**Agreement of the Heidelberg Retina Tomograph II Macula Edema Module With Fundus Biomicroscopy in Diabetic Maculopathy**

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**Objectives:** To estimate the agreement between the macular edema maps (MEMs) of the Retina Module of the Heidelberg Retina Tomograph II (Heidelberg Engineering, Heidelberg, Germany) and contact lens fundus biomicroscopy (FB) and to assess the influence of combining MEM data with the results of short-wavelength automated perimetry (SWAP) and fluorescein angiography (FA) on diagnostic test performance.

**Design:** Prospective, observational case series.

**Methods:** Twenty patients (20 eyes) with diabetic retinopathy with or without clinically manifest macular edema (11 and 9 eyes, respectively) were enrolled. All patients underwent full ophthalmologic examination and also MEM assessment, SWAP, and FA.

**Results:** Using FB as the “gold standard,” the agreement between the MEMs and FB was very good (Kendall coefficient of concordance, 0.80). Macular edema maps showed good agreement with FA and SWAP (Kendall coefficient, 0.64 and 0.65). Virtually all of the edematous areas detected with MEM but not seen clinically had decreased sensitivity on SWAP and/or fluorescein leakage.

**Conclusions:** Macular edema maps demonstrated very good agreement with FB. Combining the results of FA and SWAP with those of the MEMs provided supporting evidence of concomitant blood-retinal barrier leakage and visual dysfunction, respectively, in areas of early retinal thickening. Prospective studies are ongoing to fully assess the diagnostic test performance of MEMs in the detection of early and progressive diabetic macular edema.

_Diabetic retinopathy is the leading cause of visual impairment and blindness in the working population of Western countries._

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Diabetic patients were enrolled from the retina clinics at the Toronto Western Hospital, University Health Network, Toronto, Ontario. The study was approved by the research ethics board of the University Health Network, University of Toronto, and the Office of Research Ethics, University of Waterloo, Ontario. The research followed the tenets set out in the Declaration of Helsinki. Informed consent was obtained from all subjects. The sample comprised 20 patients (14 men, 6 women) with a mean±SD age of 59.15±7.1 years (range, 42-69 years). Nineteen patients had type 2 diabetes, and 1 patient had type 1 diabetes. The mean±SD duration of diabetes was 15±8.8 years (range, 4-42 years). Inclusion criteria comprised mild-to-moderate diabetic retinopathy, an age range of 40 to 70 years, and a logMAR visual acuity of 0.3 or better. Exclusion criteria comprised lenticular opacities that would impact substantially on fundus visualization, refractive error greater than ±6.00 diopter sphere and/or ±2.50 diopter cylinder, any other eye disorder or disease apart from diabetic retinopathy, previous laser treatment or surgery in the study eye, a family history of glaucoma in a first-degree relative, central nervous system or psychiatric diseases, systemic medications with known central nervous system effects, and unreliable automated perimetry results as defined by the Humphrey Field Analyzer II (Carl Zeiss Meditec Inc, Dublin, Calif). All patients underwent a full ophthalmologic evaluation, including logMAR visual acuity and refraction, slitlamp examination with contact lens stereo FB, FA, SWAP, and HRT II MEM. Pupillary dilation using 1.0% Mydriacyl (Alcon, Fort Worth, Tex) was undertaken for all procedures apart from logMAR visual acuity and refraction. All tests but FA were performed on the same day. One eye of each patient was randomly assigned to the study.

MEMS OF THE HRT II

The HRT II is a confocal laser scanning system for the acquisition and analysis of 3-dimensional images of the posterior segment of the eye. The laser source employed in the HRT II is a diode laser with a wavelength of 670 nm. A 3-dimensional image is generated as a series of 16 to 64 consecutive and equidistant (ie, 16 images every 1 mm of scan depth) 2-dimensional optical section images. Each of the 2-dimensional images consists of $384 \times 384$ picture elements. The scan field is $15^\circ \times 15^\circ$. Three sequential tomographic images are automatically scanned on initiation of image acquisition and are averaged to display a mean topography image. The edema index analysis developed by Flanagan and Hudson has been incorporated within the HRT II as part of the Retina Module. The HRT II Retina Module software computes reflectivity, topography, signal width, and edema maps. A full description of the edema index methodology has been detailed previously.14 The image acquisition was performed by experienced operators and 3 sets (ie, $3 \times 3$ images) of HRT II images were obtained for each patient.

The HRT II MEM images were subsequently assessed by an experienced MEM user. One of the 3 sets of images was chosen based on best image quality. The edema map was divided into 9 sectors using a grid formed by 3 concentric circles centered on the fovea and 4 radial lines extending outward from the innermost of these in the 45°, 135°, 225°, and 315° meridians (9-Zone Analysis). The radius of the innermost circle was 500 µm, and the radii of the second and the third circles were 1000 µm and 1500 µm, respectively. The total field size for the analysis was approximately $10^3$ in diameter (Figure 1). To minimize error in the positioning of the 9-sector grid on the MEM image, the foveal center was located on the basis of clinical and
FA assessments and marked on an acetate sheet that detailed each individual's retinal vascular pattern. This also ensured consistency in the positioning of the grid across all imaging modalities (FB, FA, and MEM) (Figure 2). The presence or absence of elevated edema index values was documented for each of the 9 sectors; 180 sectors (ie, 9 sectors × 20 patients) were analyzed for the group as a whole.

SHORT-WAVELENGTH AUTOMATED PERIMETRY

The macular visual field of each patient was determined with program 10-2 of the Humphrey Field Analyzer II using short-wavelength stimulus parameters and a standard full-threshold strategy. All subjects had previously undertaken at least 1 SWAP field, thus minimizing learning effects. The SWAP was assessed using a pointwise horizontal and vertical hemifield asymmetry analysis that has been detailed previously, thereby negating the influence of prereceptoral absorption. Abnormality was defined as 7 or more contiguous stimulus locations with statistically significant negative asymmetries. From the total of 68 stimulus locations, only 32 central points corresponding to a 10° field diameter were included in the comparative analysis. These 32 stimulus locations were divided into 9 predefined sectors approximately corresponding to the areas of the MEM (Figure 3). Each predefined sector comprised 4 points (4 points falling on the radial lines were double counted and included into the analysis of both adjacent areas). A given grid sector was considered abnormal if it contained at least 2 statistically significant points with negative SWAP asymmetry values, apart from the central 500-µm radius sector where only 1 abnormal point was required.

CONTACT LENS STEREO FB

Contact lens stereo FB was performed by retinal specialists masked to MEM results. For each patient, all areas of edema were drawn on an acetate sheet that detailed each individual's...
retinal vascular pattern while the patient was situated at the slitlamp. The 9-sector grid was overlaid on the sheet detailing the areas of retinal thickening to allocate the presence or absence of DME in each sector of the grid.

**FLUORESCIN ANGIOGRAPHY**

Fluorescein angiography was performed on all research patients. The interval between FA and the study tests was dictated by routine clinical care of the patient and ranged from the same day to 20 weeks (median, 8 weeks). Late phase and early phase angiograms were used to determine the presence and location of FA leakage according to Early Treatment Diabetic Retinopathy Study Research criteria. All areas of leakage on FA were drawn on an acetate sheet and sectors of involvement were documented in a similar manner to that of FB.

**STATISTICAL ANALYSIS**

Descriptive statistics such as mean, range, and standard deviation were calculated for case characteristics. Percentage of agreement and the Kendall coefficient of concordance were calculated using the pooled sectors to compare FB results with those of MEMs, SWAP, and FA.

**RESULTS**

Eleven patients had clinically evident macular edema and 9 patients had no edema by FB. Fourteen patients had an abnormal HRT II MEM. Fourteen patients had localized visual field loss using SWAP. Eleven patients had clinically evident macular edema and defined by MEMs as abnormal in 16 of 22 sectors (1.1 of 9). Similarly, FA detected a mean of 1.2 additional abnormal sectors while SWAP detected a mean of 1.75 sectors. The mean number of sectors with clinically evident retinal thickening and defined by MEMs as normal was 0.15 of 9, whereas for FA and SWAP, the mean numbers of normal sectors were 1.05 and 0.85, respectively (Table 4).

Analyzing only the sectors that were detected as abnormal by MEMs but that did not show retinal thickening on FB, the localized SWAP sensitivity loss was observed in 13 of 22 such sectors and FA leakage in 9 of 22 sectors, and decreased SWAP sensitivity and/or FA leakage was observed in 16 of 22 sectors (Table 5).

The HRT II MEMs and FB showed very good agreement in identifying areas with DME with a Kendall coefficient of concordance of 0.80 (P<.001). There was substantial agreement between MEMs and FA (Kendall coefficient, 0.64; P<.001) as well as between MEMs and SWAP (Kendall coefficient, 0.65; P<.001) (Table 3). Comparing MEMs with FA as the gold standard, MEMs demonstrated a sensitivity of 92% and specificity of 85%.

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Across the group, on average 1.85 of 9 sectors were noted as abnormal on FB. Fluorescein angiography, MEMs, and SWAP detected more abnormal sectors than FB (Table 2).

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**COMMENT**

Fundus biomicroscopy remains the clinical gold standard for the assessment of DME, but it relies on the subjective interpretation of thickening of an essentially transparent retina, has large interobserver variability, and lacks objective quantification. The development of a reproducible, objective technique to identify retinal edema and to monitor change in edema is widely recognized to be essential for the improved clinical management of DME per se and for the evaluation of new therapeutic protocols.

Currently available imaging technologies to assess DME include optical coherence tomography (OCT), the Retinal Thickness Analyzer, and the Macular Edema Module of the HRT II. Optical coherence tomography is widely used for the assessment of macular disease with different etiologies. Optical coherence tomography has very good agreement with contact lens FB, although it has been reported to be prone to artifacts arising in the process of macular surface map reconstruction. The Retinal Thickness Analyzer works on the principle of slitlamp FB and in our experience shows poor sensitivity and moderate specificity in the assessment of the retinal thickness of diabetic patients.
The Macular Edema Module represents a relatively new and promising application for the detection and follow-up of DME. The Macular Edema Module generates an edema index that reflects increase in retinal thickness and reduction in retinal reflectivity due to changes in retinal refractive index in areas of edema. The reliance of the Macular Edema Module technique on 2 optical principles for the detection of edema is thought to increase the sensitivity. Compared to OCT, the HRT II has inferior axial resolution; however, it has far superior spatial resolution and thereby avoids the undersampling in the periphery of the image that is inherent in the OCT macular maps. This study and previous work from our laboratory demonstrated that MEMs offer very good sensitivity and similar specificity in detecting macular edema compared to FB. The Macular Edema Module generates high spatial resolution topographic edema maps and, unlike any of the current imaging technologies, offers facility for the precise alignment of images acquired over successive visits, an essential feature for any sequential analysis. The extent to which all imaging technologies are influenced by the ocular media, corneal drying, and excessive eye movements is uncertain, but experience suggests that such factors impact the diagnostic test performance of every modality.

The lower specificity of MEMs when compared with FB may be due to the fact that the Macular Edema Module detects edema-related changes that are not yet clinically manifest using FB. The failure of FB to correlate with alternative objective techniques for the assessment of retinal thickness has been reported by previous investigators. Brown et al proposed the term subclinical edema for such cases. The assessment of the blood-retinal barrier integrity and short-wavelength pathway function in areas of possible subclinical DME was used in our study to validate the MEM results. The presence of edema suggests blood-retinal barrier breakdown, and areas of retinal edema largely, although not completely, coincide with areas of fluorescein leakage. Similarly, localized SWAP sensitivity loss has been shown to correspond with the clinical mapping of the area of DME, but the extent of this loss was found to be generally greater than that suggested by clinical assessment. Although SWAP visual field defects in diabetic maculopathy may also be caused by ischemic damage in the absence of DME, the larger area of defect most likely reflects subtle changes in retinal thickness, particularly given the clinical characteristics of the patients described in this study.

### Table 3. Agreement Between MEMs and FB, FA, and SWAP (in Number of Areas)

<table>
<thead>
<tr>
<th>Tests</th>
<th>Agreement</th>
<th>Total Sectors, No.</th>
<th>Sectors per Patient, Mean, No.</th>
<th>Kendall Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEMs vs FB</td>
<td>Positive</td>
<td>34/180</td>
<td>1.7/9</td>
<td>0.80 (P&lt;.001)</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>121/180</td>
<td>6.05/9</td>
<td></td>
</tr>
<tr>
<td>MEMs vs FA</td>
<td>Positive</td>
<td>24/180</td>
<td>1.2/9</td>
<td>0.64 (P&lt;.001)</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>117/180</td>
<td>5.85/9</td>
<td></td>
</tr>
<tr>
<td>MEMs vs SWAP</td>
<td>Positive</td>
<td>31/180</td>
<td>1.55/9</td>
<td>0.65 (P&lt;.001)</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>100/180</td>
<td>5/9</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: FA, fluorescein angiography; FB, fundus biomicroscopy; MEMs, macular edema maps; SWAP, short-wavelength automated perimetry.

### Table 4. Disagreement Between FB, MEMs, FA, and SWAP

<table>
<thead>
<tr>
<th>Tests</th>
<th>Total Sectors, No. (of 180)</th>
<th>Sectors per Patient, Mean, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEMs positive/FB negative</td>
<td>22/143</td>
<td>1.1/7.15</td>
</tr>
<tr>
<td>MEMs negative/FB positive</td>
<td>3/37</td>
<td>0.15/1.85</td>
</tr>
<tr>
<td>FA positive/FB negative</td>
<td>24/143</td>
<td>1.2/7.15</td>
</tr>
<tr>
<td>FA negative/FB positive</td>
<td>21/37</td>
<td>1.05/1.85</td>
</tr>
<tr>
<td>SWAP positive/FB negative</td>
<td>35/143</td>
<td>1.75/7.15</td>
</tr>
<tr>
<td>SWAP negative/FB positive</td>
<td>17/37</td>
<td>0.85/1.85</td>
</tr>
</tbody>
</table>

Abbreviations: FA, fluorescein angiography; FB, fundus biomicroscopy; MEMs, macular edema maps; SWAP, short-wavelength automated perimetry.

### Table 5. Agreement Between Modalities (MEMs, SWAP, FA) for Additional Abnormal Areas Found Within the MEMs

<table>
<thead>
<tr>
<th>Test</th>
<th>Total Sectors, No.</th>
<th>Sectors per Patient, Mean, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEMs positive/FB negative</td>
<td>22/143</td>
<td>1.1/7.15</td>
</tr>
<tr>
<td>SWAP agreed with MEMs</td>
<td>13/22</td>
<td>0.65/1.1</td>
</tr>
<tr>
<td>FA agreed with MEMs</td>
<td>9/22</td>
<td>0.45/1.1</td>
</tr>
<tr>
<td>SWAP and/or FA agreed with MEMs</td>
<td>16/22</td>
<td>0.8/1.1</td>
</tr>
</tbody>
</table>

Abbreviations: FA, fluorescein angiography; FB, fundus biomicroscopy; MEMs, macular edema maps; SWAP, short-wavelength automated perimetry.

We assessed the MEMs using a 9-sector grid rather than define the image as normal or abnormal as a whole. This approach allowed more precise assessment of MEMs and a topographic comparison of different techniques used for the detection of abnormality associated with the occurrence of DME. Macular edema maps showed excellent agreement with FB but tended to show a greater extent of abnormality. Almost all sectors identified as abnormal using MEMs but normal with FB and revealed some abnormality on SWAP and/or FA, suggesting the presence of functional and structural changes. Thus, combining the findings of FA and SWAP with the MEM scans provided supporting evidence of abnormality in areas of subclinical retinal edema. Ideally, a prospective study with a larger group of patients will determine whether these positive MEM findings will progress to clinically evident retinal edema. Such a study, also incorporating OCT, is currently in progress in our laboratory.
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REFERENCES


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