Detection of Diabetic Foveal Edema

Contact Lens Biomicroscopy Compared With Optical Coherence Tomography

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Objective: To compare contact lens biomicroscopy with optical coherence tomography (OCT) for the detection of diabetic foveal edema.

Methods: Study participants consisted of a convenient cohort of consecutive patients with diabetes mellitus seen at the Wilmer Eye Institute’s Retinal Vascular Center, Baltimore, Md. Case characteristics were recorded and eyes were examined by 1 of 4 retina specialists by means of contact lens biomicroscopy. Edema involving the center of the macula was assessed as definitely present, questionably present, or definitely not present. The OCT testing was performed and interpreted by trained technicians, masked to the physicians’ assessment of foveal edema. Agreement between OCT and contact lens examination for the absence or presence of foveal edema was evaluated.

Results: One hundred seventy-two eyes of 95 patients with diabetes were enrolled in August and September 2002. Foveal thickness was objectively measured by OCT in 170 (99%) of 172 cases. We found excellent agreement between OCT and contact lens examination for the absence or presence of foveal edema when OCT thickness was normal (≤200 µm) or moderately to severely increased (>300 µm). However, agreement was poor when foveal thickness was mildly increased on OCT (201-300 µm).

Conclusions: Agreement between contact lens examination and OCT for the detection of diabetic foveal edema is poor when OCT thickening is mild. This suggests that contact lens biomicroscopy is relatively insensitive for the detection of mild foveal thickening apparent on OCT. Additional studies are needed to investigate the natural course of cases with mildly increased foveal thickness on OCT that do not appear thickened clinically.


THE CLINICAL GOLD STANDARD for the detection of macular edema is viewing the fundus with a contact lens at the slitlamp through a pharmacologically dilated pupil. This is a complex psychomotor process that is highly dependent on observer skill and experience, patient cooperation, the degree of pupillary dilation, the amount of media opacity, and the pattern and extent of retinal edema. Recently, devices that can objectively measure retinal morphologic characteristics, such as the optical coherence tomography (OCT) scanner1 and the retinal thickness analyzer,2 have entered the commercial market. Many studies have reported that OCT3-12 and the retinal thickness analyzer6,13-16 can accurately and reliably quantify macular retinal thickening in diabetic patients.

Strom et al7 recently carried out a study that demonstrated good agreement between stereoscopic color fundus photography and OCT for the detection of retinal edema. However, a comparison of OCT with the current clinical standard of contact lens biomicroscopy for the detection of macular edema has not been reported. The goal of this study was to determine the level of agreement between OCT and contact lens biomicroscopy for the detection of diabetic foveal edema and to search for characteristics that might predict disagreement between these modalities. Because of the tremendous public health impact of diabetic retinopathy and the skill and equipment needed for biomicroscopic examination, detection of macular edema by an objective technique such as OCT followed by the prompt initiation of treatment could improve visual outcomes for many diabetic patients. The use of OCT was chosen for the objective measurement of retinal thickness in this study because of our perception that this instrument was more widely available in ophthalmic practices than other objective measurement devices.

Methods: Study interventions were performed in addition to, and not as a substitute for, routine ophthalmologic care as part of new-patient and fol-
low-up clinical encounters. All aspects of this investigation were approved by The Johns Hopkins Institutional Review Board, Baltimore, Md, and all subjects gave informed consent before enrollment in the study.

Study participants consisted of a convenient cohort of consecutive diabetic patients with varying levels of retinopathy, including the absence of retinopathy, examined in the Retinal Vascular Center at the Wilmer Eye Institute, Baltimore, during a 6-week period in August and September 2002. "Convenient" implied that every patient seen during that period in the Retinal Vascular Center with diabetic retinopathy who might meet the study’s inclusion criteria was invited to participate by one of the study investigators (J.C.B.) if that investigator was present in the clinic and not interacting with another study participant at the time. Each eye of a study participant was eligible for enrollment provided that the eye underwent ophthalmologic examination and OCT testing during the study visit. Exclusion criteria included the presence of any retinal or choroidal disease, other than diabetes, that could affect retinal thickness or preclude identification of edema involving the center of the macula. Media opacity was not an exclusion criterion provided that the investigator could assess the presence or absence of retinal edema on biomicroscopic examination.

Patient characteristics, including age, race, gender, duration of diabetes, type of diabetes, history of previous laser photocoagulation or intraocular surgery, lens status, and visual acuity, were recorded. Age was defined as that at the time of examination. Race and gender were self-reported by the patient. Duration of diabetes was defined as time between the self-reported age at initial diabetes diagnosis and the age at the time of examination. Type of diabetes was defined as early onset (age <30 years) or late onset (age ≥30 years) on the basis of age at initial diagnosis. Past ocular treatment and phakic status were determined by review of the patient’s medical records, including those of referring physicians, and the ophthalmologic examination. Visual acuity was determined by means of the patients’ habitual refractive correction with a standard Early Treatment Diabetic Retinopathy Study chart and was recorded as logarithm of the minimum angle of resolution.

Each subject was examined by 1 of 4 retina specialists (S.D.S., S.B.B., A.P.S., or N.M.B.), who performed contact lens biomicroscopy after pharmacologic pupilary dilation. The investigators assessed retinal thickness at the center of the macula in terms of edema being definitely present, questionably present, or definitely not present. The level of retinopathy was recorded as none; mild, moderate, or severe nonproliferative; or proliferative. Immediately after clinical examination, the chart note from that day was reviewed by the study coordinator (J.C.B.). The presence or absence of a vitreomacular interface abnormality was recorded. For cases without foveal thickening or with questionable foveal thickening on clinical examination, the presence or absence of definite extrafoveal macular edema was also recorded.

After clinical examination and review of the chart note were completed, OCT (OCT3; Zeiss-Humphrey Systems, Dublin, Calif) and measurement of pupillary diameter were carried out by a trained OCT technician, masked to the physician’s assessment of foveal edema. The OCT images were generated with the use of 6 µm radial scans in a spokelike pattern according to manufacturer protocol as described in the user’s manual. The OCT operator closely monitored patient fixation under direct visualization, and scanning was repeated until all reasonable attempts had been made to obtain excellent fixation maintained over the entire 1.92 seconds. Each of the 6 line scans then was reviewed individually to determine whether some or all of the scans imaged the center of the fovea. If none of the line scans imaged the foveal center, then the scan was repeated. Once all reasonable attempts had been made to obtain an adequate line scan, the foveal thickness was manually measured by placing calipers at the vitreous-retina and retina-RPE interfaces. Each scan then was interpreted by a second masked observer (C.D.), who assessed the quality of the OCT image as either adequate or inadequate and recorded the retinal thickness in microns at the center of the macula.

The clarity of media was assessed indirectly by means of stereoscopic fundus photographs obtained as part of routine care when available. Photographs were used only if obtained on the same day as the clinical evaluation and were assessed by ophthalmologists who train graders at the Wilmer Photographic Reading Center, Baltimore. The quality of media was recorded as poor, fair, or good.

Descriptive statistics such as frequency, range, mean, and standard deviation were calculated for case characteristics. Percentage agreement, weighted κ, and Pearson correlation coefficient were calculated to compare contact lens examination results with the OCT data. Logistic regression analysis using backward elimination was carried out to search for selected case characteristics that might be associated with disagreement between OCT and clinical examination or the presence of questionable foveal edema by contact lens examination. Characteristics included in the analyses were quality of media, pupillary diameter, vitreomacular interface abnormality, extrafoveal macular edema, level of retinopathy, and severity of OCT thickening.

The design of this study required a finite cutoff for the upper level of normal foveal thickness in patients without diabetes. Unfortunately, normalized data on foveal thickness in healthy control subjects obtained with the OCT3 were not available at the time of this investigation. Therefore, we reviewed the existing literature in which foveal thickness was measured by OCT in healthy controls without diabetes1,6,8,10-12 (summarized in Table 1). Our analysis suggests that 200 µm represents a reasonable and convenient cutoff for the upper level of normal foveal thickness in healthy nondiabetic adults. We defined an OCT foveal thickness of 200 µm or less as normal, 201 to 300 µm as mild thickening, 301 to 400 µm as moderate thickening, and greater than 400 µm as severe thickening.

RESULTS

We approached 107 patients and requested that they consider participation in the study. Ninety-seven patients (91%) agreed, completed the informed consent process, and were enrolled. Two patients were excluded after enrollment because one was unable to complete OCT testing during the clinic visit as a result of time constraints and another left before OCT testing without offering an explanation. One hundred seventy-two eyes of 95 patients completed the study. Case characteristics are

<table>
<thead>
<tr>
<th>Source, y</th>
<th>No. of Cases</th>
<th>Mean Foveal Thickness (95% Confidence Interval), µm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hee et al,3 1998</td>
<td>73</td>
<td>174 (138-210)</td>
</tr>
<tr>
<td>Neubauer et al,9 2001</td>
<td>21</td>
<td>153 (123-183)</td>
</tr>
<tr>
<td>Sanchez-Tocino et al,4 2002</td>
<td>26</td>
<td>145 (113-177)</td>
</tr>
<tr>
<td>Massin et al,10 2002</td>
<td>60</td>
<td>170 (154-206)</td>
</tr>
<tr>
<td>Goebel and Kretzchner-Gross,11 2002</td>
<td>30</td>
<td>153 (123-183)</td>
</tr>
<tr>
<td>Lattanzio et al,12 2002</td>
<td>50</td>
<td>162 (136-188)</td>
</tr>
</tbody>
</table>

Abbreviation: OCT, optical coherence tomography.
summarized in Table 2 and Table 3. The OCT scans were of sufficient quality for interpretation in 170 (99%) of 172 cases. In both cases of uninterpretable scans, the OCT operator attributed the poor image quality to media opacity.

Of the 172 eyes, edema involving the center of the macula by biomicroscopy was definitely present in 33 (19%), questionably present in 14 (8%), and definitely not present in 125 (73%) of the cases. Objective foveal thickness measurements were obtained by OCT in 14 (100%) of 14 cases with questionable foveal edema by contact lens examination. The clinical presence of foveal thickening demonstrated good positive correlation with increasing OCT thickness (Pearson coefficient = 0.634; P < .001).

Of 100 eyes with OCT thickness no greater than 200 µm (no OCT thickening), definite edema by biomicroscopy was detected in only 3 eyes, questionable edema in 11 eyes, and no edema in 86 eyes. Of 44 eyes with OCT thickness greater than 200 µm but no greater than 300 µm (mild OCT thickening), definite edema by biomicroscopy was detected in 8 eyes (18%), questionable edema in 2 eyes (5%), and no edema in 34 eyes (77%). Of 16 eyes with OCT thickness greater than 300 µm but no greater than 400 µm (moderate OCT thickening), definite edema by biomicroscopy was detected in 12 eyes (75%) and no edema in 4 (25%). Of 12 eyes with OCT thickness greater than 400 µm (severe OCT thickening), definite edema by biomicroscopy was detected in 10 eyes (83%), questionable edema in 1 (8%), and no edema in 1 (8%). Results organized by OCT thickness stratification are summarized in the Figure. Overall agreement between results of contact lens examination and OCT was only 119 (69%) of 172 eyes (weighted κ = 0.378; P < .001). However, the majority of disagreement occurred for cases with mild OCT thickening (>200 µm but ≤300 µm), where agreement was present in only 10 (23%) of 44 eyes. When cases of mild thickening were excluded, overall agreement was good and improved to 109 (85%) of 128 eyes (weighted κ = 0.697; P < .001).

 Logistic regression analysis was carried out to search for associations between selected case characteristics and disagreement between OCT and contact lens biomicroscopy data or the clinical determination of questionable foveal edema. False-negative clinical assessments (the absence of thickening by contact lens examination for cases with OCT thickness >200 µm) were associated with mild OCT thickening (P < .001) and milder retinopathy (P = .054). False-positive clinical assessments (the presence of thickening by contact lens examination for cases with OCT thickness ≤200 µm) were not associated with any of the characteristics evaluated. The presence of questionable foveal edema by contact lens examination was associated with the presence of definite extrafoveal macular edema (P < .001). Logistic regression associations are summarized in Table 4.

This prospective, masked, clinical case series is, to our knowledge, the first reported systematic comparison of contact lens biomicroscopy by skilled retina specialists with OCT for the detection of diabetic foveal edema in a large consecutive series of diabetic patients from one clinical center. By enrolling consecutive patients without visual acuity or media opacity restrictions, we studied a
representative cohort of diabetic patients receiving care at our center. The nearly equal numbers of men and women, inclusion of patients with both early- and late-onset diabetes, and the relatively balanced distribution of retinopathy levels supports the external validity of our findings. Whites and African Americans were well represented, but Hispanic Americans were notably absent from the study cohort.

Contact lens biomicroscopic examination was chosen over a comparison with a handheld 90- or 78-diopter lens, even though evaluation of diabetic retinopathy in clinical practice may be performed more often with non-contact lenses. There are at least 3 reasons for using contact lens biomicroscopy rather than a noncontact lens examination for assessing the presence or absence of edema clinically. First, a previous study at our clinical center demonstrated that noncontact lens biomicroscopy failed to detect questionable or definite clinically significant macular edema that was detected by contact lens biomicroscopy in approximately 10% of cases. Therefore, use of a contact lens examination is more likely to identify edema. Second, contact lens examinations facilitate the ability to avoid blinking and eye movement that might interfere with clinical assessment of macular edema compared with noncontact lens biomicroscopy. Third, the optics of the contact lens provide increased axial magnification, which facilitates the detection of subtle areas of edema that might not be detected with less axial magnification. These findings have led us to use contact lens examination routinely for evaluating the presence or absence of macular edema. (The routine use includes instillation of a drop of topical anesthetic followed by use of a contact lens with a hard contact lens wetting solution. This solution provides enough viscosity to allow coupling of the lens to the cornea, especially if the patient looks down into the lens at the time of application, with little likelihood of an air bubble to limit one's view. Also, the hard contact lens wetting solution does not interfere with subsequent examinations by indirect ophthalmoscopy or retinal photography.) In summary, the best clinical examination to assess the presence or absence of macular edema was judged to be contact lens examination clinically. We estimate that, if noncontact lens biomicroscopy of the macula had been performed, approximately 10% more cases of macular edema detected on OCT might not have been detected by clinical examination.

We found good agreement between OCT and contact lens examination for the presence or absence of foveal edema when OCT thickness was considered normal (≤200 µm) and when it was judged to be moderately to severely increased (>300 µm). However, agreement was poor when OCT foveal thickness was mildly increased (201-300 µm). It is not known whether results would have been similar if macular edema not involving the fovea had been evaluated. However, recent studies by Hee et al as well as Goebel and Kretzmar-Gross have demonstrated a strong correlation between extrafoveal and foveal thickness measurements, suggesting that results would be similar.

The failure of contact lens biomicroscopy to correlate with mild edema detected by OCT in this study is indirectly corroborated by several previous investigations. Shahidi et al showed that noncontact slitlamp biomicroscopy failed to detect retinal edema at locations with an average thickness of 1.5 times normal by examination with a retinal thickness analyzer. Yasukawa et al reported that OCT demonstrated foveal thickening in 9 (31%) of 29 eyes that appeared normal by noncontact biomicroscopic examination and 6 of 6 eyes with foveal thickening by slitlamp biomicroscopy. Oshima et al found that eyes with diabetic retinopathy and no macular edema on noncontact biomicroscopic examination had a mean foveal thickness on OCT of 283±116 µm compared with 564±168 µm for cases with clinically significant macular edema. Lattanzio et al reported that, among eyes with diabetic retinopathy, those with no macular edema on noncontact biomicroscopic examination had a mean foveal thickness on OCT of 228±53 µm, those with non–clinically significant macular edema had a mean foveal thickness on OCT of 322±124 µm, and those with clinically significant macular edema had a mean foveal thickness on OCT of 476±146 µm. All of these investigations suggest that clinical examination is relatively insensitive for the detection of mild macular edema evident by objective imaging methods.

We found a strong non–statistically significant trend toward an association between false-negative clinical assessments (the absence of thickening by contact lens examination for cases with thickness greater than 200 µm on OCT) and milder retinopathy. This was caused by 8 (35%) of 23 cases with mild nonproliferative retinopathy being labeled as having false-negative responses compared with 30 (21%) of 145 cases with more advanced retinopathy and was independent of OCT thickness measurements. The cause and significance of this association is not known. It is possible that investigators were more vigilant with biomicroscopic examinations when retinopathy was more advanced.

Pupillary diameter and media opacity were not associated with the clinician’s assessment of questionable foveal edema or disagreement between OCT and clinical examination results. However, the average pupillary diameter was 7.8 mm with a minimum of 5 mm. Furthermore, media opacity data were available only for 98

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**Table 4. Logistic Regression Analysis Results**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>False Positive</th>
<th>False Negative</th>
<th>Questionable Foveal Edema</th>
</tr>
</thead>
<tbody>
<tr>
<td>VMA</td>
<td>.95</td>
<td>.12</td>
<td>.80</td>
</tr>
<tr>
<td>Pupil diameter</td>
<td>.66</td>
<td>.96</td>
<td>.47</td>
</tr>
<tr>
<td>Extrafoveal edema</td>
<td>.91</td>
<td>.49</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td>Retinopathy level</td>
<td>.26</td>
<td>.054</td>
<td>.23</td>
</tr>
<tr>
<td>Poor media</td>
<td>.97</td>
<td>.73</td>
<td>.57</td>
</tr>
<tr>
<td>OCT mild edema</td>
<td>.85</td>
<td>&lt;.001†</td>
<td>.12</td>
</tr>
</tbody>
</table>

*Abbreviations: OCT, optical coherence tomography; VMA, vitreomacular interface abnormality.

†OCT mild edema indicates OCT foveal thickness measurements between 201 and 300 µm; false positive, the presence of thickening by contact lens examination for cases with OCT thickness by contact lens examination for cases with OCT thickness greater than 200 µm; and questionable foveal edema, the presence of questionable foveal edema by contact lens biomicroscopy.
(57%) of 172 cases, and the quality was graded as fair or good in 92 (94%) of 98 cases. Because small pupils and poor media quality were underrepresented, our study was underpowered to evaluate these characteristics adequately. However, because pupillary diameter and media quality were not specific exclusion criteria for participation, our data suggest that most patients presenting for care at a tertiary retinal center have ocular media sufficient to perform both contact lens biomicroscopy and OCT.

Optical coherence tomography, performed by skilled technicians, was able to produce interpretable thickness maps in 170 (99%) of 172 cases. This is consistent with findings of Polito et al, who recently reported obtaining retinal thickness measurements in 55 of 55 eyes with macular disease by means of OCT. The excellent technical performance of OCT supports its potential utility in clinical practice.

Contact lens examination rated the presence of foveal edema as questionable in 14 (8%) of 172 cases. Equivocal examinations were strongly associated with the presence of extrafoveal edema. This suggests that, for many cases with definite extrafoveal edema, it was not apparent whether edema was juxtafoveal or actually extended into the macular center.

There are 2 potential systematic errors that could account for the poor agreement between contact lens examination and mild thickening on OCT in this study. The first is the possibility that, for some cases without foveal edema, OCT demonstrated mild foveal thickening because of instrumentation errors. This is unlikely because Neubauer et al demonstrated that OCT yields reproducible foveal thickness measurements with a coefficient of variation of only 10% within subjects. Even if we assume that all cases with mild foveal thickening by OCT were 10% less thick than measured, agreement between contact lens examination and OCT would remain poor and the results of the study would be unaffected. The second possible systematic error is that, for many cases without foveal edema, OCT could have measured parafoveal rather than foveal thickness because of small amounts of scan decentration. This is unlikely for 3 reasons. First, the OCT technician took great care to ensure that at each scan was centered on the fovea both by asking the subject to look at the fixation target and by monitoring fixation under direct macular visualization. Second, the spokelike scanning pattern used by OCT affords a high density of thickness information at the center of the scan, making it unlikely that the foveal center would be omitted. Third, if the cases with mild thickening on OCT were not truly biologically edematous, contact lens examination would be expected to detect thickening in a proportion of cases similar to cases without thickening on OCT. Instead, clinical thickening was detected in only 3% of cases with no thickening on OCT compared with 18% of cases with mild OCT thickening.

We propose the term subclinical foveal edema to designate eyes with up to approximately a 50% increase in normal thickness (201-300 µm) by objective imaging methods, because we did not detect such thickening reliably by contact lens biomicroscopy. The short- and long-term clinical significance of subclinical edema is unknown. It does not seem reasonable at this time to extrapolate the results of the Early Treatment Diabetic Retinopathy Study to cases of subclinical edema, because it is likely that such thickening was present in cases judged to have edema and randomized to focal photocoagulation or deferral of treatment by the Early Treatment Diabetic Retinopathy Study investigators.

We recommend additional studies to determine whether subclinical foveal edema progresses to clinically apparent thickening more often than thickening develops in cases without subclinical edema. If such an outcome were found, then the presence of subclinical foveal edema could serve as a marker for eyes at higher risk for conversion to clinically apparent foveal edema and these patients could be monitored more frequently. To justify treatment of subclinical foveal edema, one would need to determine whether the treatment of subclinical thickening reduces the risk of vision loss to a greater degree than treatment at the time when the edema is apparent clinically.

In an era when ancillary testing is available to supplement clinical examination of diabetic patients, we recommend the following: (1) The presence of macular edema can be detected with noncontact lens examinations. However, the absence of macular edema with noncontact lens examinations may not necessarily indicate the absence with contact lens examinations. Therefore, if macular edema is not detected by a noncontact lens examination, the examiner may want to consider ruling out the presence of edema with a contact lens examination. (2) If macular edema is not detected by contact lens examination, the examiner may want to consider obtaining an OCT examination to determine whether “subclinical” edema (as defined earlier) is present. Eyes with “subclinical” edema may be more likely to progress to clinically evident edema for which focal laser photocoagulation may be indicated to reduce the risk of additional vision loss.

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REFERENCES

5. Yang CS, Cheng CY, Lee FL, Hsu WM, Liu JH. Quantitative assessment of retinal...


Archives Web Quiz Winner

Congratulations to the winner of our November quiz, Fatima Hamroush, MD, DO, FRCs, FRcophth(Edin), ophthalmic physician, Our Lady of Lourdes Hospital, Drogheda, Ireland, and Mater Misericordiae Hospital, Dublin, Ireland. The correct answer to our November challenge was multiple evanescent white dot syndrome. For a complete discussion of this case, see the Clinico-pathologic Reports, Case Reports, and Small Case Series section in the December ARCHIVES (Ray S, Loewenstein J. Atypical manifestation of multiple evanescent white dot syndrome with large peripapillary lesion. 2003;121:1794-1796).

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