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Assessment of Automated Screening for Treatment-Requiring Diabetic Retinopathy

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ABSTRACT *Purpose*: To evaluate fundus photographic image analysis combining automated detection of red lesions, bright lesions, and image quality as a means of identifying treatment-requiring diabetic retinopathy in a screening population of diabetic patients. *Methods*: This was a retrospective cross-sectional study of 106 patients from a diabetic retinopathy screening clinic referred for photocoagulation treatment in the period from January 1996 to May 2002 on the basis of mydriatic 60-degree 35-mm color transparency fundus photography. One fovea-centered fundus photograph and one centered nasal of the optic disk from each of a subject's two eyes was selected for digitization and analyzed using a previously tested computerized red-lesion detection algorithm in combination with a new algorithm for detection of bright lesions and image quality. The algorithm was calibrated on an independent set of fundus photographs. *Results*: Automated red-lesion detection identified 104 of 106 patients requiring photocoagulation treatment, whereas bright-lesion detection identified only 91 of the 106 patients. Two patients who were not identified by either lesion detection algorithm were automatically detected as having poor image quality in one or both eyes. In the study sample, the risk of missing treatment-requiring retinopathy patients from being detected was 0.0% (estimated CI_{95} 0.0–3.4%). **Conclusions:** The combination of automated detection of red lesions and poor image quality identified all treatment-requiring diabetic retinopathy patients in the study sample. No additional information was contributed by the automated bright-lesion detection.

KEYWORDS diabetic retinopathy; fundus photography; image analysis; screening

INTRODUCTION

Diabetic retinopathy is a late complication of diabetes for which screening is both rational and cost-effective.[1,2] The high volume of patients, the need for frequent reexamination, frequent compliance failure, and regional undersupply of ophthalmologists even in developed countries support the use of fundus photographic screening for diabetic retinopathy and, hypothetically, some level of automation of the evaluation of fundus photographs.[3]

We have previously described the effectiveness of computerized fundus image analysis in detecting diabetic retinopathy in a screening population, using

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red-lesion detection alone, and we have examined a theoretical strategy for utilizing automated fundus photographic image analysis in clinical practice.[4–6] In the hypothetical setting examined in the current study, computerized image processing was used to prescreen digital photographs in advance of grader inspection, the objective being to identify patients that can be assumed not to have diabetic retinopathy and to omit their fundus images from visual grading. Because inferior image quality increases the risk of false-negative results an algorithm for detection of poor image quality was used to also assign such images to visual grading. Additionally, we tested the utility of a new algorithm for automated bright-lesion detection as an adjunct to dark-lesion detection.

Previous studies have demonstrated performance of approximately 95% sensitivity and 70% specificity in automated detection of retinopathy in diabetic screening populations and agreement (Cohen's Kappa) with expert graders at a level comparable with the agreement between graders.[4,5] These studies were made in screening populations with a small proportion of patients in need of photocoagulation or other treatment for sight-threatening diabetic retinopathy, and the automated analysis was exclusively aimed at red lesion detection. Failure to detect any retinopathy occurred only in eyes with retinopathy of no ophthalmologic consequence in patients not in need for ophthalmologic referral. Ideally, an automated fundus photographic prescreening system should never overlook patients in need of photocoagulation or other treatment.

In the current study, we assessed the performance of automated fundus image analysis in patients who all had diabetic retinopathy of a level that required photocoagulation treatment. In addition to automated red-lesion detection as a prescreening parameter, we examined automated detection of bright lesions (hard exudates and/or cotton-wool spots) as an adjuvant target for automated detection of diabetic retinopathy, and we included automated quantification of image quality.

MATERIALS AND METHODS

This was a retrospective cross-sectional single-center study of digitized fundus photographic 35-mm transparencies from the diabetic retinopathy outpatient clinic at the Steno Diabetes Center, Denmark. Eligible patients were those that attended the Steno Diabetes Center fundus photographic screening service between January 1996 and May 2002 (both inclusive) diagnosed with a level of diabetic retinopathy that required photocoagulation treatment for clinically significant macular edema or proliferative diabetic retinopathy. Clinically significant macular edema was defined as (1) retinal thickening at or within 500 μm from the center of the macula or (2) hard exudate $\leq$500 μm from the center of the macula, if there is thickening of the adjacent retina, or (3) an area or areas of retinal thickening at least 1 disk area in size, at least part of which is within 1 disk diameter of the center of the macula. Proliferative diabetic retinopathy was defined as (1) new vessels on the optic disk $\geq$1/3 disk area with or without vitreous hemorrhage or (2) vitreous hemorrhage or preretinal hemorrhage with any new vessels on the disk or (3) vitreous hemorrhage plus new vessels elsewhere $>$1/2 disk area or (4) new vessels anywhere $\geq$1 disc area.[8,9] Patients who had previously received photocoagulation treatment in the same eye were excluded from the study. Fundus photographs were recorded after pupil dilation using a Canon CF-60UV (Canon Europa, NV, Amstelveen, The Netherlands) fundus camera set at 60 degrees angular field of view on 35-mm color transparency film (Kodak Ektachrome Elite 100, Eastman Kodak Corp., Rochester, NY). A stereoscopic set of photographs was recorded for each eye centered on the fovea, and nonstereoscopic photographs were recorded from surrounding regions to obtain partly overlapping five-field photography of the posterior pole of the eye. Screening fundus photographs were reviewed primarily by trained graders. Patients with one or two eyes of Early Treatment Diabetic Retinopathy Study (ETDRS) level 35 or higher were reviewed at the Steno Diabetes Center, Denmark (7) by a consultant ophthalmologist who referred patients for further investigations elsewhere.

During the inclusion period, the screening service was the primary eye care facility for a population of approximately 5000 outpatients who attended the Steno Diabetes Center for diabetes care. The patients underwent fundus photography under a predefined clinical protocol established in 1987 at least once per year. At the time the study was undertaken in 2004, patients who received their first photocoagulation treatment were approximately evenly distributed between diabetic macular edema and proliferative diabetic retinopathy, about 5% presenting with both conditions at or above treatment threshold at the same time. Exclusion criteria included photographs not having been taken at the visit on which the referral was based, which occurred

if patients were referred only after having been recalled to have fundus biomicroscopy performed because the photographic findings were inconclusive; absence of photographic records for patients who had concluded screening at the Steno Diabetes Center, absence of records of patients who had discontinued attendance of the Steno Diabetes Center, and referral based on eye disease other than sight-threatening diabetic retinopathy. Of a total of 466 referrals, the referral of 123 patients was based on clinical assessment that did not involve fundus photography, such as a biomicroscopic examination made at the Steno Diabetes Center, and 11 patients were referred for eye disease other than diabetic retinopathy. Of the 332 patients referred for photocoagulation treatment on the basis of fundus photography, fundus photographs of 226 patients had been transferred to other health care providers or remote archives or the patient had died. For the remaining 106 patients included in the study, a total of 1545 fundus photographic transparencies were found in the photographic files. Retinopathy grades in the eye with the most severe level of retinopathy varied between ETDRS level 35 and ETDRS level 71.[10] Two-thirds of patients referred had type 1 diabetes, and one-third had type 2 diabetes.

Digital Image Analysis

Two transparencies of each eye in each patient were selected for digitization by an ophthalmologist. To emulate the two-field EURODIAB protocol,[7] the first fovea-centered photograph of the stereoscopic set (in order of photographic sequence) and the first nasal photograph of each eye were selected, except that another peripheral field was used if no indication for treatment was found in the nasal field and lesions were present in another field, which occurred in nine eyes in eight patients. The transparencies were digitized using a Nikon Coolscan LS-2000 (Nikon Corp., Tokyo, Japan) scanner, at a resolution of 1350 dpi and 12 bits per color channel.

Digital image analysis was conducted using a proprietary software system (Retinalyze Danmark A/S, Hellerup, Denmark). We have previously described the automated red-lesion detection system.[4,5] Briefly, the automated lesion detection was based on advanced mathematical analysis of the gray-level intensity of the digital image. The circumference of potential lesions was established from each of a number of seed-points positioned at local extremes of the image. The vessel tree and the optic disk were automatically detected, and overlying candidate lesions were excluded. A measure of visibility was automatically quantified for remaining candidate lesion, expressing the densitometric steepness of the lesion edge and the lesion contrast relative to the surrounding fundus. Candidate lesions exceeding a user-supplied visibility-threshold parameter were classified as automatically detected and registered by the system. Thus, the visibility threshold controlled the balance between sensitivity and specificity of the automated red-lesion detection. The automated bright-lesion detection implemented in the Retinalyze system operated in a fashion similar to the red-lesion detection. Digital image quality was automatically quantified as a measure of contrast and detail. Loss of contrast and detail characterizes poor image quality regardless whether it is caused by inappropriate camera use or opacity of the ocular refractive media. A single user-supplied quality-threshold controlled the level at which an image was automatically deemed of unacceptable quality. Finally, as a measure of image scale, the algorithm required the expected size of the optic disk diameter in pixels as a starting parameter. The scale parameter was manually determined as the mean optic disk size of 25 macular fundus photographs of patients with no optic disk lesions.

Algorithm Calibration

Prior to automated analysis, the user-supplied adjustable thresholds were set. For red-lesion detection, the threshold was set to 1.4 arbitrary units, for bright lesion detection it was set to 2.4 arbitrary units, and for image quality it was set to 0.58 arbitrary units. This was done after titration to optimized performance in a calibration set of digitized fundus photographs from 120 diabetic patients examined at the Steno Diabetes Center. These calibration photographs were all from eyes that did not require photocoagulation treatment and represented ETDRS levels 35 to 61. All parameters were locked for further changes once the calibration had been completed; no study patients or images examined in the automated analysis were used for calibration or analyzed prior to locking of the algorithm.

Statistical Analysis

The sensitivity of the automated detection of photocoagulation-requiring diabetic retinopathy was evaluated on per-patient classifications. Each patient was classified as true positive if one or more red or

bright lesions were automatically detected in any field of a patient's two eyes and as false negative if no red or bright lesions and no images of substandard quality were automatically detected. The rationale for the per-patient classification was that whole patients, not single eyes, are referred from retinopathy screening services to clinics where full ophthalmic examinations are performed.

The statistical analysis was conducted on computer (S-plus 6.0; Insightful Corporation, Seattle, WA, USA).

This study was entirely retrospective and followed the tenets of the Declaration of Helsinki. The study did not involve patients or biological samples and as such did not require institutional review under the law of the Kingdom of Denmark.

RESULTS

Automated analysis of fundus photographs of both eyes of the 106 study patients with photocoagulation-requiring diabetic retinopathy identified fundus anomaly by detection of at least one red lesion in one eye in 104 patients (true positive; Table 1) and failed to identify two patients as being abnormal by this method (false negative; Table 1).

The automated analysis identified fundus anomaly by detection of at least one bright lesion in at least one eye in 91 of the 106 patients in the study population (Table 1). It failed to detect anomaly by bright-lesion detection in 15 patients with diabetic retinopathy (Table 1). All of the 91 patients identified by the bright-lesion detection algorithm were also identified by the red-lesion detection algorithm.

Poor image quality was automatically identified in at least one photographic field in at least one eye in 12 patients (Table 1). These included the two patients in whom no anomaly was detected by the red- or the bright-lesion detection algorithms.

TABLE 1 **Fundus photographic findings by automated image analysis in cases referred for treatment of diabetic retinopathy from a retinopathy screening clinic**

	Abnormalities of fundus morphology or image quality		
Number of patients	Yes	No	Total
Parameter			
Red-lesions	104 (98%)	2 (2%)	106
Bright-lesions	91 (86%)	15 (14%)	106
Poor image quality	12 (11%)	94 (89%)	106
Any abnormality	106 (100%)	0 (0%)	106

Consequently, the combination of automated red-lesion detection and automated detection of poor image quality identified all 106 diabetic patients in need of fundus photocoagulation treatment (sensitivity 100%, exact CI_{95} 96.6–100.0%).

The impact of the preset choice of red- and bright lesion-visibility thresholds is illustrated in Figure 1, which shows that even a substantial lowering of the thresholds for lesion detection would not have been able to substitute for poor image quality detection. Lowering the threshold for bright-lesion detection would also not have contributed any information that within the study context could have added to the performance of the red-lesion detection.

Extreme visibility (above 150 arbitrary units) of lesions categorized by the automated lesion detection algorithm as red lesions was attributable not to true red lesions but to artifacts such as dust specks and film scratches (Fig. 1). No such false-positive red lesions were found without automatically detectable true red and bright lesions being present in the same image. When extreme visibility of bright lesions was present, it was invariably attributable to true hard exudate.

DISCUSSION

In the study population of patients with photocoagulation-requiring diabetic retinopathy, automated analysis of fundus photographs achieved a per-patient detection rate of 100% when based on the combination of detection of red lesions and poor image quality. This supports that in a hypothetical prescreening application, automated image analysis may be successful in selecting patients in need of photocoagulation treatment for visual grading without false-negative results on the basis of these two modalities alone. Bright fundus lesion detection could not substitute for any of the two modalities and did not contribute independently to improve the sensitivity of the automated analysis. This study is, to the best of our knowledge, the first to assess the utility of bright-lesion detection in relation to red-lesion detection in diabetic retinopathy screening.

Patients who do not need treatment for retinopathy usually dominate diabetic retinopathy screening populations. Hence, the addition of bright-lesion detection by the method used in this study is likely to

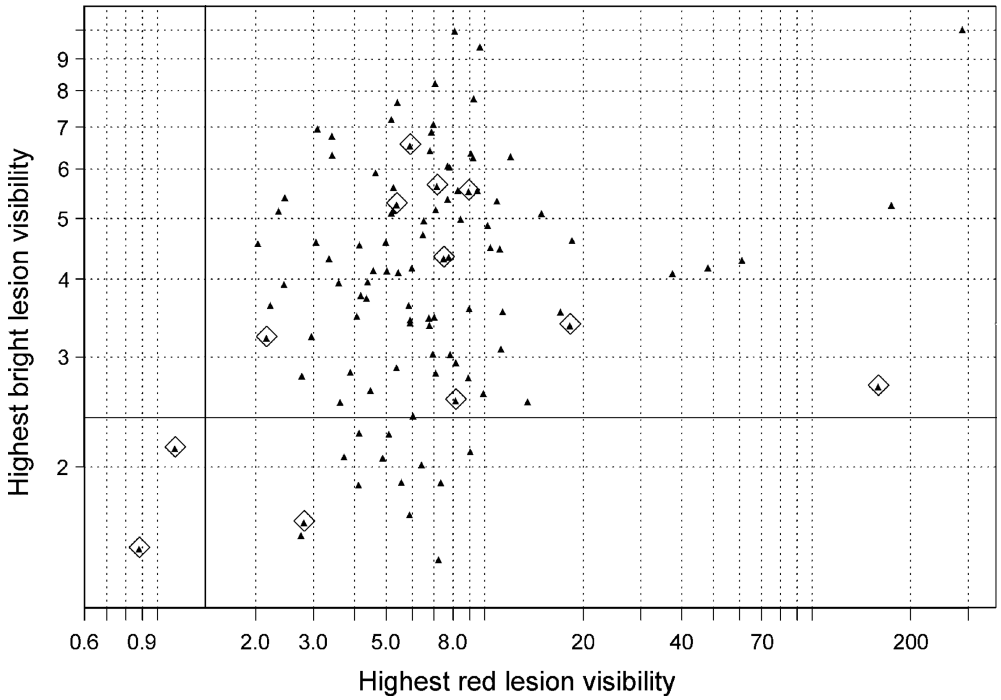

FIGURE 1 **Graphical representation of the results of the automated lesion detection, including the thresholds for lesion detection for red and bright lesions (1.4 for red lesions along the x-axis and 2.4 for bright lesions along the y-axis). A total of four images per patient from 106 patients were analyzed. Coordinates of filled diamonds represent the red lesion with the highest visibility and the bright lesion with the highest visibility per patient. Outline diamonds represent cases where poor image quality was detected in at least one of the examined photographs (two per eye).**

lower the specificity without improving the sensitivity of retinopathy detection.

In the current study, no eye with isolated bright lesions was seen. Indeed, hard exudate, the most conspicuous type of bright lesion in the retina, rarely occurs without red lesions in diabetic retinopathy. Isolated cotton-wool spots without red lesions are occasionally seen in patients with diabetes, but this condition does not require photocoagulation treatment.

The current study was conducted using a system that examines individual bright lesions without consideration of their dimension, orientation, location, pattern, chromaticity, or topographical relation to red lesions. Consequently, the full potential for bright-lesion detection in diabetic retinopathy has not been explored. The same is true for red-lesion detection, which was designed only to detect non-neovascular diabetic lesions.

Our results were achieved using a specific image analysis system, but we applied common principles of image analysis and therefore believe that our results have general value as an empirical test of the potential performance of automated fundus photographic analysis in diabetic retinopathy.

Computerized detection of diabetic retinopathy appears to have the potential of not omitting any patient who is in need of photocoagulation treatment from being selected for visual grading and/or referral for physician examination.

While the results of the current study are promising, its test value is limited by the sample size. Ultimately, automated prescreening for diabetic retinopathy in combination with visual grading of only patients found to present fundus anomalies should be made in a prospective comparison with accepted standards, be it funduscopic examination by an ophthalmologist or visual grading of fundus photographs.

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