Enhancing Nonmydriatic Color Photographs of the Retina With Monochromatic Views and a Stereo Pair to Detect Diabetic Retinopathy

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BACKGROUND AND OBJECTIVE: Nonmydriatic digital color imaging is rapidly gaining an important role in screening for diabetic retinopathy. However, it has yet to equal a dilated fundus examination or seven Early Treatment Diabetic Retinopathy Study field 35-mm photography. The authors therefore attempted to enhance efficacy and validity by adding two low-cost steps to the nonmydriatic digital image evaluation.

PATIENTS AND METHODS: The fundi of 145 consecutive patients with diabetes mellitus were evaluated for diabetic retinopathy using two different nonmydriatic reading techniques: creating a red-free view (using digital filters) and looking at a stereo pair of each field taken. These methods were each compared to a mydriatic fundus examination.

RESULTS: Although the first technique yielded views with sensitivities and specificities similar to what exists in the literature using this same technique, enhancing these photographs (second technique) yielded a statistically significant increase in sensitivity and specificity ($P < .005$).

CONCLUSION: The authors recommend using both low-cost steps when screening for diabetic retinopathy through nonmydriatic digital color imaging.

In the current literature, specificity of this technique is 72% and sensitivity is 85% (Table 1). Our aim in this study was to try to enhance the efficacy and validity of nonmydriatic images in detecting diabetic retinopathy by using two additional low-cost steps: creating a red-free view (using digital filters) and looking at a stereo pair of each field taken. Sensitivities and specificities for the two techniques were compared with a reference dilated fundus examination for each eye.

### PATIENTS AND METHODS

#### Patient Selection

The study protocol was approved by the Institutional Review Board of the American University of Beirut Medical Center and was in accordance with the declaration of Helsinki. One hundred forty-five consecutive patients with diabetes mellitus seeking medical care at the diabetes clinic of the American University of Beirut Medical Center were invited to participate in this study. Patients 18 years or older, patients with type 1 or type 2 diabetes mellitus, and patients willing to cooperate for a multiple imaging session were included. Exclusion criteria included patients with gestational diabetes mellitus, patients who had an overt corneal opacity hindering proper imaging, patients using pupillary constricting agents as a treatment modality for glaucoma, and patients in whom pupillary dilation was contraindicated. A research fellow identified and interviewed prospective participants, explained potential risks and benefits, tabulated the demographic and medical details, and had patients sign an informed consent form to participate in the study.

#### Imaging Technique

Patients about to undergo imaging were initially put in a darkened room for 7 minutes to achieve physiological pupillary dilation. Using a Topcon NW6S fundus camera (Topcon, Tokyo, Japan) linked to a 6.0 megapixel Nikon D100 camera (Nikon, Angkor, Thailand), two initial 45° nonmydriatic images for each eye were taken, one centered at the fovea and another centered at the optic nerve head. Stereo pairs of the fovea and the optic nerve head were also taken by manually shifting the camera a few millimeters horizontally from the initial fields, as is the method used in traditional mydriatic stereo imaging. Image captures were spaced 7 minutes apart, an interval necessary to avoid pupillary shadows. All images were stored in the Image-net 2000 program (Topcon) and coded to mask the patients’ names.

#### Dilated Retinal Examination and Diabetic Retinopathy Documentation

Patients’ pupils were dilated using tropicamide 1% and phenylephrine 10% instilled once in each eye after the imaging session was over. Twenty minutes later, an experienced ophthalmologist with subspecialty training in retina performed a fundus evaluation through dilated pupils initially by indirect ophthalmoscopy (using a 20-diopter lens) followed by slit-lamp biomicroscopy (using a 78-diopter lens). Diabetic retinopathy was graded initially using the traditional Early Treatment Diabetic Retinopathy Study (ETDRS) scale, then the results were tabulated following an abbreviated scale with eyes having an EDTRS score of 10 as having no diabetic retinopathy (or negative for diabetic retinopa-
Digital Image Interpretation

The same specialist (also trained for digital nonmydriatic digital image interpretation) received the photographs electronically (in tiff format) on a Sony Trinitron monitor with 1,920 × 1,200 true color resolution (Sony Corp., Tokyo, Japan) 2 weeks after image acquisition to be interpreted using the first modality and then after another 2-week interval. This reader was to look for the presence of diabetic retinopathy using the second modality.

For the first method, the reader interpreted two-color nonmydriatic images for each eye using the traditional method: one 45° field centered at the fovea and another 45° field centered at the optic nerve head. Poor quality images were labeled as ungradable and those eyes were traced back for a complete ophthalmic evaluation to determine possible causes of poor imaging. Otherwise, the above mentioned abbreviated scale for presence or absence of diabetic retinopathy was also used for this reading method.

The second modality comprised a more elaborate evaluation initially including the use of the same two previous images for each eye, then reading red-free monochromatic filtered versions of both images (using the red-free feature in Imagenet), and finally looking at a three-dimensional view of a color stereo pair for each image taken using the Berzin viewer (Proview Inc., Reseda, CA). The same simplified scale mentioned above was also employed for this modality.

Reading Techniques Analysis

For the detection of diabetic retinopathy, sensitivity, specificity, positive predictive value, and negative predictive value for each reading method were calculated. Kappa values for both techniques were also calculated using the STATA software (StataCorp, College Station, TX).

Cases in which the presence of diabetic retinopathy was missed by either reading method were identified and tabulated with their detailed ETDRS standard grading this time (false negatives). Likewise, cases that were overdiagnosed with either method were tabulated and analyzed (false positives).

To confirm statistical significance in the difference between the two reading techniques, a Student’s t test was performed.

RESULTS

A total of 145 patients were recruited for the study and 290 eyes were imaged. Table 2 summarizes the patients’ characteristics. The mean age of the patients was 54.4 years. Approximately 60% of the recruited patients were women. Of the 290 eyes from the 145 recruited patients, 248 eyes (or 85.5%) could be interpreted by nonmydriatic camera imaging. Reasons hindering proper nonmydriatic imaging are shown in Figure 1.

Table 3 summarizes the results obtained using the first evaluation technique. Using nonmydriatic color nonstereo images alone for evaluation had a sensitivity of 59.25% and a specificity of 88.0%. Positive predictive values and negative predictive values for nonmydriatic digital color imaging alone were 70.6% and 81.6%, respectively. The Kappa value for this technique was 0.49 (P < .005), indicating a significant but moderate agreement.

<table>
<thead>
<tr>
<th>Variables</th>
<th>No. or %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD (y)</td>
<td>54.4 (± 11.72)</td>
</tr>
<tr>
<td>Female</td>
<td>59.4%</td>
</tr>
<tr>
<td>Mean body mass index ± SD</td>
<td>30.1 (5.6)</td>
</tr>
<tr>
<td>Mean duration of disease (y)</td>
<td>8.6</td>
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<tr>
<td>Insulin use</td>
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<tr>
<td>HbA1C ± SD</td>
<td>8.5% (± 2.4%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>52.8%</td>
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<tr>
<td>Type 1 diabetes mellitus</td>
<td>8.7%</td>
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</table>

SD = standard deviation.
Table 3 also summarizes the results obtained using the second evaluation technique. Using the combination method increased sensitivity for detecting diabetic retinopathy to 70.0% and specificity to 93.9%. Positive and negative predictive values for this method were 85.3% and 85.6%, respectively. The Kappa value for this approach was 0.66 (P < .005), indicating a stronger agreement.

**DISCUSSION**

Previously reported advantages of nonmydriatic digital color imaging include its low cost (no running expenses of 35-mm film), easy access, user-friendly set up for the photographer and patient, immediate availability of images for reading, and the possibility of remote interpretation with telemedicine. In addition, in this study we have added a two-step enhancement technique to make nonmydriatic images more sensitive and more specific in detecting diabetic retinopathy. To our knowledge, no previous study has proved the importance, validity, and efficacy of these low-cost combined steps in nonmydriatic imaging and interpretation for detecting diabetic retinopathy.

Reasons for using these enhancement steps include the following. First, using stereo photographs gave us greater confidence in discerning changes such as cotton wool spots from artifacts of imaging, therefore detecting the mildest early retinal edema seen from vascular leakage or any neovascularization bud growing into the vitreous. Second, the use of monochromatic views helped minimize artifacts that could be mistaken at times in color photographs for microaneurysms. This combination resulted in an increase in the rate of lesion detection and a reduction in the number of overdiagnosed cases when we compared our findings with the results obtained with the traditional reading method having the same reader and monitor.

Other authors have advocated steps similar to ours. For example, Bursell et al.\(^1\) employed the three-dimensional evaluation in nonmydriatic photographs, but without using monochromatic views. In addition, although accurate and reliable, their proposed technique of stereo interpretation is costly and requires a double monitor set up. Our stereo photographs require a single screen with the portable Berzin viewer. The same method for three-dimensional evaluation has been validated for assessment of optic nerve cupping with good confidence.\(^14\)

Although our two 45° fields did not cover the entire retina, overlapping these fields on the classic seven 30° fields has them cover 70% of the ETDRS evaluated surface (Fig. 2). Other authors have used similar fields

**TABLE 3**

<table>
<thead>
<tr>
<th>Evaluation Technique</th>
<th>DFE Positive for DR</th>
<th>DFE Negative for DR</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonmydriatic digital color imaging</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive for diabetic retinopathy</td>
<td>48</td>
<td>33</td>
<td>81</td>
</tr>
<tr>
<td>Negative for diabetic retinopathy</td>
<td>20</td>
<td>147</td>
<td>167</td>
</tr>
<tr>
<td>Total</td>
<td>68</td>
<td>180</td>
<td>248</td>
</tr>
<tr>
<td>Enhanced nonmydriatic digital color imaging</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive for diabetic retinopathy</td>
<td>58</td>
<td>26</td>
<td>84</td>
</tr>
<tr>
<td>Negative for diabetic retinopathy</td>
<td>10</td>
<td>154</td>
<td>164</td>
</tr>
<tr>
<td>Total</td>
<td>68</td>
<td>180</td>
<td>248</td>
</tr>
</tbody>
</table>

DFE = dilated fundus examination; DR = diabetic retinopathy.

![Figure 2. Overlap area of the two 45° fields and the seven 30° Early Treatment Diabetic Retinopathy Study fields.](image-url)
and obtained good agreement with gold standards. Using more than two 45° fields can be taxing in terms of time consumption and pupillary constriction reflex with the repeated flash.

Our rate of ungradable images was lower than in other published studies of similar ethnic groups from the same region. For example, Penman et al. published a nonmydriatic study of an Egyptian adult diabetic population with a nongradable rate of 22%. This could be due to many factors. The recent availability of technical advances in nonmydriatic imaging, as illustrated in more recent work using the small pupil mode in modern nonmydriatic cameras, achieves an acceptable image even with 3.7 to 4.0 mm pupils. Another factor could be the relatively young age of our study group. Recent publications in which similar technologically advanced cameras were used in a population of older patients with diabetes mellitus yielded a higher ungradable rate. The selected population in our study probably has fewer lenticular opacities and larger pupils. In fact, in a more recent study than Penman et al.’s article, imaging subjects with a younger mean age than ours obtained an even lower ungradable image rate.

Table 4 describes the ETDRS grading of the false-negative readings from both techniques. Analysis reveals that most of the cases of diabetic retinopathy missed were from the mild and moderate nonproliferative diabetic retinopathy category and only one was from the proliferative diabetic retinopathy category. The latter case in particular had an unusual isolated peripheral neovessel elsewhere that could only be detected by dilated fundus examination. Even a seven ETDRS 30° field 35-mm film evaluation misses 18% of the surface of the retina, an area covered by the dilated fundus examination. With the second reading technique, the number of missed diabetic retinopathy cases was significantly lower and all missed cases belonged to the mild nonproliferative diabetic retinopathy category with the exception of the same unusual proliferative diabetic retinopathy case. Specifically with our combined interpretation technique, the more serious moderate nonproliferative diabetic retinopathy cases were no longer missed.

The seven ETDRS 30° field stereo images and the dilated fundus examination remain the ideal methods for diabetic retinopathy evaluation. However, from a practical standpoint, nonmydriatic digital color imaging is gaining momentum and popularity in diabetic retinopathy screening programs. It is a patient-friendly, cost-effective method. It is therefore advisable to consider our enhanced interpretation of digital nonmydriatic photography with the above mentioned enrichment steps (the monochromatic views and the stereo photographs) to obtain the best results from nonmydriatic imaging studies to detect diabetic retinopathy.

**REFERENCES**


2. Lin DY, Blumenkranz MS, Brothers RJ, Grosvenor DM. The sensitivity and specificity of single-field nonmydriatic monochromatic digital fundus photography with remote image interpretation for diabetic retinopathy screening: a comparison with ophthalmoscopy and