Benefits of stereopsis when identifying clinically significant macular edema via teleophthalmology

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ABSTRACT • RÉSUMÉ

Background: The need to incorporate stereopsis into a teleophthalmology system is controversial. Detection of hard exudate in the macula is suggested by some as an adequate surrogate for direct observation of retinal thickening. This study was designed to determine how accurate the detection of hard exudate is as a surrogate for stereoscopic detection of clinically significant macular edema (CSME).

Methods: 120 patients with diabetes underwent clinical retinal examination with contact-lens biomicroscopy by a retinal specialist. The presence or absence of CSME was recorded. On the same day as clinical grading, 30° stereoscopic digital photographs of the macula were captured. At least 2 months after clinical examination, the digital images were viewed by masked graders for the presence or absence of hard exudate and retinal thickening.

Results: 207 eyes of 106 patients had complete data sets for both diagnostic modalities. The sensitivity of hard exudate (93.9%) in predicting the presence of CSME was similar to that of direct stereoscopic observation of retinal thickening (90.9%), with \( p = 0.5 \). On the other hand, digital stereopsis was significantly more specific (92.9%) than was hard exudate (81.6%) in predicting the presence of CSME (\( p < 0.001 \)). This difference was maintained even when controlling for image quality.

Interpretation: Although the presence of hard exudate within the macula is a sensitive surrogate marker for CSME, it is less specific than stereoscopic evaluation. Any American Telemedicine Association category 3 teleophthalmology system that utilizes hard exudate as a surrogate marker for CSME may refer patients unnecessarily for clinical evaluation.

Contexte : Le besoin d'intégrer la stéréopsie dans un système de téléophtalmologie est controversé. Certains suggèrent que la détection d'exsudats secs dans la macula offre un substitut adéquat pour observer l'épaississement de la rétine. Cette étude a pour objet d'établir avec quelle exactitude la détection des exsudats secs peut remplacer la détection stéréoscopique d'un œdème cliniquement significatif de la macula (OCSM).

Méthodes : Un spécialiste de la rétine a procédé à l'examen clinique par biomicroscopie avec verre de contact de la rétine de 120 patients diabétiques. La présence ou l'absence d'OCSM a été notée. Le jour de la cotation clinique, des photographies numériques et stéréoscopiques à 30° ont été prises. Au moins 2 mois après l'examen clinique, les images ont été vues à l'insu par des préposés à la cotation pour vérifier la présence ou l'absence d'exsudats secs et l'épaississement de la rétine.

Résultats : 207 yeux de 106 patients ont fait l'objet d'un jeun complet de données pour les deux modes de diagnostic. La sensibilité de l'exsudat sec (93.9 %) pour prévoir la présence d'OCSM a été semblable à celle de l'observation stéréoscopique directe de l'épaississement de la rétine (90.9 %) (\( p = 0.5 \)). D'autre part, la stéréopsie numérique a été significativement plus précise (92.9 %) que l'exsudat sec (81.6 %) pour prévoir la présence d'OCSM (\( p < 0.001 \)). L'écart s'est maintenu même dans le contrôle de la qualité de l'image.

Interprétation : Bien qu'elle présente un indicateur de substitution sensible pour déceler l'OCSM, la présence d'exsudat sec dans la macula s'y avère moins précise que l'évaluation stéréoscopique. Avec les systèmes de catégorie 3 de l’American Telemedicine Association, qui utilisent l’exsudat sec comme indicateur substitut de l’OCSM, il n’est peut-être pas nécessaire de soumettre les patients à l’évaluation clinique.
Improved screening for diabetic retinopathy has been a research focus since the Diabetic Retinopathy Study and the Early Treatment Diabetic Retinopathy Study (ETDRS) proved that laser treatment improves visual outcome.\textsuperscript{1–3} Teleophthalmology has been identified as a cost-effective\textsuperscript{4} and efficacious method for assessing whether patients have treatable diabetic retinopathy.\textsuperscript{5,6}

In Canada, many communities are geographically isolated, with some locations accessible only by air. Teleophthalmology is successful in identifying diabetic retinopathy in individuals living in these remote communities.\textsuperscript{5–7} The high cost of travel within Canada has led to the development of teleophthalmology systems that are both sensitive and specific for the identification of treatable diabetic retinopathy (proliferative diabetic retinopathy, clinically significant macular edema [CSME]) and other eye disease (cataracts, glaucoma, macular degeneration).\textsuperscript{8} By referring only those patients in need of treatment, travel costs can be minimized.

There is disagreement about the value of stereopsis in a teleophthalmology system. At a recent Canadian teleophthalmology symposium,\textsuperscript{9} consensus could not be reached on whether stereopsis was essential when identifying diabetic retinopathy. Similarly, the Canadian Diabetes Association recently released its clinical practice guidelines\textsuperscript{10} but was unable to comment on whether stereopsis was necessary because “high-quality consistent protocols for digital images are still being developed.” This sentiment is echoed by a relatively recent editorial\textsuperscript{11} that stated, “most of the nonmydriatic digital cameras now available lack a stereoscopic capability that is helpful in identifying and accurately diagnosing subtle neovascularization, [and] macular edema.” In recent discussions on telehealth practice recommendations, the American Telemedicine Association’s Ocular Telehealth Special Interest Group discussed stereopsis with respect to diabetic retinopathy but did not include it as a requirement for screening systems. Instead, for the identification of diabetic retinopathy, teleophthalmology systems were divided into 4 validation categories when compared with ETDRS 7-field stereoscopic slide film photography. These validation categories ranged from category 1, which is the ability to identify presence or absence of diabetic retinopathy, to category 4, which is comparable to ETDRS standards.\textsuperscript{12}

Some researchers\textsuperscript{13} have attempted to identify CSME from digital monoscopic images, whereas others have suggested that stereopsis can be foregone if one assumes that CSME can be identified by the presence of hard exudate in the macula. Certainly, there is ETDRS\textsuperscript{14} data that indicates the presence of hard exudate in the macula is a sensitive predictor of the presence of CSME, and yet it is still unclear in the teleophthalmology community if a system with stereoscopic capabilities can perform better than a monoscopic one. It should be noted that optical coherence tomography (OCT) was not evaluated in the present study despite recent research\textsuperscript{15–17} on the benefits of OCT for the identification of CSME. Because teleophthalmology groups are not currently using OCT (nor proposing to do so), a study evaluating OCT for the teleophthalmology diagnosis of CSME would not change current clinical practice. The goal of our study was to more clearly answer the question of whether or not stereopsis is necessary for a teleophthalmology system to diagnose CSME. To achieve this, we evaluated how accurate hard exudate is as a surrogate for the stereoscopic detection of CSME.

**METHODS**

All new diabetic patients referred to a group retina practice over a 4-month period were eligible for inclusion in the study irrespective of the reason for the referral. Exclusion criteria were (1) media opacity that obscured adequate clinical evaluation, (2) inability to have fundus photographs taken, and (3) inability to have same-day photographs obtained. Power calculations were performed\textsuperscript{18} to verify that the sample size was adequate to evaluate the extent of agreement between the 2 diagnostic methods. The study was approved by the ethics committee of the University of Alberta Faculty of Medicine, and all participants gave informed consent.

Patients underwent clinical examination of the retina after pupillary dilation (1% tropicamide and 2.5% phenylephrine, Diopptic Laboratories, Markham, Ont.). A handheld contact lens (Centralis Direct, Volk Optical Inc., Mentor, Ohio) was used with a slit lamp (BM900, Haag Streit AG, Gartenstadstrasse, Switzerland) to examine each macula. The presence or absence of CSME was recorded. CSME was defined according to the ETDRS definition as thickening of the retina at or within 500 μm of the center of the macula, hard exudate at or within 500 μm of the center of the macula if associated with adjacent retinal thickening, or a zone or zones of retinal thickening of at least 1 disc area that is located at least 1 disc diameter from the center of the macula. Other diabetic retinal pathologies were identified and have been reported elsewhere.\textsuperscript{8}

Patients then underwent mydriatic digital fundus photography by a trained ophthalmic photographer using a high-resolution digital camera (Kodak/Canon DCS560, Rochester, N.Y.) attached to a 30° fundus.
camera (Zeiss FF450, Zeiss, Jena, Germany). Digital photographs measuring 3040 × 2008 pixels were obtained on the same day as clinical examination and downloaded to a Windows NT-based (Microsoft, Redmond, Wash.) Intel Pentium (Intel Corp., Santa Clara, Calif.) workstation. Nonsimultaneous stereoscopic paired images of the macula were captured (standard field 2) through a corneal-induced parallax. Image focus, composition, and exposure were evaluated at the time of capture using the DCS host software for Windows (DCS TWAIN Data Source version 5.9.3, Kodak Canada Inc., Toronto, Ont.). Multiple image sets could be captured at the discretion of the photographer. Images were saved uncompressed as left and right image files in tagged image file format (TIFF) at a file size of 7.4 MB.

The reader was masked to the clinical examination of each eye. Moreover, a minimum of 2 months separated clinical examination from photographic grading to minimize reader recall. Additionally, digital photographs of the left eye were reviewed in random order, with a minimum of 2 months before review of right eyes. Finally, graders were not aware of the primary research question of this paper when the data were obtained, namely, whether hard exudate is a sensitive and specific surrogate marker for the detection of CSME.

Images were viewed on a computer monitor through liquid crystal display (LCD) shutter goggles (StereoGraphics CrystalEyes Wired, StereoGraphics Corp., San Rafael, Calif.) using proprietary 3D viewing software (Stereoviewer, MacDonald Dettwiler and Associates, Richmond, B.C.). The screen resolution was set to 1024 × 768 pixels, and the minimal threshold for refresh rate specified by the LCD goggles was set at 120 Hz. The number of stereoscopic images viewed per eye was at the discretion of the reader, with the sharpest photo being used for the final grading. Image quality was assessed as poor, good, or excellent. CSME was defined by means of the same ETDRS definition. Hard exudate was recorded as present if any amount of hard exudate was evident within 2 disc diameters of the macular centre. The reader recorded the presence or absence of CSME and hard exudate during the same grading session.

The primary comparison was whether the digital identification of hard exudate in the macula (used as a surrogate for the presence of CSME) is as sensitive and specific as the observation of retinal thickening by stereoscopic digital imaging. We carried out this comparison by testing the hypotheses on the 2 summary measures of accuracy considered: sensitivity and specificity. The null hypothesis was that the summary measures of accuracy for the 2 diagnostic tests are the same; the alternative was that they are different. Specifically, we tested the null hypothesis that the sensitivities (or specificities) of stereoscopic digital identification of retinal thickening and the digital identification of hard exudate within the macula are equal against the alternative hypothesis that the sensitivities (or specificities) are not equal.

Because the same digital images of the eyes were considered for both diagnoses, we used the McNemar test for dependent proportions. This test takes into account the correlation between the diagnoses arising from the paired design, with the diagnostic tests evaluated on the same set of eyes. As before, the gold standard used is the clinical diagnosis of CSME based on contact-lens biomicroscopy. To test equality of sensitivities, only those eyes clinically diagnosed as CSME by contact-lens biomicroscopy for CSME were considered, and the McNemar test was carried out. Similarly, only those eyes clinically diagnosed as negative for CSME were considered to test equality of specificities. Exact p values for the tests are given by Zhou et al.

Note that while the correlation arising from the pairing of the eyes used for the 2 diagnostic tests was accounted for by the McNemar test, the inter-eye correlation between the left and right eyes was ignored. Thus, eyes from the same patients were treated as independent.

**RESULTS**

During the enrollment period, 139 new patients with diabetes mellitus were identified. Thirty-five eyes (19 patients) were not eligible for enrollment: Six patients (12 eyes) were physically unable to sit at the fundus camera due to fatigue, prior stroke, incontinence, illness, or physical size. Sixteen eyes (9 patients) had media opacities preventing adequate clinical evaluation. Three patients (6 eyes) were unwilling to be photographed on the same day as the clinical examination, and 1 eye (1 patient) had retinal pathology preventing differentiation of diabetic retinopathy. A total of 232 eyes of 120 patients were examined clinically and received same-day high-resolution stereoscopic digital fundus photography of the macula. Twenty-five eyes (14 patients) were excluded after enrollment because the digital image files were corrupt and the photos could therefore not be graded. In the final analysis, 207 eyes of 106 patients were included.

Patient ages ranged from 34 to 87 years, with a median of 60.2 years. Of the 106 patients, 39.6% were female and 82.9% had type 2 diabetes. Duration of diabetes ranged from 1 month to 38 years, with a median...
duration of 11.4 years. Thirty-three eyes had poor quality stereoscopic images, 135 were of good quality, and 39 were of excellent quality. A total of 59 eyes had underexposed digital photographs that were adjusted to proper exposure using the Kodak TWAIN software.

Four sets of calculations were performed on the data set: (1) the sensitivity and specificity (Table 1) of hard exudate (as identified from digital photographs) to identify CSME, (2) the sensitivity and specificity (Table 2) of retinal thickening, as identified by stereoscopic digital images, to detect CSME, (3) a comparison, using the McNemar statistic, of the sensitivities and specificities (Table 3) of hard exudate and retinal thickening to detect CSME, and (4) the same comparison repeated in a dataset that excluded all eyes with image sets graded as having poor quality (Table 3). This fourth calculation was performed because the University of Alberta teleophthalmology guidelines require that all patients with poor quality images be referred for clinical examination (ETDRS level 90). It is therefore useful to know how well stereopsis and hard exudate sort out the remaining patients.

All comparisons were made using CSME identified clinically by contact-lens biomicroscopy as the reference gold standard. The first 3 sets of calculations were performed on a study population of 207 eyes in 106 patients, whereas the fourth set was performed on a study population of 174 eyes in 98 patients.

The presence of hard exudate, when used as a surrogate for stereoscopic detection of CSME, was slightly more sensitive (93.9%) than digital stereoscopic identification of retinal thickening (90.9%), but this difference was not statistically significant (McNemar statistic = 2, \( p = 0.5 \)). Digital stereopsis, however, was significantly more specific (92.9%) than the hard exudate surrogate (81.6%, McNemar statistic = 16, \( p < 0.001 \)). To control for the influence of poor image quality, eyes whose images had been assigned a grade of poor were removed and the calculations repeated (Table 3). The results of this subset analysis were similar, with sensitivities being excellent and roughly equal, while stereopsis was significantly more specific than the hard exudate surrogate (McNemar statistic = 15, \( p < 0.001 \)) for identifying CSME.

**INTERPRETATION**

The results of this study help to answer the question, “Is stereopsis required in a teleophthalmology system?” A monoscopic system is able to identify CSME with high sensitivity by utilizing hard exudate as a surrogate marker for retinal thickening. On the other hand, specificity is reduced when compared with a stereoscopic system, and this could lead to a greater number of patients being referred for unnecessary clinical evaluation because no laser treatment would be necessary.

The results of this study are similar to those found by Bresnick et al. They demonstrated that hard exudate in the macula could identify CSME as diagnosed by stereoscopic film photography with a sensitivity of 89% but a specificity of 58%. It is unclear why the specificity found in their paper was so much lower than that identified in our study (81.6%). One possible explanation is that Bresnick defined CSME as present if hard exudate was within 1 disc diameter of the center of the fovea, whereas our study said CSME was present if hard exudate was anywhere within the macula (approximately two disc diameters from the center of the fovea).

Maberley et al used a monoscopic system with the specific intention of utilizing hard exudate as a surrogate identifier for CSME, and compared clinical examination with digital photos. Their surrogate definition included hard exudate within 500 µm of the fovea, and they added that if “a one disc-diameter area of exudation within one disc diameter of the center of the fovea” was present, CSME was deemed to coexist. Clinical exami-

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**Table 1—Identification of clinically significant macular edema by monoscopic digital imaging* versus clinical examination with contact-lens biomicroscopy**

<table>
<thead>
<tr>
<th></th>
<th>CLBM Total</th>
<th>Mono digital Yes</th>
<th>Mono digital No</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>62</td>
<td>26</td>
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</tr>
<tr>
<td>No</td>
<td></td>
<td>4</td>
<td>115</td>
<td>119</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>66</td>
<td>141</td>
<td>207</td>
</tr>
</tbody>
</table>

Note: CLBM = contact lens biomicroscopy.

*Identified via digital imaging by the presence of hard exudate (acting as a surrogate for the presence of retinal thickening) in the macula.

**Table 2—Stereoscopic digital imaging versus clinical examination with contact-lens biomicroscopy for identification of clinically significant macular edema**

<table>
<thead>
<tr>
<th></th>
<th>CLBM Total</th>
<th>Stereo digital Yes</th>
<th>Stereo digital No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>60</td>
<td>10</td>
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</tr>
<tr>
<td>No</td>
<td></td>
<td>6</td>
<td>131</td>
<td>137</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>66</td>
<td>141</td>
<td>207</td>
</tr>
</tbody>
</table>

Note: CLBM = contact lens biomicroscopy.
nation identified 10 eyes (5%) with CSME, although data were not reported on the number of eyes identified with CSME via digital imaging. They found that a single digital photograph correlated very well ($\kappa = 0.89$) with clinical examination and that hard exudate had a sensitivity of 90.0% (SD 13.1) and specificity of 97.1% (SD 1.7) in the detection of CSME. They studied an isolated population with a low rate of disease, however, (105 of 200, or 52.5% of eyes had ETDRS diabetic retinopathy level 20 or less and only 10 eyes were identified clinically as having CSME) and therefore their sample size may be too small to draw a statistically significant conclusion.

Lim et al.\(^{13}\) also studied the detection of CSME by digital photography. The method by which CSME was determined to be present in the nonstereoscopic digital images was not described. In comparing their digital images to standard stereoscopic 35 mm film photography, they found the diagnostic methods had fair correlation ($\kappa = 0.38$) and poor sensitivity (33%) but high specificity (97%). Again, a small sample size (6 of 40 eyes with CSME, as identified by stereoscopic 35 mm film photography) may complicate direct comparison with our results.

Is it possible to meet the needs of patients with diabetes with an efficient teleophthalmology system? Part of this question can be answered when the rate of CSME in a teleophthalmology population is considered. Research by Tennant et al.\(^6\) found that 9.1% of the subjects enrolled (11 patients) from a rural community in northern Alberta had CSME in at least 1 eye. Hard exudate was identified in 15.4% of patients (37 eyes), however, implying that nearly twice as many patients would have been referred for clinical evaluation if hard exudate alone had been utilized as the marker for CSME. In our study, if hard exudate alone had been utilized as a surrogate for the presence of CSME, 88 people instead of 70 would have been referred for clinical evaluation, representing an increase of 26%.

There is some question whether stereoscopic digital imaging may be more sensitive than clinical examination for the detection of CSME. In this study, 4 eyes of 4 patients were diagnosed with macular edema that was not clinically significant by clinical examination, but when measured with the digital software, the retinal thickening was found to lie within 1 disc diameter (equating to a diagnosis of CSME). With high-resolution video display, a reader is able to examine a macula at much greater magnification than is possible clinically or with film photographs. In addition, when grading diabetic retinopathy, the reader is allowed an unlimited and unobstructed examination of retinal detail. The examination is not affected by patient movement, discomfort of a contact lens, or outside distractions. Finally, with the 3D viewing software, retinal distances and areas can be accurately calibrated utilizing the average distance from the central fovea to the center of the optic disc.\(^{21}\) This allows accurate detection of CSME type 3, something a surrogate like hard exudate would not be able to do.

There are several limitations to this study. Because the study population was obtained from new referrals to a group retina practice, the incidence of CSME in this population was most likely higher than would exist in a broad sampling of diabetic patients. Although the rate of CSME can therefore not be used in reference to other works, the comparison between hard exudate and stereoscopic identification of retinal thickening is still valid because there were many eyes that did not have CSME. A second limitation is the possibility of having introduced bias into the grading process by grading the presence of both hard exudate and CSME during the same viewing session. This bias was minimized, however, given that the reader was not aware of the primary research question of this paper when performing the grading.

Another weakness of the study is that OCT, which is an objective measurement of retinal thickening, was not available at the time the study was carried out. Even if OCT had been available, there are no current teleoph-

### Table 3—Stereoscopic observation of retinal thickening versus identification of hard exudate via digital imaging for the identification of clinically significant macular edema

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Exact agreement (%)</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$%$</td>
<td>McNemar statistic</td>
</tr>
<tr>
<td>Retinal thickening</td>
<td>92.3</td>
<td>90.9</td>
<td>2</td>
</tr>
<tr>
<td>Hard exudate</td>
<td>85.5</td>
<td>93.9</td>
<td></td>
</tr>
<tr>
<td>Retinal thickening (no p)(^*)</td>
<td>94.8</td>
<td>98.0</td>
<td>1</td>
</tr>
<tr>
<td>Hard exudate (no p)(^*)</td>
<td>86.8</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

\(^*\)Indicates calculations performed on the dataset ($n = 174$) that excluded eyes graded as having poor quality (no p).
thalmology programs using OCT for distance evaluation of diabetic retinopathy. This is because OCT, although sensitive in the detection of retinal thickening, is not able to detect peripheral neovascularization. As such, including OCT in a teleophthalmology system would mean that a second imaging device, such as a fundus camera, would be required (thus making OCT redundant if the fundus camera can perform the same role). In addition, there remains controversy about the accuracy and reproducibility of OCT when evaluating macular thickness.\textsuperscript{22}

As efforts accelerate to identify the population burden of diabetic retinopathy, it is likely that the contribution of teleophthalmology will grow. Systems that forgo stereopsis will be able to identify CSME with high sensitivity, although they may refer significantly more patients for clinical assessment of CSME because of reduced specificity. This shortcoming, along with the ease of obtaining stereoscopic photographs with current digital imaging systems, may increase the importance of cost-effectiveness when making design choices for a teleophthalmology system.

There were no sponsors for this study. Drs. Tennant, Hinz, and Greve declare a proprietary commercial interest as directors of Secure Diagnostic Imaging Inc., a medical imaging company that provides web-based teleophthalmology services.

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**Key words:** teleophthalmology, telemedicine, stereopsis, diabetic retinopathy, macular edema