteristics
Mean CSMT approximately 400 µm
Mean VA of approximately 65 to 66 ETDRS letters
Randomization
Sham injection with prompt laser
0.5 mg intravitreal ranibizumab with prompt laser
0.5 mg intravitreal ranibizumab with deferred laser
4 mg intravitreal triamcinolone with prompt laser
Web-based system was used for supplemental retreatment guidelines
Baseline characteristics
Mean OCT CSMT of 405 µm (Zeiss Stratus TD-OCT system)
Mean baseline VA of 63 ETDRS letters (~20/63)
TD-OCT results at 1 year
Triamcinolone with prompt laser had OCT-measured CSMT reduced by 127 µm
Ranibizumab groups had reduced CSMT by 131 and 137 µm
Sham with prompt laser group had reduced CSMT by 102 µm (significantly less reduction)
OCT results were similar whether baseline CSMT was < 400 or ⩾ 400 µm
VA results at 1 year
Both ranibizumab groups gained approximately +9 ETDRS letters
Triamcinolone with prompt laser group gained approximately +4 ETDRS letters
Sham with prompt laser group gained approximately +3 ETDRS letters
Ranibizumab groups were statistically significantly greater than other groups
In the subset of pseudophakic eyes at baseline, visual acuity and OCT improvement in the triamcinolone with prompt laser group appeared comparable to that in the ranibizumab groups
Two-year visual acuity and OCT outcomes were similar to 1-year outcomes
Ranibizumab with prompt/deferred laser gained +7/+10 ETDRS letters
CSMT reduced by -144 and -170 µm, respectively
Triamcinolone with prompt laser gained 0 ETDRS letters
CSMT reduced by -78 µm
Sham with prompt laser gained +2 ETDRS letters
CSMT reduced by -133 µm
Conclusions
Intravitreal ranibizumab with prompt or deferred laser is more effective compared with prompt laser alone for the treatment of DME involving the central macula for both OCT and VA improvements
In pseudophakic eyes, intravitreal triamcinolone with prompt laser appears more effective than laser alone but frequently increases the risk of intraocular pressure elevation

VA = visual acuity; DME = diabetic macular edema; TD-OCT = time-domain optical coherence tomography; CSMT = central subfield mean thickness.
Data from Elman MJ, Aiello LP, Beck RW, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology. *2010;117:1064-1077.*

TD-OCT and SD-OCT. The results with TD-OCT had a mean of 1.33%, whereas those with SD-OCT had a significantly smaller mean of 0.66%.[49]

Limitations to OCT Analysis

To obtain clinically useful data from any OCT report, whether spectral domain or time domain, image quality must be sufficient. Signal strength is defined as the averaged intensity value of the signal pixels in the OCT image, measured on a scale of 0 to 10. Reliable OCT scans typically require higher signal strengths, although a good general understanding can often be garnered from poorer quality images.[50,51] An additional limitation to OCT data involves image artifacts that can poorly affect final image data despite high-quality images. The effect of image artifacts on macular volume scans of healthy and diseased eyes was recently evaluated.[52]

An evaluation was performed on 98 eyes of 58 patients imaged with Cirrus SD-OCT and 88 eyes of 54 patients imaged with Spectralis SD-OCT. Ar-

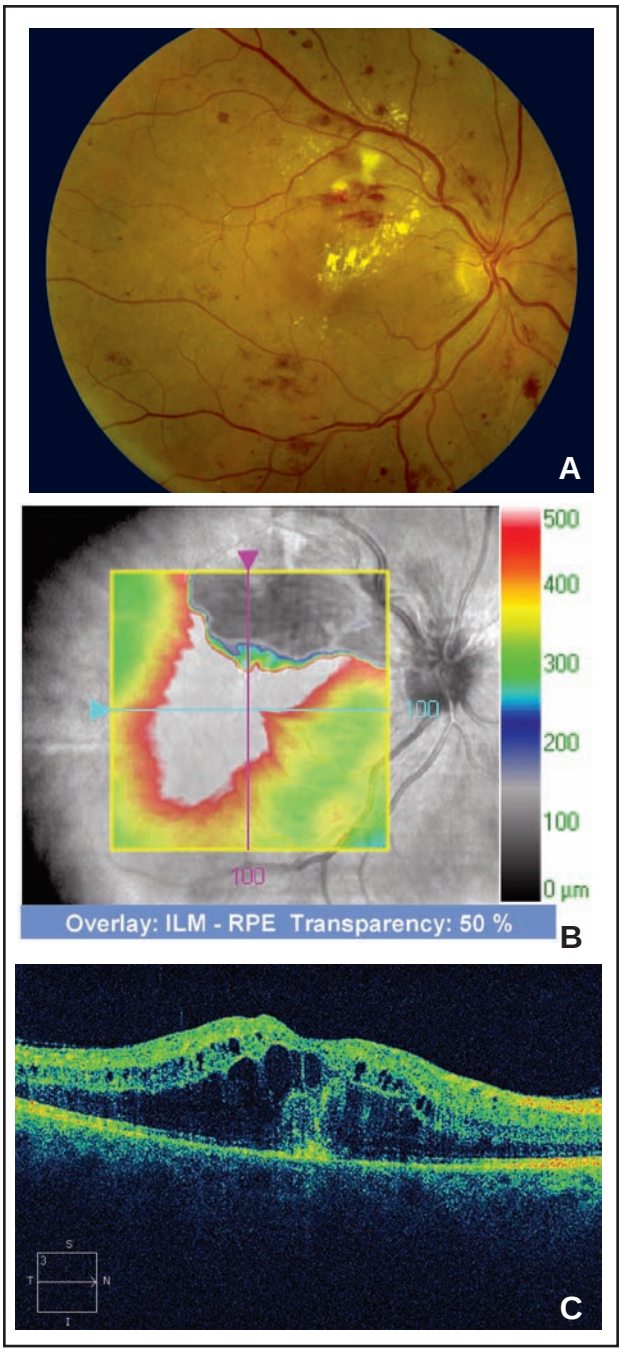

Figure 3. (A) Color fundus image of an eye with clinically significant macular edema demonstrating severe exudative changes throughout the macula. (B) Color macular thickness map obtained by spectral-domain optical coherence tomography (Cirrus HD-OCT; Carl Zeiss Meditec Inc., Dublin, CA) reveals diffuse macular thickening. (C) Representative horizontal optical coherence tomography scan with extensive macular edema and exudative changes. This is an eye of a patient with uncontrolled type II diabetes who presented with severe non-proliferative diabetic retinopathy and clinically significant macular edema prior to any treatment. Initial best-corrected Snellen visual acuity in this eye was 20/200.

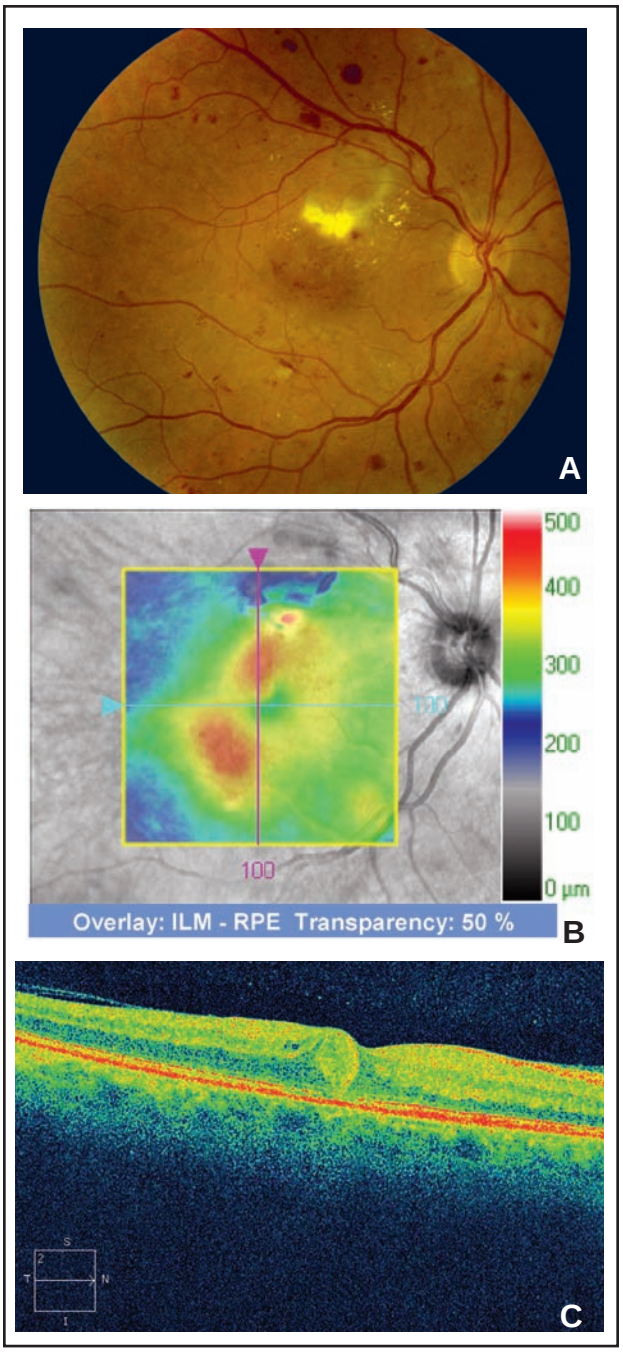

Figure 4. (A) Color fundus image of the same eye as Figure 3, six months after a single injection of intravitreal bevacizumab and prompt treatment with focal/grid photocoagulation. (B) Color macular thickness map reveals significant improvement of the macular edema and thickening. (C) Representative horizontal optical coherence tomography scan demonstrates improvement of macular edema and near-normalization of the foveal contour. Final Snellen best-corrected visual acuity in this eye was 20/60.

TABLE 4
Intravitreal Bevacizumab or Laser Therapy in the Management of Diabetic Macular Edema (BOLT)

Enrolled 80 eyes of 80 patients
Entry criteria
Nonischemic center-involving CSME
TD-OCT measured CSMT ⩾ 270 µm
Received at least 1 prior MLT
Baseline characteristics
VA of 35 to 69 ETDRS letters (~ ETDRS 20/40 to 20/200)
Mean VA of approximately 55 ETDRS letters
Mean CSMT (TD-OCT) approximately 500 µm
Randomization
Laser alone group
Treated at baseline and reevaluated every 4 months, receiving a mean of 3 lasers over the first 12 months
Bevacizumab group
Intravitreal bevacizumab monthly for the first three months and subsequently reevaluated for treatment on a "PRN" basis every 6 weeks
Received a mean of 9 injections over the first 12 months
TD-OCT results at 12 months
CSMT decreased 130 µm in the bevacizumab group
CSMT decreased 68 µm in the laser group
Result trending towards significance (P = .06)
VA results at 12 months
Laser group lost a mean of 0.5 ETDRS letters
Bevacizumab group gained a mean of 8 letters
Conclusions
The study supports the use of bevacizumab in patients with persistent nonischemic center-involving CSME
At 1 year, bevacizumab has a greater treatment effect on VA than modified ETDRS MLT in patients with center-involving persistent CSME despite previous laser therapy (OCT data not significant)

CSME = clinically significant macular edema; TD-OCT = time-domain optical coherence tomography; CSMT = central subfield mean thickness; MLT = macular laser treatment; VA = visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; PRN = as needed.
Data from Michaelides M, Kaines A, Hamilton RD, et al. A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) 12-month data: report 2. Ophthalmology. *2010;117:1078-1086.*

tifacts that resulted in errors of more than 50 µm or more than 10% of retinal thickness or that caused a misdiagnosis of macular edema or retinal thinning were defined as clinically significant and were analyzed further by the authors. Multiple categories of artifacts were observed, including misidentification of the outer and inner retina, degraded scan image, cut edge artifact (Spectralis only), incomplete segmentation error, and superior or inferior shifts of retinal images without corresponding shifts of segmentation lines. For Cirrus SD-OCT, 84.7% of scans had artifacts and 32.7% had at least 1 artifact in the center 1-mm area of the scan. For Spectralis SD-OCT, 90.9% of scans had at least 1 artifact, and 37.5% had at least 1 artifact in the center 1-mm area. Clinically significant artifacts involving the center 1-mm area were seen in 5.1% of Cirrus and 8.0% of Spectralis scans. The most common artifact in the study involved segmentation errors. Ultimately, a careful review of OCT scans for image quality and artifacts is important in the assessment of both OCT images and retinal thickness measurements in patient care and clinical trials.

FUTURE DIRECTION OF HIGH-RESOLUTION OCT

Newer OCT technology can achieve near maximum axial resolution by sweeping a narrow bandwidth of light source through a broad optical range in swept-source OCT.[53] An ultrahigh-speed SD-OCT may be able to acquire images at a speed of 70,000 to 312,500 axial scans per second, further limiting exposure time and motion artifact.[54] Doppler OCT has the potential to measure blood flow in the retinal and choroidal vasculature, whereas scattering optical coherence angiography may have the ability to create a three-dimensional view of the choroidal vasculature by segmenting the choroidal vessels.[55,56]

The use of OCT technology has revolutionized the

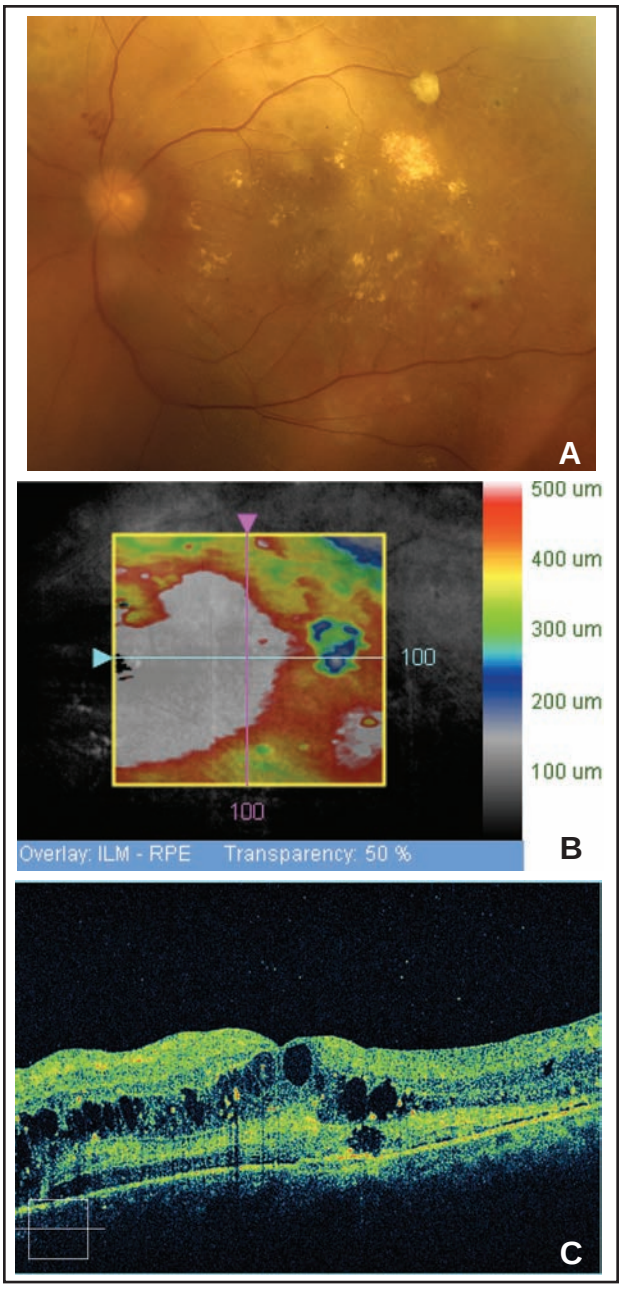

Figure 5. (A) Color fundus image of an eye with clinically significant macular edema demonstrating severe exudative changes throughout the macula. (B) Color macular thickness map obtained by spectral-domain optical coherence tomography (Cirrus HD-OCT; Carl Zeiss Meditec Inc., Dublin, CA) reveals diffuse macular thickening. (C) Representative horizontal optical coherence tomography scan with extensive macular edema and exudative changes. Note this is an eye of a patient with uncontrolled type II diabetes who presented with clinically significant macular edema and poor visual acuity prior to any treatment. Initial best-corrected Snellen visual acuity was 3/200 in this eye. The patient also had a combined tractional and rhegmatogenous retinal detachment and therefore a pars plana vitrectomy with membrane peeling was performed. (Images courtesy of Geeta Lalwani, MD.)

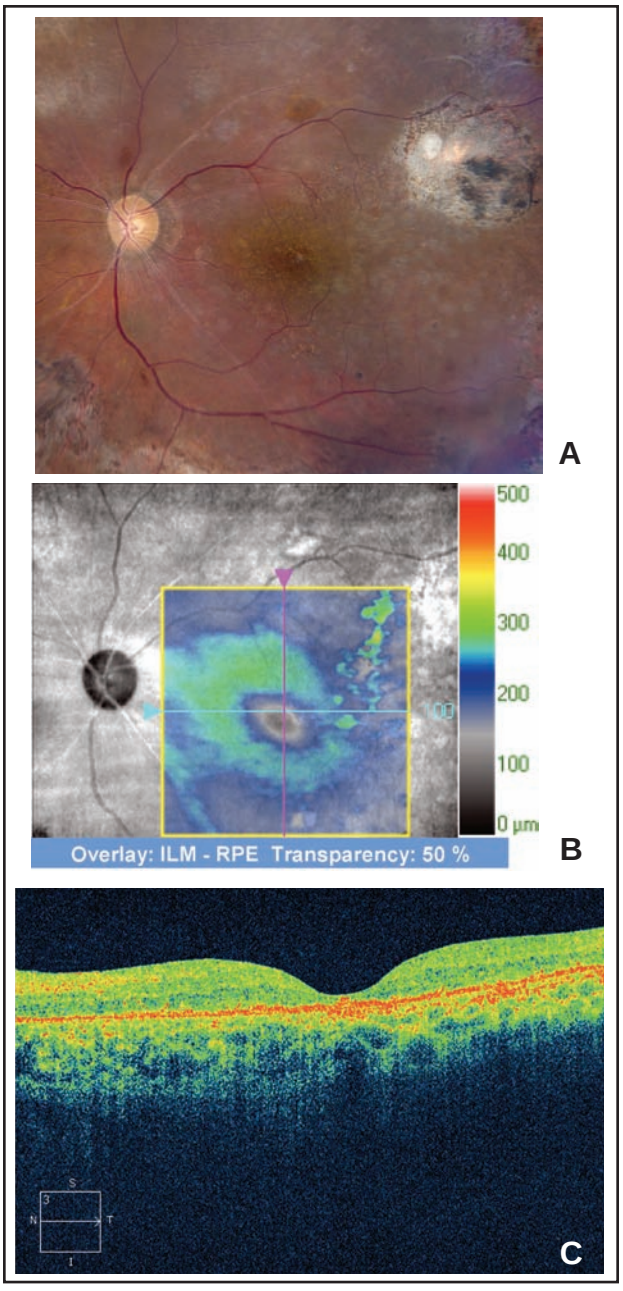

Figure 6. (A) Color fundus image of the same eye as Figure 5 after pars plana vitrectomy surgery with peeling of epiretinal membranes causing vitreomacular traction and rhegmatogenous retinal detachment. (B) Color macular thickness map reveals significant improvement of macular edema and thickening. (C) Representative horizontal optical coherence tomography scan demonstrates resolution of significant macular edema and normalization of the foveal contour. Despite improved foveal contour, significant disruption of the photoreceptor inner segment/outer segment junction is demonstrated, resulting in final Snellen best-corrected visual acuity in this eye of 20/400. (Images courtesy of Geeta Lalwani, MD.)

TABLE 5
Vitrectomy Outcomes in Eyes With Diabetic Macular Edema and Vitreomacular Traction

Enrolled 87 eyes
Entry criteria
Eyes with DME and vitreomacular traction
VA of 20/63 to 20/400
OCT-measured CSMT > 300 µm
No simultaneous cataract extraction at the time of vitrectomy
Baseline characteristics
Median VA of 20/100
Median OCT CSMT of 491 µm
Protocol
Surgery performed according to the investigator's usual routine
Follow-up visits were performed after 3 months, 6 months (primary end point), and 1 year
Additional procedures performed during the surgery included
Epiretinal membrane peeling (61%)
Internal limiting membrane peeling (54%)
Panretinal photocoagulation (40%)
Injection of corticosteroids at the close of the procedure (64%)
TD-OCT outcomes at 6 months
CSMT decreased by 160 µm
43% had CSMT < 250 µm
68% had at least a 50% reduction in thickening
VA outcomes at 6 months
Improved by ⩾ 10 letters in 38%
Deteriorated by ⩾ 10 letters in 22%
Median VA change at 6 months was an improvement of 3 letters
Similar results were noted at 6 months and 1 year for OCT and VA
Conclusions
Vitrectomy is a successful treatment in the setting of DME, VMIA, and at least moderate vision loss in reducing OCT-measured retinal thickening in most eyes

DME = diabetic macular edema; VA = visual acuity; OCT = optical coherence tomography; CSMT = central subfield mean thickness; TD-OCT = time-domain optical coherence tomography; VMIA = vitreomacular interface abnormalities.
Data from Haller JA, Qin H, Apte RS, et al. Vitrectomy outcomes in eyes with diabetic macular edema and vitreomacular traction. Ophthalmology. *2010;117:1087-1093.*

evaluation and treatment of DME. OCT-measured retinal thickness has become a primary outcome measure in most major DME-related clinical trials. SD-OCT technology allows significantly improved evaluation and monitoring of DME, including assessment of foveal microstructural changes, and has been rapidly incorporated into clinical evaluation and into most of the major clinical trials currently underway evaluating the treatment of DME. As we learn more about the disease process through large clinical trials and progressively more detailed images, OCT will continue to play an increasingly important role in the evaluation and treatment of DME.

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