Published in final edited form as:

Ophthalmology. 1998 February ; 105(2): 360–370.

Topography of Diabetic Macular Edema with Optical Coherence Tomography

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Abstract

Objective—This study aimed to develop a protocol to screen and monitor patients with diabetic macular thickening using optical coherence tomography (OCT), a technique for high-resolution cross-sectional imaging of the retina.

Design—A cross-sectional pilot study was conducted.

Participants—A total of 182 eyes of 107 patients with diabetic retinopathy, 55 eyes from 31 patients with diabetes but no ophthalmoscopic evidence of retinopathy, and 73 eyes from 41 healthy volunteers were studied.

Intervention—Six optical coherence tomograms were obtained in a radial spoke pattern centered on the fovea. Retinal thickness was computed automatically from each tomogram at a total of 600 locations throughout the macula. Macular thickness was displayed geographically as a false-color topographic map and was reported numerically as averages in each of nine regions.

Main Outcome Measures—Correlation of OCT with slit-lamp biomicroscopy, fluorescein angiography, and visual acuity was measured.

Results—Optical coherence tomography was able to quantify the development and resolution of both foveal and extrafoveal macular thickening. The mean $\pm$ standard deviation foveal thickness was $174 \pm 18 \mu\text{m}$ in normal eyes, $179 \pm 17 \mu\text{m}$ in diabetic eyes without retinopathy, and $256 \pm 114 \mu\text{m}$ in eyes with nonproliferative diabetic retinopathy. Foveal thickness was highly correlated among left and right eyes of normal eyes (mean $\pm$ standard deviation difference of $6 \pm 9 \mu\text{m}$). Foveal thickness measured by OCT correlated with visual acuity ($r^2 = 0.79$). A single diabetic eye with no slit-lamp evidence of retinopathy showed abnormal foveal thickening on OCT.

Conclusions—Optical coherence tomography was a useful technique for quantifying macular thickness in patients with diabetic macular edema. The topographic mapping protocol provided geographic information on macular thickness that was intuitive and objective.

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Presented in part at the Association for Research in Vision and Ophthalmology Annual Meeting, Fort Lauderdale, Florida, April, 1996.

Macular edema is a common cause of vision loss in patients with diabetic retinopathy. Although fluorescein angiography provides a qualitative assessment of vascular leakage in macular edema, actual macular thickening is better correlated with visual acuity¹ and is the standard by which potential laser treatment is evaluated. Macular edema is clinically significant, as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol, if retinal thickening or hard exudate associated with adjacent retinal thickening is observed within 500 μm of the center of the foveal avascular zone.²

Optical coherence tomography (OCT) is a new retinal imaging technique that has applications in the diagnosis and management of a variety of diseases of the macula and optic nerve.³⁻¹⁴ Optical coherence tomography produces cross-sectional images of optical reflectivity in the retina in analogy to ultrasound B-scan, but with higher resolution. Measurements of retinal thickness may be obtained directly from the tomograms, either by manually measuring the distance between the inner and outer retinal boundaries or by using computer image processing techniques. In patients with diabetes and diabetic retinopathy, single measurements of central foveal thickness using OCT correlate with visual acuity and provide a means of monitoring macular thickening before and after laser therapy.⁷

In this article, we extend OCT to perform retinal thickness measurements at multiple locations covering the entire macula so that retinal thickening also may be assessed in the perifoveal and surrounding macula. A standardized scanning protocol and image analysis method that displays macular thickness topographically is investigated for the early screening of macular thickening in patients with diabetes and for following the progression or regression of edema after treatment.

Materials and Methods

Over a 2-year duration, we performed OCT on 182 eyes of 107 patients with diabetic retinopathy, 55 eyes from 31 patients with diabetes but no ophthalmoscopic evidence of retinopathy, and 73 eyes from 41 healthy volunteers. All patients underwent a complete ophthalmic evaluation at the New England Eye Center of Tufts University, including indirect ophthalmoscopy and best-corrected Snellen visual acuity. Optical coherence tomograms were acquired through a dilated pupil by an experienced examiner familiar with the clinical findings.

Optical Coherence Tomography System

Optical coherence tomography is a new diagnostic imaging technique analogous to B-scan ultrasound that uses optical interferometry to resolve the distances of reflective structures within tissue.¹⁵⁻¹⁹ A superluminescent diode light source operating at 840 nm provides between 200 μW and 1 mW of probe illumination on the retina, which is consistent with the American National Standards Institute standard for intrabeam viewing.²⁰ Cross-sectional or B-mode imaging is accomplished in 2.5 seconds by acquiring a sequence of 100 interferometric A-scans while scanning the probe beam across the retina. A false-color tomogram of optical reflectivity is produced in which bright colors, such as red and white, correspond to highly reflective areas and dark colors, such as blue and black, indicate minimally reflective regions.

The OCT system is interfaced using fiber optics to a conventional slit-lamp biomicroscope and a fixed +78-diopter condensing lens for retinal examination. An infrared-sensitive video camera provides a view of the scanning probe beam on the fundus so that the location of each scan on the retina can be monitored. A computer-controlled light that fixates the eye being scanned is provided so that different areas of the retina may be imaged.

The axial or longitudinal resolution of the OCT system was determined experimentally to be 14 μm in air by measuring the full width at half maximum of the reflection obtained by imaging a mirror placed in the image plane of the slit-lamp biomicroscope. This measurement predicts a full-width-at-half-maximum resolution of 10 μm in the retina because of the difference in refractive index between air and tissue. Thus, under optimal conditions, the precision of OCT measurements of retinal thickness would be expected to be on the order of 10 μm . In practice, the average reproducibility of central foveal thickness measurements was 11 μm in normal subjects and approximately 20 μm in patients with diabetic retinopathy (see Results section and refer to Table 1). The best-case lateral resolution is determined by the probe beam diameter in the retina and was calculated to be 14 μm based on the reduced Gullstrand schematic eye. The actual lateral resolution is limited by the separation between adjacent A-scans on the retina and was 70 μm for the OCT images presented in this study. Computer image processing techniques are used to correct for patient eye motion in the longitudinal direction.¹⁹ Optical coherence tomography images in this study are displayed twice expanded in the vertical or axial direction to enhance the distinction between retinal layers.

Topographic Mapping Protocol

For each eye, six consecutive OCT scans were obtained at equally spaced angular orientations in a radial spoke pattern centered on the fovea (Fig 1A). Each of the six tomograms (B-scans) was oriented along a line intersecting the central fovea and contained 100 equally spaced axial profiles (A-scans) of optical reflectivity. Thus, retinal thickness measurements were performed at a total of 600 points along these 6 intersecting lines, with 6 of these measurements located identically through the central fovea. Each of the other measurements, or A-scans, was spaced by 70 μm from the next closest measurement. This pattern had the advantage of concentrating measurements in the central fovea where accurate information was most important. A computer algorithm was used to profile the inner and outer retinal boundaries for each tomogram (Fig 1B), and retinal thickness was computed automatically from these boundaries by assuming a constant refractive index of 1.36. Each of the six tomograms was smoothed by linear convolution with a center-weighted kernel. An edge-detection kernel then was used to locate the strongest two edges in each tomogram, which most likely corresponded to the vitreoretinal interface and the retinal pigment epithelium. After this initial estimate of the inner and outer boundaries was created, an error-checking step was performed to interpolate the posterior boundary in areas of hard exudate where no reflection from the retinal pigment epithelium–choriocapillaris was visible and to locate edges when they were poorly defined because of low contrast. The error-checking step involved identifying and replacing discontinuous line segments in each contour with a new estimate of the profile constructed by using the edge-detection kernel to locate the strongest local edge in that area.

The retinal thickness data were displayed in two complementary manners. For quantitative interpretation, the macula was divided into nine ETDRS-type regions, including a central disc of 500- μm diameter (hereafter known as the foveal region), and an inner and outer ring, each divided into four quadrants, with outer radii of 1 and 2 disc diameters, respectively (Fig 1C). An average retinal thickness was reported for each of the nine regions. The mean $\pm$ standard deviation (SD) central foveal thickness also was recorded for the six A-scans at the intersection of all the tomograms in the central macula. The SD provided a simple estimate of the measurement reproducibility. A false-color topographic display also was developed. Macular thickness was converted to a false-color value for every point within 2 disc diameters from the center, with brighter colors indicating areas of increased retinal thickness. Bilinear interpolation in polar coordinates was performed to estimate thicknesses in the wedges between each OCT scan.

Each OCT was centered on the patient's fixation, which was assumed to correspond to the central fovea. In patients with eccentric or imperfect fixation, the examiner could choose to offset each OCT after data acquisition so that the fovea would be positioned centrally. The location of the fovea was estimated from each OCT using a computer algorithm that searched for a local minimum in total intraretinal reflectivity, which usually coincided with the relative absence of plexiform layers in the foveal region. For each OCT, the examiner was given a choice of accepting either the center of the OCT (fixation) or the computer estimate of minimum intraretinal reflectivity as the position of the central fovea. For the purposes of data analysis, left eyes were considered as mirror images of right eyes.

Results

Normal Eyes

The topographic mapping protocol was performed on 73 eyes from 41 healthy volunteers (mean age, 38 years; range, 23–79 years), including 40 eyes from 23 women and 33 eyes from 18 men. The mean $\pm$ SD retinal thickness by region is displayed in Figure 1C and Table 1. The mean $\pm$ SD foveal thickness was $174 \pm 18 \mu\text{m}$ and never exceeded $216 \mu\text{m}$ in any of the normal eyes. As expected, retinal thickness reached a minimum in the fovea, was largest within 1 disc diameter of the center, and decreased toward the periphery. The temporal quadrant was thinnest. Within 1 disc diameter of the center, the superior and inferior quadrants were thickest because of the superior and inferior arcuate bundling of nerve fibers. The nasal retina was thickest 2 disc diameters from the center because of the convergence of nerve fibers approaching the optic disc. Figure 1C also illustrates a false-color topographic map from a typical healthy eye that provides an example of these normal variations.

The SD of the average thickness for each region outside the central 500- μm radius was uniformly approximately $15 \mu\text{m}$, showing that there was relatively little variability in average retinal thickness outside the fovea. The SDs of $18 \mu\text{m}$ and $21 \mu\text{m}$ for the average foveal and central foveal thickness, respectively, were slightly larger. The SD of the six central macular measurements provides a simple estimate of the measurement reproducibility for a given patient. The average value of this reproducibility estimate over healthy eyes was $11 \mu\text{m}$. Age was not significantly correlated with average foveal thickness within 500 μm of the center. However, the mean $\pm$ standard error average foveal thickness was significantly different among men ($181 \pm 4 \mu\text{m}$) and women ($169 \pm 4 \mu\text{m}$) (Student's *t* test, $P = 0.04$).

Diabetic Macular Edema

Optical coherence tomography was used to examine 182 eyes from 107 patients with diabetic retinopathy (mean age, 60 years; range, 25–81 years), including 98 eyes from 55 men and 84 eyes from 52 women. On slit-lamp examination, 148 eyes were diagnosed with nonproliferative, or background, diabetic retinopathy (NPDR) and 34 eyes had proliferative diabetic retinopathy (PDR). The mean $\pm$ SD retinal thickness by region for these eyes is reported in Table 1. As expected, the mean macular thickness was larger in all regions for eyes with NPDR or PDR compared with that of normal eyes, although these differences were not statistically significant. This difference was most significant in the average and central foveal thicknesses, indicating the predominance of central versus more peripheral edema. The SD in thickness for each region was greater among eyes with NPDR or PDR compared with that of normal eyes, which was a direct consequence of the variable extent and location of macular edema in the diabetic eyes. There were no significant differences in average thickness in any region between eyes with NPDR and eyes with PDR. Comparison of the average SD of the six measurements obtained through the central macula showed that

measurements in eyes with diabetic retinopathy appeared to be less reproducible than those from normal eyes.

Slit-lamp biomicroscopy was used to grade clinically significant macular edema based on the presence or absence of macular thickening or hard exudate within 500 μm of the central macula. Figure 2 displays a histogram of average foveal thickness within 500 μm of the center as measured by OCT. Mean foveal thickness was considered to be abnormal or clinically significant on OCT examination when it was greater than the maximum value observed for normal eyes (i.e., $>216 \mu\text{m}$). According to Figure 2, OCT evaluation agreed with slit-lamp examination results for normal and extreme values of foveal thickness but disagreed often when foveal thickness was between 200 and 325 μm . Similar results were obtained for OCT measurements of central macular thickness. Central macular thickness was highly correlated by linear regression with average foveal thickness ($r^2 = 0.97$), and these two measurements were essentially equivalent in evaluating clinically significant macular thickening.

Screening for Macular Edema

Fifty-five eyes from 31 patients with diabetes but with no evidence of retinopathy on slit-lamp examination were evaluated with OCT to determine whether macular thickening was present in this population (mean age, 55 years; range, 32–84 years). These patients included 41 eyes from 23 men and 14 eyes from 8 women. As a population, the average macular thickness in these eyes showed no significant difference from normal eyes in any of the nine regions (Table 1). Two of the diabetic eyes had foveal thicknesses of 221 μm and 230 μm , which were both greater than the maximum foveal thickness observed for any of the normal eyes (216 μm). The reproducibility figures for these eyes were 24 μm and 53 μm , respectively.

Comparison of macular thickness between right and left eyes in the same patient provides an additional means of identifying early macular edema. Among the 30 normal subjects who had both eyes imaged, left and right average foveal thicknesses were highly correlated (Fig 3). The mean $\pm$ SD absolute difference in foveal thickness between these left and right eyes was $6 \pm 9 \mu\text{m}$. In the 23 patients who had diabetes without retinopathy who had both eyes imaged, left and right average foveal thickness also was correlated (Fig 3). In these eyes, the mean $\pm$ SD absolute difference in foveal thickness was $9 \pm 8 \mu\text{m}$. Three of the patients with diabetes (Figs 3A–C), including two of the patients described above (Figs 3A, B), exhibited a difference between eyes (51 μm , 28 μm , and 26 μm , respectively), which was greater than two SDs larger than the mean for normal eyes.

Macular Thickening and Visual Acuity

Optical coherence tomography measurements of foveal thickness (averaged within a radius of 500 μm from the center) were compared with visual acuity using linear regression in 237 diabetic eyes with either no retinopathy, nonproliferative retinopathy, or proliferative retinopathy (Fig 4). The foveal thickness, averaged over eyes with the same visual acuity, correlated with visual acuity expressed on a logarithmic scale ($r^2 = 0.79$).

Case Reports

Case 1

This 55-year-old woman with a 14-year history of diabetes had moderate NPDR in her right eye associated with a visual acuity of 20/25. Severe exudate and extrafoveal macular edema that was not clinically significant was noted on slit-lamp examination (Fig 5A). Fluorescein angiography showed late leakage surrounding the fovea consistent with macular edema (Fig

5B). The OCT topographic map showed retinal thickening not involving the fovea, which generally corresponded to regions of hard exudate and fluorescein leakage (Figs 5C, D). Hard exudate was visible in the cross-sectional OCT images as focal intraretinal areas of high reflectivity.

Case 2

This 75-year-old woman with NPDR and a visual acuity of 20/70 in her right eye had cystoid macular edema centrally and hard exudate located inferior to the fovea (Fig 6A). Fluorescein angiography showed diffuse late leakage in the superior macula (Fig 6B). Optical coherence tomography showed diffuse retinal thickening, large central cysts, and intraretinal exudate (Fig 6C). The topographic map showed that the increased retinal thickness was most prominent in the superior macula in the area of fluorescein leakage (Fig 6D). Moderate thickening was noted inferonasal to the fovea, which corresponded to the exudate observed on biomicroscopic analysis. Four months later, the patient received focal laser photocoagulation treatment. Six months after the initial examination, her visual acuity in the right eye had improved to 20/60. Optical coherence tomography showed a corresponding decrease in retinal thickness throughout the macula (Fig 6E).

Case 3

A 50-year-old man with NPDR and clinically significant macular edema in the right eye was examined (Fig 7A). His visual acuity in the right eye was 20/25. Optical coherence tomography showed foveal and juxtafoveal macular thickening, which was most significant temporally and corresponded to areas of hard exudate (Fig 7B). Eight months later, the patient's visual acuity in the right eye had decreased to 20/40. Optical coherence tomography displayed a substantial increase in macular thickness centrally (Fig 7C). Focal laser photocoagulation was performed, and the patient returned 5 months later. On follow-up examination, the visual acuity in the right eye had returned to 20/20. Optical coherence tomography showed resolution of the edema with a normal foveal and central macular thickness (Fig 7D). A remaining area of minimal retinal thickening was evident nasal to the fovea.

Case 4

A 69-year-old man with NPDR had a visual acuity of 20/40 in his left eye (Fig 8A). Slit-lamp biomicroscopic analysis showed significant retinal thickening inferotemporally within 1 disc diameter of the center of the fovea and minimal clinically significant macular edema. Optical coherence tomography confirmed both regions of increased retinal thickness (Fig 8B). Grid yellow dye laser was applied to the inferotemporal region of increased retinal thickness according to leakage observed on fluorescein angiography. The patient returned 2 months later for follow-up with no improvement in his visual acuity in the left eye. Optical coherence tomography showed a regional decrease in the inferotemporal retinal thickness; however, the average foveal thickness and central foveal thickness had not changed significantly from the initial examination (Fig 8C). A significant decrease in foveal thickness was not noted until 10 months after laser treatment, at which time the foveal thickness was within the normal range (Fig 8D). The patient's visual acuity remained at 20/40.

Case 5

A 66-year-old man with NPDR had a visual acuity of 20/25 in his right eye. Slit-lamp biomicroscopic analysis showed multiple dot and blot hemorrhages but no evidence of clinically significant macular edema (Fig 9A). Fluorescein angiography was not performed. Optical coherence tomography showed two focal regions of macular thickening

superotemporal and nasal to the fovea that corresponded to areas of hemorrhage on ophthalmoscopy (Fig 9B). The foveal thickness was increased at 220 μm , which was consistent with clinically significant macular thickening.

Discussion

The diagnosis and management of diabetic macular edema depend on the traditional techniques of slit-lamp examination and fluorescein angiography. Although fluorescein angiography is sensitive to vascular leakage, which causes macular edema, actual retinal thickening is better correlated with loss of visual acuity.¹ Thus, the ETDRS guidelines for clinically significant macular edema are based on slit-lamp observation of macular thickening or hard exudate associated with macular thickening within 5.00 μm of the central fovea, independent of the angiographic findings. We previously have shown that OCT is an effective technique for monitoring central foveal thickness in patients with macular edema.⁷

Single measurements of retinal thickness in the central fovea, however, provide an incomplete clinical picture because extrafoveal macular edema is neglected. In this study, a radial spoke pattern of six optical coherence tomograms was used to obtain geographic measurements of macular thickness. Macular thickness was displayed quantitatively, averaged over nine ETDRS-type regions, and as a false-color topographic map. Although many methods could have been used to sample retinal thickness throughout the macula, the radial scanning pattern concentrated measurements in the central macula where information was most important. Additionally, the individual OCT images permitted visualization of intraretinal features such as cysts and hard exudate (e.g., Figs 5C, 6C), which would not have been available from other scanning patterns that did not have the A-scans spaced closely in one dimension.

The radial pattern of six tomograms sampled macular thickness at all clock-hours. Bilinear interpolation in polar coordinates was used to estimate thickness in the wedges between each tomogram for the false-color display. No interpolation was used to compute average thickness by ETDRS region. This protocol would be expected to miss very focal edema situated in a wedge that spanned less than a clock-hour. In our experience, the likelihood of this occurring was minimal, especially near the fovea where the tomograms were spaced more closely. With six OCT images used to radially map macular thickness, the arc length of a clock-hour 500 μm from the center was approximately 250 μm . More detailed mapping could be obtained, if desired, by increasing the number of tomograms in the radial pattern. Because each image was acquired in 2.5 seconds, the total time required to perform all six scans in a given eye usually was less than a minute. The radial scanning pattern kept the patient's fixation constant for all tomograms, which enabled the six scans to be performed in succession after the initial alignment.

The topographic mapping protocol was useful in longitudinally monitoring patients for the development of macular edema and for following the resolution of edema after laser treatment (e.g., cases 2–4). Geographic information was helpful because edema often presented or began to resolve outside of the fovea before affecting central macular thickness (e.g., case 3). The false-color map of retinal thickness provided an intuitive and efficient method of comparing retinal thickness over several visits, which could be directly compared with slit-lamp observation.

The OCT topographic map of retinal thickness generally correlated with conventional clinical examination. Retinal thickening or hard exudate observed on slit-lamp biomicroscopic analysis almost always correlated with increased thickness on OCT, but there were some occasions in which OCT detected thickening in the absence of any

abnormality on slit-lamp examination. Both measurements of central macular thickness and measurements of foveal thickness averaged over a central disk of 500- μm radius appeared to be more sensitive than slit-lamp examination for evaluating clinically significant macular edema. Edema was difficult to detect clinically when there was no hard exudate in the central macula and diffuse rather than focal macular thickening was present, reducing the variation in retinal surface contour. Optical coherence tomography retinal thickness also generally correlated with regions of fluorescein leakage; however, increased macular thickness occasionally was evident on OCT in the absence of leakage. Both single measurements of central foveal thickness and measurements averaged over the 500- μm central disc essentially were equivalent in detecting clinically significant thickening. Optical coherence tomographic measurements of macular thickness averaged over eyes with the same visual acuity correlated with visual acuity in diabetic patients both with and without retinopathy. The correlation between central thickness and visual acuity ($r^2 = 0.79$) corroborated previous studies.⁷

Optical coherence tomography appears to be a promising method for screening for the early development of diabetic macular edema. Optical coherence tomography is without contact and noninvasive, and the apparent brightness of the predominantly infrared light is significantly less than the visible illumination from conventional indirect ophthalmoscopy. Macular edema can be detected by comparing thickness measurements with values from a normal population, with earlier baseline measurements from the same patient, or with measurements from the contralateral eye. In our series, the normal variation (SD) in average retinal thickness was small (15 μm outside the fovea and approximately 20 μm centrally). Macular thickness was not correlated with age, but was slightly larger in males compared to females. The effect of axial eye length on foveal thickness was not investigated. Left and right eyes also were highly correlated among healthy subjects. Among normal subjects, the mean $\pm$ SD absolute difference in left and right foveal thickness was $6 \pm 9 \mu\text{m}$. In contrast, absolute foveal thickness varied over a range ($\pm$ SD) of 36 μm . The difference between the inpatient and outpatient variation was evidence of the high precision of the OCT measurements and suggested that the comparatively larger outpatient variability was because of differences in actual thickness rather than measurement errors. Both the small variation in thickness among normal eyes and the high correlation between right and left eyes suggested that OCT was highly sensitive to small increases in macular thickness that would characterize early macular edema.

These results indicate that OCT has potential to screen patients with early nonproliferative retinopathy for the development of macular thickening. We also attempted to investigate whether some patients with diabetes might have early macular edema develop before the onset of ophthalmoscopically visible retinopathy. Abnormal macular thickening was suspected if either the absolute macular thickness was greater than the maximum observed for normal eyes (i.e., >216 μm) or if the difference in foveal thickness between the right and left eyes was greater than two SDs larger than the mean difference for normal eyes (i.e., >24 μm). (Alternatively, a two-SD figure of 210 μm could have been used to screen absolute macular thickness.) Three patients with diabetes (Figs 3A–C) and one normal subject showed a suspicious difference in foveal thickness between right and left eyes based on these criteria. Two of the patients with diabetes (A, B) also had abnormally thick foveae in one eye according to these criteria. One of these two suspicious patients (A) had an unacceptable reproducibility figure of 53 μm , indicating a low reliability for that measurement. Patient B, however, exhibited acceptable reproducibility and a left foveal thickness, which was both greater than all normal eyes and increased significantly compared to the patient's contralateral eye. Although patient B had a visual acuity of 20/20 in this eye, based on these findings, we believe that patient B would be a candidate for more frequent and detailed follow-up in his left eye, perhaps including fluorescein angiography.

Because all OCT images in the radial pattern intersected in the center, the SD of the six central thickness measurements provided an estimate of the test reproducibility and reliability. This reproducibility figure typically varied between 5 and 20 μm for normal subjects. Eyes with retinopathy tended to exhibit poorer reproducibility. Larger deviations suggested imperfect fixation and could be used to quantify the reliability of the OCT images. In patients with eccentric or varying fixation, the central fovea often was displaced laterally slightly from the center of the OCT image. In these cases, the computer provided an estimate of the lateral displacement by identifying the position of minimum total intraretinal reflectivity, which usually was characteristic of the relative absence of plexiform layers in central fovea. The examiner then was given a choice to offset the center of the OCT to this position. Human intervention was necessary because the computer occasionally would confuse the reduced intraretinal reflectivity, characterizing a cyst for the reduced reflectivity within fovea. We found that the examiner was able to identify the fovea based on its characteristic cross-sectional morphology in most eyes without severe edema. Thus, whereas complete manual identification of the fovea would have been feasible, the computer algorithm permitted a binary decision that minimized examiner bias. Future developments in the feature recognition algorithm should lead to a completely automated identification technique. In any case, imperfect fixation was a concern mostly for patients with advanced disease (e.g., case 2) and generally was not a factor in patients with more mild edema (e.g., cases 1, 3–5). Furthermore, the reproducibility figure provided an objective context within which one could interpret the OCT results from the patients with more problematic fixation.

Other potential sources of artifacts included refractive error and saccadic eye motion. The length of each OCT on the retina was computed from the angular deviation of the scanning mirrors by assuming a constant axial length for each eye. Differences in refractive power or magnification could therefore lead to inaccurate measurements of transverse dimensions that would affect the actual size of the nine ETDRS regions on the macula. This error could potentially be corrected in future studies with a simple multiplicative scaling factor derived from ultra-sonographic measurements of axial eye length or the glass refraction or both.²¹ Measurements of central macular thickness were not affected by refractive error, and these measurements also could have been used to assess clinically significant macular thickening. Saccadic eye motions that occurred during the 2.5 seconds required for each of the six OCT images could result in inaccurate measurements of retinal thickness if there was significant local variation in thickness. Transverse eye motion was more problematic in patients with advanced disease and poor fixation. However, the influence of eye motion could be assessed in the central fovea with the reproducibility figure in a manner similar to fixation losses. A commercial OCT system is available with a scanning time of less than 1 second, which should reduce the impact of eye motion.

In summary, we found that OCT was a useful technique for quantitative measurement of retinal thickness in patients with diabetic macular edema. The topographic mapping protocol provided geographic information on macular thickness that was intuitive and objective. Future improvements in scanning time will allow more OCT images to be compiled into a more detailed and sensitive topographic map. This pilot study suggests that this method may become an effective diagnostic tool for screening patients with diabetes for the early development of macular thickening. Further studies are warranted to investigate the possibility of detecting retinal thickening before ophthalmoscopically evident retinopathy and to evaluate the impact of OCT on treatment outcome.

Acknowledgments

Supported in part by NIH Grant 9-RO-I-EY11289-10, Bethesda, Maryland; MFEL Grant N00014-94-1-0717, Arlington, Virginia; an unrestricted departmental grant from Research to Prevent Blindness, Inc., New York, New York; and the Massachusetts Lions Eye Research Fund, Inc, Boston, Massachusetts.

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Figure 1.

A, radial spoke pattern of six optical coherence tomograms. **B**, retinal thickness is computed automatically from the inner and outer retinal boundaries (purple) for each optical coherence tomogram. Arrows indicate the center of the fovea, which is chosen either to lie at fixation (denoted by an “F”) or at a location determined by a feature recognition algorithm (denoted by an “R”). **C**, macular thickness is displayed as a false-color topographic map and as numeric averages over several regions covering the macula. The three circle radii are 500 μm, 1 disc diameter, and 2 disc diameters. The false-color map for a prototypical healthy eye is shown on the left. Mean ± standard deviation thickness in micrometers is reported for the population of healthy eyes on the right.

Figure 2.

Histogram of foveal thickness in eyes with diabetic retinopathy averaged over a 500-μm radius disc and stratified by results from slit-lamp biomicroscopic analysis. CSME = clinically significant macular edema. The maximum normal foveal thickness observed is indicated by a vertical bar placed at 216 μm. Eyes to the right of this bar were considered abnormally thickened by optical coherence tomography.

Figure 3.

Right versus left average foveal thickness in healthy eyes (left) and in eyes with diabetes but no evidence of retinopathy (right). Dashed lines indicate the maximum foveal thickness observed for normal eyes ($216\ \mu\text{m}$). Solid lines demarcate a strip within which the difference between left and right foveal thickness was less than 2 standard deviations away from the mean difference in normal subjects ($\pm 24\ \mu\text{m}$). One normal and three diabetic eyes (**A–C**) showed a suspicious difference between right and left foveal thickness. In two of these eyes (**A,B**), the larger foveal thickness was greater than the maximum observed for normal eyes.

Figure 4.

Foveal thickness averaged over eyes with the same visual acuity correlates linearly with visual acuity on a logarithmic scale. The numbers in parentheses indicate the number of eyes averaged for each Snellen visual acuity. Error bars denote standard error. MAR = minimum angle of resolution.

Figure 5.

Case 1. Macular edema and exudate not clinically significant. **A**, fundus photograph showing severe extrafoveal exudate. **B**, fluorescein angiography showing late leakage surrounding the fovea. **C**, cross-sectional optical coherence tomograms showing retinal thickening and intraretinal hard exudate. **D**, optical coherence tomography topographic map displaying extrafoveal macular thickening.

Figure 6.

Case 2. Cystoid macular edema before and after treatment. **A**, fundus photograph showing hard exudate inferior to the fovea. **B**, fluorescein angiography showing diffuse leakage in the superior macula. **C**, large central cysts and intraretinal hard exudate are observed on optical coherence tomography (OCT). **D**, OCT topographic map displays increased macular thickness throughout the macula, especially in the area of fluorescein leakage. **E**, OCT

topographic map obtained 4 months after focal laser photocoagulation showing a decrease in macular thickness.

Figure 7.

Case 3. Development and resolution of clinically significant macular edema. **A**, fundus photograph showing areas of hard exudate and hemorrhage temporal and inferior to the fovea. **B**, optical coherence tomography topographic map showing clinically significant macular thickening, which is most prominent temporal to the fovea. **C**, 8 months later, the macular thickening has increased substantially. **D**, 5 months after focal laser photocoagulation, the edema is almost completely resolved in the central fovea.

Figure 8.

Case 4. Extrafoveal resolution of clinically significant macular edema. **A**, fundus photograph. **B**, optical coherence tomography shows mild clinically significant macular thickening and severe macular edema inferotemporal to the fovea. **C**, (2, 2 months after grid laser treatment, the inferotemporal edema has begun to resolve, but the central thickening persists. **D**, the central thickening has resolved 10 months after laser treatment.

Figure 9.

Case 5. Minimal clinically significant macular thickening. **A**, fundus photograph showing dot and blot hemorrhages but no clinically significant macular edema. **B**, optical coherence tomography showing abnormal foveal thickening and edema both superotemporal and nasal to the fovea.

Table 1**Macular Thickness in Healthy and Diabetic Eyes**

Region	Retinal Thickness (mean $\pm$ SD; μm)			
	<i>Normal</i> (<i>N</i> = 73)	<i>Diabetes</i> (<i>N</i> = 55)	<i>NPDR</i> (<i>N</i> = 148)	<i>PDR</i> (<i>N</i> = 34)
<500 μ m radius				
Fovea	174 $\pm$ 18	179 $\pm$ 17	256 $\pm$ 114	254 $\pm$ 133
Center	152 $\pm$ 21	158 $\pm$ 20	244 $\pm$ 125	236 $\pm$ 140
Reproducibility	11 $\pm$ 6	14 $\pm$ 9	20 $\pm$ 12	19 $\pm$ 11
Inner ring (500 μ m to 1 DD radius)				
Superior	264 $\pm$ 15	261 $\pm$ 18	296 $\pm$ 72	308 $\pm$ 108
Inferior	263 $\pm$ 16	263 $\pm$ 16	298 $\pm$ 71	299 $\pm$ 113
Temporal	248 $\pm$ 15	246 $\pm$ 16	285 $\pm$ 74	281 $\pm$ 96
Nasal	260 $\pm$ 16	255 $\pm$ 18	292 $\pm$ 70	311 $\pm$ 121
Outer ring (1 DD to 2 DD radius)				
Superior	238 $\pm$ 14	237 $\pm$ 16	264 $\pm$ 55	284 $\pm$ 89
Inferior	225 $\pm$ 15	223 $\pm$ 14	255 $\pm$ 56	253 $\pm$ 92
Temporal	229 $\pm$ 15	228 $\pm$ 14	257 $\pm$ 50	259 $\pm$ 55
Nasal	255 $\pm$ 16	252 $\pm$ 17	273 $\pm$ 46	304 $\pm$ 97

DD = disc diameter (1.5 mm); Diabetes = diabetic eyes with no slit-lamp evidence of retinopathy; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; Reproducibility = standard deviation of the six measurements intersecting at the center of the fovea.