Diabetic Macular Edema Assessed with Optical Coherence Tomography and Stereo Fundus Photography

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PURPOSE. To compare retinal thickening in diabetic macular edema assessed subjectively by evaluation of stereo fundus photographs with that assessed objectively by optical coherence tomography (OCT).

METHODS. Forty-degree stereo fundus photographs of the macular field and OCT scans in 84 eyes of 47 patients with diabetes were compared in terms of both location and area of retinal thickening. Six radiating 6-mm OCT scans at intervals of 30° were obtained, and the retinal thickness was compared with the mean retinal thickness ± 2 SD of healthy control subjects (33 eyes). Subsequently, retinal thickness was mapped topographically and the subjectively assessed retinal thickening map was overlaid. The degree of agreement on location was evaluated as retinal thickening present or absent in nine subfields of the fundus. Area of retinal thickening was divided into four categories: no retinal thickening, less than 1 disc area (DA), less than 2 DAs, or less than 3 DAs, expressed as the \( \kappa \) statistic.

RESULTS. Exact agreement on location was found in 676 of 756 (84.1%) observations (89.4%; \( \kappa = 0.69 \); 95% confidence interval [CI]: 0.63–0.75). Two eyes in which both methods assessed the same amount of retinal thickening showed no agreement on location. These eyes were compared only in terms of location. Exact agreement on area was found in 69 (84.1%) of 82 eyes. Weighted \( \kappa (\kappa_w) = 0.79 \); 95% CI: 0.76–0.82).

CONCLUSIONS. The degree of agreement between subjectively and objectively assessed retinal thickening was very good, implying that changes in diabetic macular edema can be accurately and prospectively measured with OCT. (Invest Ophthalmol Vis Sci. 2002;43:241–245)

Diabetic retinopathy accounts for much of the visual impairment in the Western world. Among patients with type 2 diabetes, macular edema is the most common cause of visual impairment and legal blindness. The diagnosis of macular edema is obtained by binocular view of the fundus performed by slit lamp biomicroscopy, indirect fundoscopy, or stereo fundus photography. Stereoscopic vision is necessary for all three assessments. Both observational and interventional studies of diabetic macular edema require fundus photographs in stereo pairs. Although this is a generally accepted gold standard for the evaluation of macular edema, the drawback to this method is that it requires skilled personnel for both photography and photograph grading. In addition, patients generally find this procedure fairly uncomfortable. The OCT scanning procedure described herein takes 10 minutes, including instruction of the patient. Inconvenience to the patient is minimal. The OCT is user friendly, and an operator needs only minimal training to perform reproducible and high quality OCT scans. OCT was previously shown to be useful in detecting and quantitating various diseases of the macula, including clinically significant diabetic macular edema (CSME), central serous chorioretinopathy, cystoid macular edema, epiretinal membranes, and macular holes.1–3 Generally, OCT scans are sensitive enough to detect foveal involvement of diabetic macular edema. However, the subtle changes in macular thickness in cases of non-CSME are less likely to be detected by OCT scans. Moreover, it is necessary to evaluate whether increases in thickness detected by OCT are in concordance with the subjective assessment of retinal thickening of the same fundus. OCT is now available in many eye clinics throughout the western world. However, this method still needs validation before it can be implemented in clinical trials and used as an objective tool for measuring changes in retinal thickening in cases of diabetic macular edema.

The objective of this study was to compare subjective evaluation of retinal thickening in stereo fundus photographs with objective assessment of retinal thickening by OCT in patients with diabetes with macular edema and to evaluate the degree of agreement between the two methods.

PATIENTS AND METHODS

Ninety-six eyes of 48 patients with diabetes were studied. All patients were diagnosed as having diabetic macular edema less severe than CSME or as having untreated CSME in one or both eyes by slit lamp biomicroscopy (before data collection). Twelve eyes were excluded for the following reasons: epiretinal fibrosis (\( n = 1 \)), missing OCT scan (\( n = 3 \)), poor photograph quality (no stereo effect) in Early-Treatment Diabetic Retinopathy Study (ETDRS) standard field 2 (\( n = 4 \)), poor photograph clarity due to lens opacification (\( n = 4 \)), and poor quality of the OCT scans due to cataract (\( n = 1 \)). Thus, a total of 84 eyes (45 right and 41 left eyes) in 47 patients underwent analysis. Baseline patient characteristics were as follows: mean age, 53 years (range, 24.5–69.3); female-to-male ratio, 11:36; type 1-to-type II diabetes mellitus ratio, 7:40; mean duration of diabetes: type I, 13.8 years (range, 2–26.7), type II, 23.5 years (range, 16–32.2).

CSME, meeting the ETDRS criteria of retinal thickening 500 \( \mu \)m or less from the center of the fovea, was diagnosed in two eyes by fundus examination.2 Two eyes had previously had focal laser photocoagulation for CSME, and both eyes were clinically assessed as still having retinal thickening. Non-CSME (\( n = 71 \); defined as retinal thickening present at or within 2 disc diameters [DD] from the fovea, but not

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meeting the criteria of CSME or no definite retinal thickening \( (n = 9) \) was diagnosed in the remainder of the eyes by fundus examination. 4

The control group consisted of 33 eyes in 25 healthy control subjects (15 right eyes, and 18 left eyes): mean age, 48.2 years (range, 25–75); female-to-male ratio, 17:8.

**Stereo Fundus Photography**

ETDRS 7 standard 40° field stereo fundus photographs were obtained in all patients with a fundus camera (CF–60 Uvi, Canon USA, Lake Success, NY) by a photographer certified for stereo fundus photography with this camera by the Fundus Photography Reading Center (University of Wisconsin, Madison, WI). Photographs in which sufficient stereo effect, clarity, and correct positioning had not been obtained (because of poor patient cooperation, excessive tearing, poorly dilated pupils, or unclear media) were excluded.

The stereo color slides were mounted in transparent slide holders in stereo pairs, and retinal thickening was evaluated in ETDRS standard field 2 (centered on the macula) of each photograph set. Retinal thickening was evaluated with a stereo viewer and assessed with respect to area and location of retinal thickening by the first author (CS). These assessments were drawn on transparent maps, one map for each eye. For improving the assessment of the retinal thickening in the fundus photographs, a detailed grid (Fig. 1C), calibrated for 40° fundus photographs, was used (kindly provided by the Fundus Photography Reading Center).

**Optical Coherence Tomography**

OCT scans were performed with the Optical Coherence Tomograph (Zeiss-Humphrey Inc., Dublin, CA, with software application version A4.1). The principle of the OCT has been described by Hee et al.1 and Puliafito et al.2

In each eye, six radiating cross-sectional B scans of 6 mm, matching the size of the grid (Fig. 1C) used for assessing retinal thickening by stereo fundus photographs, were obtained, with the center of each scan being the center of the fovea. The procedure used for obtaining OCT scans in this study was standardized by retaking all scans for which correct fixation had not been obtained. An internal fixation spot was available to the patient, and the fixation was monitored on the fundus photograph. The fovea was overrepresented in measuring points with the scanning procedure used in this study. This may to some degree compensate for small deviations from the correct fixation spot, which were not detected immediately by the technician.

**Figure 1.** (A) Fundus photograph of the right eye of a patient with diabetes with non-CSME and retinal thickening in the upper temporal quadrant. (B) Corresponding OCT topographic map. Red: a definitely thickened area (i.e., a thickness exceeding the mean retinal thickness +2 SD of healthy control eyes); blue: a definitely nonthickened area (i.e., a thickness below the mean retinal thickness of healthy control eyes); and green: moderate thickening (i.e., a thickness exceeding the mean value of healthy control eyes, but below the +2 SD value). (C) The detailed grid used for evaluation of stereo fundus photographs and OCT. The measuring points of the grid are the first fully drawn circle from the center, representing a radius of 500 µm; the second fully drawn circle, radius of 1500 µm; and the outer fully drawn circle, radius of 3000 µm from the center of the fovea. Several marker (dotted) lines are added to these measuring points for the purpose of enhancing the assessment of retinal thickening. This figure is an overlay of retinal thickening assessment by OCT and subjective evaluation of stereo fundus photographs of the eye shown in (A) and (B). Yellow: area of definite retinal thickening subjectively assessed on stereo fundus photographs; red: definitely thickened area on OCT; hatching: area of overlap between the two methods; and green: area on OCT surrounding the definitely thickened area, representing a thickness above the mean retinal thickness of healthy control eyes, but below the mean +2 SD. (The grid in C is reprinted with permission from Larry Hubbard, Fundus Photography Reading Center, University of Wisconsin, Madison, WI.)

The scanning procedure, with the six radiating 6-mm scans, was chosen as the standard procedure for this instrument3 and also for completion within a reasonable amount of time. All scanning sessions were performed by one trained technician.
Comparison of Study Eyes and Healthy Control Eyes

The algorithm used for interpolation of the OCT scans in this study compared the retinal thickness of the study eyes to a mean value ± 2 SD of healthy control eyes. The scans were topographically mapped in a color code, with red indicating a definitely thickened area (i.e., a retinal thickness exceeding the mean retinal thickness +2 SD of healthy control eyes), blue indicating a definitely nonthickened area (i.e., a retinal thickness below the mean retinal thickness of healthy control eyes), and green indicating a thickness in between (i.e., a retinal thickness greater than the mean value of healthy control eyes, but below the mean +2 SD value, Figs. 1B). The range of standard deviations for the 100 A scans of healthy control subjects was 7 to 14 μm.

To ensure that anatomic differences in retinal thickness in the control subjects (e.g., nasal versus temporal, right versus left) would not interfere with the comparison to diabetic eyes, right and left eyes were treated separately.

Comparison of Location of Retinal Thickening

On the comparison of location (i.e., placement of retinal thickening), the transparent, subjectively assessed retinal thickening map was compared with the OCT color-coded map, and the area or areas definitely thickened on OCT were added to the transparent map. For the purpose of analyzing the degree of agreement on location of retinal thickening, the fundus was divided into nine subfields, as suggested by Hee et al.3 allowing for a differentiated evaluation of agreement on location of retinal thickening in one eye (Fig. 2).

Comparison of Area of Retinal Thickening

The degree of retinal thickening was arbitrarily evaluated as being in one of four categories: no retinal thickening, less than 1 disc area (DA), less than 2 DAs, and less than 3 DAs. The area (i.e., the extent) of retinal thickening was based on a sum of all areas of retinal thickening in one eye and the assumption that 1 DD is equal to 1500 μm. No eyes had more than 3 DAs of retinal thickening.

The OCT maps and subjective evaluation of stereo fundus photographs were assessed by the same person with a minimum of 7 days between the two assessments. The subjective assessment of retinal thickening on the fundus photographs took place before assessment of the OCT topographic maps.

Informed Consent

The study adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from the subjects after explanation of the nature and possible consequences of the study. The research was approved by the institutional human experimentation committee.

Statistics

The κ statistic is interpreted as the chance-corrected proportional agreement between two groups. The weighted κ (κw) is the weighted proportional agreement corrected for chance.6 The usage of the κw is preferable to κ for comparison of the area of retinal thickening, because the degree of disagreement is taken into account. Thus, in this data set, the categories were ordered, and disagreements were given weights according to the size of the discrepancy. However, the comparison of the location of retinal thickening yielded only two categories. Thus, κw analysis was not required. In addition, a binomial test, also known as the McNemar test, was performed as a test for bias in symmetry of the disagreements.

The κ statistic has a maximum of 1.00 when agreement is perfect, and κ = 0 indicates no agreement better than chance. The interpretation of κ values cannot be absolutely stated; only guidelines to interpretation can be given. Those given by Landis and Koch7 suggest that κ = 0.61 to 0.80 indicates that agreement between groups is substantial, and κ = 0.81 to 1.00 indicates that agreement is almost perfect. Although the degree of acceptable agreement depends on circumstances, for most purposes a κ or κw < 0.5 indicates poor agreement.

Reproducibility

Intraobserver Agreement in Grading Stereo Fundus Photographs. One hundred sixty-two observations were made (nine per eye in 18 eyes) and entered in a 2 × 2 table. The χ2 statistic gave a P < 0.0001. A high correlation between the first and second evaluation by grader 1 (CS) was found, with χ2 = 0.841 (95% confidence interval [CI]: 0.79–0.88) and P < 0.0001. There were no disagreements between the first and the second evaluation of grader 1 on the area of retinal thickening.

Interobserver Agreement between Grader 1 (CS) and Grader 2 (ML). Ninety-nine observations were made (nine per eye in 11 eyes) and the interobserver agreement on location of retinal thickening showed exact agreement in 90 observations (91%) with κ = 0.91 (95% CI: 0.84–0.96). Only 1 of 11 eyes showed disagreement on area of retinal thickening from grader 1 to grader 2.

Optical Coherence Tomography. Intraobserver reproducibility obtained in healthy control eyes in the same scanning position, in the same eye, on the same day was 7%, comparable to earlier studies.5

Results

Comparison of Location of Retinal Thickening

A total of 756 (nine per eye in 84 eyes) observations were made. Exact agreement was found in 676 (89.4%) observations. The κ statistic was 0.69 (95% CI: 0.63–0.75), between evaluation of stereo fundus photographs and OCT, for location of retinal thickening.

The McNemar test for symmetry of the data showed that four fields (2, 3, 4, and 5) had significant bias in the symmetry of the observations of discrepancies in favor of the presence of
Comparison of Area of Retinal Thickening

Exact agreement on the area of retinal thickening was found in 69 (84.1%) of 82 eyes (κ = 0.79; 95% CI: 0.76–0.82). Two eyes in which both methods detected retinal thickening, but showed no agreement on location were omitted from the results (Table 2).

Two eyes with CSME showed retinal thickening with central involvement, both by OCT and stereo fundus photography. Nine eyes, which had no detectable retinal thickening as determined by stereo fundus photographs, also showed no retinal thickening by OCT. In addition, three eyes were found to have definite retinal thickening on subjective stereo fundus photograph evaluation, but no retinal thickening was detected on OCT.

DISCUSSION

Quantitation of retinal thickness and topographic mapping of the retina have previously been useful in assessing retinal thickness in both non-CSME and CSME. In the present study, direct comparisons of the extent and the localization of macular edema as assessed by OCT and subjective grading of stereo fundus photography were performed. A significant degree of agreement was found between the methods for both the area and the location of retinal thickening.

Comparing an Objective and a Subjective Method

Determining the exact thickness of a thickened area in stereo fundus photographs is difficult, because it is dependent on the stereopsis of the observer and the quality of the fundus photographs. Sometimes, retinal thickening is underestimated in stereo fundus photographs when compared with binocular ophthalmoscopy. Empirically, the fovea is subject to the most pronounced edema, a comparison between perceived thickness on stereo fundus photographs and absolute thickness (even volume), as determined by OCT, is probably feasible. Although volume measurements could provide additional information, a direct comparison between the two methods in terms of both area and location of retinal thickening would provide the most useful information in cases of more subtle disease such as those assessed in this study.

**Table 1.** Comparison of Location of Retinal Thickening by Stereo Fundus Photography and OCT

<table>
<thead>
<tr>
<th>Field</th>
<th>OCT</th>
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<th>−RT</th>
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<tr>
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<td>0</td>
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</tr>
<tr>
<td></td>
<td>−RT</td>
<td>6</td>
<td>45</td>
</tr>
</tbody>
</table>

Retinal thickening (RT) was assessed in stereo fundus photographs, shown horizontally, and by OCT, shown vertically. The McNemar test was used for testing symmetry of the data. H(0) is a null hypothesis, merely stating that κ is different from 0. The lower limit of the CI adds more credibility to the result. Exact agreement (n = 84); 89.4%; κ = 0.69; 95% CI: 0.63–0.75; H(0) test: Z = 21.13; *significant at P < 0.0001.

**Table 2.** Comparison of Area of Retinal Thickening by Stereo Fundus Photography and OCT

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<tr>
<th>OCT</th>
<th>No RT</th>
<th>&lt;1 DA</th>
<th>&lt;2 DAs</th>
<th>&lt;3 DAs</th>
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<tr>
<td>Total</td>
<td>9</td>
<td>45</td>
<td>18</td>
<td>6</td>
<td>82</td>
</tr>
</tbody>
</table>

Retinal Thickening (RT) was assessed in stereo fundus photographs, shown horizontally, and by OCT, shown vertically. The four categories were: No retinal thickening, <1 disc area (DA), <2 DAs, and <3 DAs. H(0) is a null-hypothesis, merely stating that κ is different from 0. The lower limit of the CI adds more credibility to the result. Exact agreement (n = 82); 84.1%; κ = 0.79; 95% CI: 0.76–0.82; H(0) test: Z = 22.1; *significant at P < 0.0001.
One of the advantages of stereo fundus photography is that it has a large lateral resolution over the whole photographic field. OCT does not have this large lateral resolution, unless an immense amount of scans are performed. Thus, by making the comparison on the terms of the subjective stereo evaluation, the approximation of mapping the retina from the six OCT scans seems reasonable. The advantage of the OCT is that it facilitates quantitation of the retinal thickness in an objective way.

The radiating six scans that were performed in this study, with estimated values of retinal thickness in the wedges between scans, covered an area of 28.5 mm². This area matched the area covered by the grid used for subjective evaluation of stereo fundus photographs. Objective assessments of the retinal thickness with mapping of the posterior pole has also been demonstrated by Gieser et al. This technique is different from the OCT technique in optical principle, scanning procedure, and analysis methods of the computer software. Until now, no other studies in this group of patients have been available for comparison to the present study.

Is subjective assessment of retinal thickening in stereo fundus photographs more sensitive than OCT? Table 1 shows that, in this study, stereo fundus photographs tended to be more sensitive than OCT for the detection of retinal thickening. Thus, in five of nine fields, the majority of disagreements were in favor of retinal thickening present on stereo fundus photographs but absent on OCT. Two fields showed no bias on disagreements, and two fields were biased toward OCT being the more sensitive method, yet not significantly. Table 2 shows that 9 of 82 eyes showed a larger area of retinal thickening on stereo fundus photographs than on OCT, whereas only 4 of 82 eyes were found to have a larger area of retinal thickening on OCT than on stereo fundus photographs. In addition, in three eyes, OCT showed no retinal thickening, whereas thickening was present on stereo fundus photographs. Given that the OCT retinal thickness was compared with a mean value of retinal thickness in healthy control subjects + 2 SD and not just with the mean retinal thickness, the bias toward fundus photographs showing retinal thickening more often than OCT was expected. Very subtle lesions (i.e., above mean retinal thickness, yet below mean retinal thickness + 2 SD in healthy control subjects’ eyes) simply would not be detectable on the topographical OCT map. However, these subtle changes can be observed on individual OCT retinal profiles.

Previously, OCT has been reported to be more sensitive than slit lamp biomicroscopy for detection of small changes in retinal thickness (i.e., changes of <100 μm greater than the mean retinal thickness in normal subjects). Changes of this magnitude are too subtle for the human eye to detect on stereo fundus photographs as well as on binocular slit lamp biomicroscopy, the latter presumably being the better way of assessing retinal thickening. The sensitivity of OCT for detection of subtle retinal lesions could be enhanced by generating a topographical scan using mean values of retinal thickness in healthy control subjects + 1 SD (instead of + 2 SD) as a baseline comparison. A longitudinal study of changes in retinal thickening could measure very small changes in retinal thickness, given that the study eye is compared with itself at baseline. However, in this study and for clinical purposes, retinal thickening of less than the mean healthy control value + 2 SD was considered not to represent macular edema.

Hard exudates can be an important factor in relation to the detection of retinal thickening by subjective assessment of edema on fundus photographs. ETDRS report 5 describes hard exudates as very likely to be associated with retinal thickening, even if the thickening is not apparent on the fundus photograph. The fundus photographs in this study were strictly evaluated with respect to definite retinal thickening. Appreciable macular hard exudates by themselves were not sufficient to qualify the eye as having retinal thickening. Hard exudates increase retinal thickness in the OCT software algorithm. However, the effect of shadowing caused by exudates on the RPE is modest. Typically, a maximum increase of 5% in retinal thickness is found just beneath the hard exudate.

Lens opacification could also present a problem for both methods. Decreased clarity of the photographs was seen with increasing lens opacification, and the quality of OCT scans could also have been impaired. In the present study, three eyes were excluded from the data set due to poor photograph quality. In addition, in one eye with lens opacification, the OCT signal was too impaired, and no retinal profile could be assessed. This eye was also excluded. However, in general, the OCT did not seem to be prone to impairment by cataract (JL Hougaard et al., Department of Ophthalmology, Herlev Hospital, Copenhagen, Denmark, personal communication, November 2000).

OCT is a noninvasive, patient- and operator-friendly technique that has the advantage of quantitating retinal thickness, and it has been shown to be reproducible by several authors. In addition, the results of this study show that OCT assessment of retinal thickening corresponded very well to subjective assessment of retinal thickening by grading of stereo fundus photographs and that the OCT was reliable for determining the location and extent of retinal thickening. These results suggest that changes in diabetic macular edema can be accurately and prospectively measured with the OCT in both clinical trials and clinical practice.

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References