

Nonmydriatic screening for diabetic retinopathy by ultra-widefield scanning laser ophthalmoscopy (Optomap)

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Received: 18 March 2007 / Accepted: 14 June 2007
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Abstract

Purpose To compare the diagnostic properties of a nonmydriatic 200° ultra-widefield scanning laser ophthalmoscope (SLO) versus onsite mydriatic ophthalmologic examination for diabetic retinopathy.

Methods A consecutive series of 51 eyes of 51 patients with different levels of diabetic retinopathy (DR) was examined. Grading of diabetic retinopathy and macular edema obtained on stereoscopic dilated funduscopy by a retina specialist was compared against grading obtained from Optomap Panoramic200 SLO images. All SLOs were performed with an undilated pupil, and no additional clinical information was used for evaluation of the Optomap images by three independent, masked expert graders.

Results A total of five images (9.8%) were not gradable due to insufficient quality. Clinically 4 eyes had proliferative diabetic retinopathy (PDR), while 9 had none, 5 mild, 19 moderate and 14 severe nonproliferative diseases (NPDR). Of the gradable 46 images, a clinically significant macular edema (CSME) was present in 28 eyes clinically. On Optomap, all eyes with PDR were detected as being proliferative, and a sensitivity of 94% at a specificity of 100% was obtained for all graders to detect more than mild DR. Agreement between Optomap retinopathy grading and

clinical assessment was good with unweighted kappas of 0.68, 0.68 and 0.51. Assessment of CSME yielded sensitivities of 93, 93 and 89% at specificities of 89, 72 and 83%.

Conclusions The Optomap Panoramic200 nonmydriatic images are of sufficient quality to assess DR and CSME validly and therefore fulfill the basic requirements for telescreening programs.

Keywords Retinopathy screening · Retinal screening · Telemedicine · Imaging · Diabetes

Introduction

Diabetic retinopathy is a leading cause of visual impairment and blindness in developed countries. The incidence and prevalence are high and will continue to increase [18]: it is currently estimated that 10.2 million adults in the United States aged 40 years or older currently have diabetes mellitus (DM). The prevalence rates in this group of patients are approximately 40.3% for retinopathy and 8.2% for vision-threatening retinopathy [10]. Diabetic retinopathy impairs vision due to two main complications: macular edema and proliferative retinopathy [13]. To avoid vision loss, an annual clinical examination with dilated pupils is the current best standard of care in patients with no or mild diabetic retinopathy [7]. In the Early Treatment Diabetic Retinopathy Study (ETDRS), regular examination, combined with timely treatment, led to a reduction of moderate visual loss by 50% [6].

Current screening coverage for diabetic retinopathy is unsatisfactory in most Western countries. In the United States, only approximately 40–60% of patients with diabetes are annually seen by an ophthalmologist [2]. The

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The authors do not have any commercial interest in any of the materials and methods used in this study.

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main reasons are perceived difficulty and inconvenience in visiting an ophthalmologist and the contributing fact is that conventional screening by an ophthalmologist requires pupil dilation, which is time-consuming and impairs the patient's ability to drive a vehicle on that day.

Nonmydriatic screening techniques are available—these are usually based on photography and allow for tele-ophthalmologic networks. While such nonmydriatic photography screening is being successfully used [1], some problems exist with this technique: with increasing age media opacities (especially cataracts) increase and pupil diameters decrease, both of which degrade image quality. Therefore a 20% rate of ungradable images can be considered average [17], reducing the effectiveness of screening programs based on nonmydriatic photography. Another important issue is that coverage of the retina is limited, with most cameras taking one or two 45° or 60° images for diabetic retinopathy screening. The current best known standards for photography, the ETDRS photographs, consist of seven single (stereoscopic) 30° images taken after pupil dilation; they cover 75–65° of the central retina. While two 60° fundus photographs, one macula-centered and one optic disc-centered, cover 80% of this area imaged and make it unlikely that areas of neovascularisation will be missed [20], most screening programs cover significantly less retina area. Although these programs still offer good screening characteristics [19], this fact might reduce their sensitivity.

Recently, a novel nonmydriatic fundus imaging device, the Optomap Panoramic200 (Optos PLC, Dunfermline, Fife, Scotland, UK) has become widely available with currently more than 2,500 systems installed worldwide. The system allows nonmydriatic imaging not only of the posterior pole but even extending over the equator. It covers 180–200° without the need for pupil dilation, which by far exceeds the area covered by the ETDRS photographs. This is made possible by a special optical design of the scanning laser ophthalmoscope (SLO), which also has the advantage of being much less susceptible than fundus cameras to any media opacities such as cataracts [12, 15]. Therefore the Optomap widefield SLO appears to be a promising technology to screen for diabetic retinopathy. In this study we investigate the diagnostic properties to correctly grade diabetic retinopathy by nonmydriatic Optomap imaging assessed by three expert ophthalmologists versus onsite routine ophthalmologic examination in diagnostic mydriasis.

Methods

Patients

Consecutive patients were recruited from the outpatient clinic of the Department of Ophthalmology, Ludwig-Maximilians-

University, Munich. Patients were included if they had diabetes (based on WHO criteria) for at least 3 years. One eye of each patient was randomly selected to avoid any bias by intra-individual correlation between the two fellow eyes. Eyes were excluded if there were eye diseases involving the posterior pole other than diabetic retinopathy (such as age-related macular degeneration), but not for media opacities. All patients underwent complete ophthalmological examination including a dilated (1% tropicamide) stereoscopic fundus exam with slit-lamp biomicroscopy (78 D lens) by an experienced retina physician. The levels of diabetic retinopathy and macular edema were assessed using the International Clinical Diabetic Retinopathy (ICDR) severity scale [2]. Additionally the presence of clinically significant macular edema (CSME) was assessed independently. The lens opacity was assessed clinically by slit-lamp grading based on a simplified clinical scale ranging from 0 (clear lens) to 5 (very mature cataract) [5, 11]. Additional tests such as fluorescein angiography were performed if needed.

Optomap imaging

After informed consent, Optomap imaging was performed without pupil dilation before and independently of the clinical examination. The study fully conformed to the principles expressed in the Declaration of Helsinki, and Institutional Review Board approval was obtained. Optomap imaging consisted of taking several images; the best image per eye was saved on the server for grading. The instrument takes one image in approximately 0.25 s thus avoiding motion artifacts. Total scanning requires approx-



Fig. 1 Example of Optomap imaging of a patient with PDR. Despite panretinal laser coagulation, a preretinal hemorrhage can be seen at the lower temporal vessel arcade due to significant neovascularization there and at the upper temporal vessel arcade. In the lower part of the image, some lashes from imaging are present

imately 3–5 min including patient positioning and was performed by an experienced technician or one of the authors (MK).

The Optomap Panaoramic 200 consists of a scanning laser ophthalmoscope (SLO), with two laser wavelengths: one green (532 nm) and one red (633 nm) laser. The two images are then either viewed separately or superimposed by the software to yield semi-realistic color imaging (see Fig. 1). The instrument requires a small optical path of only 2 mm and, by a special mirror design, is able to obtain wide-field images of approximately 180–200° without pupil dilation. The optical resolution with the instrument used in this study was 1,984×1,984 pixels for that angle, resulting in approximately 10–11 pixels per degree. In keeping with the SLO principle, images of high contrast and sharpness are obtained, which show less susceptibility to media opacities than conventional photography [12].

Image grading

The retina images were loaded from the server to a viewing station (equipped with a conventional cathode-ray 17" noncalibrated color monitor) via network and assessed with the Optomap viewing software. This software allows important image manipulations such as changing contrast and brightness and zooming. It also offers viewing in both the composite color image and the single wavelengths (Fig. 2). The images obtained by the different wavelengths was compared to better differentiate the level at which lesions were located, as the green laser cannot penetrate significantly below the retinal pigment epithelium, while the longer red laser wavelength will (see Fig. 2).

The images were graded independently by three experienced retina specialists (ASN, CH and SGP; randomly named graders A–C). The graders had previously not

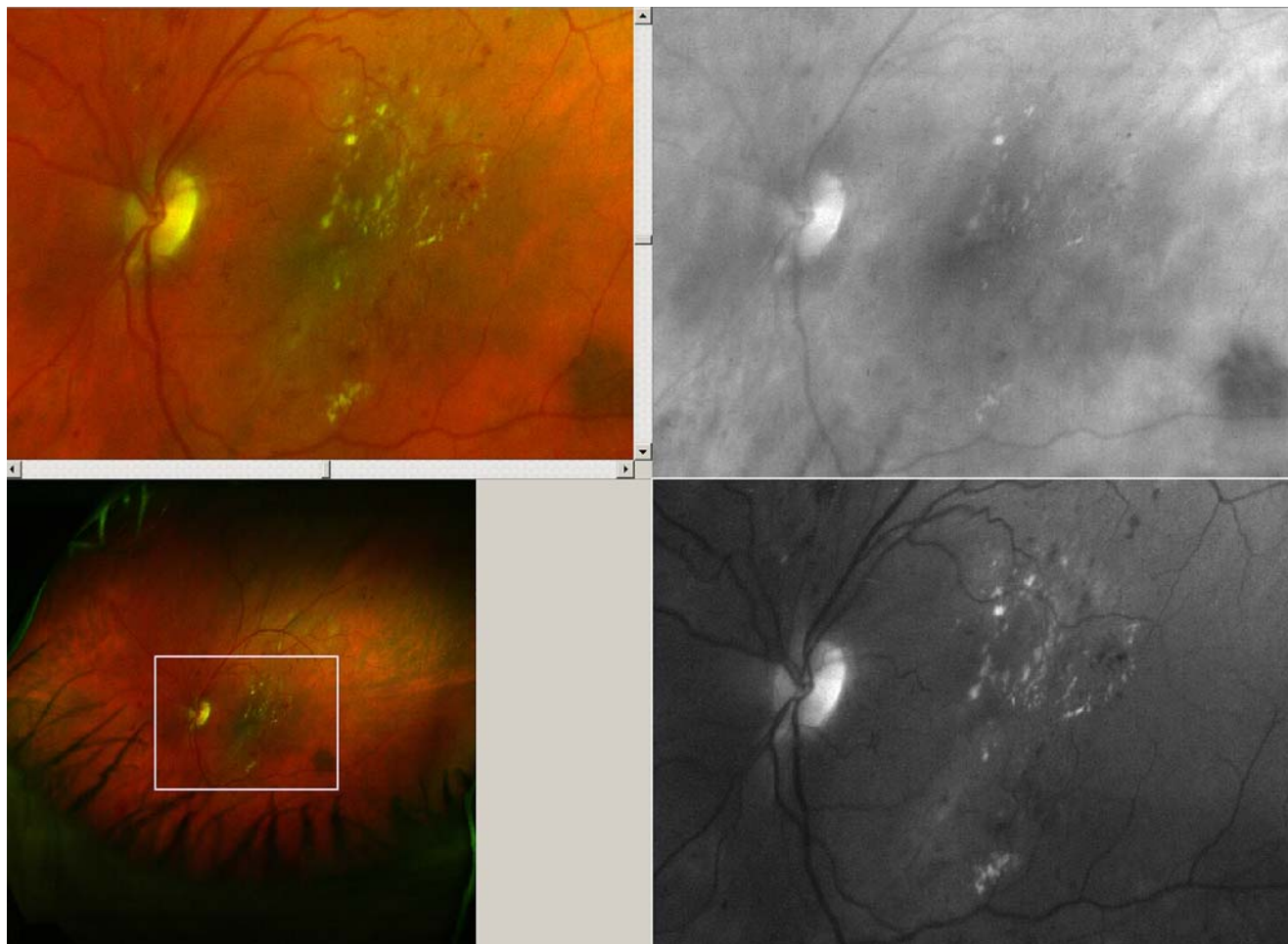


Fig. 2 Zoomed Optomap image to better assess the clinically significant macular edema. In the *upper left* part of the image the composite color view is seen, which is composed by the viewing software from the single red laser (*upper right* part of image) and

green laser (*lower right* part of image) images. Note how differently the exudates show up under the two different wavelengths. The *lower left* picture shows the complete Optomap image, with the currently zoomed part marked by a *white box*

participated in examination of the patients and were masked to all additional information such as visual acuity, duration of diabetes, or clinical symptoms. The grader, however, could decide not to grade due to insufficient image quality, which was defined as not covering at least the central 60° and without both the macula and the optic disc in good quality.

As with the clinical grading, the levels of diabetic retinopathy and macular edema were assessed using the ICDR severity scale [2]. Independently from this assessment, the presence of CSME was graded. The two laser wavelengths were viewed separately to better assess the level at which changes were located especially in the macula on the two-dimensional display of the Optomap. This—together with the two-dimensional signs such as exudates—allows macular edema to be assessed to some degree.

Statistics

All data were collected in an MS Excel 2000 spreadsheet (Microsoft, Redmond, WA, USA) and analyzed using SPSS 13.0 for Windows (SPSS, Chicago, IL, USA). On all tests $P < 0.05$ was considered significant, and nonparametrical testing was applied where appropriate. Kappa statistics were calculated and assessed as proposed in [3]: < 0.20 poor, $0.21–0.40$ fair, $0.41–0.60$ moderate, $0.61–0.80$ good, and $0.81–1.00$ very good agreement. Unweighted kappa was used thus avoiding any bias by weighting.

Results

Patients

A total of 51 eyes, 25 right and 26 left, of 51 patients were included in the study. Mean patient age (\pm SD) was 60 ± 12.1 years (range 24–75 years). Mean visual acuity was 0.48 ± 0.40 LogMAR ranging from 0 to 1.40. Diabetes duration ranged from 3 to 40 years, mean 11 ± 10.1 years. Of all patients, 53% were using insulin, while 47% were on oral medication. Mean HbA_{1c} was $7.0 \pm 1.3\%$ (range 5.4–10.5).

On clinical grading, 9 eyes (18%) showed no retinopathy, 5 mild (10%), 19 moderate (37%), 14 severe NPDR (28%) and 4 PDR (8%). Macular edema was absent in 12 eyes (24%), mild in 11 (22%), moderate in 17 (33%) and severe in 11 eyes (22%). CSME was present in 31 eyes (61%), while 20 eyes did not have clinically significant macular edema. The lens was clear in 2 cases (4%), 17 eyes had mild (33%), 15 moderate (29%) and 8 severe (16%) cataracts. One eye had very advanced cataracts, and in 8 eyes (16%), an intraocular lens was present.

Technical quality of imaging

Optomap imaging could technically be performed in all patients, however the graders assessed the resulting images of three to five eyes as “not gradable” due to insufficient imaging quality (5.9–9.8%): images did not cover at least

Table 1 Clinical grading of diabetic retinopathy (DR) after pupil dilation versus assessment from Optomap images. Data are the number of eyes in each category for the three graders A, B and C

Optomap grading	No DR	Mild NPDR	Moderate NPDR	Severe NPDR	PDR	Sum
No DR	7	2	0	0	0	9
	6	2	0	0	0	8
	7	1	0	0	0	8
Mild NPDR	2	0	2	0	0	4
	3	0	2	0	0	5
	2	1	2	0	0	5
Moderate NPDR	0	0	16	1	0	17
	0	0	14	1	0	15
	0	0	10	4	0	14
Severe NPDR	0	0	0	8	0	8
	0	0	2	11	0	13
	0	0	5	8	1	14
PDR	0	0	0	4	4	8
	0	0	0	1	4	5
	0	0	1	1	3	5
Not gradable	0	3	1	1	0	5
	0	3	1	1	0	5
	0	3	1	1	0	5
Sum	9	5	19	14	4	51

Overall a good concordance was found among the three independent graders of Optomap imaging as well as for individual graders with the clinical assessment (kappa 0.68, 0.68 and 0.51). NPDR Nonproliferative diabetic retinopathy, PDR proliferative diabetic retinopathy

Table 2 Clinical assessment of diabetic retinopathy (DR). Data are number of eyes in each category for the three graders A, B and C

Optomap grading	More than mild DR	No or mild DR	Sum	
More than mild DR	33	0	33	PPV 100%
	33	0	33	100%
	33	0	33	100%
No or mild DR	2	11	13	NPV 85%
	2	11	13	85%
	2	11	13	85%
Sum	35	11	46	
	Sensitivity 94, 94, 94%	Specificity 100, 100, 100%		

Good screening characteristics regarding the presence of significant (> mild) diabetic retinopathy were obtained, which is illustrated by the sensitivity, specificity, and positive (*PPV*) and negative predictive values (*NPV*)

the central 60° and both the macula and the optic disc. The reasons were mainly inability for the patients to keep their eyes open and be positioned in front of the instrument, which results in improper focus. Because of the non-confocal SLO design of the instrument, the resulting images are sharp, but the angle covered is reduced. The five eyes not showing a sufficient angle of 60° covered were therefore excluded from further analysis. Media opacities due to cataracts did not correlate significantly with the probability that an image would not be gradable. The degree of lens opacification, however, correlated significantly with increasing age ($r=0.36$, $P=0.02$) and decreasing visual acuity ($r=0.33$, $P=0.03$), but not with diabetes duration or retinopathy level in our patient cohort.

Grading of retinopathy

Table 1 summarizes the results for grading diabetic retinopathy. The five nongradable eyes were excluded from further analysis. For the remaining 46 eyes, a good agreement with a kappa of 0.68 for grader A, 0.68 for grader B and 0.51 for grader C was obtained compared to the clinical retinopathy level as a reference. Among the three graders, good kappas were also obtained: 0.72

between grader A and B, 0.49 between grader B and C, and 0.66 between grader A and C. The screening characteristics in terms of sensitivity and specificity for significant DR (> mild DR) are summarized in Table 2.

Grading of macular edema

When considering the four-level grading scale for the degree of macular edema, the kappa values indicate only a fair agreement with clinical assessment yielding 0.20 for grader A, 0.27 for grader B and 0.25 for grader C. Detailed data are given in Table 3 for the more relevant and sight-threatening condition of CSME. A good sensitivity between 89 and 93% at specificities between 72 and 89% was obtained from the Optomap images.

Discussion

In this study, we were able to show that a special color scanning laser ophthalmoscope allowing 200° ultra-widefield imaging, the Optomap Panoramic200, can be applied to validly assess diabetic retinopathy without the need for pupil dilation. It should be noted, however, that assessment of the

Table 3 Clinical assessment of clinically significant macular edema (CSME). Data are the number of eyes in each category for the three graders A, B and C

Optomap grading	CSME present	No CSME	Sum	
CSME present	26	2	28	PPV 93%
	26	5	31	84%
	25	3	28	89%
No CSME	2	16	18	NPV 89%
	2	13	15	87%
	3	15	18	83%
Sum	28	18	46	
	Sensitivity 93, 93, 89%	Specificity 89, 72, 83%		

Good screening characteristics for vision-threatening CSME were obtained, as illustrated by the sensitivity, specificity, and positive (*PPV*) and negative predictive values (*NPV*)

images was performed in this study by experienced retina specialists and the available reviewing features such as separate viewing of the single laser color images and zooming on the images were used extensively during grading. On the other hand, owing to the clinic-based patient selection in our study, most patients showed high levels of diabetic retinopathy: 61% had sight-threatening macular edema, and only 27% had no or mild retinopathy. In a typical primary care screening setting over 60% normal eyes and only about 7% sight-threatening changes are usually observed [8], which means that grading results may be even better in such a setting. Despite this negative bias in our study, the screening characteristics obtained for the Optomap SLO are comparable to those obtained by ophthalmologists [16] or by on-site trained optometrists in a primary setting, where 87% sensitivity and 91% specificity for sight-threatening eye disease were achieved [8].

The percentage of nongradable images in this study ranged between 6 and 10% although a high percentage of eyes had significant media opacities. The mean patient age of 60 years was also relatively high. Both advanced age and media opacities are known to cause problems with nonmydriatic imaging [17]. Despite this the percentage of nongradable images compared favorably to the usual 10–20% [17] or up to 35% obtained with nonmydriatic fundus cameras [1]. This is attributed to the laser scanning principle, which allows better penetration through hazy media, creates high contrast images by point-wise scanning, and allows the use of extremely narrow optical pathways at the pupil level. On the other hand, the optical resolution of SLOs is usually less than with high-quality fundus cameras. The Optomap Panoramic200 offers 10–11 pixels per degree, which is less than, for example, the 20 pixels per degree recommended for fundus cameras by the United Kingdom's National Screening Committee (<http://www.nscretinopathy.org.uk>). However, such comparisons are misleading as the SLO resolution cannot be compared directly to a fundus camera; for instance it is widely accepted that an SLO used for fluorescein angiography, the Heidelberg HRA (Heidelberg Engineering, Heidelberg, Germany), yielding “only” 768×768 pixels images outperforms megapixel photography systems in terms of sharpness and contrast of the images. This is due to the different principles of illumination and image taking between SLO and fundus photography.

Limitations of the Optomap system have been described, such as missing or misdiagnosing lesions [4], which may apply to peripheral lesions but were not observed in our study. On the other hand, the ultra-widefield nonmydriatic coverage of the images allows for new applications [9, 14, 15], potentially improving patient care. Further systematic validation is necessary for each application as performed in this pilot study for diabetic retinopathy.

In summary, the Optomap Panoramic200 SLO nonmydriatic images are of sufficient quality to assess the diabetic retinopathy level validly as compared to dilated clinical examination. Vision-threatening CSME is also detected reliably. The rate of <10% nongradable images is acceptable. Overall the performance characteristics of nonmydriatic Optomap examination may fulfill the basic requirements of telescreening programs for diabetic retinopathy and justify larger scale studies.

Acknowledgements The authors thank Mrs. S. Guthmann and Mrs. N. Ehsani for expert technical assistance with Optomap imaging.

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