Shedding new light on diabetic retinopathy with optical coherence tomography

van Dijk, Hille

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 2

Variability in photocoagulation treatment of diabetic macular edema

Hille W. van Dijk 1, Frank D. Verbraak 1,2, Pauline H.B. Kok 1, Sarit Y. Lesnik Oberstein 1, Reinier O. Schlingemann 1,3, Stephen R. Russell 4,6, Michael D. Abràmoff 4,5,6

1 Dept. of Ophthalmology, Academic Medical Center, Amsterdam, The Netherlands
2 Dept. of Biomedical Engineering and Physics, Academic Medical Center, Amsterdam, The Netherlands
3 Dept. of Clinical and Molecular Ophthalmogenetics, The Netherlands Institute for Neuroscience, Royal Netherlands Academy of Arts and Sciences (KNAW), Amsterdam, The Netherlands
4 Dept. of Ophthalmology and Visual Sciences, The University of Iowa Hospital and Clinics, Iowa City, USA
5 Dept. of Electrical and Computer Engineering, The University of Iowa, Iowa City, USA
6 Department of Veterans Affairs, Iowa City, USA

ABSTRACT

**Purpose:** To establish whether differences in the assessment of diabetic macular oedema (DME) with either optical coherence tomography (OCT) or stereoscopic biomicroscopy lead to variability in the photocoagulation treatment of DME.

**Methods:** The differences in the assessment of DME with either OCT or stereoscopic biomicroscopy were analysed by calculating the surface areas and the overlap of retinal thickening. Photocoagulation treatment plans of retinal specialists were compared by evaluating the number and location of planned laser spots.

**Results:** The threshold for and dosage of photocoagulation differ depending upon whether the basis of retinal thickness diagnosis is clinical observation or OCT. The overlap in laser spot location based on the assessment of DME with OCT or biomicroscopy averages 51%. Among retinal specialists, the treatment plans differed in the laser spot count by six- to 11-fold.

**Conclusion:** Diabetic macular oedema photocoagulation treatment threshold and dosage of laser spots differ depending on whether thickness assessments are based on stereoscopic slit-lamp biomicroscopy or OCT. In addition, retinal specialists differed in the number and placement of planned laser spots even when given identical information concerning DME and treatable lesions. This variability in the photocoagulation treatment of DME could lead to differences in patient outcome and laser study results.
INTRODUCTION

Diabetic macular oedema (DME) is the most common cause of visual loss in patients with diabetic retinopathy. DME is characterized by retinal thickening, hard exudates and capillary microaneurysms. The Early Treatment Diabetic Retinopathy Study (ETDRS) showed that careful patient selection and timely treatment by photocoagulation of thickened retinal areas slow visual loss from DME. The ETDRS defined DME as being “clinically significant” based upon the distribution and extent of retinal thickening and the presence of hard exudates. In the ETDRS, photocoagulation treatment was directed at all “treatable lesions” identified by ophthalmoscopic examination and/or fluorescein angiography (FA) within two disc diameters of the centre of the macula if they were associated with retinal thickening. FA is used in the standard photocoagulation workup to exclude other causes of visual loss, such as ischaemic maculopathy, as well as to identify “treatable lesions”. The characteristics of these treatable lesions are discrete points of retinal hyperfluorescence, focal leakage, areas of diffuse leakage and thickened retinal avascular zones.

Adequate stereopsis of the treating physician is an assumed prerequisite for analysis of DME with stereoscopic slit-lamp biomicroscopy. Stereoscopic slit-lamp biomicroscopy is highly dependent on the skills and experience of the observer, dioptic power and type of the examining lens, patient cooperation, media opacities, pupil dilation, and the location, gradation and extent of retinal oedema. Optical coherence tomography (OCT) is a non-invasive, non-contact technique that creates cross-sectional images of the retina. OCT enables evaluation of the macular contour and intra- and subretinal fluid collections and allows objective and accurate measurement of retinal thickness. Previous studies show that OCT provides a more sensitive measure of retinal thickening than stereoscopic biomicroscopy and stereoscopic fundus photography. Macular thickness measurements obtained with the Stratus OCT using the fast macular mapping protocol have been shown to be repeatable and reproducible in previous studies.

Optical coherence tomography can be used in addition to or even instead of stereoscopic biomicroscopy to determine the location of DME. In practice, and because of physician time constraints, many clinicians already substitute OCT for contact lens examination. We are not aware of any comprehensive studies that address the difference in threshold and dosage of photocoagulation treatment when OCT is used to judge thickening instead of clinical biomicroscopy. The purpose of this pilot study is to determine whether photocoagulation treatment for DME would differ based on these different assessment techniques.
MATERIALS AND METHODS

Patients and Consent Process
In January 2006 until March 2006 and September 2007 until January 2008, patients recruited from the outpatient clinic of the Department of Ophthalmology at the Academic Medical Center (University Hospital, Amsterdam, The Netherlands) were asked to participate in this observational study. The study adhered to the tenets of the Declaration of Helsinki. Investigative review board approval was obtained at the AMC, and all participants gave written informed consent. Study observations were made in addition to standard ophthalmologic care. The study did not interfere in any way with the standard care.

Inclusion and Exclusion Criteria
Patients were included if they had a diagnosis of diabetes mellitus (DM) and a clinical suspicion of DME as determined by a retinal specialist through slit-lamp stereoscopic biomicroscopy after pupil dilation with 0.5% phenylephrine hydrochloride and 1.0% tropicamide. Exclusion criteria were significant media opacities, refractive errors over SE+5 or under SE-8 diopters, previous ocular surgery including previous photocoagulation treatment, or a previous diagnosis of glaucoma, uveitis, or retinal disease. Best-corrected visual acuity was measured using an Early Treatment Diabetic Retinopathy Study chart at 4 meters and recorded as Snellen equivalent. All patients underwent colour fundus photography (TRC-50IX; Topcon Corporation, Tokyo, Japan), FA, stereoscopic slit-lamp biomicroscopy and OCT.

Stereoscopic slit-lamp biomicroscopy
A medical retinal specialist, masked to the OCT readings, performed stereoscopic biomicroscopy utilizing a 78-D hand-held lens (Volk Optical, Inc., Mentor, OH). Any observed retinal thickening defined as CSME by the ETDRS was sketched on a fundus photograph.

Optical Coherence Tomography
All subjects were imaged with the Stratus OCT (Model 3000; Carl Zeiss Meditec, Dublin, CA, USA, software version 4.0.1), using the fast macular thickness OCT scan protocol. The macular mapping algorithm interpolates the thickness measurements of the six radial OCT scans resulting in a topographic map of the central ETDRS regions. Colour coding was used to compare local thickness to a proprietary normative database of the Stratus OCT (Fig 1). Areas of DME were measured from the OCT topographic map, based on criteria as close as possible to those of the ETDRS. The term “treatable macular oedema” (TME) is used to differentiate the assessment of DME utilizing OCT from the assessment utilizing biomicroscopy or stereoscopic fundus photography. TME is analogous to CSME, but thickening is derived from OCT (Table 1). For the presence of TME, specific thresholds were chosen for “thickening”: an area within 500 µm of the fovea, either 2 SD greater than normal or more
than 50 µm thicker than retinal thickness equidistance from fovea. Contour maps indicating the presence, location and extent of TME were outlined by a second retinal specialist, masked to the stereoscopic biomicroscopy examination, on a second colour fundus photograph of each patient (Fig 1).

![Fig. 1. (A) Colour fundus photography; (B) OCT topographic map; (C) Presence, location and extent of CSME as assessed on OCT and hand-sketched on a colour fundus photograph.](image)

<table>
<thead>
<tr>
<th>Table 1. Definition of treatable macular oedema</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Areas of retinal thickness (RT) &gt; 2 standard deviations (SD) thicker than mean RT of normal controls, larger than 50 µm in diameter, of which any part is within 500 µm of the fovea</td>
</tr>
<tr>
<td>2) Areas of RT more than 50 µm thicker than equidistant foveal retina, larger than 50 µm in diameter, of which any part is within 500 µm of the fovea</td>
</tr>
<tr>
<td>3) Hard exudates at, or within, 500 µm of the fovea, if associated with an area of retinal thickening as described in criteria 1 and 2</td>
</tr>
<tr>
<td>4) Areas of retinal thickening of 2 SD, one disc area or larger in size, any part of which is within one disc diameter of the centre of the macula</td>
</tr>
</tbody>
</table>

**Photocoagulation treatment plans**

Using the Truthseeker (IDx LLC, Iowa City, IA, USA) program, four retinal specialists independently reviewed the fundus images with the contour map of either TME or CSME (Fig 2). The fundus images with contour map of CSME were horizontally mirrored prior to presentation to improve masking. They used early/mid/late phases of FA in a standardized format and order to localize the treatable lesions. They then marked the position, and number of planned photocoagulation spots on the corresponding colour fundus photograph.

**Data Analysis**

The extent and location of CSME and TME were compared using Imagenet I-base (version 3.5.4; Topcon Europe Medical, Capelle a/d/IJssel, the Netherlands). Both the CSME and TME areas were marked in the corresponding fundus image. With Imagenet I-base, it is possible to accurately calculate surface areas of CSME, TME and the CSME-TME overlap in mm².
For each individual retinal specialist, the photocoagulation treatment plans based on CSME or TME were evaluated and compared as follows. For each retinal specialist, the number and location of planned laser spots were calculated and evaluated individually. The treatment overlap was defined as the fraction of identical planned laser spot locations for each retinal specialist to the total number of laser spots. Placement of laser spots was considered identical when the laser spots were marked within an area of approximately 0.5 mm$^2$ of each other.

Thirdly, the photocoagulation treatment plans of the four retinal specialists, who were provided with identical information concerning presence and location of DME and treatable lesions, were analyzed and compared. The overall number of laser spots and the number of laser spots confined to the area of retinal thickening - CSME or TME - were counted for each retinal specialist. The agreement between the four different retinal specialists concerning the number of laserspots was defined using the intraclass correlation coefficient.

![Image](image.png)

**Fig. 2.** Documented example of a laser treatment plan using the Truthseekerj program. Biomicroscopy or OCT determined thickening are indicated by red circles. The retinal specialists marked all the locations where they would apply focal laser coagulation with yellow targets. The program shows a fundus photograph with and without marked thickening, a red-free photograph and early- and late-phase fluorescein angiogram images.

**RESULTS**

Of the 16 subjects (24 eyes) with diabetes analysed, the age was 60 ± 12 years (mean ± SD). Sixty-two percent were women. Fifteen subjects were patients with type 2 diabetes. One subject was patient with type 1 diabetes. The mean duration of diabetes was 15 ± 7 years (mean ± SD). Mean visual acuity in study eyes was 20/32 (ETDRS chart: 77 ± 11 letters).
Variability in photocoagulation treatment of diabetic macular edema

Comparison of TME and CSME
The assessment of DME differed between stereoscopic slit-lamp biomicroscopy and OCT. In only 16 of 24 eyes (67%) both methods detected DME. In three of these 16 eyes, the assessment of TME and CSME was identical in both area and location. In Fig. 3, four examples of the differences between the assessment of TME and CSME are depicted. In four eyes, CSME was marked, while no TME was marked anywhere (see Subject 1 in Fig. 3). In four eyes, TME was marked, but no CSME was marked (see Subject 2 in Fig. 3). In the remaining 13/16 eyes both CSME and TME were marked, but their location and area were different (see Subjects 3 and 4 in Fig. 3). The mean surface area of DME assessed with OCT was 5.89 ± 4.95 mm². The mean surface area of DME assessed with stereoscopic biomicroscopy was 4.02 ± 4.93 mm². The mean area of overlap (2.31 ± 2.49 mm²) between the two assessments was 30% of the total area of thickening of the two assessments combined (7.60 ± 4.95 mm², see Table 2).

Table 2. The area of DME assessed by biomicroscopy and OCT

<table>
<thead>
<tr>
<th></th>
<th>Biomicroscopy</th>
<th>OCT</th>
<th>OCT+biomicroscopy</th>
<th>Overlap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean DME</td>
<td>4.02 ± 4.93 mm²</td>
<td>5.89 ± 4.95 mm²</td>
<td>7.60 ± 4.95 mm²</td>
<td>2.31 ± 2.49 mm²</td>
</tr>
</tbody>
</table>

Values are the mean ± standard deviation. DME = diabetic macular edema, OCT = optical coherence tomography.

Comparison of photocoagulation treatment plans
Differences in the assessment of DME with OCT or stereoscopic biomicroscopy appeared to lead to different photocoagulation treatment decisions. Figure 4 demonstrates that the photocoagulation treatment plans of four retinal specialists differ depending on whether thickness assessments are based on stereoscopic slit-lamp biomicroscopy or OCT. The overlap in location of laser spots based on CSME or TME averages 51% (Table 3).

Table 3. The overlap in laser spot location based upon CSME versus TME scenarios.

<table>
<thead>
<tr>
<th>Retina Specialist</th>
<th>Specialist 1</th>
<th>Specialist 2</th>
<th>Specialist 3</th>
<th>Specialist 4</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overlap in laser spot location</td>
<td>43 ± 45%</td>
<td>49 ± 44%</td>
<td>57 ± 45%</td>
<td>53 ± 43%</td>
<td>53 ± 42%</td>
</tr>
</tbody>
</table>

The treatment overlap was defined as the proportion of identical planned laser spot locations for each retina specialist in relation to total number of laser spots. Values are the mean ± standard deviation. S1, S2, S3 and S4 represent the different individual retina specialists. CSME = clinically significant macula edema, TME = treatable macular oedema.
Fig. 3. Four examples of the differences between the assessment of treatable macular oedema (TME) and CSME. Each panel represents one subject. Within each panel, the subpanels are marked as follows: (A) Optical coherence tomography (OCT) - based TME; (B) Stereoscopic slit-lamp biomicroscopy based CSME; (C) Early-phase fluorescein angiography (FA) image; (D) Late-phase FA image. In Example 1, CSME is shown, while assessment with OCT did not show TME. In Example 2, TME is shown while assessment with stereoscopic slit-lamp biomicroscopy did not show CSME. In Example 3 and 4, both CSME and TME are shown, but the extent and location differ considerably.

Table 4. Placement and number of laser spots by retinal specialist

<table>
<thead>
<tr>
<th>Assessment method</th>
<th>Stereoscopic biomicroscopy</th>
<th>OCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinal specialist</td>
<td>S1</td>
<td>S2</td>
</tr>
<tr>
<td>Average number of laser spots</td>
<td>5.1</td>
<td>23.4</td>
</tr>
<tr>
<td>Average number of laser spots within retinal thickening</td>
<td>1.7</td>
<td>10.1</td>
</tr>
</tbody>
</table>

S1, S2, S3 and S4 represent the different individual retinal specialists. OCT = optical coherence tomography.

Of equal or greater importance was that retinal specialists markedly differed in the number and placement of planned laser spots when given identical information concerning presence and location of DME and treatable lesions (see Table 4). Identical information was used differently by different specialists. For CSME-based scenarios, the average
Variability in photocoagulation treatment of diabetic macular edema

number of proposed laser spots varied from 5.1 to 30.8 per patient. Within the region of retinal thickening, the number of laser spots ranged between 1.7 and 18.0. Similarly, large variances were found for the TME-based map scenarios. Average number of proposed laser spots varied from 4.3 to 31.2, and spots within retinal thickness area ranged from 1.3 to 14.5. These averages suggest that the dosage of laser application, given identical information concerning presence and location of DME and treatable lesions, may vary by six- to 11-fold. The intraclass correlation coefficient between the four different retinal specialists for the number of planned laserspots was 0.41 (95% CI 0.22 – 0.62). Examples of location, amount and pattern of planned laser spots marked by the different medical retinal specialist are shown in Fig. 4. Inspection of the treatment plans suggests that two medical retinal specialists tended to treat strictly focal lesions contiguous to retinal thickening, while the other two had the tendency to also treat discrete points of retinal hyperfluorescence or leakage irrespective of retinal thickening.

Fig. 4. The photocoagulation treatment plans of four retinal specialists. The top row represents photocoagulation treatment plans based on stereoscopic slit-lamp biomicroscopy. The bottom row represents photocoagulation treatment plans based on optical coherence tomography. Each column represents the photocoagulation treatment of a different retinal specialist based on identical information concerning retinal thickening and treatable lesions. Early- (top) and late-phase (bottom) fluorescein angiogram images of this patient are shown at right.

DISCUSSION

This study addresses two major contributions to the variability of photocoagulation treatment for DME. Firstly, we have shown that the threshold for and dosage of photocoagulation differs depending upon whether the basis of retinal thickness diagnosis is clinical observation or OCT. Secondly, we have shown that the dosage of laser application may vary by six- to 11-fold among retinal specialists, given identical information concerning presence and location of DME and treatable lesions.

For clinicians utilizing primarily OCT rather than clinical examination to assess regions of diabetic macular thickening and treatment initiation, these results should be concerning. We found a concordance rate of 67% in diagnosing retinal thickness by clinical examination and OCT. Even in the majority of concordant cases, the areas of agreement were
only 31%. The extent of TME was 46% greater than CSME. More importantly, these variances between CSME and TME assessment for the same patient appeared to lead to different photocoagulation treatment decisions. The overlap in laser spot location between plans based on CSME or TME averages 51%. We are not aware of any study that has proven the effectiveness of photocoagulation on DME, in which treatment initiation was based upon thickening as measured by OCT. Therefore, we cannot know whether outcomes similar to the ETDRS can be achieved using these methods.

We had expected this variation in the threshold for and dosage of photocoagulation when comparing the different DME assessments. Surprisingly, however, we also found large and unexpected differences in treatment plans between retinal specialists when given identical information concerning presence and location of DME and treatable lesions. Perhaps the most notable finding is that clinical retinal experts can vary in their application of photocoagulation treatment dosage by six- to 11-fold. Although we have been impressed by the large variations found within this study, especially in delivery of laser doses, we anticipate that more variation may exist among retinal specialists in diverse practice settings and between training programmes, countries and continents; however, this pilot study was not powered to answer such questions.

We have assumed that a determination of TME can be made using a set of criteria that is analogous to the ETDRS definition of CSME. Our definition of TME is analogous to CSME, but the specific thresholds chosen for “thickening” (2 SD greater than normal, or more than 50 µm thicker than retinal thickness equidistance from fovea within 500 µm of the fovea) may affect our results. Also, we utilized Stratus OCT rather than newer spectral domain OCT, which may underestimate or overestimate the area or degree of retinal thickening. However, the magnitude of the variances that we have found suggests that our general findings are likely to be correct, even if alternative thickness thresholds or OCT instruments were chosen.

The agreement between stereo biomicroscopy and OCT for the detection of diabetic foveal oedema is poor when OCT thickening is mild (Brown et al. 2004). We included patients that had not previously been treated with laser photocoagulation. The greater part of the included patients had mild DME (i.e. no more than 200-300 µm thickness). We found a concordance rate of 67% in diagnosing retinal thickness by clinical examination and OCT. The concordance rate would possibly be greater if more patients with severe diabetic macular edema were included (i.e>300 µm thickness).

This study was limited to the analysis of initial photocoagulation treatment plans that each retinal specialist would provide to patients with DME. However, in clinical practice, if DME persists after the first photocoagulation treatment, additional laser is commonly applied during follow-up. Although retinal specialists can differ in their first approach, applying more or less photocoagulation spots during follow-up could eventually result in more similar end-points.

As shown by our application of Truthseeker, the recording of fictional photocoagula-
Variability in photocoagulation treatment of diabetic macular edema
tion treatment plans provides a powerful tool to compare individual plans. However, without some means to deliver these treatment plans to a subject with CSME or TME in an objective way, comparative determinations on visual outcome and consequences of ophthalmologist-related variability in photocoagulation treatment may be difficult. Application of automated treatment planning and custom laser pattern application offers the potential for more uniform treatment guideline application.\textsuperscript{15,16}

In summary, this study shows that DME treatment threshold and dosage of laser spots differs depending upon whether the basis of retinal thickness diagnosis is clinical observation or OCT. What was even more striking was that individual retinal specialists diverge in their management and intensity of photocoagulation therapy of DME. There is a need for a better and renewed definition of treatable DME and consensus regarding standardization of photocoagulation treatment for macular oedema. This is particular relevant to clinical trials investigating new treatment modalities like anti-VEGF in DME in comparison, or conjunction with photocoagulation treatment. In the absence of additional or comprehensive studies the divergence of the individual retinal specialists has the potential to affect patient outcome and laser study results.
REFERENCES