Screening for diabetic retinopathy using digital colour photography and oral fluorescein angiography

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Abstract

Purpose To evaluate digital colour photography and oral fluorescein angiography (OFA) for diabetic retinopathy screening.

Methods Thirty-seven patients were selected from either a diabetic retinopathy screening or a medical retina clinic. Three 45° colour digital images and a single macula 45° OFA image were taken from each eye. Standard seven-field stereo photography with ETDRS grading was used as a gold standard for data comparison. The images were assessed by two graders and the results of each method compared using the McNemar test.

Results Five eyes had no diabetic retinopathy, 50 had background diabetic retinopathy, 3 had pre-proliferative diabetic retinopathy, 11 had proliferative disease and 3 had quiescent post-treatment disease. Clinically significant macular oedema was present in 25 eyes and absent in 48. For grading diabetic retinopathy digital colour photography produced a sensitivity of 0.87 (specificity 0.83); OFA produced a sensitivity of 0.87 (specificity 0.80) ($p = 0.1$). For the detection of diabetic maculopathy, the sensitivity of digital colour photography was 0.48 (specificity of 0.95) and for OFA was 0.87 (specificity 0.87) ($p < 0.01$).
Conclusion This pilot study has shown that both digital colour photography and OFA compare well with conventional methods for diabetic retinopathy screening. The results encourage the further evaluation of OFA in the screening for diabetic maculopathy.

Key words Diabetic retinopathy, Digital photography, Oral fluorescein angiography, Screening

Screening for diabetic retinopathy is good clinical practice and cost-effective health care.¹⁻⁵ Screening methods vary widely and they have been extensively assessed.⁶⁻⁸ The use of direct ophthalmoscopy is now recognised as a poor method and photography or biomicroscopy are

advocated. Photography has the advantage that permanent retinal images are produced allowing for rapid diagnosis and also audit/quality assessment.

We appraised two new photographic methods for diabetic retinopathy screening: digital colour photography and oral fluorescein angiography (OFA). Digital colour photography was chosen as it is replacing conventional colour photography.⁹ This technique gives high-definition images which are easily stored on, and enhanced by, computers. Digital images may also be used for automated diabetic retinopathy detection using artificial neural networks.¹⁰ The other test was OFA, imaged with a digital camera. Intravenous (i.v.) fluorescein angiography is a sensitive technique for the detection of early diabetic retinopathy.¹¹ However, fluorescein need not be administered intravenously. OFA has been performed for many years and is currently used for children and in patients with no intravenous access.¹²⁻¹⁴ It benefits from being non-invasive and having fewer side effects than the i.v. method,¹⁵ although there is a case report of allergic reaction following OFA.¹⁶

OFA has not been widely used because it produces poorer quality images than i.v. angiography. The OFA images have less contrast (due to a lower plasma concentration of fluorescein¹⁷) and OFA does not produce early-phase angiogram images. However, early-phase shots are not necessary for the detection of many conditions such as diabetic maculopathy, neovascularisation and papilloedema.¹⁸

The development of digital cameras has overcome some of the drawbacks of OFA. These cameras are more light-sensitive, so lower levels of fluorescence can be detected, and the images may be digitally enhanced giving good final results. These considerations encouraged us to re-evaluate OFA as a method of detecting retinal disease.

This study aimed to assess the feasibility of using colour digital photography and OFA to detect sight-threatening diabetic retinopathy.

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Fig. 1. An enhanced oral fluorescein angiogram, demonstrating the reasonable quality and high contrast that can now be afforded by this technique.

Methods

Thirty-seven patients were recruited from a diabetic retinopathy clinic and a diabetic screening service. After explanation and consent the patients were dilated with 1% tropicamide. They were given a dose of fluorescein sodium (between 1 and 2 mg/kg) orally which was diluted in 250 ml of orange juice. Blood pressure and pulse were monitored by the trial nurse. Thirty minutes later, three 45° digital colour photographs were taken with a Zeiss FF450 camera (Carl Zeiss, UK), corresponding to ETDRS grading fields F1, F4 and F5.¹⁹ A single 45° macula angiogram image was taken at 35–40 min (Fig. 1). The patients were then transferred onto a standard 30° retinal camera for seven-field stereo photography. Each patient gave informed consent for retinal photography and OFA, and the trial was performed under the auspices of the local ethics committee.

The digital images were graded by two ophthalmologists, and the seven-field stereo photographs by an ETDRS trained grader as the gold standard. Images were graded as: (i) no retinopathy, (ii) background retinopathy, (iii) pre-proliferative retinopathy (iv) proliferative retinopathy and (v) post-treatment group. A separate grade was given for the presence or absence of clinically significant macular oedema (ETDRS).¹⁹

Table 1. Digital colour photography grading of diabetic retinopathy

	True positive	True negative	Total
Test positive	53	1	54
Test negative	8	5	13
Total	61	6	67

Sensitivity = 0.87, specificity = 0.83, PPV = 0.98, NPV = 0.83. Ungradable images 5/72 (6.9%).

Statistical methods

The sensitivities, specificities, positive predictive value (PPV) and negative predictive values (NPV) were calculated for each test. The proportion of true positives versus false positives for each test were compared using McNemar's test. Statistical advice was obtained from the Department of Statistics, Kings College Hospital, London.

Results

Thirty-seven patients were recruited (age range 25–70 years). Two of the gold standards were ungradable: one because of inadequate field capture and the other because of media opacities. The gold standard with poor field capture was still unusable for assessment of macular oedema. Of the other 72 eyes, 5 had no diabetic retinopathy, 50 had background diabetic retinopathy, 3 had pre-proliferative diabetic retinopathy, 11 had proliferative disease and 3 had quiescent (post-treatment) disease, 25 had diabetic maculopathy and 48 had no maculopathy.

During the test 3 patients complained of a bitter taste following the fluorescein administration; however, no patient vomited, complained of nausea or suffered any allergic symptoms.

The grading results (for 72 eyes) were compared with seven-field stereo photography for both the grade of retinopathy and the presence or absence of clinically significant diabetic maculopathy. Five of the colour

Table 2. Oral fluorescein angiography grading of diabetic retinopathy

	True positive	True negative	Total
Test positive	54	1	55
Test negative	8	4	12
Total	62	5	67

Sensitivity = 0.87, specificity = 0.80, PPV = 0.98, NPV = 0.50. Ungradable images 5/72 (6.9%). Inter-test McNemar = 2.17 ($p > 0.1$).

Table 3. Digital colour photography detection of diabetic macular oedema

	True positive	True negative	Total
Test positive	12	2	14
Test negative	13	41	54
Total	25	43	68

Sensitivity = 0.48, specificity = 0.95, PPV = 0.86, NPV = 0.95.
Ungradable images 5/72 (6.9%).

Table 4. Oral fluorescein angiography detection of diabetic macular oedema

	True positive	True negative	Total
Test positive	20	6	26
Test negative	3	39	42
Total	23	45	68

Sensitivity = 0.87, specificity = 0.87, PPV = 0.77, NPV = 0.87.
Ungradable images 5/72 (6.9%).
Inter-test McNemar = 10.32 ($p < 0.01$).

digital images and 5 of the oral fluorescein angiograms were ungradable. The results are presented on 67 colour digital gradings and fluorescein angiograms for the grading of retinopathy and on 68 images for the detection of macular oedema. The results are shown in Tables 1–4.

Table 1 shows the results for the grading of diabetic retinopathy using digital colour photography: a sensitivity of 0.87 with a specificity of 0.83. The result for OFA was comparable (Table 2), with a sensitivity of 0.87 and a specificity of 0.80; the inter-test McNemar result was 2.17 ($p > 0.1$). When digital colour photography was used to assess macular oedema (Table 3) a sensitivity of 0.48 (specificity of 0.95) was found. In comparison OFA (Table 4) was more sensitive (0.87; specificity 0.87), the inter-test McNemar result being 10.32 ($p < 0.01$).

Discussion

We have demonstrated that digital OFA and digital colour photography are sensitive methods for the detection of diabetic retinopathy. Digital colour photography yielded a sensitivity of 0.87 (PPV 0.98) and OFA a sensitivity of 0.87 (PPV 0.99). These compare well with the previously published data using 35 mm colour photography and Polaroid photography. Moss *et al.*²⁰ showed that four-field stereo 30° images have a sensitivity of 89% for the detection of diabetic retinopathy. Others have further simplified this method by using a three-field non-stereo pattern²¹ and maintained a high of sensitivity of 89%.²² These results reflect the best in conventional photography, using high-definition 35 mm film. Kerr *et al.*²³ found the sensitivity of digital colour photography to be 90% when compared with a clinician and now use it routinely to follow up patients with established or treated diabetic retinopathy (26% of their clinic). Our results with digital colour photography are in broad agreement (sensitivity of 0.85);

however, we used seven-field stereo as a gold standard, which is generally more sensitive for detecting diabetic retinopathy.

Detection of diabetic maculopathy

The best method of screening for macular oedema is still unclear. Many screening programmes use non-stereo retinal images, which may underestimate the incidence of diabetic macular oedema. Some programmes rely on a reduction of acuity to trigger referral for macular oedema.²¹ This is unfortunate as the ETDRS clearly showed that only a minority of patients treated with macular grid experienced an improvement in vision; most patients experienced a stabilisation or moderate acuity loss. Patients referred late for treatment did worse. Conversely, patients with little or no visual loss still benefited from laser treatment compared with those with deferred treatment.²⁴ We found non-stereo colour digital images were relatively insensitive for detecting diabetic macular oedema (sensitivity of 0.48). OFA, however, yielded a sensitivity of 0.87. Few studies have reported rates for the detection of diabetic macular oedema. Using slit-lamp biomicroscopy the ETDRS reported that macular oedema was detected 82% of the time with a specificity of 79% when compared with stereo photography. This is similar to the sensitivity of OFA.

Photographic failures

Several techniques have problems with photographic failures. Klein *et al.*²⁵ found that 50° non-mydratic cameras had an 86% sensitivity compared with the gold standard; however, the number of photographic failures increased from 2% to 12.7%. In our group photographic failure occurred in 2.8% of patients undergoing 30° colour photography, compared with 6.9% for 45° digital colour images and 6.9% of OFA images. This failure rate is similar to other methods such as Polaroid photography.²⁶

Conclusion

We have shown, in this pilot study, that digital colour photography and oral fluorescein angiography are highly sensitive for the detection of diabetic retinopathy. However, non-stereo digital colour images are relatively insensitive for detecting clinically significant diabetic maculopathy. Oral fluorescein angiography was as effective as clinical examination in the detection of maculopathy. As early detection of maculopathy is key for preserving vision in these patients, these results highlight the need for a two-stage screening process where patients with a suspicious macula could be referred for further assessment.

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