A Telemedical Approach to the Screening of Diabetic Retinopathy: Digital Fundus Photography

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OBJECTIVE — The importance of screening for diabetic retinopathy has been established, but the best method for screening has not yet been determined. We report on a trial of assessment of digital photographs by telemedicine compared with standard retinal photographs of the same fields and clinical examination by ophthalmologists.

RESEARCH DESIGN AND METHODS — A total of 129 diabetic inpatients were screened for diabetic retinopathy by slit-lamp biomicroscopy performed by an ophthalmologist and by two-field 50° non-stereo digital fundus photographs assessed by six screening centers that received the images by electronic mail. Conventional 35-mm transparencies of the same fields as the digital photographs were assessed by a retinal specialist and served as the reference method for detection of diabetic retinopathy. Slit-lamp biomicroscopy was the reference method for the detection of macular edema.

RESULTS — The prevalence of any form of diabetic retinopathy was 30% (n = 35); of sight-threatening retinopathy including macular edema, the prevalence was 6% (n = 7). The assessment of digital images by the six screening centers resulted in a median sensitivity of 85% and a median specificity of 90% for the detection of moderate nonproliferative or sight-threatening diabetic retinopathy. Clinically significant macular edema (n = 4) was correctly identified in 15 of the 24 grading reports. An additional seven reports referred the patients for further investigation because of concurrent diabetic retinopathy.

CONCLUSIONS — Telescreening for diabetic retinopathy by an assessment of two-field 50° non-stereo digital images is a valid screening method. Although detection of clinically significant macular edema using biomicroscopy is superior to digital or standard non-stereo photographs, only few patients with sight-threatening diabetic retinopathy are missed.

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Diabetic retinopathy in its early easily treatable form is asymptomatic (1). Because it is a common cause of preventable blindness—if treated adequately—it is important to establish effective screening programs for its detection (2,3). Although there is consensus concerning the cost-effectiveness of screening (4–8), the best screening method has not been established.

Digital fundus photographs have the advantage that they can be taken at minimal cost and inconvenience to the patient (9–13) and can be transmitted by electronic mail through the Internet to distant experts (14,15). Valid assessment requires uniformity of terminology and methodology. For this purpose, the Field Guide Book (16) is useful, since it has been validated against standard 30°, seven-field stereo photographs (17) and has been shown to be useful in a community-based study in Wales (18).

In the study reported here, we adopted the Field Guide Book and compared a combination of slit-lamp biomicroscopy performed by an ophthalmologist and evaluation of two-field 35-mm transparencies with the assessment of two-field digital fundus images sent to distant screening centers in a telemedical setting.

RESEARCH DESIGN AND METHODS

Subjects

From 1 October 1997 to 31 January 1998, 194 consecutive diabetic inpatients were screened for eligibility for the study at Bogenhausen Hospital, Munich. According to criteria defined before the study, 65 patients were excluded from the screening program for one of the following conditions: previous photocoagulation for diabetic retinopathy (n = 26), inability to cooperate (n = 19), blindness (n = 2), refusal to participate in a study (n = 10), mature cataract (n = 3), glaucoma (n = 2), and other (n = 3). Informed consent was given by all study participants. The study was approved by the Ethical Committee of the Bavarian Chamber of Physicians (no. 97179) and was conducted in accordance with the 1983 Helsinki Declaration.

The clinical characteristics of the 129 patients included were: type 1 diabetes 48% (n = 62), type 2 diabetes 52% (n = 67), men 45% (n = 58), mean age 46.6 ± 17.5 years, mean duration of diabetes 9.9 ± 8.2 years, and mean HbA_{1c} 8.4 ± 1.9%.

The 65 patients who did not participate were older (59.0 ± 16.0 years), had a longer duration of diabetes (17.6 ± 12.4 years), and had more severe retinopathy (43% no, 33% mild or moderate, and 24% sight-threatening diabetic retinopathy). The proportion of men (50%) and patients with type 2 diabetes (58%) did not differ from the included patients. These patients were examined by an ophthalmologist only.

Experimental protocol

After the assessment of best corrected visual acuity, each patient was screened for the presence of diabetic retinopathy after dilation of pupils (tropicamide 1%) and subsequent slit-lamp biomicroscopy by an experienced ophthalmologist. During the study period, six senior ophthalmologists, not specializing in diabetic retinopathy, performed the funduscopies.

Subsequently a Topcon TRC 50X fundus camera (Topcon Europe, Rotterdam, the Netherlands) was used to take two 50° digital images (768×576 pixels) and two transparencies (35 mm, Kodak Ektachrome 100) per eye according to the standard protocol defined in the Field Guide Book (16) with dilated pupils. One field covered the temporal area including macula and disc whereas the second covered the nasal field including the disc. Digital and conventional photographs showed identical sections of the fundus. The images were captured by medical personnel or by nonmedical personnel who had a 1-day introductory course on fundus photography and 1 month of subsequent daily practice.

The digital images were sent as electronic mail via the Internet to five different grading centers in Europe with special expertise in diabetic retinopathy. The graders at the five centers comprised two diabetologists, two ophthalmologists, and an expert retinal grader. The transmission was performed using standard Internet protocols. Additional information on type of diabetes, diabetes duration, visual acuity, diabetes therapy, and HbA$_{1c}$ was added to the reports in most cases. Screeners were not allowed to manipulate the digital images. The reports were returned via electronic mail to the Bogenhausen Munich Hospital.

Several months after the recruitment period, the ophthalmologists who performed the biomicroscopy graded the digital fundus images of the patient they had seen months earlier using the same structured report as previously mentioned. They were masked for the grading results of the

other screeners and had no access to their previous reports.

Reference methods and screening threshold

A "mixed gold standard" was used for analysis. To obtain the gold standard for the diagnosis of diabetic retinopathy excluding macular edema, two-field non-stereo 35-mm transparencies of each eye were graded by one expert (E.K.) in April 1998 without knowledge of visual acuity, diabetes duration, HbA$_{1c}$, or the previous telescreening reports. The gold standard for diagnosis of macular edema was the slit-lamp biomicroscopy of the ophthalmologist. The screening threshold was defined as moderate nonproliferative or more severe diabetic retinopathy and/or clinically significant macular edema. Patients with this degree of retinopathy would be referred for ophthalmologic examination.

Classification of diabetic retinopathy

The results of funduscopy and of the assessments of the digital and the 35-mm transparencies were documented on identically structured forms. All graders received written definitions of the stages of diabetic retinopathy before the study began and were asked to classify pathological findings according to this protocol. The protocol was a modified version of the Field Guide Book (16) and comprised eight diagnoses: 1) no retinopathy, 2) mild nonproliferative, 3) moderate nonproliferative, 4) severe nonproliferative, and 5) proliferative diabetic retinopathy, 6) high-risk proliferative diabetic retinopathy (2), 7) advanced eye disease, and 8) clinically significant macular edema (19). Sight-threatening diabetic retinopathy included any form of clinically significant macular edema and/or any stage of diabetic retinopathy that was severe nonproliferative or higher in at least one eye.

Technical quality of the screening methods

Reports on 14 of the 129 (11%) sets of 35-mm transparencies were not available because slides were lost (n = 5), were not of sufficient image quality (n = 7), or were not taken according to Field Guide Book criteria (16) (n = 2). Therefore the analysis was based on 115 patients. Between 0 and 15% of 129 digital image sets per telemedical screener were not gradable because of image quality

(mean 5%). No loss of digital images was observed. Image sets of a patient that were not graded by a telescreener were considered positive screening results because severe retinopathy was not excluded. The ophthalmologist was able to perform funduscopy on all 129 patients.

Statistical analysis

Sensitivity and specificity can be calculated per patient as well as per eye. Here we report only patient-based values and we use a "mixed gold standard" (see REFERENCE METHODS AND SCREENING THRESHOLD). Since the sample size for estimating sensitivity was small, we calculated 95% confidence limits by the exact method.

RESULTS

Detection of diabetic retinopathy and maculopathy

The prevalence of retinopathy is presented in Table 1.

Considerable variations of sensitivity and specificity between telemedical screeners were observed (Table 2). The quality of the screening results was not related to the medical specialty of the screeners (diabetologists in centers 1 and 6, ophthalmologists in centers 3, 4, and 5). The medical photographer with long expertise in screening (center 2) had the second-best result.

Macular edema

Clinically significant macular edema was diagnosed by biomicroscopy in six eyes of four patients. A total of 15 of the 24 screening reports on digital images and 2 of the 4 reports on 35-mm transparencies of these patients correctly identified macular edema. An additional seven reports graded patients as having at least moderate nonproliferative diabetic retinopathy while not mentioning the presence of macular edema. Therefore a total of 22 of 24 telescreening reports on patients with maculopathy had a positive screening result according to the previously defined screening threshold.

One additional patient with clinically significant macular edema in both eyes was not diagnosed by clinical examination but was identified by 35-mm transparencies and by three of five telescreeners. The diagnosis was ascertained by a second biomicroscopy, and laser treatment was initiated. Best corrected visual acuity was reduced to at least 50% in the affected eyes of all patients with clinically significant macular edema (data not shown).

Table 1—Prevalence of diabetic retinopathy including clinically significant macular edema (n = 115)

Stage of diabetic retinopathy	n	Prevalence (%)
No diabetic retinopathy*	80	70
Mild nonproliferative diabetic retinopathy*	22	19
Moderate nonproliferative diabetic retinopathy†	6	5
Sight-threatening diabetic retinopathy†	7	6

Data are n or %. *No referral for further evaluation indicated. †Referral to ophthalmologist for further examination indicated. The group with sight-threatening retinopathy also comprised four patients with macular edema in one or both eyes with or without proliferative diabetic retinopathy.

Sight-threatening diabetic retinopathy

Applying the threshold "at least moderate nonproliferative diabetic retinopathy or clinically significant macular edema" for referral to an ophthalmologist, three tele-screening centers correctly identified seven, one center identified six, and two centers identified five of seven patients with sight-threatening diabetic retinopathy.

CONCLUSIONS — In Germany, only a minority of eligible diabetic patients are screened annually (20) and the incidence of blindness and severe visual loss remains high (21). In other Western countries, continuously high or increasing prevalence of diabetic retinopathy has been reported (22–24). Most screening in Europe is currently done by ophthalmologists frequently using biomicroscopy; therefore the new telemedical approach to screening had to be compared to this as the usual standard of care.

Some professional bodies demand a sensitivity of 80% and a specificity of 95% to accept a screening method for sight-threatening diabetic retinopathy (25). We demonstrated that the telemedical assessment of digital images closely matches these criteria. Screening for diabetic retinopathy leads to an increase in person-years of sight and savings to national budgets, with little more gain obtained above 60–80% sensitivity (4,5).

It was not possible to exclude clinically significant macular edema in all affected eyes on the basis of non-stereo two-field digital or 35-mm fundus photographs alone. Stereo fundus photography and slit-lamp biomicroscopy are the best noninvasive methods to detect early macular edema (5). On the other hand, all patients with macular edema had significant reductions of best corrected visual acuity so that a combination of photography and measurement of visual acuity might define a sensible screening threshold. Moreover, in our study, many patients with macular edema had a positive screening result due to concurrent significant retinopathy alone.

Recent developments in retinal thickness analysis (RTA) using laser technique allow accurate topographical measurements of the retina (26). RTA was found to be superior to slit-lamp biomicroscopy and stereo fundus photography in comparison with the gold standard fluorescein angiography to detect macular edema (27), but at present RTA is not suitable for screening. Ischemic maculopathies will not be detected by RTA but in many cases can currently not be treated successfully.

Visual loss in clinically significant macular edema is closely related to the thickness of the retina (27). In the U.K. Prospective Diabetes Study, 60% of laser treatments were indicated because of clinically significant macular edema (E.K., unpublished observations). Simple devices like the Amsler grid might be used to increase detection of clinically significant macular edema (28,29) in telemedical screening settings.

Limitations of the study include the low mean age of patients and the low proportion of type 2 diabetes, which are not representative for the general population with diabetes. Moreover, the sample size of our study was small and therefore did not include large numbers of cases of diabetic retinopathy. Nevertheless, the total prevalence of diabetic retinopathy of all 194 consecutive patients screened for eligibility to the study was 38% (sight-threatening 11%), which is in line with recent screening results of 40% total prevalence in a more rural area of Bavaria (30). Other investigators also found a total prevalence of 40–45% of diabetic retinopathy and of 10–14% of sight-threatening diabetic retinopathy in the general diabetic population (31,32).

The low average failure rate of telescreening of 5% for the digital screening in our study was probably influenced by the low prevalence of cataract or corneal opacity, which can dramatically increase the number of unreadable photographs reported in studies using conventional photography (30,33). The fact that 85–90% of the diabetic population has type 2 diabetes with frequent coexistence of cataract would limit the method's sensitivity in the general population. On the other hand, 11% of the 35-mm transparency sets used in our study were not gradable. The British Diabetic Association recommends a maximum failure rate of 5% for any photographic method to be acceptable (25).

Conventional fundus photography has been implemented successfully in various screening scenarios (18,34–36). Digital imaging of the eye opens new perspectives: it is now possible to send some or all images for instant review by a retinal expert supported by a retinal photographer who needs training and auditing but no medical degree. Screening costs would be expected to decrease, since no film material is necessary and compressed digital images preserve image quality (10). Algorithms for automated detection of retinal pathology on digital images are being developed (14,15).

In conclusion, assessment of digital fundus photography following the methodology of the Field Guide Book (16) is of suf-

Table 2—Sensitivity and specificity for the detection of at least moderate nonproliferative or sight-threatening diabetic retinopathy (n = 13), including clinically significant macular edema, using digital fundus photography in 115 patients

Observer	Sensitivity	Specificity
Center 1	92 (64–99)	95 (89–98)
Center 2	85 (55–98)	94 (88–98)
Center 3	85 (55–98)	91 (84–96)
Center 4*	85 (55–98)	88 (80–94)
Center 5	77 (46–95)	73 (62–81)
Center 6	70 (39–91)	88 (80–94)
Median	85	90

Data are % (95% CI). The reference methods were two-field 50° 35-mm non-stereo color transparencies for diabetic retinopathy and slit-lamp biomicroscopy for diabetic maculopathy. The centers were ranked according to sensitivities obtained. *Center 4 consisted of the six ophthalmologists who had performed the slit-lamp biomicroscopies but were masked for these results. All other centers had one screener only. Calculation was based on screening results per patient.

ficient quality to detect sight-threatening diabetic retinopathy and can add telemedical support to urgently needed screening programs. However, because clinically significant macular edema cannot be excluded using this methodology, the measurement of visual acuity is also indicated. The detection of macular edema requires further investigation.

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