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The value of digital imaging in diabetic retinopathy

PF Sharp

J Olson

F Strachan

J Hipwell

A Ludbrook

M O'Donnell



S Wallace

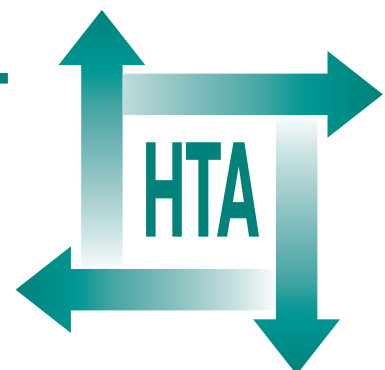
K Goatman

A Grant

N Waugh

K McHardy

JV Forrester





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The value of digital imaging in diabetic retinopathy

PF Sharp^{1*}

J Olson²

F Strachan^{3,4}

J Hipwell³

A Ludbrook⁵

M O'Donnell⁶

S Wallace⁶

K Goatman³

A Grant⁶

N Waugh⁷

K McHardy⁸

JV Forrester⁹

¹ Department of Medical Physics, University of Aberdeen, UK

² Department of Ophthalmology, Grampian Universities NHS Trust, UK

³ Department of Biomedical Physics and Bioengineering, University of Aberdeen, UK

⁴ Departments of Ophthalmology and Diabetes, Grampian Universities NHS Trust

⁵ Health Economics Research Unit, University of Aberdeen, UK

⁶ Health Services Research Unit, University of Aberdeen, UK

⁷ Scottish Health Purchasing Information Centre, Grampian Health Board, UK

⁸ Consultant, Grampian University Hospitals NHS Trust, UK

⁹ Department of Ophthalmology, University of Aberdeen, UK

*Corresponding author

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Initially, six HTA panels (pharmaceuticals, acute sector, primary and community care, diagnostics and imaging, population screening, methodology) helped to set the research priorities for the HTA Programme. However, during the past few years there have been a number of changes in and around NHS R&D, such as the establishment of the National Institute for Clinical Excellence (NICE) and the creation of three new research programmes: Service Delivery and Organisation (SDO); New and Emerging Applications of Technology (NEAT); and the Methodology Programme.

This has meant that the HTA panels can now focus more explicitly on health technologies ('health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care) rather than settings of care. Therefore the panel structure was replaced in 2000 by three new panels: Pharmaceuticals; Therapeutic Procedures (including devices and operations); and Diagnostic Technologies and Screening.

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Abstract

The value of digital imaging in diabetic retinopathy

PF Sharp,^{1*} J Olson,² F Strachan,^{3,4} J Hipwell,³ A Ludbrook,⁵ M O'Donnell,⁶ S Wallace,⁶ K Goatman,³ A Grant,⁶ N Waugh,⁷ K McHardy⁸ and JV Forrester⁹

¹ Department of Medical Physics, University of Aberdeen, UK

² Department of Ophthalmology, Grampian Universities NHS Trust, UK

³ Department of Biomedical Physics and Bioengineering, University of Aberdeen, UK

⁴ Departments of Ophthalmology and Diabetes, Grampian Universities NHS Trust

⁵ Health Economics Research Unit, University of Aberdeen, UK

⁶ Health Services Research Unit, University of Aberdeen, UK

⁷ Scottish Health Purchasing Information Centre, Grampian Health Board, UK

⁸ Consultant, Grampian University Hospitals NHS Trust, UK

⁹ Department of Ophthalmology, University of Aberdeen, UK

*Corresponding author

Objectives: To assess the performance of digital imaging, compared with other modalities, in screening for and monitoring the development of diabetic retinopathy.

Design: All imaging was acquired at a hospital assessment clinic. Subsequently, study optometrists examined the patients in their own premises. A subset of patients also had fluorescein angiography performed every 6 months.

Setting: Research clinic at the hospital eye clinic and optometrists' own premises.

Participants: Study comprised 103 patients who had type 1 diabetes mellitus, 481 had type 2 diabetes mellitus and two had secondary diabetes mellitus; 157 (26.8%) had some form of retinopathy ('any') and 58 (9.9%) had referable retinopathy.

Interventions: A repeat assessment was carried out of all patients 1 year after their initial assessment. Patients who had more severe forms of retinopathy were monitored more frequently for evidence of progression.

Main outcome measures: Detection of retinopathy, progression of retinopathy and determination of when treatment is required.

Results: Manual grading of 35-mm colour slides produced the highest sensitivity and specificity figures, with optometrist examination recording most false negatives. Manual and automated analysis of digital images had intermediate sensitivity. Both manual grading

of 35-mm colour slides and digital images gave sensitivities of over 90% with few false positives. Digital imaging produced 50% fewer ungradable images than colour slides. This part of the study was limited as patients with the more severe levels of retinopathy opted for treatment. There was an increase in the number of microaneurysms in those patients who developed from mild to moderate. There was no difference between the turnover rate of either new or regressed microaneurysms for patients with mild or with sight-threatening retinopathy. It was not possible in this study to ascertain whether digital imaging systems determine when treatment is warranted.

Conclusions: In the context of a national screening programme for referable retinopathy, digital imaging is an effective method. In addition, technical failure rates are lower with digital imaging than conventional photography. Digital imaging is also a more sensitive technique than slit-lamp examination by optometrists. Automated grading can improve efficiency by correctly identifying just under half the population as having no retinopathy. Recommendations for future research include: investigating whether the nasal field is required for grading; a large screening programme is required to ascertain if automated grading can safely perform as a first-level grader; if colour improves the performance of grading digital images; investigating methods to ensure effective uptake in a diabetic retinopathy screening programme.



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Glossary and list of abbreviations

Glossary

Biomicroscopy A technique for examining the structures of the eye.

Capital costs The costs associated with items that remain useful beyond the period in which these costs are incurred, for example, for equipment and buildings.

Cost-effectiveness A comparison of the cost of an intervention with the effect on the patient.

Creatinine A component of urine.

Diabetic retinopathy A complication of diabetes in which the retina of the eye is affected by blocking off of its small blood vessels.

Exudate Masses of macrophages containing lipids formed at the edges of where plasma has leaked from the capillaries.

Field A single image taken of the retina.

Fluorescein angiography A technique for visualising the blood flow through the vessels of the eye. A fluorescent dye is injected intravenously and images of the eye are taken as it flows through the blood vessels.

Fovea A small pit or depression in the retina. The very centre of the macula.

Fundus The portion of the interior of the eye visible through the ophthalmoscope.

Fusiform Spindle shaped.

Glycated haemoglobin A test to show how well controlled diabetes has been in the preceding months.

Haematocrit The percentage of a blood sample occupied by cells.

Haemorrhage Bleeding.

HbA_{1c} Glycated haemoglobin. See above.

Ischaemia Reduction of blood supply.

Laser photocoagulation The use of a highly focused laser to treat diseased tissue.

Macula The area of the retina that is the centre of sight.

Macular oedema Fluid in the macula.

Maculopathy A pathological condition of the macula.

Microalbuminuria Abnormally increased excretion of albumin in the urine. An early marker of diabetic kidney disease.

Microaneurysms Localised dilations of retinal capillaries. They may leak, causing oedema and haemorrhage in the retina.

Mydriasis The use of drops to dilate the pupil.

Neovascularisation The formation of new blood vessels.

Oedema A collection of fluid.

Ophthalmoscopy The use of an optical instrument for examining the interior of the eyeball.

Prognosis A forecast of the probable course and outcome of the disease.

Proliferative retinopathy Diabetes can result in small blood vessels being blocked off, so depriving the retina of oxygen and nutrients. The eye tries to grow new vessels, proliferative retinopathy, that may bleed and detach the retina.

Recurrent costs Costs which occur regularly.

Retina The light-sensitive layer at the back of the eye.

Risk factor A clearly defined occurrence that increases the probability that a person will get a disease.

Sensitivity The probability of correctly identifying that a disease is present.

Slit-lamp biomicroscopy A method of examining the eye using a special microscope.

continued

Glossary continued

Specificity The probability of correctly identifying that a disease is not present.

TIFF format Tag(ged) Image File Format – an image file popular owing to its platform independence, extendibility and great flexibility.

Type 1 (insulin-dependent) diabetes The type of diabetes that develops when the body cannot produce any insulin.

Type 2 (non-insulin-dependent) diabetes The type of diabetes that develops when the body can make some insulin but not enough, or when the insulin that is produced does not work properly.

Visual acuity A measure of how well a person sees distant and close objects.

VS2 Greater than or equal to Airlie House Photograph 2B in the equivalent of two Airlie House standard photographic fields.

List of abbreviations

BDR	background diabetic retinopathy	IRMA	intra-retinal microvascular abnormality
CCD	charge-coupled device	MeSH	medical subject headings
CI	confidence interval	NPDR	non-proliferative diabetic retinopathy
CSMO	clinically significant macular oedema or maculopathy	PC	personal computer
ETDRS	Early Treatment of Diabetic Retinopathy Study	PDR	proliferative diabetic retinopathy
FAZ	foveal avascular zone	PIA	perifoveal intercapillary area
FD	fractal dimension	RAM	random access memory
FROC	free response receiver operating characteristic	RCT	randomised controlled trial
ICG	indocyanine green	ROC	receiver operating characteristic
		SLO	scanning laser ophthalmoscope

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.



Executive summary

Objectives

To undertake a systematic literature review followed by a primary study to assess the performance of digital imaging, compared with other modalities, in screening for, and monitoring the development of, diabetic retinopathy.

The study addressed three questions:

1. Can a digital imaging system detect retinopathy irrespective of sort or level?
2. Can a digital imaging system detect progression of retinopathy?
3. Can a digital imaging system determine when treatment is required?

Design

Question 1

All imaging was acquired at a hospital assessment clinic. Subsequently, study optometrists examined the patients in their own premises.

Questions 2 and 3

In addition to the above, a subset of patients had fluorescein angiography performed every 6 months.

The gold standard was clinical examination by an ophthalmologist.

All questions were also addressed using automated analysis of digital red-free images.

Subjects

The study invited 1114 patients undergoing direct ophthalmoscopy at the diabetic clinic in Aberdeen; of these, 727 agreed and 387 declined. Of the former, 586 attended. Of these 103 patients had type 1 diabetes mellitus, 481 had type 2 diabetes mellitus and two had secondary diabetes mellitus; 157 (26.8%) had some form of retinopathy ('any') and 58 (9.9%) had referable retinopathy.

Results

Question 1: can a digital imaging system detect retinopathy irrespective of sort or level?

Any retinopathy

Manual grading of 35-mm colour slides produced the highest sensitivity (89%) and specificity (89%) figures, with optometrist examination recording most false negatives (sensitivity 75%). Manual and automated analysis of digital images had intermediate sensitivity.

Referable retinopathy

Both manual grading of 35-mm colour slides and digital images gave sensitivities of over 90% with few false positives (specificity 89 and 87%, respectively).

Digital imaging produced 50% fewer ungradable images than colour slides.

Question 2: can a digital imaging system detect progression of retinopathy?

This part of the study was limited as patients with the more severe levels of retinopathy opted for treatment.

There was an increase in the number of microaneurysms in those patients who developed from mild to moderate.

There was no difference between the turnover rate of either new or regressed microaneurysms for patients with mild or with sight-threatening retinopathy.

Question 3: can a digital imaging system determine when treatment is warranted?

Since there was no definite answer to question 2, then the answer must be 'no' at present.

Conclusions

Implications for healthcare

Digital imaging

In the context of a national screening programme for referable retinopathy, digital imaging is an effective method. In addition, technical failure rates are lower with digital imaging than conventional photography. Digital imaging is also a more sensitive technique than slit-lamp examination by optometrists.

Automated grading of digital images

Automated grading can improve efficiency by correctly identifying just under half the population as having no retinopathy.

Recommendations for future research

1. Is the nasal field required for grading? Our study would suggest not. Single-field imaging could potentially reduce the time taken to perform retinal screening and the number of technical failures.
2. Can automated grading safely perform as a first-level grader? Our study would suggest 'yes', but this needs to be confirmed in a large screening programme.
3. Does colour improve the performance of grading digital images? Although high-resolution colour digital images are now routinely available, their role in screening for diabetic retinopathy has yet to be assessed.
4. Can patient recruitment be improved? Future research is required to ensure effective uptake in a diabetic retinopathy screening programme.

Chapter I

Introduction

Background

Despite advances in diabetic care, visual impairment in diabetes remains a devastating complication, in terms of both personal loss for the patient and socio-economic costs to the community. It remains the commonest cause of blindness in the working population.¹ It is potentially preventable, but this presents an immense challenge to the NHS, principally because the timing of treatment is critical. If laser photocoagulation is delayed until there is symptomatic visual loss, the outcome may be poor, but too early referral will overload ophthalmology departments, leading to inefficient practice.

Two essential components of an effective and efficient system of diabetic care within the NHS are therefore first, regular retinal assessment, and second, a method of assessment that allows optimal timing of therapy.

The current arrangements within the NHS for identifying diabetic eye disease are widely perceived as being costly and inefficient and this leads to pressure for change. The development of digital cameras is a promising step forward. As it may not need a skilled operator, then regular assessment is more feasible and its diagnostic performance may be as good as, or even superior to, current methods. It is ideally suited to quality assurance as it produces a hard copy. However, the introduction of this technology into the NHS will have major logistical and resource implications and it should be a prerequisite that it demonstrably performs better than existing systems.

Key features of diabetic retinopathy

Klein and colleagues² were the first to suggest that baseline microaneurysm counts in patients with no other evidence of retinopathy can provide a useful predictor of long-term progression to proliferative retinopathy, independent of the effects of glycaemic control and blood pressure. Kohner and Sleightholm³ have provided evidence supporting the importance of microaneurysm detection and quantification from their analysis of fluorescein

angiograms. They showed a significant correlation between microaneurysm number and the presence of haemorrhages and cotton-wool spots and, to a lesser extent, the severity of hard exudates and intra-retinal microvascular abnormalities (IRMAs). From examination of the natural progression of fundus changes in diabetics with at least moderate diabetic retinopathy, key features were identified as having a high predictive value in heralding a deterioration to a proliferative state. The severity of IRMA, venous beading and the number of haemorrhages and microaneurysms were thought to be of the greatest significance in identifying individuals who are likely to develop neovascularisation.⁴

Early Treatment of Diabetic Retinopathy Study

The Early Treatment of Diabetic Retinopathy Study (ETDRS) was designed to provide answers as to how the devastating morbidity from visual loss could be reduced. The benefits to long-term visual outcome for patients with high-risk proliferative retinopathy undergoing laser panretinal photocoagulation have been recognised and adopted into standard clinical practice.⁵ However, the authors concluded that for those with mild to moderate retinopathy, and a low risk of progression to severe visual loss, early panretinal photocoagulation was inappropriate given its potentially detrimental effect on the peripheral visual field. They emphasised that the key to successful management was early identification of retinopathy with the meticulous monitoring of progression to allow optimum timing of intervention when a high-risk proliferative stage had been reached.

Risk factors in development of retinopathy

The Diabetes Control and Complications Trial⁶ has shown that strict metabolic control can both offset the development and slow the progression of diabetic retinopathy in type 1 diabetes. Whilst acknowledging the limitations of their cross-sectional study of 3250 European type 1 diabetes

patients, Sjolie and colleagues⁷ have also suggested that, in the later stages of retinopathy, the adjustment of blood pressure, fibrinogen and triglyceride levels may affect outcome. The cessation of cigarette smoking may also have a beneficial effect, although the evidence is conflicting.^{8–10}

However, as intervention at both primary and secondary level can now be contemplated, the need for careful screening of diabetic populations and monitoring of established retinopathy becomes even more crucial. The recognition of very early diabetic fundal change may provide the impetus to patients to make positive lifestyle changes and tighten glycaemic control. Accurate grading of retinopathy and recognition of high-risk features are essential to providing appropriately timed laser therapy.

An overview of existing screening methods

Adhering to the principles of the St Vincent Declaration,¹¹ the European Retinopathy Working Party defined a protocol of screening for diabetic retinopathy in 1991, advocating that all patients with diabetes should have an annual eye examination. This was broadly defined as ophthalmoscopy through pharmacologically dilated pupils or by retinal photography.¹² In the absence of evidence to support a definitive method of performing retinal examination, a study of 3318 patients with diabetes was undertaken on behalf of the NHS by Buxton and colleagues. A comparison was made between direct ophthalmoscopy, performed by general practitioners (GPs), ophthalmic opticians and hospital physicians, and consultant ophthalmologist assessment of images acquired with a non-mydriatic Polaroid fundus camera.¹³ They concluded that all participants showed relatively poor sensitivities (hospital physicians 67%; GPs 53%; ophthalmic opticians 47%) although specificities were higher (hospital physicians 97%; GPs 91%; ophthalmic opticians 95%), indicating that relatively few inappropriate referrals to ophthalmology services would occur. However, it was apparent that direct ophthalmoscopy alone was likely to miss a significant proportion of patients with evidence of retinopathy, regardless of who performed the examination. Comparable results were obtained from analysis of fundus photographs, with sensitivities ranging from 35 to 67% and specificities marginally higher than those of the

primary screeners at 95–98%. Although subsequent reports indicate that the quality of photography from a non-mydriatic camera may have been improved by use of mydriatic agents,¹⁴ the authors were unable to recommend a specific technique for routine screening of a general diabetic population. These results also reflect the outcome of work by previous authors^{15–19} and suggest that, at present, no individual method of routinely available fundus examination can be judged superior for clinical screening. Although the findings of Klein and colleagues¹⁵ seem encouraging, the wide confidence intervals calculated for their relatively small patient population warrant caution in interpretation of these results. Combining the modalities of ophthalmoscopy and retinal photography appears effective in detecting sight-threatening retinopathy according to O'Hare and colleagues,¹⁹ however, their technique does not achieve the recommended threshold of a minimum 80% sensitivity and 95% specificity for detecting mild retinopathy, suggested as an audit standard by the British Diabetic Retinopathy Working Group.²⁰

Commission from NHS Health Technology Assessment Programme

Aims of investigation

Given the above background, there has been significant interest in developing screening techniques and in particular in exploring the potential of digital imaging. As there was no clear information as to how these techniques would fit into a clinical setting, the work in this report was commissioned in 1996 by the NHS Health Technology Assessment Programme. The intention was first to undertake a systematic literature review and then carry out a primary study to assess the performance of digital imaging in screening for, and monitoring the development of, diabetic retinal disease. The study aimed to show: (1) whether further technical development will be required, (2) what the diagnostic performance of current digital systems is in comparison with alternative approaches, (3) whether there is any evidence of clinical effectiveness and (4) whether it is likely to be cost-effective as a screening or disease monitoring (diagnostic) test.

Overview of the study

The purpose of the study was to address three questions: (1) can a digital imaging system detect retinopathy irrespective of sort or level?; (2) can a digital imaging system detect progression of

retinopathy, in particular warranting further investigation?; and (3) can a digital imaging system determine when treatment is required?

Diabetologists and GPs wish to know the answer to question 1 as they can use this information to motivate patients to improve their metabolic control and prevent, or slow, the progression of retinopathy and other microvascular complications of diabetes – nephropathy and neuropathy. Diabetologists, GPs and optometrists wish to know the answer to question 2, as this will help reduce the enormous workload of screening for sight-threatening retinopathy. Ophthalmologists wish to know the answer to question 3 as this will help them decide when to initiate laser treatment.

We had previously developed software that could analyse digitised retinal images from fluorescein angiograms for the presence of the cardinal features of diabetic retinopathy, namely microaneurysms/haemorrhages and exudates.²¹⁻²⁴ This current project involves using a digital fundus camera, which would provide direct digital images, in conjunction with our software modified to analyse red-free images not only to detect retinopathy but to answer the three questions raised above.

The study was preceded by a systematic review of the literature to assess the value of currently

available digital imaging techniques and compare them with alternative methods.

Layout of the report

In the following chapter we will discuss the design of the study, centred around the three cardinal questions, and patient recruitment. The factors influencing the choice of the digital fundus camera system and the results of an assessment of the quality of the images produced by it will be presented in Chapter 3.

In Chapter 4, the principles behind the software used to detect microaneurysms and hard exudates automatically will be set out.

The study is divided into two branches. The role of digital imaging in screening will be looked at in Chapter 5, addressing question 1 and, in part, question 2. In Chapter 6 the value of digital imaging in monitoring progression of disease will be investigated. This will explore the answers to questions 2 and 3.

Finally, costs and consequences will be examined in Chapter 7 and conclusions and proposals for further research are presented in Chapter 8.

The systematic literature review is included as Appendix 1.

Chapter 2

Study design and patient recruitment

Aim of study

The systematic literature review (Appendix 1) concluded that digital photography offered a promising alternative to conventional photography and that its diagnostic performance was not impaired by the lower resolution of currently available systems. It confirmed that further studies were required to compare digital photography with conventional photography, when both sets of images are manually assessed by trained observers. In addition, it recommended that digital photography should be assessed against the performance of those currently providing retinopathy screening by direct ophthalmoscopy. As a result, the original proposal for investigating the value of digital imaging in diabetic retinopathy was followed.

Three cardinal questions were to be addressed in this study:

- Question 1: can a digital fundus camera system detect the presence of diabetic retinopathy (of any sort/level)?
- Question 2: can a digital fundus camera system detect progression of retinopathy?
- Question 3: can a digital fundus camera system determine when treatment is required?

In pilot studies it was shown that the contrast of microaneurysms/haemorrhages in digitised red-free images was sufficient to allow accurate quantitative analysis. Hence a digital fundus camera would probably allow the detection of the presence of retinopathy, assuming that the patient has sufficiently clear media to give digital images of sufficiently high quality. The question is whether it is more effective than conventional photography or slit-lamp examination by non-ophthalmologists.

Study design

An outline of the study is shown in *Figure 1*.

Patients were recruited whilst attending for their routine eye screening assessment at the diabetic clinic in Aberdeen. Routine screening usually

involved direct ophthalmoscopy with mydriasis. As direct ophthalmoscopy is known to be an insensitive technique, the information from this procedure was not used in the study as it was not felt to be an acceptable screening method.

Once patients had agreed to take part, they were all asked to attend a research clinic at the hospital eye clinic. There, patients had their visual acuity measured, their fundi photographed and fundi assessed by one of the study ophthalmologists. All patients were then asked to attend one of the study optometrists in the optometrists' own premises. This appointment was arranged by the research registrar. The information from these first assessments was used to answer question 1, can a digital system detect the presence of diabetic retinopathy (of any sort/level)? The second question, can a digital system detect progression of retinopathy?, was to be answered by repeat assessment of all patients 1 year after their initial assessment.

In addition to the above, a subset of patients who had more severe forms of retinopathy were monitored more frequently for evidence of progression. This subset had the following criteria when examined by the study ophthalmologists:

- moderate non-proliferative or worse retinopathy
- retinal thickening within a one disc diameter radius of the centre of the macula.

This subset was also studied to answer question 3, Can a digital system determine when treatment is required?

Question 1: can a digital system detect the presence of diabetic retinopathy (of any sort/level)?

This question has two components. First, can a digital system detect the presence of any retinopathy, and second, can it be used to decide automatically that the disease has progressed to a stage where the patient should be transferred to the eye clinic for further action? As it has been estimated that 'only' 30% of all patients with

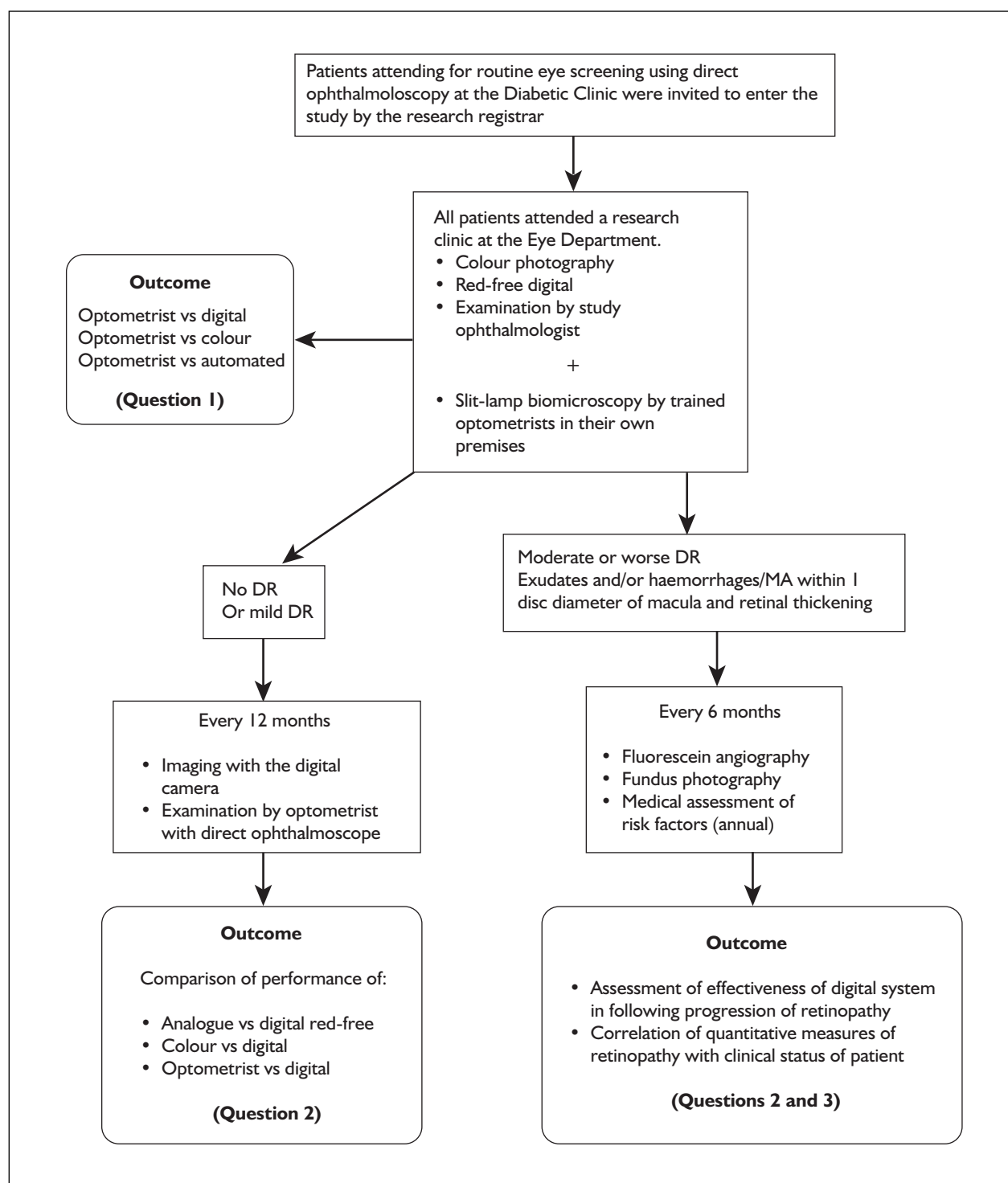


FIGURE 1 Experimental design. DR, diabetic retinopathy; MA, microaneurysm.

diabetes at any one time have retinopathy, then such a system could be of great benefit in reducing clinical workload.²⁵

All patients were studied every 12 months. As shown in *Figure 1*, they underwent digital imaging on the Topcon™ system, where red-free images were acquired using two 45° fields, a macular field

and a disc/nasal field. These digital images were transferred to a SUN™ system, where the programmes which had been developed for analysing for microaneurysms and haemorrhages were used.

In addition, analogue red-free and colour images were taken. Conventional mydriatic retinal

photography was performed using a Topcon 50X fundus camera with 35-mm transparencies on Kodachrome 64 film.

Patients were also examined at this visit by an ophthalmologist using slit-lamp biomicroscopy, this being the only widely agreed clinical gold standard for assessing severity of retinopathy. The use of two 45° fields allowed direct comparison with the proposed European grading system developed for the EURODIAB study. This method is directly comparable with the Airlie House grading system – the present gold standard for grading diabetic retinopathy – and has been proposed as a particularly suitable method for large epidemiological studies.²⁶ This study is described in detail in Chapter 4.

All patients also had an additional assessment by a study optometrist for fundus examination using slit-lamp biomicroscopy. This was performed on a separate occasion in the optometrist's own premises.

Question 2: can a digital system detect progression of retinopathy?

Question 3: can a digital system determine when treatment is required?

This arm of the study looked at the ability of the digital system to provide the ophthalmologist with a reliable, quantitative measure of retinal pathology which will allow him or her to monitor the progression of the disease. The crucial questions were whether a digital system could detect progression of retinopathy and whether it could be used to determine when treatment was required. As for the detection of any retinopathy, it was felt that the answer to the first question was probably 'yes'. That to the second question may be 'yes' if the measurement of area of haemorrhage and number of microaneurysms at VS2 (greater than or equal to Airlie House Photograph 2B in the equivalent of two Airlie House standard photographic fields) is the end-point.

An important facet of these two questions was to look at the natural history of retinopathy. Therefore, in addition to the subset of those patients initially assigned to this study, that is, those diagnosed on the initial screening study as having moderate proliferative retinopathy or worse, or clinically significant macular oedema

(maculopathy), a group of patients with lesser degrees of retinopathy was included.

All patients underwent fluorescein angiography and fundus photography every 6 months. Software to measure the number of microaneurysms and area of exudate from such images had previously been developed by our group.²¹⁻²⁴

Finally, it was planned to correlate the changes reported from the computer measurements against clinical status. All patients were assessed medically once a year as various risk factors are known to be associated with the progression of retinopathy. Patients had body mass index, blood pressure, HBA_{1c} and microalbuminuria measured.^{6,15,27-29} In addition to smoking and alcohol consumption, obstetric history, past medical history and drug history were also ascertained.^{30,31} This was done to allow the natural history of retinopathy to be put into clinical context and to help identify those patients needing more frequent screening than eye signs alone will suggest.

Patient recruitment

The numbers of patients required for the study were estimated as follows. For the community screening group, assuming that 30% (240) actually have retinopathy, the area under the receiver operating characteristic (ROC) curve will be estimated to $\pm 2\%$. Differences in specificity of $>6\%$ could be identified (80% power, $2p = 0.05$).

Assuming 560 participants of whom 10% (56) progress, the area under the ROC curve will be estimated to $\pm 4\%$. Comparisons with analogue image, colour slide and optometrist will identify differences in specificity of $>7\%$ (80% power, $2p = 0.05$).

For the hospital monitoring group, assuming 160 patients, of whom 10% (16) progress, the area under the ROC curve will be estimated to $\pm 7\%$. Differences in specificity of $>13\%$ could be identified (80% power, $2p = 0.05$).

For the purposes of analysis, this group may be combined with those with mild diabetic retinopathy. Assuming the combined sample, giving 720 participants of whom 10% (72) may progress, the area under the ROC curve will be estimated to $\pm 3\%$. Differences in specificity of $>6\%$ could be identified (80% power, $2p = 0.05$).

TABLE 1 Patients attending Grampian diabetic medical clinics on 10 January 1995

Diet controlled	1852
Tablet controlled	2858
UK Prospective Diabetes Study	294
Insulin treated	2620
Total	7624

The ability of digital imaging to identify progression to retinopathy that warrants treatment will be explored within the cohort of people found to have moderate/severe retinopathy at the first ‘inception’ examination. Assuming 80 participants of whom 40% (32) progress, the area under the ROC curve will be estimated to $\pm 5\%$.

Patients were recruited from those referred to the hospital diabetic clinic. At present 1.4% (7624) of the population of Grampian (528,100) attends these clinics (Table 1).

Previous studies have shown that, for Aberdeen patients, almost 100% of those on insulin and 96% of all patients with diabetes are registered at the clinic.³¹ As a consequence, our study reflected the local diabetic population as a whole; in other parts of the country hospital diabetic medical clinics are mainly attended by those with complications or on insulin. It was estimated that over the 36-month period of this study, about 800 patients could be studied. It was expected that approximately 30% would have abnormal retinal pathology, depending upon duration and level of control.³¹

The study invited 1114 patients undergoing routine funduscopy at the diabetic clinic to participate; 727 patients were recruited and 387

declined. Of the former, 586 patients attended an optometrist trained in slit-lamp biomicroscopy and also a hospital assessment clinic where digital and conventional photography was performed. Slit-lamp examination by an ophthalmologist was performed as the gold standard. These examinations were then repeated 1 year later.

Patients failing to attend for an appointment were offered a second appointment, but not followed up further.

Copies of the consent form, patient information sheet and letter of invitation are provided in Appendix 2.

Of the patients, 103 had type 1 diabetes mellitus (17.6%), 481 had type 2 diabetes mellitus (82.1%) and two had secondary diabetes mellitus (0.3%). The male-to-female ratio was 398:214 (65:35%). The average age at the start of the study was 56.5 years (median 59.3 years) (Table 2).

Table 3 summarises the alcohol consumption and smoking history. The definition of level of retinopathy is discussed in the section ‘Photography and digital imaging’ (p. 21).

TABLE 2 Age distribution of patients entering the study

Age range (years)	Percentage
<25	2.6
25–34	6.5
35–44	9.2
45–54	20.8
55–64	30.0
65–74	27.3
>75	3.6

TABLE 3 Smoking history and alcohol consumption of patients entering the trial

Level of retinopathy	Alcohol consumption (units per week) (mean and range)	Smoking history		
		Non-smoker	Smoker	Ex-smoker
None	5.4, 0–60 (n = 427)	209	80	140
Mild	6.4, 0–42 (n = 107)	59	12	37
Moderate	5.3, 0–56 (n = 36)	17	6	13
Severe	10.2, 0–28 (n = 6)	3	1	2
Very severe	–	0	0	0
Early PDR	4, 0–15 (n = 4)	2	1	1
High-risk PDR	8 (n = 1)	1	0	0

PDR, proliferative diabetic retinopathy.

Conclusions

For historical reasons, a larger number of patients attend the hospital diabetic clinic than might be expected in other areas. This is reflected in the demographics of the population studied, which has a higher prevalence of type 2 diabetes than might be expected in a hospital clinic. Although

the majority of people in the study were of a working age, it is of concern that 528 of 1114 patients approached either declined to take part or failed to attend once recruited. It can be speculated that this is due to the fact that patients were already being screened and might have implications for any stand-alone retinopathy screening programme.

Chapter 3

Photography

Choice of digital fundus camera

The choice of digital fundus camera is central to the project. At the time the study started, August 1996, there were few systems from which to choose. The defining parameters for selection were as follows:

- A digital image resolution of at least 1024×1024 pixels. Previous work by the Aberdeen group on the automated detection of diabetic retinopathy from fluorescein angiograms had used 35-mm film digitised off-line using a Kodak Megaplug camera with a resolution of 1024×1024 , a pixel size being equivalent to $13 \mu\text{m}$. A coarser digitisation than this was unlikely to yield comparable results.
- Monochrome image acquisition with a pixel depth of at least 8 bits. The project utilised red-free and fluorescein images. Although colour images might contain more information than monochrome images, at the time of the study commercial systems offered colour charge-coupled device (CCD) cameras with a coarser image digitisation, typically 640×480 pixels.
- Images must not be compressed prior to storage. Some types of compression can result in loss of information.
- Image file structure must be such that images can be extracted for analysis on a SUN workstation. Previously programs had been developed using the Unix™ environment on SUN workstations and time constraints meant that converting it to a personal computer (PC) environment was unrealistic.

The only system able to meet those specifications was the Topcon retinal camera and IMAGENet™ windows system (Topcon UK, Newbury, Berkshire, UK). The system, shown in *Figure 2*, consists of a Topcon TRC-50XT™ retinal camera with digital images being acquired with a Kodak Megaplug™ 1.4I CCD camera, with a digitisation of 1024×1024 pixels in monochrome with a pixel depth of 8 bits. A colour film back was available for the colour slides which were captured on to Kodak Kodachrome 64 film. Data were acquired on a PC for analysis, display and archiving under the IMAGENet hardware and software. Acquired images were archived on CD-ROM and



FIGURE 2 Topcon retinal camera with IMAGENet system

transferred to the SUN workstation for image analysis.

The Topcon TRC-50XT camera was chosen for this study as it had the finest image digitisation of the digital fundus cameras commercially available at the time. The images from other manufacturers (such as Canon) were not comparable, principally because they used colour cameras which gave a more coarsely digitised image (e.g. 768×576 pixels). In our experience, the larger monochrome (red-free) images with their potentially higher resolution at a given field of view, and greater contrast, were more appropriate for computer analysis than smaller colour images.

In addition to finer image pixellation from the Topcon camera, an earlier model photographic fundus camera from the same company was already being used in the eye clinic. The ophthalmic photographers were familiar with the operation of this camera and the quality of the slides they produced was consistently high. It was these slides, digitised using a Kodak Megaplug 1.4I CCD camera (the same CCD camera as fitted to the Topcon TRC-50XT digital fundus camera), which had been used to develop our automated techniques. Thus the ability to acquire the same images directly using the TRC-50XT camera was a logical progression.

The EURODIAB protocol

For this study we adopted the photographic protocol developed for the EURODIAB IDDM

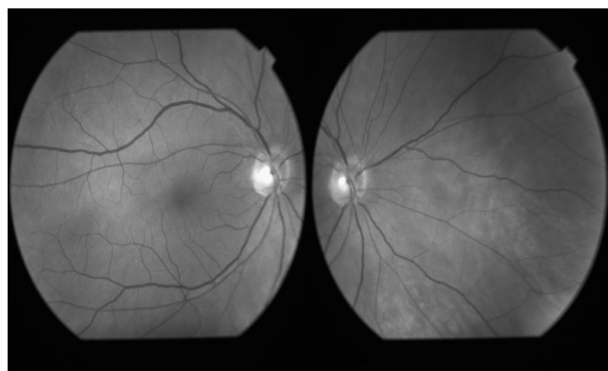


FIGURE 3 Two 50° red-free images of the right eye taken according to the EURODIAB IDDM Complications Study protocol. Left, macular view; right, nasal disc.

Complications Study in which two fields of each eye are obtained for each patient.²⁶ The first, the macular field, extends from the optic disc to the temporal retina and the second, the nasal-disc field, covers the region from the disc to the nasal retina; 50° fields were obtained, as opposed to the 45° fields used in the EURODIAB study, because this field of view was closest to that available on the Topcon TRC-50XT fundus camera used (Figure 3). The difference, however, is negligible and will, if anything, increase the area of the retina examined.

The EURODIAB protocol was validated against the recognised gold standard of the modified Airlie House system,³² with which it ‘compared favourably’. In the latter, seven pairs of 30° stereo photographs are obtained for each eye of each patient. Clearly the four images per patient of the EURODIAB scheme are vastly preferable to the 28 photographs of the modified Airlie House system if either is being considered for use in a large-scale screening programme.

The same protocol was used for both colour slide photography and acquisition of the digital images, permitting their direct comparison. An initial concern was the quality of images produced by the digital fundus camera. In the following section is reported a study of the overall quality of the images with respect to the visibility of structures such as the nerve-fibre layer and the retinal vessels.

Image artefacts due to camera dust

Soon after patient photography got under way, it became apparent that the digital images acquired

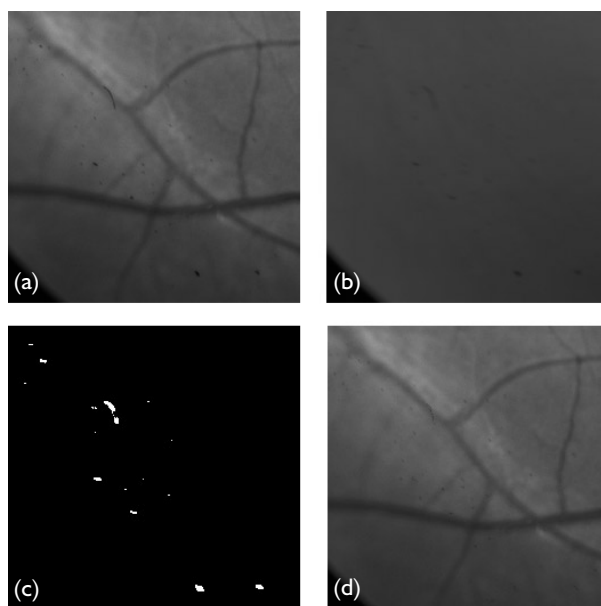


FIGURE 4 Removal of camera dust artefacts from the region of interest in an image. (a) Part of the original image showing the presence of dust as small dark shadows. (b) The average of all images taken on the same day's photography. After processing this average image a 'mask' is generated giving the locations of the image dust artefacts (c). This dust mask can then be used to remove the corrupting dust artefacts in the image (d).

were being corrupted by the presence of dust inside the camera (Figure 4a) and that this dust threw shadows on the images which closely resembled small, dark microaneurysms.

In the 5 months it took to identify and solve the problem, a total of 158 subjects had been photographed. In order to salvage the images collected and prevent the costly and time-consuming recall of subjects, a program was written to remove these dust artefacts from the images.

Although the dust in the camera could be disturbed on a day-to-day basis, it was found that on any given day the pattern of dust was relatively stationary. Hence, if the average of all the images collected on a given day was calculated, then the superimposed dust would produce a large response whereas non-coincident features, such as the retinal vessels, would be suppressed (Figure 4b). From this average image, a 'mask' could be generated (by shade-correcting and thresholding the average image; Figure 4c). This mask could then be used to eliminate the dust artefacts in each image by replacing the image pixels at these locations with the average (actually the median) of its neighbours (Figure 4d).

TABLE 4 Scheme used to grade 35-mm colour slide and digital image quality

Grade	Definition
Q1	Nerve-fibre layer visible
Q2	Nerve-fibre level not visible
Q3	Small vessels blurred
Q4	Major arcade vessels just blurred
Q5	Significant blurring of major arcade vessels in over one-third of the image in the absence of visible referable retinopathy

Grading image quality

To assess the quality of the digital images a grading scheme was developed that was adapted from the scoring system for vitritis.³³ The categories used to grade the quality of both the colour slides and digital images are listed in Table 4.

Q1 indicates the highest quality images in which the fine structure of the nerve-fibre layer is clearly visible. In images of grade Q2, the nerve-fibre layer is not visible but the smallest vessels in the image are in sharp focus. In Q3 images, these small vessels are blurred but the larger vessels are well defined. Q4 indicates that the large blood vessels in the major arcades are just blurred and, finally, if the image is judged to be of insufficient quality for a classification of retinopathy to be made, then grade Q5 is assigned to the image. This last grade is also assigned to images for which there is significant blurring of major arcade vessels in one-third or more of the image, in the absence of visible referable retinopathy. This might occur, for instance, as a result of shadows falling across the image such caused by misalignment of the eye.

For an overall grade of retinopathy to be assigned to a patient, quality grades between Q1 and Q4 were required for all four fields photographed. This ensures that lesions present in an obscured or degraded region of the retina are not overlooked, leading to potentially serious undergrading of the patient's retinopathy. In practice, we would expect these patients whose images are graded as Q5 to be referred for separate examination using slit-lamp biomicroscopy by a trained individual such as an optometrist or an ophthalmologist.

Grading of the digital images and colour slides was performed solely by the research fellow. As a result, direct comparison could be made between

TABLE 5 Comparison of quality of the digital and 35-mm colour slide images

Colour slide	Digital image					Total
	Q1	Q2	Q3	Q4	Q5	
Q1	492	329	64	35	1	921
Q2	138	669	287	172	5	1271
Q3	41	249	159	156	2	607
Q4	55	354	242	458	28	1137
Q5	6	45	26	83	51	211
Total	732	1646	778	904	87	4147

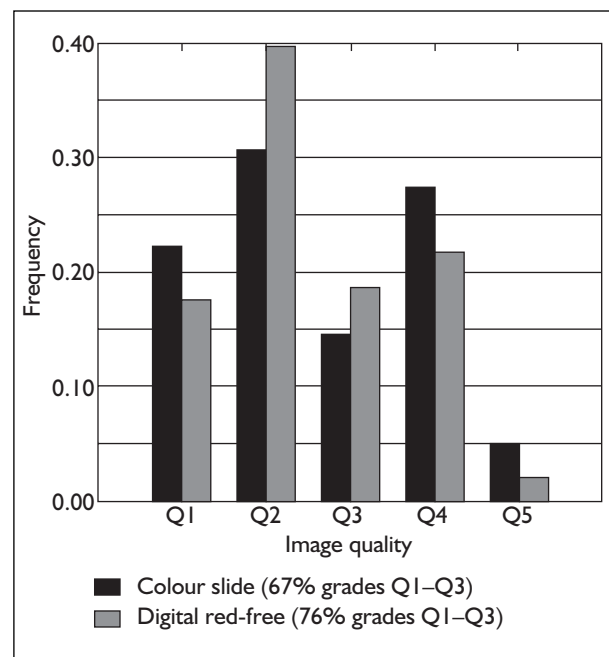


FIGURE 5 Colour slide and digital image quality distributions (data as in Table 4)

the grades assigned to each method of photography, avoiding concerns about inter-observer variability.

The data in Table 5 are replotted in Figure 5 to show overall image quality for both fields. In Figure 6, the difference in image quality between colour slide and digital image is shown. Individual colour slides had a higher frequency of the highest quality grade Q1 slides (22%) than digital images (18%) ($p < 0.001$), but also a higher frequency of the lowest quality grade compared with digital images (5% versus 2%). If one examines the number of images falling into categories Q1, Q2 and Q3 then there is a higher proportion of digital images than colour slides (76 and 67% respectively, $p < 0.001$).

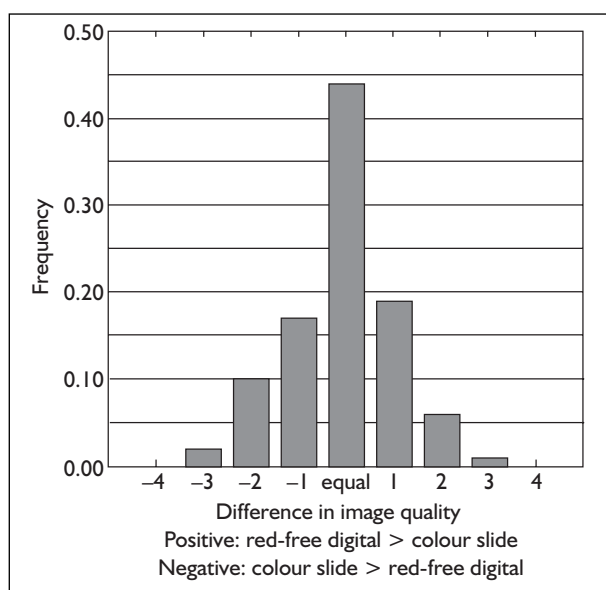


FIGURE 6 Comparison of colour slide and digital image quality

Failure to obtain gradable images

In *Figure 7*, the number of patient visits for which one, two, three or four ungradable fields were obtained for the two modalities are compared. Of the 1041 patient visits for which both colour slides and digital red-free photographs were obtained, twice as many visits for colour slide photography (107 or 10%) generated one or more ungradable fields compared with digital photography (54 or 5%). This was statistically significant ($p < 0.001$).

Colour slide photography would result in a large number of patients having to be recalled for photography and, of course, this has associated costs.

Conclusions

One of the main concerns with using digital images is that quality would be impaired by the digitising process. The choice of the Topcon fundus camera and IMAGENet software was made primarily on the basis that the Kodak Megaplug CCD camera used by this system had the finest image digitisation available at that time, 1024×1024 pixel image array. To reduce possible problems with image quality further it was specified that the software should not utilise any form of image compression.

Image quality can only be defined in terms of the use to which the image is to be put,³⁴ in this case the detection of diabetic retinopathy. This will be explored further in later chapters. However as an

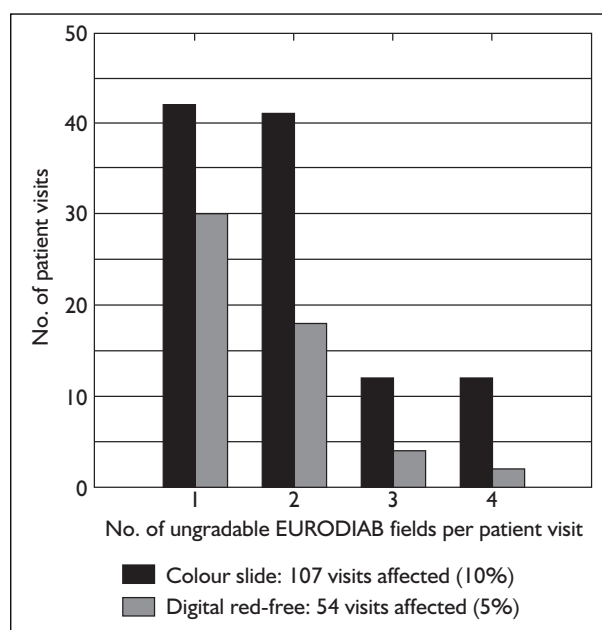


FIGURE 7 The number of patient visits for which one, two, three or four EURODIAB fields were ungradable

initial step, a grading system was used that utilised the clarity of features such as nerve-fibre layer and vessels as a measure of overall image quality. This demonstrated that the finest quality photographs were produced by conventional photography. This is not surprising as the maximum resolution of conventional photographs is approximately 2–3 times better than the digital camera used in this study. However, if the first three categories of quality are regarded as acceptable, then the digital images were superior to the colour slides. When the image quality was analysed in terms of field, then the poorest quality field tended to be the nasal field, reflecting the need for a widely dilated pupil and the absence of peripheral cortical cataract, a common clinical finding, to obtain high-quality images.

Digital photography produced fewer ungradable images, approximately half the number of visits for digital photography producing one or more ungradable images compared with colour slide photography. This was mainly due to the photographer having instant feedback on image quality by being able to view them instantaneously on the computer screen. If the image was not of sufficient quality the photographer simply repeated the photograph until one of sufficient quality could be obtained. This meant that approximately 50% fewer individuals would need to be recalled for repeat photography if a digital rather than a conventional photographic camera were used for image capture.

Chapter 4

Automated detection of retinopathy

Why automate?

Establishing a photographic screening programme has workload implications. In addition to the time taken to photograph the diabetic population, trained personnel are then required to view and grade all the acquired images.

The acquisition of digital images reduces the time previously associated with conventional photography, because it eliminates the overhead associated with the development of photographic slides. This also accounts for the higher proportion of digital images which are of reasonable quality; they may be viewed immediately and retaken if necessary without the need to recall the patient.

There is clearly a case to be made for an automated analysis of images to eliminate the need for tedious and costly manual grading of the images. Digital images are uniquely suited to this task since a well-designed computer program is able to read these images and process them directly, without the need for human intervention. Automated analysis also offers a consistency and reliability of interpretation that is not found with the human observer who is prone to fatigue.

What lesions should we detect?

Microaneurysms

Previous screening programmes have focused on the need to detect sight-threatening retinopathy; however, opinion has more recently shifted to the detection of any retinopathy. Microaneurysms are the earliest detectable signs of diabetic retinopathy and their numbers correlate closely with the severity of the disease.^{3,35,36} They are a logical choice for a screening programme, enabling patients with all degrees of disease severity to be detected. Furthermore, since the number of lesions increases with the severity of the disease, the likelihood of detecting patients with more severe retinopathy will increase, helping to ensure that those in need of referral are not missed.

The process of manually identifying individual microaneurysms in a fundus image is tedious and

prone to operator error. Although computer-assisted localisation of these lesions can help to reduce intra- and inter-observer errors,³⁷ a fully automated and entirely objective approach is clearly preferable.

Hard exudates

Diabetic maculopathy (clinically significant macular oedema) is the most common cause of visual impairment in diabetic patients and is indicated by the presence of retinal thickening or hard exudates within one disc diameter of the fovea. Current screening methods favour non-stereoscopic photography owing to the increased complexity of acquiring and interpreting stereo photographs. These techniques, however, offer no information about the presence of retinal thickening. The reliable detection of patients with macular exudates is of increased importance, therefore, if patients with potential clinically significant macular oedema are not to be overlooked.

The established means of manually quantifying exudate presence, via comparison with two standard photographs,³⁸ is unavoidably subjective, has limited precision and, consequently, is inherently inaccurate. Computerised detection, on the other hand, offers the benefits of a fully automated, and therefore objective and repeatable, analysis with accurate quantification of the extent of the pathology.

Automated detection of retinopathy

We have previously developed programs for the automated detection and quantification of microaneurysms in retinal fluorescein angiographic images.^{22,24,39} It has been demonstrated that this automated system detects microaneurysms almost as well as clinicians.³⁹ This program was used to analyse the fluorescein images taken in the disease monitoring part of the study (Chapter 6). For the screening study (Chapter 5), we needed to adapt the technique to the more challenging task of detecting microaneurysms in digital red-free images.

The general philosophy of our approach is to construct a definition of the appearance of a

microaneurysm or hard exudate. As will be described below, this is done on the basis of defining a number of features of the pathology, such as those relating to shape and intensity. By means of a training set of images, in which the pathology has been identified by an experienced observer, a set of rules is constructed for combining the values of these features in such a way as best to discriminate genuine from false pathology. As will be seen later in this chapter, the choice of an operating point for the program still requires a decision to be taken as to what constitutes an acceptable level of true and false-positive responses.

Microaneurysm detection

The definition of a microaneurysm

We have defined microaneurysms as small (25–200 μm in diameter), circular features with an approximately Gaussian or ‘bell-shaped’ profile. In red-free images they appear dark against the background whereas in the frames of a fluorescein angiogram they are bright. In both cases, however, we have attempted to mimic the decisions of clinicians viewing these images by measuring each microaneurysm identified by them in a training set of diverse images.

Thirteen measurements of each object are taken into account, including size, perimeter, circularity, aspect ratio, intensity and similarity to the ideal Gaussian profile. We do more than simply setting limits on these parameters, however. For instance, circularity is less significant for small microaneurysms that lie at the limit of the resolving power of the camera. The criteria for classifying an object as a microaneurysm will therefore vary with the size of the object.

Operation of the program

The initial processing of each image is performed in three stages. First the image is ‘shade-corrected’ to remove differences between images caused by changes in the illumination conditions under which each was obtained. Second, large features such as vessels and haemorrhages are removed by excluding all structures which are greater than a particular linear extent and, finally, only those remaining features which resemble the approximate shape and size of a microaneurysm are retained for subsequent classification.

At this stage of the processing, the image contains a number of candidate microaneurysms only some of which will be genuine. For each of these

candidates the program makes 13 measurements of intensity and shape, such as perimeter length, aspect ratio and circularity. These measurements are then tested using a set of rules which, if all are satisfied, identify the candidate as a microaneurysm. For example, a large object with insufficient average intensity might be rejected whereas a smaller, less prominent object is accepted owing to its greater circularity.

At this stage, it was necessary to draw up the rules for the program by examining the performance of the program on a set of genuine microaneurysms identified by the consultant ophthalmologist. Unsurprisingly, it was not possible to classify correctly all the microaneurysms identified by the consultant without also detecting a large number of spurious objects. As a result, it was necessary to decide on the degree of sensitivity and specificity which would be clinically acceptable.

Calibrating and testing the microaneurysm detector

Figure 8 illustrates the performance of the program for the detection of individual microaneurysms. It is expressed in terms of a free response receiver operating characteristic (FROC) curve that plots the sensitivity of the program in detecting microaneurysms as a function of the number of false positives per image, that is, the average number of spurious microaneurysms reported as being present in the image. The data were generated by analysing a set of images consisting of 44 normals, 41 mild, 12 moderate,

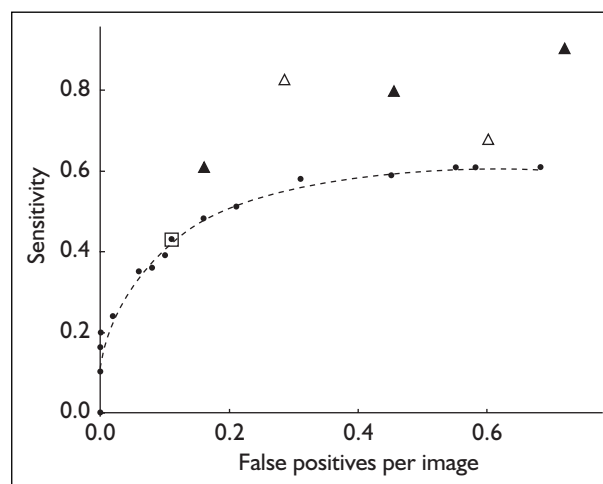


FIGURE 8 FROC curve comparing the performance of the microaneurysm detector (filled circles and dashed line) on digital red-free images with that of five clinical observers (filled and open triangles), with an ophthalmologist as the gold standard. The operating point of the detector is indicated by the open square.

three severe and two early. By varying the program's criteria for what constitutes a microaneurysm, by relaxing or tightening the rules used to classify each detected candidate microaneurysm, the effect on specificity of increasing the program's sensitivity can be investigated. The outcome from the program is compared with the results from five observers looking at the same images: two ophthalmologists, two diabetologists and one physicist experienced in interpreting retinal images. The gold standard was generated by an experienced ophthalmologist. Clearly, the opinions of the human observers vary in sensitivity and specificity (number of false positives per image). For instance, the observer with the highest sensitivity has achieved this result at the expense of the greatest number of false positives (identification of objects that the ophthalmologist did not consider to be microaneurysms).

The program's FROC curve shows how changing the rules affects the sensitivity and specificity of microaneurysm detection. Obviously, it is necessary for the purpose of this study to select one operating point. Although a high sensitivity for a screening task is clearly desirable, specificity is also important. This is because the use of four fields per patient increases the likelihood of detecting a falsely positive microaneurysm and hence incorrectly concluding that a normal patient has retinopathy.

By relaxing the rules, the number of genuine microaneurysms identified, and hence the sensitivity, could be increased. On the other hand, tightening the rules reduces the number of spurious objects erroneously classified as microaneurysms, so increasing specificity. An estimate of the best compromise between these two parameters was made, based on the analysis of the training set, and this version of the rules was chosen as the 'operating point' of the program shown in the *Figure 8* by the open square. This corresponded to a sensitivity of 43% and 0.11 false positives per image.

Automated detection of hard exudates

Hard exudates are composed of lipoprotein and lipid-filled macrophages. This gives them a yellow, waxy appearance which is highly reflective and, as a consequence, they appear as regions of high local intensity in digital red-free photographs. Owing to their being formed by leakage from microvascular lesions, they have no characteristic

shape but may be distinguished from similarly intense lesions such as cotton-wool spots or drusen by the strength of their boundary definition. In contrast, cotton-wool spots and drusen are diffuse structures with considerably less intense edges.

This information has been used to classify bright objects in the images according to their size, perimeter length, overall intensity and edge definition. Once again the choice of appropriate classification rules is dictated by the exudates manually identified by an ophthalmologist in a training set of images. This set consisted of 42 images containing 479 exudate objects.

Operation of the exudate detector

In order to enhance those features with strong edge definition (i.e. potential exudates), the images are first 'sharpened' by application of an appropriate filter. This sharpening operation also helps to ensure that the detected features are accurately delineated prior to their measurement (see below). Shade correction is then performed as described above to eliminate the effects of illumination.

The next stage in the processing is to locate the optic disc to enable it to be eliminated from subsequent analysis of the image. This is achieved by searching the image for the region which best matches a model disc. This model consists of a bright circle, representing the surface of the disc, bisected by a dark, diverging, vertical stripe which mimics the pattern of the dark blood vessels leaving and entering the eye via the central retinal artery and vein.

Having identified the optic disc, the remaining area of the image is thresholded to identify any features which are brighter than the background and therefore could be hard exudates. Once again these candidates are classified by comparing their measurements with those of the exudates identified by a clinician in the set of training images. This comparison generates a number of rules based on the values, or pairs of values, of these parameters.

Testing the hard exudate detector

As for the microaneurysm detection program, the ability of the program to detect hard exudate objects was assessed using an FROC experiment, the results being shown in *Figure 9*. A test set of images was used consisting of 50 images in which a total of 215 individual exudates were identified by the clinical research fellow. The performance of the program is varied by relaxing or tightening the rules used to define an exudate in a manner



FIGURE 9 FROC curve comparing the performance of the hard exudate detector (filled circles and dashed line) with that of five clinical observers (filled triangles), with an ophthalmologist as the gold standard. The operating point of the detector is indicated by the open square.

identical with that used for the microaneurysm program. Once again the performance of a number of clinicians asked to perform the same task was also included for comparison and the gold standard against which both are judged is provided by an ophthalmologist.

The operating point is chosen to give an extremely low false-positive detection rate, 0.2 false-positives per image, so as to maximise the discrimination between exudates and cotton-wool spots or drusen. Consequently, the sensitivity will be low, 44%. However, it must be appreciated that the clinical significance of sensitivity and specificity will vary according to the total number of exudate objects which are actually present in a given image. For example, a single false positive detected in a normal image is much more serious than a single false positive detected in an image with 30 real lesions present.

Lesion location and maculopathy

Diabetic maculopathy (clinically significant macular oedema) is an important cause of visual impairment in patients with diabetes.^{40–42} It is indicated by a thickening of the retina, which can only be positively identified using stereo photography. In the absence of stereo photographs, however, a patient will be referred for further examination if he or she exhibits microaneurysms or hard exudates within one disc diameter of the fovea.

By locating the fovea in the macular images obtained, we are able to define this region in the image and hence potentially identify patients with referable macular lesions. The position of the fovea is identified in a similar manner to the optic disc position described above, finding the location in the image which best matches a model of the fovea. This model is simply a small, dark cone which mimics the increase in pigmentation in this area of the retina. Although an estimate of the macula size (one disc diameter or 1500 μm) can be made given the approximate resolution of the image, differences in optical power between patients means that this value is unreliable. A second estimate is therefore made based on a fraction (0.38) of the distance between the fovea and the centre of the optic disc. The average of these two measurements is then used to specify the size of the macular area.

Because the locations of any microaneurysms or hard exudates detected in the image are known, we are able to calculate the numbers of each which lie within one disc diameter of the fovea. In Chapter 5 we will investigate whether this information enables us to detect patients with notable macular lesions and how many of the same were, on subsequent examination, found to have clinically significant macular oedema.

Turnover of microaneurysms

We have proposed investigating whether automated digital image processing techniques can follow the progression of retinopathy. Although the total number of microaneurysms has been shown to correlate with the severity and progression of early retinopathy,^{2,3,43} it has also been observed that these lesions are not static but appear and disappear over a period of time.^{44–46}

This turnover of microaneurysms is not well understood but it has been suggested that the rate of their formation and regression might be related to the progression of retinopathy.⁴⁶ In Chapter 6 we will calculate the turnover of microaneurysms detected in the three 6-monthly fluoresceins obtained from these patients and examine how these figures relate to the severity and progression of retinopathy present.

Image registration

In order to calculate turnover of microaneurysms, it is necessary to align or ‘register’ the images concerned. This allows corresponding microaneurysms which have been detected in the

different images to be identified according to whether they overlap (by $>10\%$). Owing to the small size of these lesions, the registration is required to be very accurate and a cross-correlation algorithm⁴⁷ with minor modifications has been found to give good results for these images. Once registered, each pair of the three 6-monthly fluorescein frames is analysed to give the number of static microaneurysms (those present in both images), new microaneurysms, (those on the second image only), and regressed microaneurysms (those on the first image only).

Conclusions

In this chapter we have described the algorithms for the automated detection of microaneurysms and hard exudates that have been used in this study. In the following chapters we will describe the results of our investigation into whether these automated analyses of digital red-free photographs may be used as a screening

tool for diabetic retinopathy, and whether changes in the numbers of lesions present can be used to follow the progression of the disease.

In addition, by identifying the locations of the fovea and optic disc in each image, the positions of the detected lesions can be related to the location of the macula. Using this information we are able to investigate whether the detection of macular microaneurysms or hard exudates or both provides useful markers for the referral of patients with suspected clinically significant macular oedema.

Finally, we are able to calculate the turnover of microaneurysms in individual frames of consecutive fluorescein angiograms. Using this technique, we hope to show that the rate of new and regressed microaneurysms can provide useful information about the natural history of diabetic retinopathy, and that this information might allow the point when treatment is required to be determined.

Chapter 5

Question 1: can a digital system detect the presence of diabetic retinopathy (of any sort/level)?

Introduction

This study aims to look at the role of digital imaging in screening for diabetic retinopathy so that timely intervention, both medical and surgical, can be applied before significant visual impairment occurs.

The patient population was described in the section 'Patient recruitment' (p. 7); to recap, 586 patients attended a hospital assessment clinic where digital and conventional photography was performed. Slit-lamp examination by an ophthalmologist was performed as the gold standard. Patients then attended a study optometrist who performed an examination of the fundi using slit-lamp biomicroscopy. These examinations were then repeated 1 year later.

Slit-lamp biomicroscopy

Six high-street optometrists were recruited through the auspices of the Aberdeen and North-east Scotland branch of the Association of Optometrists. Each underwent a specially devised training programme consisting of a day of lectures, a day of slide examination, practical demonstration of slit-lamp biomicroscopy and regular eye clinic attendance, culminating in a formal examination of their ability to recognise the features of diabetic retinopathy using slit-lamp biomicroscopy.

The optometrists examined the subjects using slit-lamp biomicroscopy through dilated pupils in their own premises. A poster with examples of the various features of retinopathy was provided for reference. Patients were graded according to a modified interim ETDRS severity scale. This scale is based on the grading of features of diabetic retinopathy detected in seven-field stereoscopic 35-mm colour slides against standardised slides. The presence of four blot haemorrhages in any one quadrant was used as the definition of severe retinal haemorrhages, as this is a rough

TABLE 6 Definitions of NPDR grades

Level	Retinopathy features
Mild	At least one microaneurysm
Moderate	Severe haemorrhages (≥ 4 blot haemorrhages) in one quadrant and/or cotton-wool spots or venous beading or IRMA definitely present
Severe	Any one of the following: severe haemorrhages in four quadrants; venous beading in two quadrants; severe IRMA in one quadrant
Very severe	Any of the two 'severe' categories

approximation to the reference slide used by the ETDRS. The definitions of non-proliferative diabetic retinopathy (NPDR) used in the study are given in *Table 6*.

Proliferative diabetic retinopathy (PDR) was defined as the presence of new vessels in the fundus. Clinically significant macular oedema was defined as the presence of retinal thickening within a one-disc diameter radius of the centre of macula.

The reference standard was taken as slit-lamp biomicroscopy performed by consultants or their specialist registrars with a special interest in medical retina. The clinical grading protocol was the same as the optometrists'. This is referred to as the 'ophthalmologist gold standard'.

Photography and digital imaging

Conventional mydriatic retinal photography was performed using a Topcon 50X fundus camera with 35-mm transparencies on Kodachrome 64 film. High-resolution (1024×1024 pixels) red-free digital photography was performed on the same camera using the IMAGEnet 1.53 1024 digital image acquisition system as described in the section 'Choice of digital fundus camera' (p. 11).

TABLE 7 EURODIAB retinopathy grading protocol

Level	Retinopathy features
Mild	HMA and/or hard exudates
Moderate	Very severe HMA in one field, or HMA plus CWS and/or IRMA and/or VB
Severe	Very severe HMA in both fields, or severe HMA in one field plus very severe CWS and/or severe IRMA and/or severe VB
Photocoagulated	Photocoagulation scars
Proliferative	New vessels and/or fibrous proliferations, and/or pre-retinal haemorrhage, and/or vitreous haemorrhage

HMA, haemorrhages and microaneurysms; CWS, cotton-wool spots; IRMA, intra-retinal microvascular anomalies; VB, venous beading; severe, lesion present \geq standard photograph 1 but $<$ standard photograph 2; very severe, lesion present \geq standard photograph 2.

Photographs were taken according to the EURODIAB protocol (see the section ‘The EURODIAB protocol’, p. 11).

All photographs and digital images were graded by a trained research registrar for image quality (see the section ‘Grading image quality’, p. 13) and for retinopathy severity according to the EURODIAB protocol (Table 7). This is referred to as ‘manual grading’. The research registrar was trained by attending weekly diabetic clinics for 6 months under consultant supervision. Her effectiveness at grading images was then formally evaluated by the consultant before any of the study images was graded.

Digital images were stored in their original loss-less TIFF format on CD-ROMs and manually

transferred to the Department of Bio-medical Physics, University of Aberdeen. The images were analysed using the software described in Chapter 4. The presence of any retinopathy and the quantity of retinopathy were recorded. The presence of exudates and/or haemorrhages within one disc diameter of the centre of the fovea in the macular field were used to infer the possible presence of diabetic macular oedema as retinal thickening cannot be visualised in monocular images.

Distribution of retinopathy amongst patients

The levels of retinopathy and clinically significant macular oedema detected by the ophthalmologists in patients on their first visit are given in Table 8. Figure 10 shows the distribution of retinopathy amongst eyes and fields.

Detection of retinopathy

The performance of the optometrists, the manual grading of red-free digital images and manual grading of 35-mm colour slides were determined by using the ophthalmologists’ clinical grading as the gold standard. Table 9 shows the sensitivity and specificity achieved for the different screening modalities in terms of whether or not an image was reported as having retinopathy. The actual agreement as to the level of retinopathy is shown in Figure 11.

The results have been analysed for all retinopathy, that is, all patients irrespective of the degree of retinopathy, and for early retinopathy, which uses the results from those patients who have either mild or no retinopathy. Of course, the specificity will be the same in both cases.

TABLE 8 Frequency of retinopathy levels and clinically significant macular oedema (maculopathy) in patients at the first visit

Retinopathy level	No.	Clinically significant macular oedema	No.
None	429	Absent	559
Mild	108	Present	24
Moderate	36		
Severe	6		
Very severe	0		
Early PDR	5		
High-risk PDR	2		

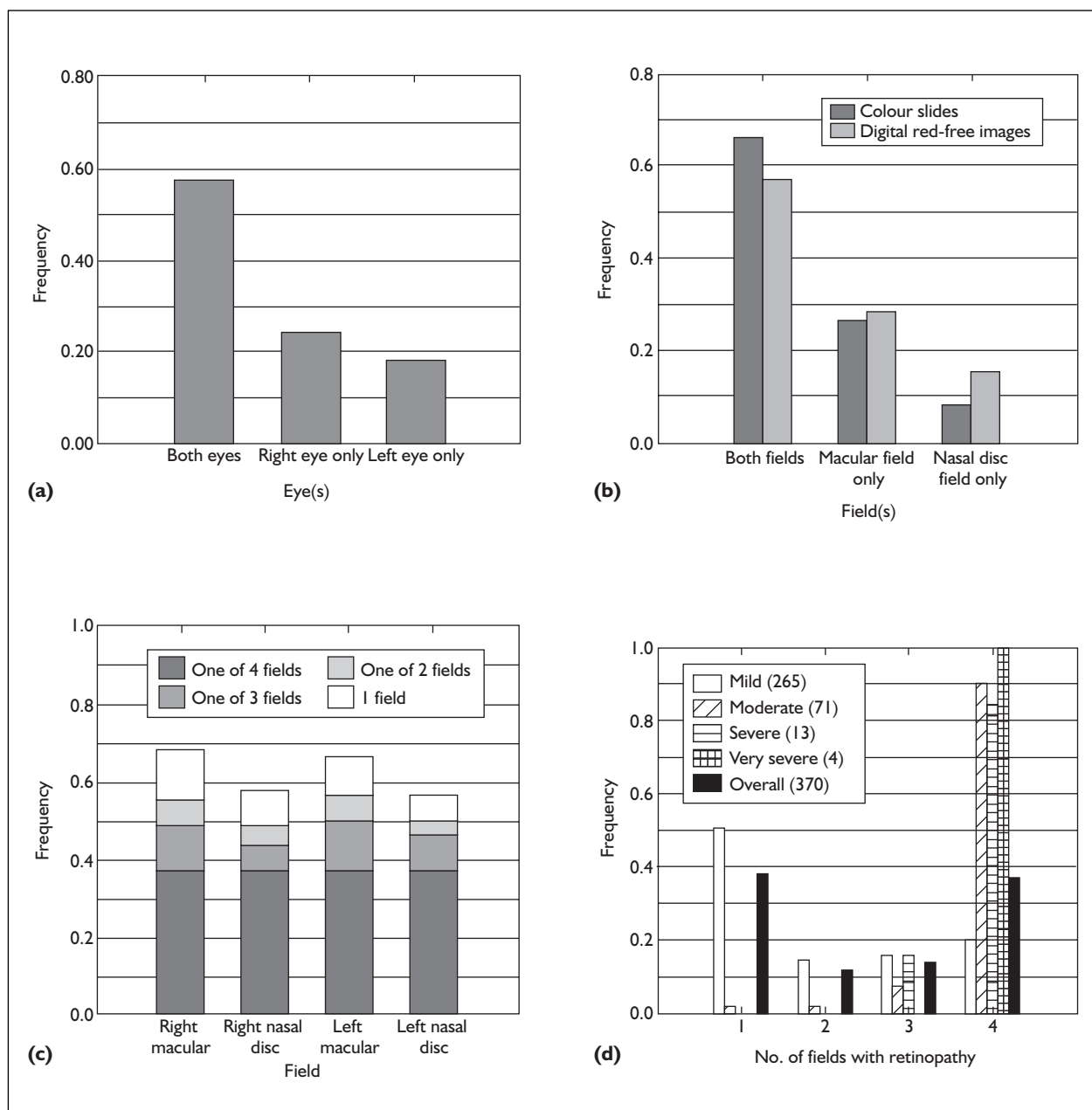


FIGURE 10 (a) The proportion of patients with manually graded retinopathy present in the left eye only, the right eye only, or both. (b) The proportion of digital red-free eye-field pairs with manually graded retinopathy present in either the macular field only, the nasal-disc field, or both. (c) The distribution of retinopathy throughout the four fields obtained using the EURODIAB protocol. (d) The number of fields exhibiting retinopathy according to the level of retinopathy.

TABLE 9 The detection of any retinopathy

Screening modality	All retinopathy		Early retinopathy	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
35-mm colour slide	89	89	85	90
Manual grading of digital images	83	79	81	81
Optometrists	75	82	71	82
Automated grading of digital images	83	71	82	71

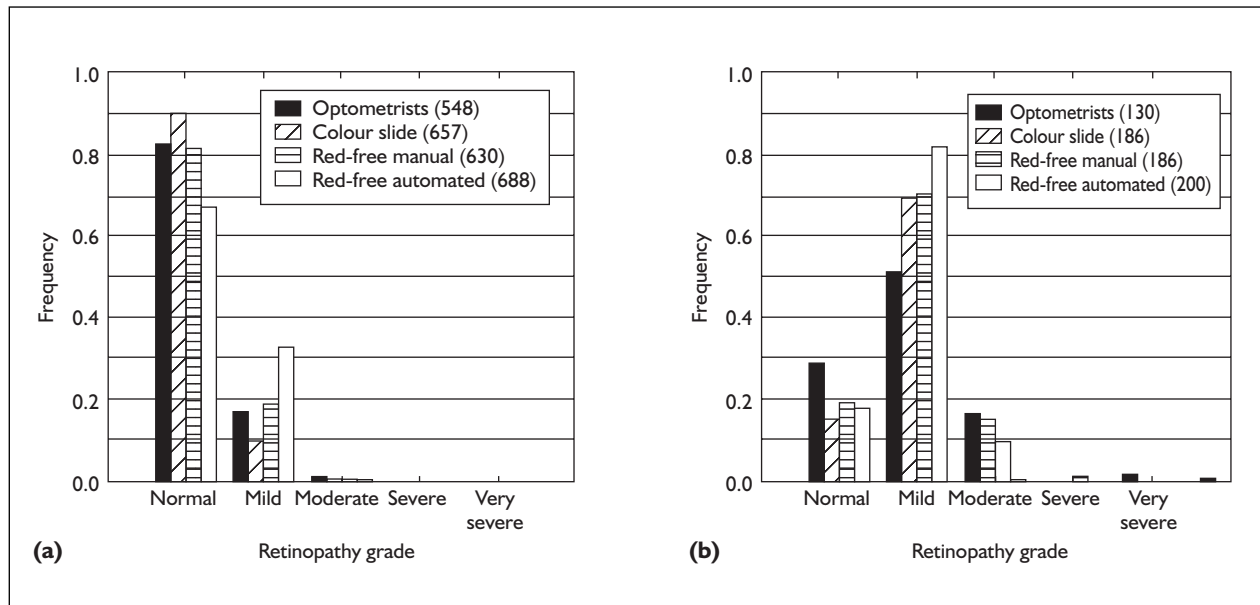


FIGURE 11 Comparison of grading produced by screening techniques with the ophthalmologist gold standard for patients with (a) no retinopathy and (b) mild retinopathy

Automated analysis in diabetic macular oedema

In this part of the study, 583 patients were entered; 24 cases of clinically significant macular oedema (retinal thickening within one disc diameter radius of the geometric centre of the eye) were diagnosed by the ophthalmologists (Table 8).

The performance of the optometrists, the manual grading of red-free digital images and manual grading of 35-mm colour slides were determined using the ophthalmologists' clinical grading as the gold standard (Table 10).

Sight-threatening retinopathy

Sight-threatening retinopathy was defined as that classed as moderate or worse on the retinopathy

TABLE 10 The detection of clinically significant macular oedema by optometrists, by grading 35-mm colour slides and by grading digital images

Screening modality	Sensitivity (%)	Specificity (%)
35-mm colour slides	83	84
Manual grading of digital images	83	83
Optometrists	46	92
Automated grading of digital images	76	85

rating scale and/or the presence of clinically significant macular oedema. The performance of the optometrists, the manual grading of red-free digital images and manual grading of 35-mm colour slides at detecting retinopathy in such patients, irrespective of agreement in grading, is shown in Table 11. Once again, the ophthalmologists' clinical grading is taken as the gold standard.

In these results sight-threatening retinopathy for the automated analysis is defined as patients with microaneurysms or exudates in the macula. As such it does not grade the severity of the retinopathy.

Is the nasal-disc field required?

Many established screening protocols obtain only a macular view, chiefly because detection of sight-

TABLE 11 The detection of sight-threatening retinopathy by optometrists, by grading of 35-mm colour slides and by grading of digital images

Screening modality	Sensitivity (%)	Specificity (%)
35-mm colour slides	96	89
Manual grading of digital images	93	87
Optometrists	73	90
Automated grading of digital images ^a	77	88

^a Clinically significant macular oedema only.

threatening retinopathy has been the main objective in the past. As *Figure 10(b)* shows, according to a clinician interpreting the 35-mm colour slides 8% (45/580) of eye-field pairs showed retinopathy in either nasal-disc field only and 14% (91/644) when digital photography was used. If the data are analysed in terms of patients, then if single-shot macula-only fields had been used, 22/322 (7%) patients with any retinopathy would have been undetected and 6/214 (3%) patients with sight-threatening retinopathy would have been undetected (*Table 12*). The corresponding results for manual analysis of the red-free images were 59/366 (16%) for any retinopathy and 1/217 (0.5%) for sight-threatening retinopathy. In terms of sensitivity and specificity (*Table 13*), the use of a single macula field has no significant effect for sight-threatening retinopathy.

Comparison of optometrist with ophthalmologist

The difference between optometrists and ophthalmologists in grading of retinopathy (gold standard) is shown in *Figure 12*. In 74% (531/718) of patients there is agreement over the grading whereas the optometrists have a sensitivity of 76%

and a specificity of 82% for the task of deciding whether or not the images are abnormal (*Table 9*), levels comparable with the other modalities.

For the detection of macular oedema, there is more of a problem. The overall agreement on grading is 90% (631/696 excluding three 'did not attend') but this largely reflects the 93% agreement over the 676 normals that were present. The optometrists failed to detect clinically significant macular oedema in over half of abnormal (11/22). This probably reflects the lack of experience in detecting macular oedema, as in everyday practice optometrists would see mainly normal eyes.

Discussion

For historical reasons, a larger number of patients attend the hospital diabetic clinic in Aberdeen than might be expected in other areas. This is reflected in the demographics of the population studied, which has a higher prevalence of type 2 diabetes than might be expected in a hospital clinic. Although the majority of people in the study were of working age, it is of concern that 528 of 1114 patients approached either declined

TABLE 12 Number of patient visits with retinopathy by field: analysis made using 35-mm colour slides

Nasal field	Macular field			Total
	No retinopathy	Mild retinopathy	Sight-threatening	
No retinopathy	616	22	34	672
Mild retinopathy	22	64	84	170
Sight-threatening	0	6	90	96
Total	638	92	208	938

TABLE 13 Effect of using a single macular view for any retinopathy and sight-threatening retinopathy

Condition	Screening modality	All fields		Macula only	
		Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Any retinopathy	35-mm colour slides	89	89	86	92
	Manual grading of digital images	83	79	80	88
	Automated grading of digital images	83	71	79	80
Sight-threatening retinopathy	35-mm colour slides	96	89	95	89
	Manual grading of digital images	93	87	93	87
	Automated grading of digital images	77	88	77	88

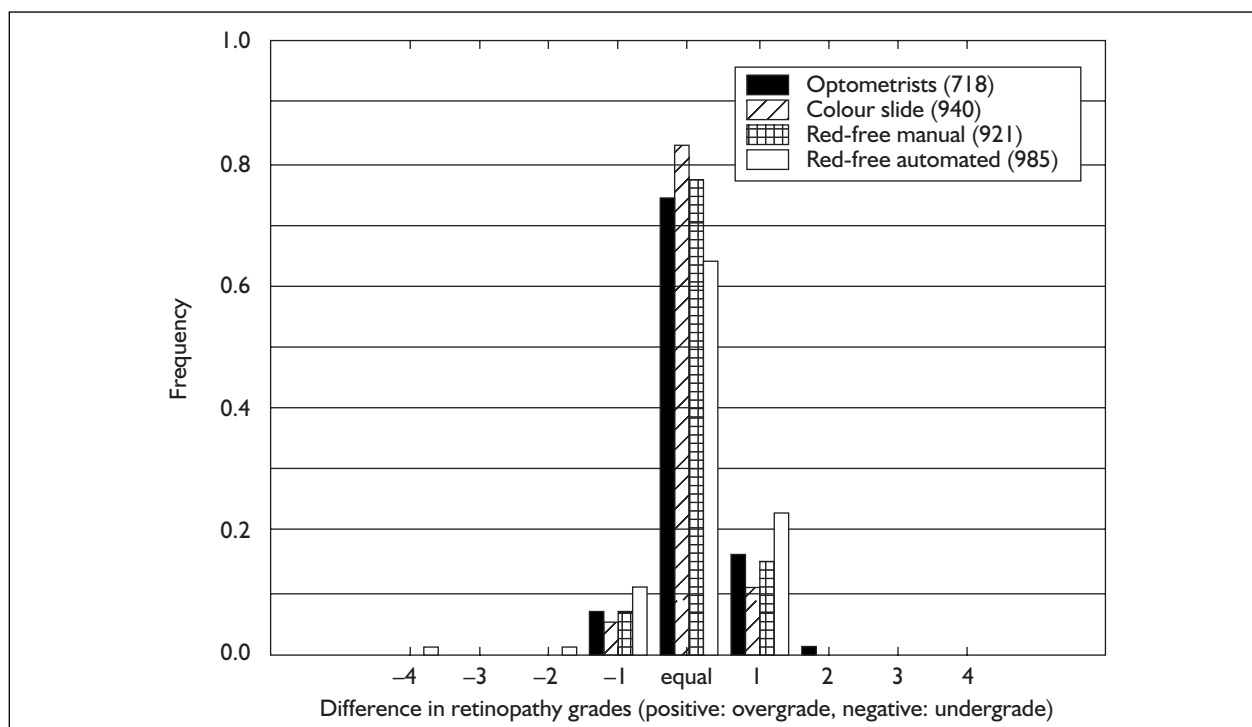


FIGURE 12 Comparison of retinopathy grades derived by optometrists with those produced by grading 35-mm colour slides or digital red-free images

to take part or failed to attend once recruited. This probably reflects the fact that patients were already being screened and might have implications for any stand-alone retinopathy screening programme.

The reference standard chosen was that of a consultant, or his or her specialist registrar, performing slit-lamp biomicroscopy. Although seven-field stereoscopic photography is often used as a reference in research programmes, it is too cumbersome for everyday clinical practice. Slit-lamp biomicroscopy is the standard tool used by ophthalmologists to examine for diabetic retinopathy and was felt to be the most relevant reference standard for screening. It is also potentially the most sensitive standard as more retina is visualised than by the two 50° fields of the EURODIAB photographic protocol or of the seven 35° fields of the ETDRS photographic protocol.

Two grading protocols were used, one for the 35-mm colour slides and the digital images and the other for slit-lamp biomicroscopy. The EURODIAB grading protocol was used for the slides and the digital images as it has been shown to correlate with the interim ETDRS retinopathy severity grades. The interim ETDRS retinopathy severity scale was modified for slit-lamp biomicroscopy, thus allowing comparison between

the two techniques despite the different fields of view. From a practical point of view the presence of four blot haemorrhages in any one quadrant was used as the definition of severe retinal haemorrhages as this is a rough approximation to the reference slide used by the ETDRS.

In terms of sensitivity and specificity there was little to choose between conventional photography and digital photography for detecting any or early retinopathy. For sight-threatening retinopathy the optometrists had the lowest overall sensitivity (73%) although their specificity (90%) was comparable to that of the other modalities.

When looking at clinically significant macular oedema (maculopathy), a sub-set of sight-threatening retinopathy, optometrists performed particularly badly with a sensitivity of only 46%. The specificity of 92% was comparable to the other modalities. Detection of macular oedema is difficult and with hindsight requires more practice than they received.

Automated detection of diabetic retinopathy has progressed rapidly in the last decade, and commercial programs are now becoming available.⁴⁸⁻⁵⁰ Recently, Lee and colleagues⁴⁹ have published their work with apparently similar good results. Unfortunately, no details of the methods used or the resolution of the images were

published as they wished to protect this information prior to commercialisation. Our own work started with fluorescein angiography, but for this study it was realised that this was not a practical modality for screening and the computer algorithms were modified to work with high-resolution red-free digital images instead.

Automated techniques have the advantage of repeatability. Individual human graders tend to have their own varying internal reference standards that are difficult to make conform, despite training, leading to intra- and inter-observer variability. However, with the algorithm used in our automated detection program it is necessary to select the particular combination of sensitivity and specificity at which the algorithm operates, as discussed in the section 'Calibrating and testing the microaneurysm detector' (p. 16).

Grading of photographs or digital images is a repetitive task and where two-thirds are expected to be normal this leads to fatigue and boredom. Computers suffer from none of these complaints, although they are heavily reliant on images being of a sufficient quality to permit analysis. Images will therefore have to be graded for image quality before being processed. This is, however, a far simpler and quicker task than actually grading the image. Also, as was shown in the section 'Grading image quality' (p. 13), it is easier to obtain good quality images with the digital system.

We have been able to achieve significant sensitivity and specificity for the detection of the presence of any diabetic retinopathy. That in itself may at face value not seem a great achievement, but when one considers the vast numbers of patients with diabetes in the UK that require screening, then this is no mean achievement. In a previous study comparing the automated detection of retinopathy, using only microaneurysms, with 35-mm colour slides graded by a research fellow⁴⁸ we were able to achieve a sensitivity of 85% and a specificity of 76% for detecting whether or not a patient had retinopathy. As pointed out in that paper, since the decision on the presence of retinopathy requires four images to be analysed, this task will have a higher sensitivity but lower specificity than for detecting retinopathy in a single image. Assuming a prevalence for diabetic retinopathy of 30%, this would have meant that 51% of this population would be correctly classified as having no retinopathy. In this current study, in which ophthalmologists using stereo biomicroscopy were used as the gold standard, then if we consider all grades of retinopathy we

have achieved a sensitivity of 87% but a lower specificity of 71% with the automated system. Despite this, the automated grading would still correctly classify 48% of a theoretical diabetic population as having no retinopathy.

Clearly, such results depend on the population examined. For sight-threatening retinopathy, the specificity rises to 88% whereas the sensitivity is lower than that achieved by other modalities at 77%. The problem is that we have not been able to detect all forms of sight-threatening retinopathy as we do not as yet have a computer algorithm to detect new vessel formation. Obviously, automated grading cannot be used on its own, but in the context of a manual grading system it will still greatly reduce the workload by correctly identifying just under half the population as having no retinopathy.

In addition, it would appear that automated grading is able to detect the presence of clinically significant macular oedema (maculopathy) (using a combination of the microaneurysm detection program and the exudate program), with a specificity comparable to other modalities. This allows graders to target their attention to images with potentially sight-threatening retinopathy.

The use of the automated hard exudate detector as a tool for detecting any retinopathy was not found useful. Used in conjunction with the microaneurysm detector program it reduced the specificity from 71 to 67%, a result not surprising given the specificity shown in *Figure 9*. As mentioned above, it does have an important role in detecting maculopathy where the analysis is limited to retinopathy within a one disc diameter radius of the centre of the fovea.

We used the two-field protocol of the EURODIAB study as this has been validated against the seven-field stereoscopic protocol of the ETDRS. Although the EURODIAB retinopathy levels do appear to correlate with the interim ETDRS retinopathy levels, it should be remembered that it was only validated against 24 patients and thus it cannot be certain that a two-field protocol is sufficient to detect all sight-threatening retinopathy. Using only one field would have failed to detect a significant number of patients with any retinopathy. However, in the case of sight-threatening diabetic retinopathy, up to 3% of patients were missed. As the sensitivity and specificity changed little, then in some circumstances the use of macular fields only might be regarded as acceptable.

Chapter 6

Question 2: can a digital system detect progression of retinopathy? Question 3: can a digital system determine when treatment is required?

Introduction

The previous chapter examined the effectiveness of the digital system in providing the ophthalmologist with a reliable, quantitative measure of retinal pathology. In this chapter, the value of this information as a tool for monitoring the progression of the disease will be evaluated. The important clinical questions are whether a digital system can detect progression of retinopathy and whether it can be used to determine when treatment is required.

An additional facet of this study is to look at the natural history of retinopathy. Therefore, in addition to those patients initially assigned to this study, that is, those diagnosed on the initial screening study as having moderate proliferative retinopathy or worse, or clinically significant maculopathy, a group of patients with no or mild retinopathy are included.

Study protocol

It had originally been planned to study only patients with sight-threatening retinopathy. It proved impossible to obtain sufficient patients, mainly because those with such retinopathy usually underwent treatment before progression could be measured and so the entry requirement was relaxed. Thirty-seven patients, having mild or no retinopathy, who were participating in the screening arm also agreed to take part in this study. A total of 81 patients attended for the first appointment; the spread of retinopathy is shown in *Table 14*. Of these, 38 patients, 16 of whom had sight-threatening retinopathy, completed the full series of three fluorescein angiograms and fundus photographs every 6 months over a period of 12 months.

The fluorescein angiograms were analysed for the presence of microaneurysms and the number of

TABLE 14 Retinopathy of those patients entering the study

Level of retinopathy	No. of patients	
	Total ^a	Those undergoing three fluorescein studies
None	1	0
Mild ^b	36	22
Moderate	31	13
Severe	6	3
Very severe	0	0
Early PDR	5	0
High-risk PDR	2	0

^a Of these patients, 21 also had maculopathy.
^b Of these patients, eight also had maculopathy.

new, static and regressed microaneurysms, as described in the section 'Turnover of microaneurysms' (p. 18).

Patients also had a variety of potential risk factors measured, including body mass index, blood pressure, HBA_{1c} and microalbuminuria. These data will be presented in the section 'Risk factors' (p. 31).

Can digital red-free photography monitor progression of retinopathy?

Crucial to using the digital fundus camera to measure change in retinopathy is an assessment of the reproducibility of retinopathy gradings. *Figure 13(a)* shows how the results from a clinician manually grading the digital red-free images varies when assessed against the gold standard; the results for 35-mm colour slides are shown in *Figure 13(b)*. There can be significant variation in the grading given; between 10 and 18% of images classified as mild are graded as moderate and up

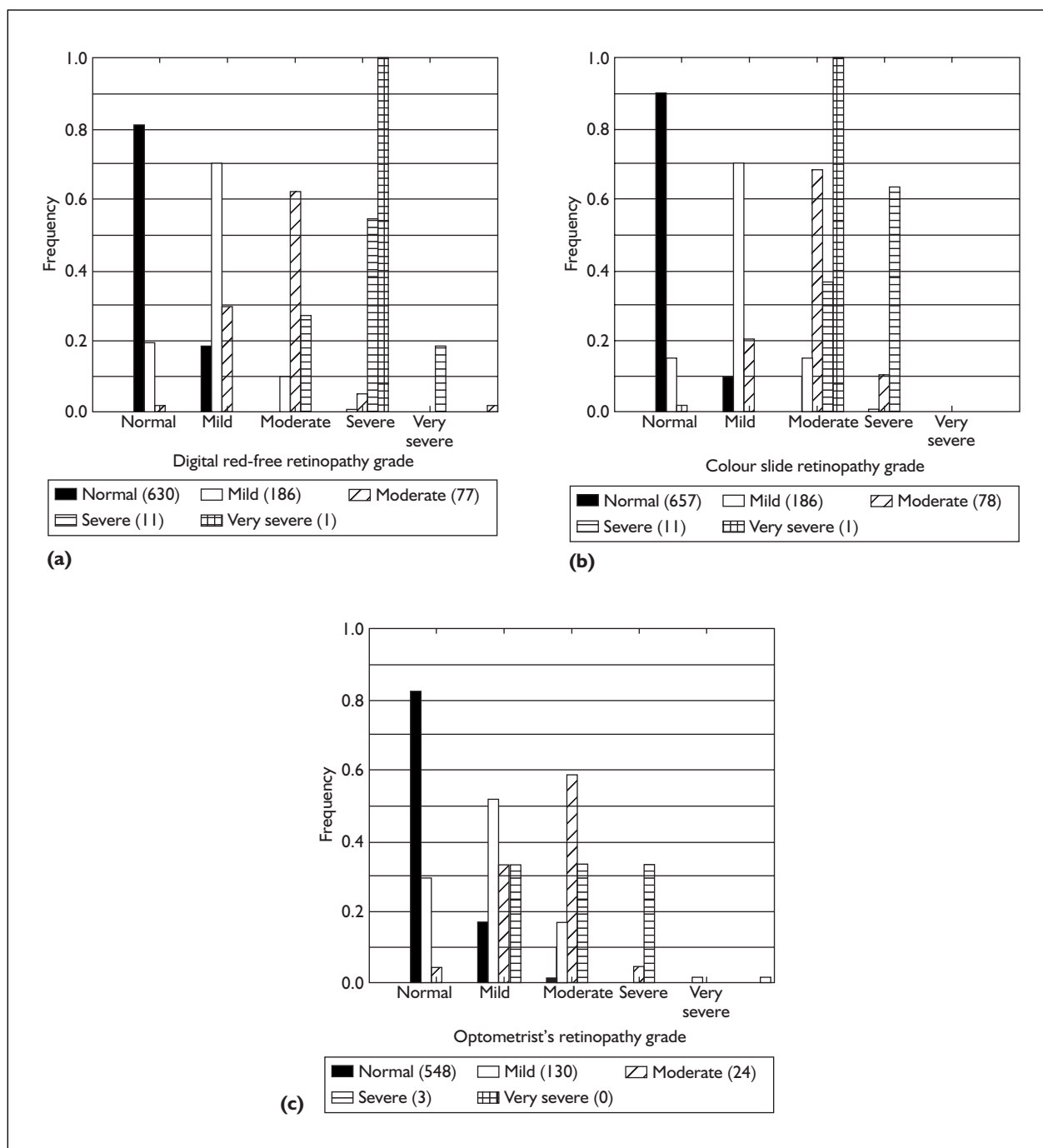


FIGURE 13 The ability of a clinician grading (a) digital images and (b) 35-mm colour slides to monitor the progression of diabetic retinopathy. The x-axis indicates the reference grade assigned by the ophthalmologist viewing the patient's retina directly and each set of bars indicates the corresponding spread of values assigned by a clinician grading the 35-mm colour slides of each retinopathy severity group. The numbers in parentheses indicate the population in each group. In (c) the results of optometrist grading are given.

to 30% of moderates are graded as mild. This intrinsic variability in grading reproducibility will provide a limit to the extent to which a change in retinopathy level can be measured. The optometrists' results (Figure 13c) show a greater spread in gradings; for example, only 52% of the milds were correctly classified.

Can automated analysis of digital images follow progression of retinopathy?

It was postulated in the proposal for this study that a more objective measure of retinopathy, in

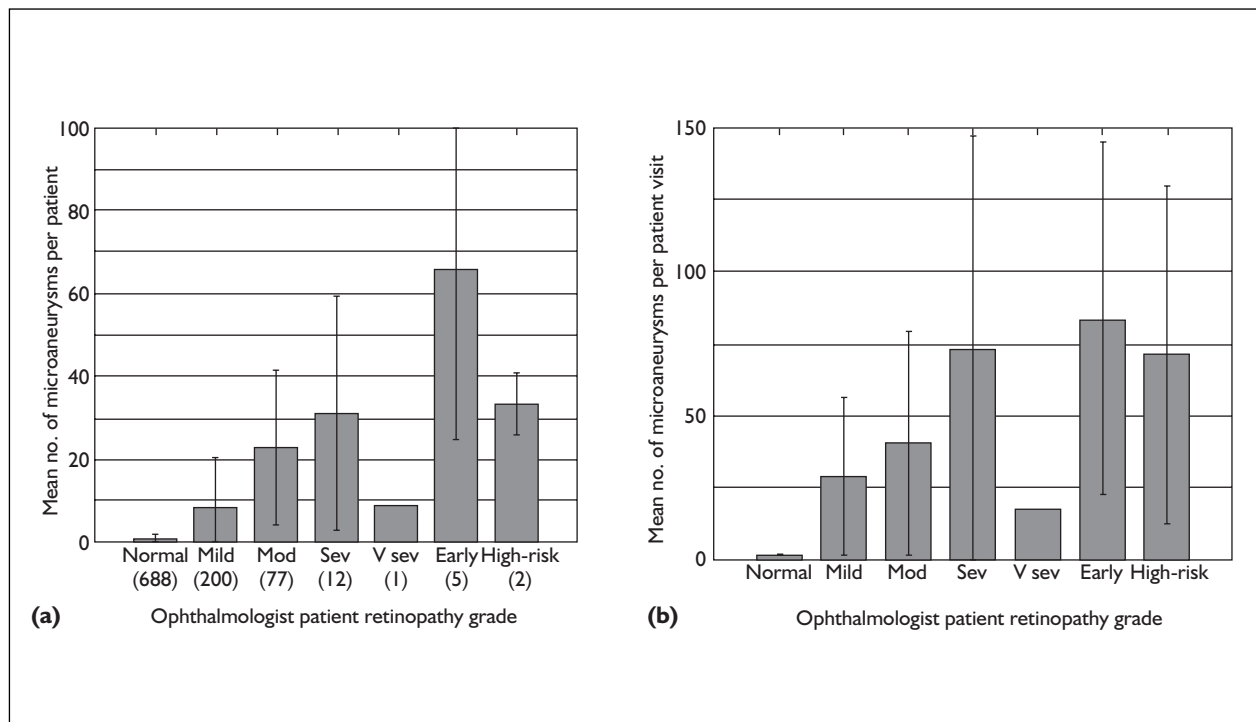


FIGURE 14 The mean number of microaneurysms per patient detected in (a) digital red-free and (b) fluorescein angiographic images. Each patient has been graded by an ophthalmologist according to the overall level of retinopathy present. Error bars are the standard deviations.

particular the number of microaneurysms, might provide a means for assessing progression of the disease. *Figure 14* shows, for each patient retinopathy grade, the mean number of microaneurysms per patient and the variation in that number. Results are given for both red-free (a) and fluorescein angiograms (b). Although there is a general trend towards more microaneurysms with increasing retinopathy grade, there is considerable variability in the mean number per patient in any group.

These results, of course, reflect the ability to use the average number of microaneurysms to measure differences in retinopathy grading. It can be argued that measuring the changes in the number of microaneurysms is likely to be more effective. Red-free digital images were taken at a 12-month interval and the data are shown (*Figure 15*) as a function of the change in grade of retinopathy between the two studies. In *Figure 15(a)* the mean number of microaneurysms is plotted and in *Figure 15(b)* the data are shown as a percentage change. Only two of the groups in which the retinopathy showed a deterioration had sufficient patients to do a statistical analysis. There was a statistically significant increase in the number of microaneurysms in those patients who developed from mild to moderate retinopathy (paired *t*-test, $p = 0.02$) and from none to mild ($p = 0.01$).

Problem of microaneurysm turnover

Figure 16 demonstrates the dynamic nature of microaneurysms in fluorescein angiograms. Taking all levels of retinopathy (*Figure 16a*), only 45% of the microaneurysms seen on the first visit are present 6 months later and 36% of those at the 6-month visit are still seen at the 12-month visit. Similar turnover is seen in *Figure 16(b)* for the sight-threatening retinopathy group (42 and 36%, respectively). As the overall total number of microaneurysms shows relatively little change, then the regressed microaneurysms are being balanced by new ones.

If one examines the microaneurysm turnover rate for individual patients (*Figure 17*), where turnover rate is calculated as the ratio of (a) new or (b) regressed microaneurysms to the total number of microaneurysms, then a large spread of values is found. There is no statistically significant difference between the turnover rate of either new or regressed microaneurysms for patients with mild or with sight-threatening retinopathy.

Risk factors

As mentioned in the section on questions 2 and 3

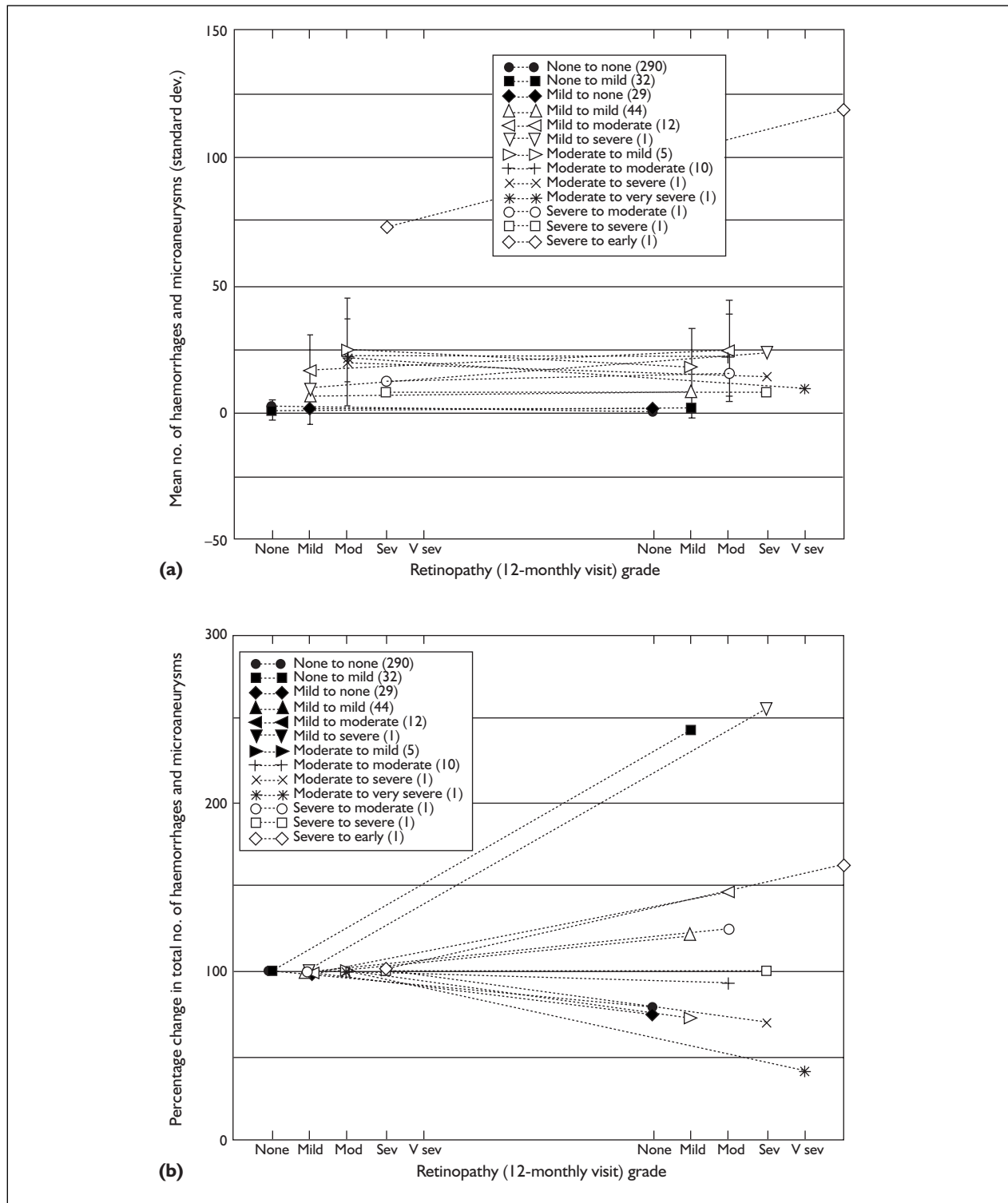


FIGURE 15 (a) Change in the mean number of microaneurysms with progression of retinopathy, and (b) percentage change in the total number of microaneurysms with progression of retinopathy

(p. 7), all patients were assessed medically once a year as various risk factors are known to be associated with the progression of retinopathy. Patients had various parameters measured, including body mass index, blood pressure, HBA_{1c} and microalbuminuria.

Table 15 shows the results of a one-way analysis of variance to study the relationship between risk factors and level of retinopathy. As can be seen, only triglyceride approaches a level of statistical significance. The main reason for this is that, as mentioned earlier, the number of patients with the

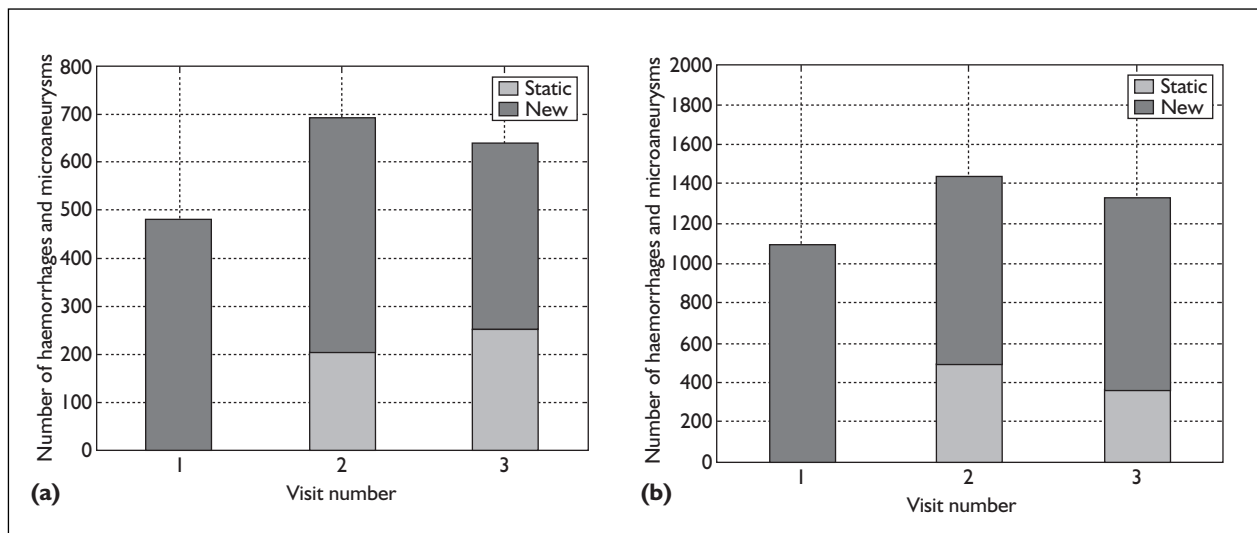


FIGURE 16 Microaneurysm turnover as measured from fluorescein angiograms for patients with (a) any retinopathy (38 patients) and (b) sight-threatening retinopathy (16 patients) on their first visit

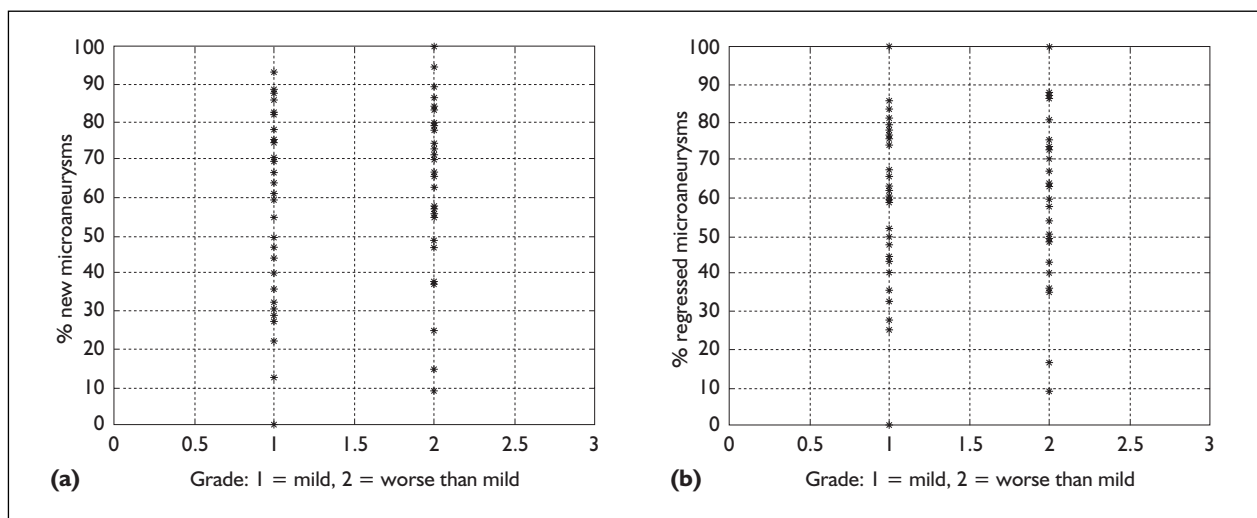


FIGURE 17 Rate of turnover of microaneurysms, each point showing the number of (a) new microaneurysms and (b) regressed microaneurysms expressed as a percentage of the total. Each point shows the results for one patient and the patients are classified as having either mild (n = 32) or sight-threatening retinopathy (n = 40).

more severe levels of retinopathy is very limited as they would be treated rather than remain in the study. This can be seen from the graph showing triglyceride against level of retinopathy (Figure 18), where most patients are in the mild or moderate groups. Further analysis of this data therefore did not appear to be of value.

Discussion

Microaneurysms are a key lesion in studies on early diabetic retinopathy since the counts are said to correlate with severity of early retinopathy and its likely progression.^{2,3,43} However, if microaneurysm change is to be used on a patient

by patient basis to make a clinical decision, there are a number of other factors to consider.

First there is the question of the consistency in the grading of the level of retinopathy. It has been shown that there is a significant variation in the ratings produced by clinicians and optometrists from the gold standard of the ophthalmologist. Hence the actual definition of the degree of retinopathy has an error associated with it.

Second, although the number of microaneurysms in general increases with the severity of the retinopathy, there is considerable variation in the mean number per patient. Thus the actual number of microaneurysms does not, in itself,

TABLE 15 Significance of relationship between risk factors and level of retinopathy

Risk factor	p-Value	No. of readings
Body mass index	0.13	55
Creatinine	0.29	76
Systolic BP	0.25	38
Diastolic BP	0.5	41
Fasting cholesterol	0.92	66
Haematocrit	0.69	69
Haemoglobin	0.59	79
HbA _{1c}	0.61	71
HDL	0.92	71
LDL	0.4	73
Microalbuminuria	0.21	52
Platelet count	0.33	73
White cell count	0.79	73
Triglyceride	0.076	73

BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

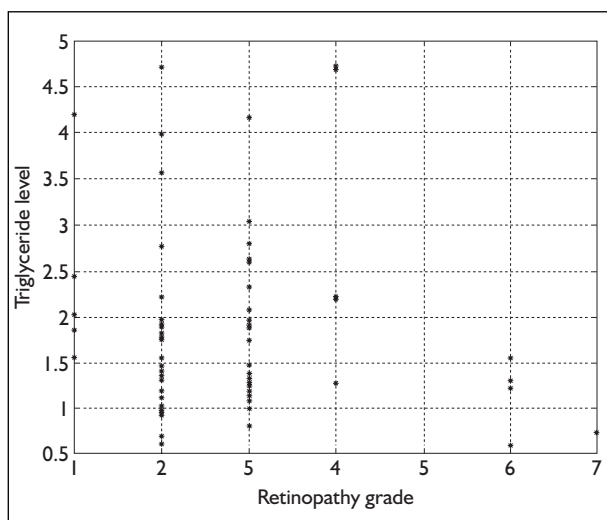


FIGURE 18 Triglyceride level as a function of level of retinopathy (n = 73)

allow the retinopathy to be graded. An analysis of how the average number of microaneurysms changed as the disease developed did show an increase in the number of microaneurysms in these groups of patients whose condition had changed from none to mild and from mild to moderate retinopathy. There were insufficient patients in the other groups. However, as can be seen from the error bars (standard deviations) in *Figure 15(a)*, this was not sufficient to predict the change in retinopathy from microaneurysm counts alone.

In keeping with the results of other studies, it was shown that on fluorescein angiography there is a

significant turnover in the number of microaneurysms even over a period of 6 months, with some disappearing between visits and new ones being formed. Hence it is perhaps not surprising that the absolute number of microaneurysms does not provide an accurate measure of the level of retinopathy.

The use of fluorescein angiograms raises the question of the time in the sequence that gives the best image for detecting microaneurysms. Jalli and colleagues⁵¹ have suggested that the actual phase of the angiogram studied has an important bearing on microaneurysm counts. They looked at microaneurysms in the arterial and late phases of fluorescein angiograms. Other microaneurysm counting studies have also used the arterial phase for counting microaneurysms.^{46,52} This approach is surprising as microaneurysms develop from capillaries and therefore to be sure that all microaneurysms are perfused with fluorescein then the arteriovenous/early venous phase, as we have used, seems more appropriate. Microaneurysms appearing only in the late phase probably contain thrombus and thus are partially occluded. Fully occluded microaneurysms do not fluoresce at all.

In this study we only looked at microaneurysms present in the early venous/arteriovenous phase as we felt that this ensured that all microaneurysms present had been perfused. The mean and range of times (in seconds) at which the images were analysed were 37.2 (11.4–111.8) for visit 1, 32.8 (8.3–57.6) for visit 2 and 30.7 (17.7–52.8) for visit 3. For a particular patient the difference in the time (in seconds) of the analysed image was 4.5 (range 0.60–73.8) for visits 1 and 2 and 2.1 (range 0.10–32.2) between visits 2 and 3. In essence, this means that we only identified perfused microaneurysms, namely those of a fusiform or saccular nature. By doing so we have included the very beginnings of microaneurysm formation, namely fusiform capillary dilation, and excluded the very late stages where microaneurysms are occluded and no longer increasing in size. This is important as poorly perfused microaneurysms may exist in this state indefinitely but are no longer ‘active’.

Given the dynamics of microaneurysms on fluorescein images, the potential of the rate of microaneurysm turnover as a marker of retinal progression was investigated. Although relatively small numbers of patients were available for analysis, there appeared to be no correlation between turnover rate and level of retinopathy over a 6-month period.

Chapter 7

Costs and consequences of screening for diabetic retinopathy

Introduction

This chapter is concerned with the economic evaluation of three alternative methods of providing screening for diabetic retinopathy as used in this study: digital photography, analogue photography and direct ophthalmoscopy carried out by trained optometrists. The methods have already been described in Chapter 2. The requirements of the research programme were such that some costs were incurred that would not be part of a normal service setting (research costs) and where possible these have been adjusted for, or are explained in the text. The comparison of the screening methods does not include the costs of administering a call and recall system, and the equipment does not include visual acuity charts and light boxes, as both of these would be common to all screening programmes. Costs for the photographic screening methods were calculated as a cost per session and converted to a cost per patient using a baseline assumption of 10 patients per session.

Digital photography costs

Capital costs

The photography was carried out in a Portacabin dedicated to the project, although it is possible for this technology to be provided on a mobile basis. The equipment consists of a basic fundus camera with a digital attachment and associated computer equipment and software. The building cost was discounted over 20 years and the equipment cost was discounted over 7 years, although it is recognised that technical obsolescence may set in much earlier. Other assumptions will be considered in the sensitivity analysis.

Running costs

Running costs for the building were allocated from hospital costs on the basis of the floor area. Staff costs per session took into account a nurse to carry out initial visual acuity checks and administer eye drops and the photographer and a senior registrar to read and report on the results. (The research registrar undertook some of these tasks but the grades of staff for the costing are those considered

appropriate to the tasks.) The session time for the photographer allows for the carrying out of related administrative tasks.

Consumables

Consumables consisted of eye drops.

Automated grading costs

The costs for screening include the cost of medical staff time to read and report the results. This project developed the software for automated grading of digital images. The development costs consist of staff time and this cost has been discounted over 7 years, to be consistent with the equipment costs, and replaces the medical staff time in the cost of the screening.

Colour slide photography costs

Capital costs

The photography was carried out in the same setting as the digital photography. Equipment consists of a basic fundus camera with a 35-mm slide attachment. The same fundus camera was used for both types of photography but the full cost was included both times as only one type of photography would be carried out in practice. The building cost was discounted over 20 years and the equipment cost was again discounted over 7 years, in the first instance.

Running costs

Running costs for the building and staff costs per session were the same as for the digital photography.

Consumables

Consumables consisted of eye drops, film and developing materials.

Optometrist screening costs

Optometrists carrying out screening in the project were given training at the start of the project as

described in the section ‘Slit-lamp biomicroscopy’ (p. 21) and a poster showing the various features of retinopathy was provided for reference. A standard fee of £18.00 per patient was paid for the screening. The optometrists were using facilities and equipment that would be used for normal sight testing.

Results

The costs for digital and analogue screening are shown in *Table 16*. The digital camera system is slightly cheaper and both camera systems were less costly than the payment to optometrists. However, these costs are simply for the initial screening visit and the reading of the results. The number of repeat visits, because of poor images, and the referral rate for assessment have to be taken into account. A cohort analysis has been carried out for this purpose and the results are shown in *Table 17*.

Repeat screens are only relevant for photographic screening and the rates were 5% for digital and 10% for analogue photography. The number of patients called for an assessment visit depends upon the sensitivity and specificity of the screening test. Based on the figures given in the section ‘Detection of retinopathy’, and assuming a prevalence of sight-threatening diabetic retinopathy of 6%, the number of assessment visits would be 175 for digital (graded by research registrar), 159 for digital (automated grading), 171 for 35-mm colour slides and 138 for optometrists. These visits have been costed at £51

each, the average cost for an outpatient attendance.

From *Tables 16* and *17*, it can be seen that digital screening with automated grading has the lowest cost per screen, and remains the least costly method when the additional factors of repeat visits and number of assessment visits are included. However, it is more expensive than digital imaging with medical staff reading the images or 35-mm colour slide photography in terms of cost per true positive detected. This is largely due to having a much lower sensitivity in reading the digital images.

The assumptions for *Table 16* were as follows:

- Building area based on two standard rooms plus circulation space giving 33.8 m².
- Building cost discounted over 20 years gives an annual equivalent cost of £2653 (for comparison, the capital charge on the area assumed would be £2501).
- Session costs based on 460 sessions per year to allow for holidays/sickness/equipment breakdowns, etc.
- Cost per patient based on 10 patients per session.
- Camera costs allocated between fundus/digital/analogue as £54,000 for the entire digital system and £35,000 for the analogue system.
- Running costs cover cleaning/maintenance/rates and power.
- Film costs £9.82 per film and has been assumed to include processing.

TABLE 16 Screening costs (£ 1998–9)

	Manual interpretation of digital images		Automated grading of digital images		35-mm Colour slides	
	Cost per session	Cost per patient	Cost per session	Cost per patient	Cost per session	Cost per patient
Building	5.77	0.58	5.77	0.58	5.77	0.58
Equipment						
digital	21.03	2.10	21.03	2.10		
analogue					13.63	1.36
Running costs	4.41	0.44	4.41	0.44	4.41	0.44
Drops	0.50	0.05	0.50	0.05	0.50	0.05
Film and processing					24.55	2.46
Staff						
nurse	38.91	3.89	38.91	3.89	38.91	3.89
photographer	27.58	2.76	27.58	2.76	27.58	2.76
senior registrar	42.87	4.29			42.87	4.29
Automated grading of digital images			26.09	2.61		
Total	141.07	14.11	124.29	12.43	158.22	15.82

TABLE 17 Costs for a cohort of 1000 patients screened (£ 1998–9)

	Manual grading of digital images	Automated grading of digital images	35-mm Colour slides	Optometrist
Screening cost	14110	12430	15820	18000
Repeat screens	706	621	1582	
Assessment visits	8721	8109	8721	6477
Total	23537	21160	26123	24477
True positives detected (from 60)	56	46	58	42
Cost per true positive detected	420	460	450	583

- Nurse costed as grade E working 46 weeks per year and allocating 3.5 hours per session to allow for time getting ready or over-running. Salary based on scale average including employer's on-costs.
- Photographer cost based on MLSO-grade salary.
- Senior registrar cost based on scale average including employer's on-costs. One session taken as 0.1 of working week; reads 17.5 patient films; session cost calculated for 10 patients.
- Development costs for software taken as the whole of 3 years' salary for grade RA1.

TABLE 18 Model for a cohort of 1000 patients – automated grading combined with medical staff grading

Screening cost – automated grading of digital images	£12430
Regrading of positives by medical staff (324 × 4.29)	£1390
Repeat screens	£621
Assessment visits	£8313
Total	£22754
True positives detected (from 60)	£48
Cost per true positive detected	£474

Combining modalities – a modelling exercise

It is possible that automated grading could be used in conjunction with medical staff and this can be modelled using results from this study. The automated system would be used to report any retinopathy, as it has a better sensitivity rate of 87%, although specificity is worse, 71%. Medical staff carrying out a reading of the reported positives would eliminate some false positives. The medical staff would have to read images for 324 out of 1000 patients (based on a prevalence of 6% for sight-threatening diabetic retinopathy). It is assumed that in this model 48 true positives would be detected (automated grading would detect 52 and medical grading would identify 93% of these). It is further assumed that medical reading would continue to grade as false positive the same absolute number of patients (113) as were graded false positive when reading all 1000 cases. These are the least favourable assumptions to be made about the effect of combining the two modalities of reading. The results in *Table 18* show that the cost per true positive remains higher than for digital imaging and medical staff grading alone.

Altering the assumption about the combined sensitivity of the reading methods makes little

difference. However, if the absolute number of false positives was reduced, this could affect the result. The most optimistic assumption would be that medical staff would continue to achieve 87% specificity when reading only the positives selected by automated grading. This would reduce the number of false positives to 36, giving a combined specificity of 96%, and would reduce the cost per true positive to £375. Hence it is the combined specificity of the two modalities that is important in estimating the relative cost-effectiveness of the screening.

Sensitivity analysis

Prevalence

Increasing the assumed prevalence of sight-threatening diabetic retinopathy reduces the cost per true positive of all screening methods without affecting the ranking between methods (*Table 19*).

Throughput per session

The estimates in *Table 16* are based on a throughput of 10 patients per session for both methods of photographic screening. The number of patients per session would have to fall below seven before all of the photographic methods

TABLE 19 Costs for a cohort of 1000 patients screened (£ 1998–9) (prevalence of 12% in normal font and 8% in italics)

	Manual interpretation of digital images	Automated grading of digital images	35-mm Colour slides	Optometrist
Screening cost	14110	12430	15820	18000
Repeat screens	706	621	1582	
Assessment visits	11271	10098	11322	8364
	9537	8772	9588	7089
Total	26087	23149	28724	26364
	24353	21823	26990	25089
True positives detected	112	92	116	84
	75	62	78	56
Cost per true positive detected	232	252	248	314
	325	352	346	448

TABLE 20 Effect of throughput on cost per screen

No of patients per session	Cost per patient screened (£)		
	Manual interpretation of digital images	Automated grading of digital images	35-mm Colour slides
10	14.11	12.43	15.82
9	15.67	13.81	17.58
8	17.63	15.54	19.78
7	20.15	17.76	22.60
6	23.51	20.72	26.37

became more expensive than optometrist screening, per patient screened (Table 20). The throughput per session would have to fall below six before it became more expensive than optometrist screening, per true positive detected. The ranking of alternative photographic methods would be the same unless different throughput rates were assumed for different methods. It may be that throughput would be lower for digital imaging because of the opportunity for patient education using the captured images. If throughput per session was eight or less for digital imaging, and remained at 10 for analogue imaging, then analogue imaging would be less expensive in terms of cost per screen and cost per true positive detected.

Assumed life of equipment

Equipment costs have been given as assumed life of 7 years, but replacement may occur much earlier because of developments in technology. This is more likely to affect the digital systems and the costs were recalculated using 5 years and 3 years as the assumed life (Table 21). If digital equipment is replaced after 3 years, the cost per

screen becomes more expensive than analogue screening. The cost per true positive remains just below the figure for the analogue screening, at £447 compared with £450.

Automated grading – software costs

The development costs for the software have been treated as equipment costs and have been spread over 7 years. Reducing this time period would further increase the costs of automated reading. However, the costs have also been applied to screening in one location only. If the system were adopted more widely, the cost per screen would fall. In order for the cost per true positive to equate with the cost based on medical staff grading, the cost per screen for the software would have to fall to £0.24. This is equivalent to screening 50,000 patients per year.

Conclusions

The costing information presented above reflects those costs incurred in the trial. Their extrapolation to a more general context of a national screening programme needs to be taken cautiously.

TABLE 21 Effect of alternative assumptions about replacement of digital equipment

	Cost per patient screened (£)		
	Manual interpretation of digital images	Automated grading of digital images	35-mm Colour slides
Baseline (7 years)	14.11	12.43	15.82
5 years	14.79	13.11	
3 years	16.40	14.72	

Optometrist analysis was the least cost-effective. As mentioned in the section 'Comparison of optometrist with ophthalmologist' (p. 25) to some extent this probably reflects the lack of practice in detecting macular oedema, as in everyday practice optometrists would see mainly normal eyes. Care was taken in training optometrists for this study, but performance would be expected to improve with further experience.

The automated system, either on its own or in conjunction with medical staff, is more expensive per true positive detected than manual grading. To make it competitive, the cost per patient has to be reduced to £0.23, which, with the current cost implies an annual screening of 50,000 patients, a number that could be encountered in a national

screening programme. The main problem was the relatively low sensitivity of the software for detecting sight-threatening diabetic retinopathy and, in part, this was because the software was unable to detect new vessels. Undoubtedly the sensitivity of software can be expected to improve as further development continues.

Although manual grading appeared most cost-effective, the main problem, that has not been investigated, is the cost of setting up a manual screening service and ensuring that the quality of reporting remains consistent. Although it is not unreasonable to expect a trained grader to perform as well as the senior registrar used in this study, introducing quality control measures will have a cost implication.

Chapter 8

Conclusions

Current study

It is estimated that there are 1100 new cases of blindness every year secondary to diabetic retinopathy. Early detection of sight-threatening retinopathy enables laser therapy to be performed to prevent or slow the onset of visual loss. At present the commonest cause of visual impairment is ischaemic maculopathy, which is untreatable by surgical means. Early detection of retinopathy with aggressive management of metabolic control and blood pressure will therefore be the most effective way of meeting the St Vincent targets for visual impairment, thus reducing the social and economic toll of this complication. The European Retinopathy Working Party recommended a sensitivity of 80% and a specificity of 95% for screening programmes, but conventional screening modalities are failing to achieve these targets and, in addition, the provision of conventional screening modalities is inadequate and inequitable in the UK.

The digital fundus camera is a promising development. It makes regular assessment more feasible since, unlike current approaches, it does not require a skilled assessor to see each patient. It also offers the potential for introducing automated screening of retinal images with the associated consistency in interpretation. It is ideally suited to quality assurance as it produces a hard copy that can be assessed, unlike subjective techniques such as slit-lamp biomicroscopy. One potential disadvantage is whether the quality of the digitised image is sufficiently high for the purpose of screening.

Ergonomically, digital imaging was found to be more effective than colour slides. Digital photography produced fewer ungradable images and the number of individuals needing to be recalled for repeat photography if a digital rather than a conventional photographic camera was used for image capture was reduced by about 50%. This was mainly due to the fact that the photographer had immediate feedback on the quality of the images by being able to view them instantaneously on the computer screen. If the image was not of sufficient quality the photographer simply repeated the photograph until one of sufficient quality could be obtained.

So far as image quality was concerned, a grading system, based on the clarity of features such as nerve-fibre layer and vessels, demonstrated that the finest quality photographs were produced by conventional photography. This is not surprising as the maximum resolution of conventional photographs is approximately 2–3 times better than the digital camera used in this study. However, in terms of producing images of a quality acceptable for screening, then the digital images were superior to the colour slides. When the image quality was analysed in terms of field, then the poorest quality field tended to be the nasal field, reflecting the need for a widely dilated pupil and the absence of peripheral cortical cataract, a common clinical finding, to obtain high-quality images.

Caution must also be exercised over the effect of artefacts on image quality. The presence of dust on images simulating microaneurysms was one problem that we encountered.

Previous publications on screening have tended to compare one modality with another but not all modalities together. In this study we have compared trained optometrists using slit-lamp photography against conventional mydriatic photography and digital photography. We did not use direct ophthalmoscopy as this has been shown to be an insensitive technique, although it may have a role in sporadic screening or where no screening at all occurs. Red-free digital images were used as they provide the greatest contrast for red abnormalities on a red background. Although other clinicians may not be used to such monochrome images, it is the standard imaging modality for fluorescein angiography where the highest quality images are required. It was also felt important to attempt to train the optometrists to the same standard as the ophthalmologists in the clinic.

In terms of sensitivity and specificity, there was little to choose between conventional mydriatic photography and digital photography for detecting any or early retinopathy. For sight-threatening retinopathy the optometrists had the lowest overall sensitivity (73%), although their specificity (90%) was comparable to that of the other modalities. Digital imaging and

conventional photography are acceptable methods for screening. Screening by trained optometrists is not sufficiently sensitive for detecting either any retinopathy or sight-threatening retinopathy.

In the context of a national screening programme, automated analysis techniques offer the advantages of repeatability and consistency. Individual human graders tend to have their own varying internal reference standards which are difficult to make conform, despite training, leading to intra- and inter-observer variability.

In a previous study comparing the automated detection of retinopathy, using only microaneurysms, with colour slides graded by a research fellow,⁴⁸ we were able to achieve a sensitivity of 85% and a specificity of 76% for detecting whether or not a patient had retinopathy. In this current study, in which ophthalmologists using stereo biomicroscopy was used as the gold standard, we have achieved a slightly higher sensitivity of 83% but a slightly lower specificity of 71%. Although the sensitivity exceeds the 80% recommended by the European Retinopathy Working Party, the specificity falls short of their value of 95%. Assuming a prevalence for diabetic retinopathy of 30%, this means that 48% of this population would be correctly classified as having no retinopathy. This is a significant achievement when one considers the large number of patients with diabetes in the UK who require screening.

Clearly, such results depend upon the population examined. For sight-threatening retinopathy, the specificity rises to 88% whereas the sensitivity is lower than that achieved by other modalities at 77%. The problem is that we have not been able to detect all forms of sight-threatening retinopathy as we do not as yet have a computer algorithm to detect new vessel formation.

In addition, it would appear that automated grading is able to detect the presence of clinically significant maculopathy (using a combination of the microaneurysm detection program and the exudate program), with a specificity of 85%, which is comparable to other modalities, thus enabling graders to target their attention on images with potentially sight-threatening retinopathy.

We conclude that automated grading cannot, at present, be used on its own but in the context of a manual grading system it will still greatly reduce the workload by correctly identifying just under half the population as having no retinopathy.

For this investigation, we used the two-field protocol of the EURODIAB study. Although more patients had retinopathy confined to the macular field compared with the nasal field, using the macular field only would significantly reduce the chances of detecting any retinopathy, with between 8 and 14% of cases being missed. In the case of sight-threatening diabetic retinopathy, however, the number of missed patients drops to 3% or less, with the sensitivity and specificity being almost the same for one as for two fields. This raises the possibility of adopting a screening programme based on taking only a macular field. Such a decision will depend on the likely incidence of more advanced retinopathy in the screened population. It should also be noted that the sensitivity and specificity achieved by the automated system will depend upon the number of images taken per patient; analysis of four images will lead to a higher sensitivity but lower specificity than for detecting retinopathy in two images.

The role of automated grading for assessing the progression of disease was also explored. The value of this approach was fundamentally limited by two factors. First, there is an intrinsic variability in the grading of level of retinopathy by ophthalmologists and optometrists compared with the gold standard. Second, microaneurysms, as assessed on fluorescein angiography, are subject to a rapid turnover, with only about 45% of the microaneurysms being still seen 6 months later. There was a statistically significant increase in the number of microaneurysms in the group of patients whose condition changed from none to mild and the group who progressed from mild to moderate. However, when the actual individual rate of turnover was analysed, there was no significant difference between the group of mild and sight-threatening retinopathy. However, this aspect of the study was limited by the small number of patients completing it.

At the start of the study (see the section 'Overview of the study', p. 2), three questions were posed. First, can a digital imaging system detect retinopathy irrespective of sort or level? The answer is that employing a manual analysis of the images, a sensitivity of 83% and a specificity of 79% can be achieved, and using an automated analysis, these become 83% and 71%. Second, can a digital imaging system detect progression of retinopathy? The answer is that although it can measure turnover, it has not been shown that this follows the progression of retinopathy. Third, can a digital imaging system determine when

treatment is warranted? Since there was no definite answer to question 2, then that to the third question must be 'no' at present.

Relevance to the NHS

Digital imaging is already succeeding conventional photography in eye departments. This study has demonstrated that the digital fundus camera does indeed have a significant role to play in ophthalmology. The finest quality photographs were produced by conventional photography, in terms of producing images of a quality acceptable for screening, but the digital images were superior to colour slides. Most important, digital imaging was found to be more effective than colour slides, producing fewer ungradable images. With the development of higher resolution digital cameras, it is to be expected that conventional photography may eventually be superseded by digital imaging.

Digital imaging and conventional photography are acceptable methods for screening; in terms of sensitivity and specificity there was little to choose between conventional mydriatic photography and digital photography for detecting any or early retinopathy. Screening by trained optometrists is, however, not sufficiently sensitive for detecting either any retinopathy or sight-threatening retinopathy.

In the context of a national screening programme, automated analysis techniques offer the advantages of repeatability and consistency. The cost-effectiveness of the study showed that although the automated analysis had the lowest cost per screen, in terms of cost per true positive it was more expensive than clinical staff manually reading digital images or colour slides. However, this analysis did not take account of the cost of training screeners and maintaining the quality of their reporting. Also, the cost would drop to that of other approaches in a system which was screening 50,000 patients or more per year.

The performance of the software developed for this project meant that, assuming a prevalence for diabetic retinopathy of 30%, 48% of this population would be correctly classified as having no retinopathy. This suggests a two-step procedure for any screening programme. Where no retinopathy is detected by the software, then the patient would be recalled in 1-year's time for repeat screening. Where retinopathy is detected,

the image would be manually graded. Thus automated first-level grading could considerably reduce the burden of manual grading.

Research recommendations

1. The two-field protocol of the EURODIAB study was used, but analysis of the data shows that the detection of referable retinopathy was as reliable using only the macular field. Single-field imaging could potentially reduce time taken to perform retinal screening. This observation requires confirmation with a larger number of patients and different referral criteria.
2. The value of an automated grading system to assist in a screening programme has been demonstrated. Further work is required to improve the sensitivity and specificity of such programmes. In particular, it would be of value to develop software to detect new vessel formation and to investigate the potential of using colour information.
3. An insufficient number of patients was recruited to investigate the value of automated grading for the evaluation of disease progression. This should be studied further in conjunction with the development of automated systems.
4. Patient recruitment was poor. Future research is required to ensure effective uptake in a diabetic retinopathy screening programme.

The future

Any screening programme must be able to detect retinopathy with a significant level of accuracy and confidence. The European Retinopathy Working Party recommendations are achievable in terms of sensitivity, although the required specificity was not achieved by any of the modalities tested. The recommendations of 80% sensitivity and 95% specificity are not based on any scientific evidence and whether such high levels are actually required has yet to be determined.

Perhaps the major advantage that digital imaging has over all other screening modalities is its suitability for quality assurance. For any screening programme this must be a major concern. Until the skills of slit-lamp biomicroscopy can be raised to those of the ophthalmologist then the role of high-street ophthalmologists might be limited to digital retinal photography as part of a national screening network.

The cost-effectiveness of the automated approach will be affected by developments in technology. On the hardware side, the major development is the arrival of digital cameras with a higher resolution than the 1024×1024 acquisition matrix of the Topcon system we used. For example, the

current generation (2002) of cameras offer a resolution of 2160×1440 pixels. There will undoubtedly be improvements in automated analysis software and this has been identified as an area for further research.



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Contributions of the authors

PF Sharp (Professor of Medical Physics) was overall project coordinator.

J Olson (Senior Registrar in Medical Ophthalmology) was coordinator for clinical research.

F Strachan (Research Fellow) was a clinical researcher and lead for the systematic literature review.

J Hipwell (Research Fellow) carried out software development and image analysis.

A Ludbrook was responsible for health economics aspects.

M O'Donnell (Research Assistant) and S Wallace (Research Assistant) provided assistance with the systematic literature review.

K Goatman (Research Fellow) undertook data analysis.

A Grant (Unit Director) gave advice on the systematic literature review.

N Waugh (Director) provided expertise on purchasing perspectives of screening for diabetic eye disease.

K McHardy (Consultant General Physician/Diabetologist) and JV Forrester (Professor) gave advice on clinical aspects of diabetic retinopathy screening.



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Appendix I

Systematic literature review (completed 1998)

Introduction

Background

Despite advances in diabetic care, visual impairment in diabetes remains a devastating complication, in terms of both personal loss for the affected individual and socio-economic costs to society. Of the 12 million citizens of the USA who are recognised as suffering from diabetes mellitus, it has been estimated that the prevalence of those with proliferative retinopathy is 700,000 (6% of the population) with an anticipated further 65,000 cases occurring per annum.¹ For the insulin-dependent diabetic population of Europe, a cross-sectional study of patients attending 31 diabetes centres revealed a prevalence of pre-proliferative retinopathy of 35.6% (mild 25.8%; moderate-to-severe 9.8%) and proliferative retinopathy of 10.6%.² The complications arising from diabetic retinopathy are an estimated 8000 new cases of blindness per year in the USA¹ and 1100 new cases per annum in the UK,³ giving rise to a significant problem in the working-age population.

Although it remains difficult to quantify the devastating effect of blindness with regard to personal loss, the economic cost to society in terms of unemployment and disablement benefits has been calculated as £3575 for each affected individual per annum in the UK.⁴ This was weighted against the estimated cost of treatment of £387 for each person at risk of blindness, indicating the economic advantages of successful treatment of those high-risk individuals.

Pathogenesis and key features of diabetic retinopathy

The natural history of retinopathy has been well defined, following a predictable course from the early stage of microaneurysm development to moderate retinopathy, with evidence of cotton-wool spots, intra-retinal microvascular abnormalities and venous beading indicating a deterioration in retinal blood supply. Hard exudates define areas where retinal capillary leakage is occurring in the presence of endothelial damage. Ultimately, in response to worsening ischaemia, growth of new blood vessels is stimulated. This proliferative stage of retinopathy poses a high risk for the patient as fragile new

vessels have a tendency to haemorrhage, causing potentially significant visual impairment.

Baseline microaneurysm counts in people with diabetes with no other evidence of retinopathy may provide a useful predictor of long-term progression to proliferative retinopathy, independent of the effects of glycaemic control and blood pressure.⁵ The importance of microaneurysm detection and quantification is supported by the analysis of fluorescein angiograms by Kohner and Sleightholm.⁶ This analysis has shown a significant correlation between microaneurysm number and the presence of haemorrhages and cotton-wool spots and, to a lesser extent, the severity of hard exudates and IRMAs. From examination of the natural progression of fundus changes in individuals with at least moderate diabetic retinopathy, it was found that the severity of IRMA, venous beading and the number of haemorrhages and microaneurysms present were of the most significance in identifying those people who are likely to develop subsequent neovascularisation.⁷

ETDRS

The ETDRS was carried out to provide answers to the problem of reducing the devastating morbidity from visual loss secondary to diabetes.⁸ As a consequence of the trial, the benefits of laser panretinal photocoagulation for patients with high-risk proliferative retinopathy have been recognised and adopted into standard clinical practice. However, the authors concluded that early panretinal photocoagulation was inappropriate for those with mild to moderate retinopathy and a low risk of progression to severe visual loss, given its potentially detrimental effect on the peripheral visual field. They emphasised that the key to successful management was early identification of retinopathy with the meticulous monitoring of progression to allow optimum timing of intervention when a proliferative stage had been reached.

Risk factors in development of retinopathy

There are, however, other ways in which careful screening of diabetic populations and monitoring of established retinopathy may be beneficial. The

Diabetes Control and Complications Trial has shown that strict metabolic control can both offset the development and slow the progression of diabetic retinopathy in type 1 diabetics.⁹ In addition to acknowledging the limitations of their cross-sectional study of 3250 European type 1 diabetics, Sjolie and colleagues have also suggested that, in the later stages of retinopathy, the adjustment of blood pressure, fibrinogen and triglyceride levels may affect outcome.² The cessation of cigarette smoking may also have a beneficial effect although further prospective studies are required for clarification.^{10,11} The recognition of very early diabetic fundal change may provide the impetus to patients to make positive lifestyle changes and tighten glycaemic control.

An overview of existing screening methods

Based on the principles of the St Vincent Declaration,¹² the European Retinopathy Working Party defined a protocol of screening for diabetic retinopathy.¹³ This advocated that all diabetic patients should have an annual eye examination by ophthalmoscopy through pharmacologically dilated pupils or by retinal photography.

In 1991, the Department of Health commissioned a study of 3318 diabetic patients to establish the definitive method of performing fundal examination.¹⁴ A comparison was made between direct ophthalmoscopy, performed by GPs, ophthalmic opticians and hospital physicians, and an assessment of images acquired with a non-mydiatic Polaroid fundus camera by a consultant ophthalmologist. A fundal examination by an ophthalmologist with access to the Polaroid photographs was used as the 'gold standard'. Buxton and colleagues concluded that direct ophthalmoscopy by all groups showed relatively poor sensitivities (hospital physician 67%; GP 53%; optician 47%), although specificities were higher (hospital physician 97%; GP 91%; optician 95%), indicating that relatively few inappropriate referrals to ophthalmology services would occur.¹⁴ However, it was apparent that direct ophthalmoscopy alone was likely to miss a significant proportion of patients with evidence of retinopathy, regardless of who performed the examination. Analysis of fundus photographs resulted in sensitivities ranging from 35 to 67% with specificities marginally higher than those of the primary screeners at 95–98%. Although it has been suggested that the performance of non-mydiatic cameras may be enhanced by the use of mydiatic agents,¹⁵ Buxton and colleagues' findings are consistent with the findings of other comparative studies.^{16–20} These studies,

summarised in *Table 22*, suggest that at present no individual method of routinely available fundus examination can be judged superior or indeed satisfactory for clinical screening.

Although the findings of Klein and colleagues seem encouraging for a single non-mydiatic photograph, the wide confidence intervals calculated for their relatively small patient population warrant caution in interpretation of these results.¹⁶ Combining the modalities of ophthalmoscopy and retinal photography appears effective in detection of sight-threatening retinopathy for O'Hare and colleagues.²⁰ However, even their technique does not achieve the recommended threshold of a minimum 80% sensitivity and 95% specificity for mild retinopathy as suggested for audit standards by the British Diabetic Retinopathy Working Group.²¹

An overview of digital technology

Given the recognised limitations of existing retinopathy screening techniques, there has been a great deal of interest in exploring the potential role of digital photography and imaging techniques which can allow computer-assisted analysis of fundal images.

Initially, digital techniques required the use of scanners to convert conventionally acquired images to a digital format. More recently, on-line direct acquisition of images has become increasing commonplace as technology advances. Within a digital camera system, photographic film has been replaced with CCD sensor, which is composed of a grid of individual picture elements or pixels.²² As reflected light from a fundus image falls on this sensor, each pixel generates a discrete numerical value that is representative of the level of luminance to which it is exposed. This numerical or digital signal is then relayed to the computer's imaging system, and subsequently stored temporarily in random access memory (RAM). As monochrome and colour images require 1 and 3 MB of memory for storage, respectively, the number of images acquired before transfer to hard drive is necessary will be limited by computer RAM size. Therefore, there may be an advantage in systems that allow direct storage on to enhanced hard drives. As the number of pixels in the CCD is increased, image resolution is improved.

Commission from the NHS Health Technology Assessment Programme

It is against the above background that there has been significant interest in developing digital imaging techniques in the field of diabetic eye

TABLE 22 Sensitivity and specificity of retinopathy detection techniques

Screening test	Reference/gold standard test	Study population	Definition of positive test	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Reference
Non-mydratiac fundus cameras						
45° non-mydratiac Polaroid image read by ophthalmologist	Fundal examination by ophthalmic clinical assistant (technique not specified) with access to Polaroid images	3318 diabetic patients	Referral with STDR	56 (48 to 63)	97 (96 to 97)	Buxton, 1991 ¹⁴ UK
Single non-stereoscopic 45° photograph centred between disc and fovea – 35-mm, non-mydratiac	30° stereoscopic colour photographs according to ETDRS fields 1, 2 and 3 read by trained ophthalmic graders	99 diabetic patients – single eye examined	A. Presence of any retinopathy B. Detection of PDR	A. 100 (92 to 100) B. 93 (66 to 100)	A. 91 (59 to 100) B. 98 (87 to 100)	Klein, 1995 ¹⁶ USA
Non-mydratiac Polaroid photography – number of images taken not specified	Comparison with direct ophthalmoscopy examination by hospital physician participating in diabetic clinic (overall sensitivity/specificity not calculated). Patients diagnosed with maculopathy referred for examination by ophthalmologist	2159 adults attending general diabetic clinics	Presence of retinopathy/maculopathy by either test	For new vessels detected by either method: camera 65, ophthalmoscopy 77.5. For diagnosis exudative maculopathy: camera 74.2, ophthalmoscopy 57.4	For new vessels detected by either method: camera 60.3, ophthalmoscopy 39.7. For diagnosis exudative maculopathy: camera 55.3, ophthalmoscopy 67.0	Taylor, 1990 ¹⁷ UK
Mydratiac fundus cameras						
Three 35-mm non-stereoscopic 45° overlapping images of each fundus (Canon CR4-45NM camera)	Examination by slit-lamp biomicroscopy by consultant ophthalmologist	395 diabetic patients	Presence of STDR	89 (76 to 96)	86 (82 to 90)	Harding, 1995 ¹⁸ UK
Single non-stereoscopic 45° photograph centred between disc and fovea – 35-mm, with mydratics	30° stereoscopic colour photographs according to ETDRS fields 1, 2 and 3 read by trained ophthalmic graders	99 diabetic patients – single eye examined	A. Presence of any retinopathy B. Detection of PDR	A. 98 (90 to 100) B. 93 (68 to 100)	A 100 (77 to 100) B 100 (93 to 100)	Klein, 1995 ¹⁶ USA
Single 60° colour slide photography centred on the macula – photographs graded by clinicians	Clinical examination by experienced ophthalmologist	Patients attending general diabetic clinic (subgroup of 48 patients underwent ophthalmologist examination in addition to photography)	Presence of retinopathy and assessment made of grading accuracy	Detection of any retinopathy 93 Detection of severe retinopathy 100	Detection of any retinopathy 89 Detection of severe retinopathy 75	Joannou, 1996 ¹⁹ South Africa

continued

TABLE 22 Sensitivity and specificity of retinopathy detection techniques (cont'd)

Screening test	Reference/gold standard test	Study population	Definition of positive test	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Reference
Direct ophthalmoscopy						
Direct ophthalmoscopy by i. hospital physicians ii. opticians iii. GPs	Fundal examination by ophthalmic clinical assistant (technique not specified) with access to Polaroid non-mydriatic photographs	3318 diabetic patients	Referral with STDR	i. 67 (50 to 84) ii. 47 (23 to 71) iii. 53 (44 to 62)	i. 97 (96 to 99) ii. 95 (93 to 97) iii. 91 (90 to 92)	Buxton, 1991 ¹⁴ UK
Direct ophthalmoscopy by i. opticians ii. GPs	Fundal examination by staff-grade ophthalmologist (technique not specified) with review of fundus photograph	493 patients examined by opticians; 517 patients examined by GPs	A. Detection of background retinopathy B. Referral with STDR	A. i. 43 ii. 22 B. i. 75 ii. 56	A. i. 94 ii. 94 B. i. 93 ii. 98	O'Hare, 1996 ²⁰ UK
Direct ophthalmoscopy through an <i>undilated</i> pupil by experienced ophthalmic assistant	30° stereoscopic colour photographs according to ETDRS fields 1, 2 and 3 read by trained ophthalmic graders	99 diabetic patients	A. Presence of any retinopathy B. Detection of PDR	A. 84 (72 to 93) B. 53 (37 to 69)	A. 75 (51 to 91) B. 90 (79 to 96)	Klein, 1995 ¹⁶ USA
Combined techniques						
Direct ophthalmoscopy combined with single photograph centred on the macula (field size not specified)	Fundal examination by staff-grade ophthalmologist (technique not specified) with review of fundus photograph	i. 493 patients examined by opticians ii. 517 patients examined by GPs	A. Detection of background retinopathy B. Referral with STDR	A. i. 71 ii. 65 B. i. 88 ii. 80	A. i. 94 ii. 92 B. i. 99 ii. 98	O'Hare, 1996 ²⁰ UK
CI, confidence interval; ETDRS, Early Treatment of Diabetic Retinopathy Study; PDR, proliferative diabetic retinopathy; STDR, sight-threatening diabetic retinopathy.						

disease. As no clear information was in existence as to how these techniques would fit into a clinical setting, we were commissioned in 1996 by the NHS Health Technology Assessment Programme to undertake both a systematic literature review and a primary study to assess the performance of digital imaging in screening for and monitoring the development of diabetic retinal disease. This document reports the findings of the systematic literature review.

Ultimately, the principal interest of the NHS will be the clinical effectiveness and efficiency of digital imaging for screening for diabetic retinopathy and monitoring its progression. Assessing these qualities requires reliable information about the impact of digital imaging on clinical management of diabetic retinopathy and on later health (for example, sight-years saved), relating these to the resources used and comparing them with alternative policies for screening. However, it was our view that the technology had not yet reached the point of development where these parameters could be assessed reliably. Certainly, a search of MEDLINE using the standard Cochrane search strategy failed to identify any randomised controlled trials (RCTs) of digital imaging in this context.

The review was therefore restricted to studies of the diagnostic performance of digital imaging in diabetic retinopathy, compared where possible with existing recognised techniques. In view of the difficulty in defining a gold standard in this field, we allowed the inclusion of comparative studies (studies comparing one 'test' with another, in this case, digital imaging). We had hoped to present a meta-analysis of results using ROC curves, thereby allowing consideration of performance of digital techniques against alternatives. Such curves allow direct comparisons of tests while varying the assumption on which normal and abnormal test results might be defined. However, owing to the diverse nature of the studies and the differing techniques under investigation, no meta-analysis of study results was possible and a qualitative analysis was carried out instead.

Methods

Aim and objectives of the review

The overall aim of the systematic review was to assess the value of currently available digital imaging techniques and compare them with alternative methods.

The objectives of the review were as follows:

- to identify the number and quality of primary studies of digital imaging techniques in diabetic eye disease
- to identify the range of available digital techniques applicable in this field
- to determine whether current digital imaging techniques can detect early diabetic retinopathy when screening a population with no known retinopathy
- to determine whether current digital imaging techniques can detect the progression of established retinopathy
- to determine whether current digital imaging techniques can determine when patients require treatment of retinopathy
- to evaluate 'experimental' techniques that may have a future clinical application
- to compare current digital imaging techniques with alternative methods.

Background

The studies considered in this review investigated the diagnostic performance of digital imaging techniques in the field of diabetic retinopathy. The research methodologies of the studies considered therefore were different from those in reviews of effectiveness where the emphasis is solely on RCTs. The nature of the review was, however, systematic in the sense that there were explicit search strategies for identifying studies, explicit selection criteria for the studies that were considered, a systematic way of appraising the studies and a standard format was chosen for presentation of the data.

Development of protocol

A protocol was written at the start of the project that explicitly described the objectives of the review, the criteria required of studies for inclusion, the search strategy to be used for identification of studies and the methods of quality assessment, data abstraction and presentation of results.

Systematic electronic bibliographic database searching

The following electronic bibliographic databases were searched systematically:

- MEDLINE (National Library of Medicine, electronic version of Index Medicus, USA) on OVID, CD PLUS.
- EMBASE (Elsevier Science Publishers, electronic version of Excerpta Medica, Amsterdam) on BIDS and OVID.

- Science Citation Index (electronic version, paper version of same name, produced by ISI, Institute for Scientific Information, Philadelphia, PA, USA) on BIDS.
- Ei Compendex Plus (Computerized Engineering Index, electronic version of The Engineering Index, produced by Engineering Information, Hoboken, NJ, USA) on BIDS.
- Cochrane Library (database on disk and CD-ROM). The Cochrane Collaboration; 1997, Issue 3. Oxford: Update Software; 1997. Updated quarterly.
- National Research Register (NRR), 14th consolidation, September 1996.

The search strategy was first developed in MEDLINE as this is one of the best indexed and 'user-friendly' electronic bibliographic databases. Two sets of search terms were devised: one set to describe diabetic retinopathy and the other to describe digital imaging techniques. These were developed by the research team that included ophthalmologists, diabetologists, medical physicists and health services researchers experienced in literature searching. These two sets of terms were combined together using the Boolean operator 'and'. (The use of a third set of study design terms was considered but was not included, in line with the decision to search for all possible study designs.)

These sets of search terms were built up by investigating the medical subject headings (MeSH) terms using the MeSH tree with scope notes and Permuted Index as well as textword searching (searching for terms in the title and abstract). As new search terms were added to the search strategy, details of the first 50 titles and abstracts were scanned to assess their relevance to diabetic retinopathy and digital imaging. Terms that retrieved only irrelevant articles were further modified or rejected.

The MEDLINE search strategy was modified for searching other databases. The modifications involved changing the syntax to suit that of the search software of the other databases and interrogating the thesaurus or indices of each database to identify equivalents of the MeSH terms (keyword system) used in MEDLINE. A more focused search was conducted on the other databases partly because they had less of a medical emphasis and partly because the strategy used on MEDLINE was fairly broad, resulting in many abstracts being assessed but few proving relevant.

Searching the Internet

We also searched the World Wide Web with the browser Internet Explorer and located relevant websites by using the advanced search options of the search engines Excite and Yahoo. The set of keywords entered into the query box were: *digital imaging* and *diabetic* and *retinopathy*. These keywords were combined together using the Boolean operator 'and'.

Handsearching

Recent issues of three journals, *British Journal of Ophthalmology* (Volume 81, Issues 7–12, 1997), *Graefe's Archive for Clinical and Experimental Ophthalmology* (Volume 235, Issues 7–12, 1997) and *Investigative Ophthalmology and Visual Science* (Volume 38, Issues 9–13, 1997), were handsearched for relevant publications that would not yet have appeared on the electronic databases owing to delays in indexing. Handsearching was performed by a health services researcher with an interest in the methodology of systematic reviews. This involved going through every page of each issue and reading through letters, editorials and conference reports in addition to published papers.

Other methods of ascertainment of studies

Reference lists of relevant studies

The reference lists of relevant studies identified from the electronic databases were searched for references to other studies that might be relevant. Relevance was assessed from a hard copy of each article. We limited these searches to the 'first-generation' references only; in other words, we did not search the reference lists of studies originally identified from a previous reference list search.

Contacting authors of key articles identified through the electronic searches

Authors of key articles were contacted and asked if they were aware of any other relevant studies. A number of authors were also contacted for further information in relation to their publications.

Other

In addition the Proceedings of the British Diabetic Association's Education and Care Section Annual Conference, 8–10 October 1997, and the British Diabetic Association's Medical and Scientific Section Autumn Meeting, 9–10 October 1997, and the Spring Meeting, 25–27 March 1998, were searched for relevant abstracts or poster presentations.

Identification of possible studies

All possibly relevant studies were electronically imported or manually entered into the reference managing software package Reference Manager (Version 7.01N; Research Information Systems, Carlsbad, CA, USA). Subject keywords and source of article were added.

Register of possible studies

Initially, all electronically derived abstracts and study titles were read by a diabetologist and a health services researcher with an interest in the methodology of systematic reviews to assess subject relevance. However, because of the high degree of concurrence and the greater speed at which abstracts could be assessed by the diabetologist, it was decided that the diabetologist alone should assess the abstracts. All relevant studies were assigned specific topic keywords on Reference Manager and the full published paper was obtained.

Assessment of studies for inclusion

Hard copies of studies were assessed for subject relevance and eligibility by a diabetologist. The assessor was not blinded to author, institution or journal. Studies were included if they reported on the use of either direct or indirect digital imaging techniques in the field of diabetic retinopathy and involved patients with either type 1 or 2 diabetes. Owing to the early stage of development of digital technology, poster and abstract presentations were included in the review. Given the original remit of the review, early experimental techniques which were applied to animal models only were not included. Studies used to monitor response to treatment were also not included as we were primarily interested in digital techniques which could be applied to diabetic retinopathy screening and monitoring of retinopathy progression.

Quality assessment of studies to be included

Comparative studies where digital imaging was assessed against an alternative technique were graded on the following methodological criteria proposed by Carruthers and colleagues:²³

- use of a recognised gold reference standard
- independent assessment of test under review and gold reference standard
- test applied to an appropriate study population, that is, diabetic patients suspected but not known to have retinopathy, diabetic patients with established retinopathy and non-diabetic control groups
- avoidance of verification bias, that is, reference standard applied to all patients under study

- reproducible description of both the test and the reference standard given.

Studies were graded depending on the number of these criteria met, with a score of V being awarded when a study met all five criteria and a score of I being given when only one of the above criteria was met. Posters and abstract presentations generally received a low grading owing to a lack of available information on study methodology. It is accepted that this grading may not reflect the value of future publications derived from this work. The difficulty in defining a gold standard for evaluation of techniques in this field is recognised by the reviewers; in this context, it is accepted to be either biomicroscopic examination by an experienced ophthalmologist or the use of the seven-field Airlie House photography protocol.

Grading of results section in studies to be included

In addition to the above methodological criteria, an assessment was made of the interpretation of study results by authors based on the following criteria adapted from those proposed by Carruthers and colleagues:²³

- that sensitivity and specificity could be correctly calculated from comparison with a recognised gold standard as defined above
- test reproducibility calculated by the authors to determine the consistency of results obtained
- appropriate statistical method of analysis applied to results
- data presented to allow confirmation of authors' findings.

Those studies meeting the above four criteria for grading of results were given a grading of IV, those meeting three of the four a grading of III, etc. The grading was carried out by a diabetologist and then, independently, by two expert in health services research. No significant difference was found between the graders. Posters and abstract presentations generally received a low grading owing to a lack of available information on the authors' interpretation of results. It is accepted that this grading may not reflect the value of future publications derived from this work.

Data abstraction

The following information was extracted from the individual studies: technique under review; population studied; study aim; description of gold standard or comparative method used; summary of results; summary of reviewer's comments;

TABLE 23 Results of systematic literature review

Source	No. of reports identified ^a	No. of published abstracts/posters assessed ^b	No. of studies possibly relevant to review	No. of studies included in final review
Electronic searches				
MEDLINE	733	679	72	25
EMBASE	1273	771	35	3
Science Citation Index	626	368	15	2
Ei Compendex	215	156	3	0
Cochrane Library	32	32	0	0
National Research Register ^c	12	N/A	3	0
Subtotal	2891	2006	128	30
Other				
Proceedings	371	371	6	5
Experts contacted	38	N/A	2	3
Bibliographies checked	36 ^d	N/A	19	2
WWW search:				
Excite	50	N/A	0	0
Yahoo	155	N/A	0	0
Handsearching	390	390	0	0
Subtotal	1040	761	27	10
Total	3931	2767	152	40

^a Some reports were identified from more than one source.
^b The number of abstracts assessed after duplicates had been removed by the Reference Manager database. This is only applicable to searches carried out on the electronic databases.
^c A national database of information about ongoing research currently taking place in, or of interest to, the NHS.
^d Number of reference lists checked.

reference; and methodological and results grading. This information has been presented in tabular form for ease of reference.

Data analysis

The original research proposal was for a quantitative analysis of digital imaging techniques as applied to diabetic retinopathy assessment. In view of the early stage of evolution of digital technology in this field, no statistical meta-analysis of study results was possible owing to their diverse nature and differing techniques. Therefore, only a qualitative analysis was possible. The results of the individual studies were summarised systematically and the consistency of similar studies was then considered formally.

Derivation of included studies

Results of systematic literature review

Around 2767 published abstracts and poster presentations were considered for inclusion. A total of 40 studies met the criteria for inclusion; 28 of these were comparative studies comparing digital imaging techniques with alternative methods and 12 were studies describing previously

evaluated digital techniques being used in research. Twenty-five studies were found in MEDLINE after reading 679 abstracts, a further five were found among 1327 abstracts generated by the systematic searches in the other electronic databases and the remaining nine were found in other ways. *Table 23* summarises how studies were first identified, how many were judged to be possibly relevant to the review and how many were confirmed suitable for inclusion.

Reporting the findings of the systematic review

The following three sections will provide a qualitative description of the results of the search strategy, broadly discussed under the categories of digital fundus photography, digital angiography and the scanning laser ophthalmoscope. Each section contains a descriptive text, outlining the development of the digital technique and its application to the detection of diabetic retinopathy.

The role of the search strategy was to identify papers where a digital imaging technique had been compared with existing screening and diagnostic techniques or, once validated, used to further our understanding of the pathogenesis of

diabetic retinopathy. These papers have been summarised in tabular form as techniques under evaluation or validated techniques used in research. Where digital imaging has been compared with alternative techniques, an assessment of the study methodology and the authors' interpretation of results is presented.

Publications identified by the review that did not fulfil the above criteria but were felt to be of importance for their contribution to the overall development of digital imaging in this field have been referred to in the text only. Papers relating to the treatment of retinopathy or confined to animal models have not been included in the final review.

Digital fundus photography

Number and quality of eligible studies

Seventeen relevant publications were identified relating to digital fundus photographic techniques, using both indirect and on-line image acquisition. Four of the 17 included publications were in poster or abstract format. These studies are summarised in *Table 24* and evaluated in *Table 25*.

Manual evaluation of images

Digital imaging versus colour slide photography

Indirect digitisation of original colour slides to facilitate easier storage and computer analysis does not seem to affect image quality adversely to a degree affecting clinical use, as demonstrated by George and colleagues²⁴ (*Table 24*). Diagnosis from digitised images displayed on a high-resolution video monitor was in agreement with that from the original colour slides in 95% of cases of sight-threatening retinopathy and 100% of non-sight-threatening retinopathy. It was noted that cotton-wool spots were underdiagnosed in the digital images although the authors concluded that the decision to refer for specialist advice was unaffected.

Realising the potential for improved storage and retrieval of images, Friberg and colleagues (*Table 24*) attempted an early evaluation of the quality of directly acquired images against conventional imaging modalities.²⁵ Ten diabetic patients, with fundal appearances ranging from mild background retinopathy to proliferative retinopathy, were included in an assessment of 50 patients with retinal pathology. Using a digital system capable of generating images composed of 512×512 pixel array, giving rise to a quarter of a

million pixel elements per picture, the authors conceded that picture resolution was less than that of conventional slide photography (standard 35-mm transparency film may contain up to 4 million pixel elements per image). However, a correct clinical diagnosis was made for each diabetic patient from reviewing digital images alone and the authors concluded that the system appeared to give sufficient detail for clinical purposes. As they predicted, the technology has advanced rapidly since the time of this early study and commercial cameras delivering an image of 1024×1024 pixels are now readily available. Cameras that can image 2036×3060 pixel array are beginning to enter the market but are likely to be limited in their use at present owing to their higher cost.²⁶

A Canon CR5 45NM-based digital imaging system has been compared against the results of 35-mm colour slide photography by Ikram and colleagues (*Table 24*), using slit-lamp biomicroscopy to provide a reference standard for validation of the techniques.²⁷ From a population of 66 diabetic patients attending a mobile screening unit, clinical examination confirmed the presence of background diabetic retinopathy (BDR) in 48%, pre- or proliferative diabetic retinopathy (PDR) in 3% and clinically significant macular oedema or maculopathy (CSMO) in 15%. The results of photography were graded by a consultant diabetologist and found to be comparable for detection of retinopathy using both techniques (35-mm colour slide, BDR 38%, PDR 3% and CSMO 13%; digital imaging system, BDR 44%, PDR 3% and CSMO 14.5%). All patients with sight-threatening retinopathy were identified by each photographic technique. Although there has been no direct calculation of sensitivity and specificity, the authors conclude that digital imaging is at least comparable to colour slide photography from their study.

A similar conclusion was reached by George and colleagues (*Table 24*) using a Canon CR5 retinal camera in an extension of their earlier work on retinopathy detection.²⁸ Using a study group of 40 patients with a wide spectrum of diabetic retinopathy, the results of directly acquired digital images were compared with conventional slide photography. An exact agreement in grading was achieved in 93.3% of eyes. When the images of those undergraded as non-sight-threatening retinopathy were evaluated, this discrepancy was attributed to the lower resolution of digital photography. In two of the three cases, this was due to the failure to capture IRMAs, clearly visible on colour slide images. In one case, cotton-wool

TABLE 24 Evaluation of digital photography techniques

Technique under review	Population studied	Study aim	Gold standard or comparative method	Results	Reviewers' comments	Reference	Methodology and results grading
Digital imaging in comparison with colour slide photography							
Digitisation of 45° macular view colour transparencies	150 retinal images from diabetic patients, covering a spectrum of retinopathy and including those with normal fundi	To compare the detection of DR from digitised images displayed on a high-resolution video monitor with diagnosis made from colour slide examination	Comparative method Assessment made against diagnosis from original slide	Low intra-observer variation of 7% noted when assessing quality control images from both techniques. Of patients diagnosed with STDR on colour slide, 95% similarly diagnosed from digital images (84/88; 95% CI 88 to 99%); for those with NSTDR, 100% (62/62; 95% CI 93 to 100%) diagnosed from digital images. 4 cases of STDR undergraded to NSTDR by digital image analysis. (Difficulties in identification of CWS and macular hard exudates masked by light reflection noted in digital images. Initial poor quality slide prevented macular haemorrhage being identified on corresponding digitised image)	Within a clinical setting, the authors report close agreement between the interpretation of images from both techniques. The under-reporting of STDR is likely to be overcome by direct digital image acquisition, which may have prevented the problems with image quality reported in these particular patients. 100% agreement for patients with NSTDR suggests both photographic techniques would be equally attractive for screening programmes, although validation against existing techniques has not been performed	George, 1997 ²⁴	Methodology Grade IV Results Grade III

continued

TABLE 24 Evaluation of digital photography techniques (cont'd)

Technique under review	Population studied	Study aim	Gold standard or comparative method	Results	Reviewers' comments	Reference	Methodology and results grading
<p>Direct acquisition of digital fundus photographs and fluorescein angiograms using a TOPCON TRC 50 camera interfaced with a PAR IS2000 imaging system via a high-resolution video camera</p>	<p>10 diabetic patients included in a preliminary study of 50 consecutive patients attending retinal specialists clinics</p>	<p>To evaluate the role of directly acquired digital imaging in comparison with conventional photography in diagnosis of retinal disease, including DR</p>	<p>Comparative study Comparison of diagnosis made by retinal specialist from digital images with that of colleague using conventional photographs – any discrepancies reviewed by third specialist using both sets of images and patient history</p>	<p>In all 10 patients with DR under study, both specialists were in agreement – 1 diagnosed with mild NPDR; 7 diagnosed with exudative retinopathy; 2 diagnosed with neovascularisation (1 neovascularisation elsewhere; 1 neovascularisation of disc)</p>	<p>Although patient numbers under study are inadequate to influence clinical practice, the authors have demonstrated agreement of both photographic techniques across a spectrum DR. Despite the limitations of the relatively low-resolution system under review, lesions including neovascularisation were detectable. The study population was biased towards those with exudative or PDR; these results may not reflect the outcome for a general screening population. However, they illustrate that digital imaging has significant advantages over conventional photography in terms of instant availability of images with ready correction of alignment and focusing problems</p>	<p>Friberg, 1987²⁵</p>	<p>Methodology Grade III</p> <p>Results Grade I</p>

continued

TABLE 24 Evaluation of digital photography techniques (cont'd)

Technique under review	Population studied	Study aim	Gold standard or comparative method	Results	Reviewers' comments	Reference	Methodology and results grading
Direct acquisition of digital images using a Canon CR5 45NM fundus camera and electronic imaging system	66 diabetic patients	To evaluate the role of digital imaging in comparison with standard 35-mm colour slide photography in evaluation of DR	Gold standard Fundal examination by slit-lamp biomicroscopy	Clinical examination was used to define the prevalence of BDR at 48%, PDR at 3% and CSMO at 15%. Detection of retinal disease was comparable using both camera techniques. Digital imaging: BDR 44%, PDR 3% and CSMO 14.5%. 35-mm colour slides: BDR 38%, PDR 3% and CSMO 13%	The authors concluded that digital imaging is at least comparable to conventional 35-mm slide photography in detection of retinopathy. No patients with STDR were undetected using either photographic technique. Although not presented by the authors, sensitivity was calculated from available data as: Digital imaging: BDR 91.7%; PDR 100%; CSMO 96.7% 35-mm colour slide: BDR 79.2%; PDR 100%; CSMO 86.7% Unfortunately, data were not presented in a manner which clarified whether specificity was also comparable with both techniques. This may be available in subsequent publication but would clearly have implications for clinical application. However, given the initial results, further assessment against current screening methods should be supported	Ikram, 1997 ²⁷ (Poster and personal correspondence with author)	Methodology Grade V Results Grade I

continued

TABLE 24 Evaluation of digital photography techniques (cont'd)

Technique under review	Population studied	Study aim	Gold standard or comparative method	Results	Reviewers' comments	Reference	Methodology and results grading
Direct acquisition of images using a Canon CR5 retinal imaging system (2 X 45° fields)	40 diabetic patients with wide spectrum of established retinopathy including normal controls (5 patients)	To compare the results of directly acquired digital images with conventional colour slide photography	Gold standard EURODIAB photographic protocol of 2 × 45° overlapping fields used in this study has been validated as comparable to gold standard Airlie House 7 × 35° fields for 35-mm colour slides	Exact agreement in grading in 93.3% of eyes (95% of STDR and 100% of NSTDR correctly identified) Undergrading of STDR in 3 cases (IRMA not identified in 2 cases; CVS misclassified in 1 case). System limited by current pixel density of 768 × 512 with loss of fine detail structures. IRMA clearly evident in colour slide film	Using the data presented by the authors, digital imaging sensitivity and specificity can be calculated: detection of NSTDR; sensitivity 96.3%; detection of STDR, sensitivity 93.8%. Although the 5 patients without retinopathy were correctly identified, the patient population is biased towards those with established retinopathy. Therefore, results obtained are not applicable to a screening programme. However, given the limitations of lower resolution, the digital system has performed well in comparison with 35-mm colour slide photography. The detection rate of 95% of STDR is superior to that of alternative screening techniques in current use	George, 1998 ²⁸	Methodology Grade V Results Grade II

continued

TABLE 24 Evaluation of digital photography techniques (cont'd)

Technique under review	Population studied	Study aim	Gold standard or comparative method	Results	Reviewers' comments	Reference	Methodology and results grading
Digital imaging in comparison with Polaroid photography							
On-line acquisition of digital fundus images – electronic imaging system attached to a Canon CR5 45NM fundus camera	107 diabetic patients photographed after mydriasis – 213 images obtained	To evaluate the diagnosis of STDR from digital images compared with Polaroid	Comparative study The overall prevalence of retinopathy was determined from examination of both sets of images. No other independent clinical examination appears to have been performed from the information available	DR was present in 58 eyes, of which 55/58 (95%) were detected on digital images and 49/58 (84%) were detected on Polaroid. Thirty-four eyes showed retinopathy meriting ophthalmologist referral – 34/34 (100%) were evident with digital imaging and 24/34 (71%) evident on Polaroid	Digital images were superior to Polaroid in the detection of retinopathy and identification of those patients requiring ophthalmologist referral. The authors have also highlighted the advantages of electronic imaging systems in terms of patient comfort, enhanced storage and retrieval of images and the potential for transfer for off-site analysis. Future comparison against other screening modalities using a gold standard for validation would be required prior to a recommendation for clinical practice	Ryder, 1996 ²⁹	Methodology Grade IV Results Grade I
Direct acquisition of digital images using a TOPCON non-mydriatic camera and Imagenet system or Frost Medical Systems Ris-Lite system	118 patients photographed after mydriasis	To determine the effectiveness of digital imaging in detecting DR against Polaroid photography performed with a Canon CR4 camera – for both techniques single 45° field centred between macula and disc analysed	Gold standard Standard seven-field 35° fundus photography	Detection of any retinopathy Digital imaging sensitivity 74% and specificity 96% (Polaroid, sensitivity 72% and specificity 88%) Detection of retinopathy meriting referral for ophthalmologist review: digital imaging sensitivity 85% and specificity 98% (Polaroid sensitivity 90% and specificity 98%)	For single image comparison, digital images appear as effective as Polaroid systems	Taylor, 1998 ³¹ <i>(Poster and personal correspondence with author)</i>	Methodology Grade V Results Grade III

continued

TABLE 24 Evaluation of digital photography techniques (cont'd)

Technique under review	Population studied	Study aim	Gold standard or comparative method	Results	Reviewers' comments	Reference	Methodology and results grading
Digital imaging in comparison with retinal examination							
On-line digital photographs – three 30° fields. Diagnosis made by retinal specialist from examination of photographs	11 consecutive patients with diabetic retinopathy attending an ophthalmologist clinic	To determine value of digital fundus camera as a screening tool for DR	Comparative study Clinical examination by another retinal specialist in masked fashion	Of 22 eyes examined, classification agreed on in 19. Digital image detected one case new vessels missed on examination; examination confirmed one case of new vessels less distinct on photograph. One patient defined diabetic maculopathy by image and background DR on examination	The study population presented is inadequate to allow implications for clinical practice to be determined. Although the authors suggest that the study provides support for the use of digital imaging as a screening tool, the population studied were all known to have retinopathy and do not fit the criteria for a general diabetic population. The potential advantages of electronic image transfer are recognised	Gupta, 1996 ³³ <i>(Poster and personal correspondence with author)</i>	Methodology Grade IV Results Grade I
Direct acquisition of digital fundus images	611 consecutive patients attending a general diabetic clinic randomised for assessment by either protocol	To determine whether digital imaging enhanced detection of retinopathy when added to routine screening	Comparative study Results of direct ophthalmoscopy and visual acuity assessment alone compared with results of routine screening plus digital image analysis	For the detection of early background retinopathy: detection rate in type 1 DM 42.6% with digital imaging vs 26.7% with routine screening; type 2 DM 33.2% with digital imaging vs 20.3% with routine screening	The addition of digital imaging significantly increased the detection rate of mild retinopathy in the group undergoing only routine screening. The authors concluded that the detection of early DR is enhanced by fundus photography. These findings did not apply to other degrees of retinopathy. Although the study was weakened by the lack of a gold standard for validation of results, this preliminary report shows a role for digital photography in early detection of retinopathy. As advances are made in the prevention of progression of retinopathy, this finding will be of significance should the emphasis in screening move from detection of referable eye pathology to detection of retinopathy at onset	Lindsay, 1998 ³⁴ <i>(Poster)</i>	Methodology Grade III Results Grade II

continued

TABLE 24 Evaluation of digital photography techniques (cont'd)

Technique under review	Population studied	Study aim	Gold standard or comparative method	Results	Reviewers' comments	Reference	Methodology and results grading
Automated detection of diabetic retinopathy							
60° red-free fundus photographs of posterior pole digitised using a Nikon Coolscan slide reader to provide 700 × 700 pixel images. Prospective study	200 images from patients with diabetic retinopathy and 101 images from non-diabetics with normal fundi	Evaluation of the ability of an artificial neural network to detect DR after optimisation of computer protocols	Gold standard Evaluation of conventional images by an experienced retinal specialist	For detection of DR, system achieved sensitivity of 88.4% and specificity of 83.5% in comparison with specialist. Ability to differentiate exudates or haemorrhage/microaneurysms from normal retina (or normal retinal image containing vessels only) 93% and 73.8%, respectively. To ensure that all patients referred by specialist for evaluation are also detected by the system would require increasing sensitivity to 99% at the expense of reducing specificity to 69%. At present, authors feel the system is comparable to results achieved by optometrists, Polaroids from non-mydiatic cameras and diabetologists using direct ophthalmoscopy	Although the neural network can differentiate blood vessels, hard exudates and haemorrhages/microaneurysms with relative accuracy from background retina, the basis for subsequent decision to refer patients remains unclear. No features of moderate (CWS, IRMA, VB) or proliferative (neovascularisation) are being detected using the system described. A comparison of the technique with an established screening method would be valuable to determine the role in future clinical management. At present, the system remains untested in a clinical setting	Gardner, 1996 ³⁵	Methodology Grade V Results Grade II

continued

TABLE 24 Evaluation of digital photography techniques (cont'd)

Technique under review	Population studied	Study aim	Gold standard or comparative method	Results	Reviewers' comments	Reference	Methodology and results grading
Directly acquired on-line digital fundus photographs or digitised colour photographs – seven 35° fields according to Airlie House criteria	100 diabetic patients	To develop an automated method of lesion identification and quantification of severity of DR	Gold standard Diagnosis by retinal specialist from seven 35° colour fundus photographs	For microaneurysms, dot-and-blot haemorrhages and striate haemorrhages, computer showed 99% specificity compared with retinal specialist; sensitivity better than retinal specialist. For CWS, exudates, IRMA and neovascularisation, sensitivity was 93% and specificity 90%. The authors believe that the use of computer-based analysis is comparable to retinal specialists for the interpretation of fundus photographs	The authors have attempted to develop a fully automated computer-driven analysis system, with detection of lesions across the whole spectrum of DR. We have been unable to identify subsequent formal publication of this presented abstract to provide clarification of the methodology used in this study. The authors have stated an intention to develop a commercially available system in the near future. While highlighting this work as an area of future interest, no comment can be made at present regarding implications for patient management based on the available data	Sinclair, 1996 ³⁶ <i>(Abstract and personal correspondence with author)</i>	Methodology Grade IV Results Grade II

continued

TABLE 24 Evaluation of digital photography techniques (cont'd)

Technique under review	Population studied	Study aim	Gold standard or comparative method	Results	Reviewers' comments	Reference	Methodology and results grading
Automated detection of hard exudates							
Direct acquisition of digital fundus images	134 images taken from those routinely acquired at a general diabetic screening clinic	To develop an automated DR screening programme, applying a statistically based pattern recognition program	Not stated in report	Pattern recognition allowed correct identification of optic disc and fovea in 78.4% of images. Microaneurysms, haemorrhages, exudates and CWS were identified with success rates of 66, 89, 97 and 63%, respectively	Authors found difficulty differentiating between microaneurysms and haemorrhages and between exudates and CWS at this preliminary stage. They suggest a successful role for their novel statistical approach to pattern recognition in future automated screening programmes. Further development and clinical assessment will be required before this is likely to impact on patient management	Ege, 1997 ³⁷ (Abstract)	Methodology Grade II Results Grade I
Digitisation of colour transparency slides to yield black and white image with 512 × 512 pixel array	Standard photographs used in the ETDRS for classification of retinal exudates	The semi-automated detection of retinal exudates	Gold standard Exudate area determined by program assessed against standard photograph grading of severity	With shade correction and contrast enhancement, program could identify 3 distinct grades of severity which correlated with those used in the ETDRS grading. With serial analysis of individual images, standard deviations of calculated exudate area were significantly lower in grade I compared with grade 3 images, i.e. reproducibility of technique decreased as number of exudates increased		Ward, 1989 ³⁹	Methodology Grade II Results Grade II

continued

TABLE 24 Evaluation of digital photography techniques (cont'd)

Technique under review	Population studied	Study aim	Gold standard or comparative method	Results	Reviewers' comments	Reference	Methodology and results grading
Indirect digitisation of 30° or 50° field colour slides centred on macula after projection through a red-free filter	Diabetic patients with exudative retinopathy. No normal controls were included in this paper	Automated detection and quantification of retinal exudates	Gold standard Manual estimation of false positive and negative by experienced ophthalmologist	Sensitivity 87% (range 61–100%) Coefficient of variation for reproducibility 3% for confluent areas of exudate and 17% for small scattered areas	<p>Authors have suggested that results may be improved by using directly acquired digital images. The region of interest was manually delineated prior to processing. It is anticipated that program refinement could enable this function to be automated.</p> <p>The speed of data acquisition and analysis and lack of user interaction will lead to enhanced objectivity in the assessment of exudative retinopathy. This has potential in both screening for retinopathy and in the monitoring of response to treatment. The program presented appears robust and well validated. Evaluation of its performance in a study population with and without exudative retinopathy would be of interest</p>	Phillips, 1991, ⁴⁰ 1993 ⁴¹	<p>Methodology Grade IV</p> <p>Results Grade IV</p>

continued

TABLE 24 Evaluation of digital photography techniques (cont'd)

Technique under review	Population studied	Study aim	Gold standard or comparative method	Results	Reviewers' comments	Reference	Methodology and results grading
Secondary digitisation of colour transparency photographs using filters to give images in three colour planes (red, green and blue) with 512 × 480 pixel resolution	Retrospective analysis of images from 30 patients, specifically chosen to contain both the lesion under investigation plus a random distribution of other variables such as background pigmentation. 10 images each with either CWS , exudates or drusen were identified	To determine whether fundus lesions can be identified on the basis of colour alone. The effect of luminance on colour was removed to overcome variability in exposure. This allowed a 2-dimensional vector to be used to assign position of individual lesions on a chromaticity scatter diagram	Gold standard Examination of colour transparencies by a retinal specialist	Different lesions appeared to occupy distinct regions of the chromaticity scatter diagram, with a degree of overlap between CWS and drusen. This was reflected in the greatest error in discrimination between these lesions after application of the Mahalanobis classifier and jackknife technique for assessment of separability of lesions into correct groups (exudates, sensitivity 70%, specificity 95%; CWS, sensitivity 70%, specificity 65%; drusen, sensitivity 50%, specificity 85%; calculated from data presented by the authors)	The authors propose that their technique alone is insufficient as a discriminator when lesions are of similar colour. They propose to investigate the use of additional features of size, shape, edge sharpness and texture to aid lesion recognition. At this stage in development, it is unlikely that this program will enhance automated image analysis	Goldbaum, 1990 ⁴²	Methodology Grade IV Results Grade I

continued

TABLE 24 Evaluation of digital photography techniques (cont'd)

Technique under review	Population studied	Study aim	Gold standard or comparative method	Results	Reviewers' comments	Reference	Methodology and results grading
Automated detection of VB							
Colour transparencies processed by digital slide scanner. Regions of interest corresponding to 64 × 64 pixels manually identified for analysis	Prospective study of patients attending an ophthalmology department for assessment of diabetic retinopathy. 54 vessel segments from 18 sets of photographs processed for further evaluation	Automated assessment of VB	Gold standard Assessment by professional photographic graders, using adaptation of the Airlie House criteria for classification and studying slide reproductions of the digitised vessel segments	51 slides considered assessable by 2 graders, achieving exact match of clinical grade in 76% of cases. For remaining images, grading differed by one level of severity with 7 of 12 being in the 'questionable vs definite' category and definitive grading made by a senior colleague. Computer-based VB index was able to differentiate significantly advanced beading from each of the other 3 categories, definite beading from both advanced beading and normal vessels, and normal vessels from both definite and advanced beading ($p = 0.05$, Tukey's non-parametric test)	The application of Fourier analysis to the measurement of variation of vessel diameter allows quantitative assessment of VB which has been shown to reflect clinical grading. It is recognised that VB is a difficult lesion to differentiate clinically and a method of reducing subjectivity is welcomed. Integration with additional lesion detection programs would be beneficial for use in clinical practice. Validation in a clinical setting would assist definition of its role in future use	Kozousek, 1992 ⁴⁴	Methodology Grade V Results Grade I
							<i>continued</i>

TABLE 24 Evaluation of digital photography techniques (cont'd)

Technique under review	Population studied	Study aim	Gold standard or comparative method	Results	Reviewers' comments	Reference	Methodology and results grading
Automated detection of neovascularisation							
Low-angle fundus photographs from the optic disc enlarged to allow manual tracing of vessel patterns. Images digitised and density-density correlation method used to calculate fractal dimensions	10 retinal vessel patterns from patients with known new vessels fulfilling criteria of NVD \geq EDTRS Grade 3; images from 14 healthy fundi as control group	To use the principles of fractal geometry to differentiate normal retinal vasculature from the development of neo-vascularisation	Gold standard Professional photographic graders using modified Airlie House criteria for the definition of neovascularisation	Assuming 100% accuracy by graders, FD = 1.8 yields a sensitivity for detection of NVD \geq EDTRS Grade 3 of 90%. With these conditions, specificity is 93% with false-positive value of 7% and false-negative value of 10%	The method of deriving digital images of vessel patterns is cumbersome and may be improved by the use of direct acquisition digital images. The technique is limited by an inability to identify NVD Grade 2, which also pose a risk of haemorrhage, and the presence of vitreous haemorrhage which obscures fundal detail. The area under review is a low-angle 10° view centred on the optic disc, which will not allow detection of early peripheral neovascularisation. The technique may have implications for automated screening strategies but will require further clinical validation	Daxer, 1993 ⁴⁷	Methodology Grade V Results Grade III

continued

TABLE 24 Evaluation of digital photography techniques (cont'd)

Technique under review	Population studied	Study aim	Gold standard or comparative method	Results	Reviewers' comments	Reference	Methodology and results grading
Automated detection of vessel diameter							
Digitisation of serial 30° 35-mm photographs via high-resolution video camera and Context Vision GOP-302 image-analysing computer	53-year-old normotensive male type I diabetic with mild background retinopathy and normal renal function	Evaluation of a semi-automated computer-driven method of assessing vessel diameter – vessel segment manually selected. Vessel diameter analysis by calculating average grey profile across vessel at 12 neighbouring parallel cut lines adjacent to region of interest	Comparative study Comparison with observer-dependent evaluation using graphics-digitising table and manual definition of vessel diameters	Co-efficient of variation of single image 1.5–7.5% for semi-automated method; 6–34% for observer method (noted to be dependent on vessel size). Standard diameter of variation from the mean 4.2 µm for automated method (cf. 18.9 µm for observer), with 95% CI being 3.2 to 6.0 and 14.6 to 27.1 µm, respectively ($p < 0.001$)	Image analysis method appears more reproducible and accurate, particularly with small-diameter vessels. ECG-triggered photography may reduce variability in serial photography analysis by minimising effect of cardiac cycle on perfusion pressure. This technique will enhance research in retinal blood flow parameters and the pathogenesis of retinopathy. It is unlikely to provide a useful tool in general retinopathy screening and management	Newsom, 1992 ⁵⁵	Methodology Grade III Results Grade II
CWS, cotton-wool spots; DM, diabetes mellitus; DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; NSTDR, non-sight-threatening diabetic retinopathy; NVD, new vessels disc; VB, venous bleeding.							

TABLE 25 Assessment of study methodology and results – evaluation of digital photography techniques

Reference	Methodology						Results				
	Use gold standard	Independent assessment	Appropriate study population	No verification bias	Reproducible description	Grading	Correct sensitivity/specificity	Reproducibility calculated	Statistics appropriate	Data presented	Grading
George, 1997 ²⁴		✓	✓	✓	✓	IV		✓	✓	✓	III
Friberg, 1987 ²⁵		✓		✓	✓	III				✓	I
Ikram, 1997 ²⁷	✓	✓	✓	✓	✓	V				✓	I
George, 1998 ²⁸	✓	✓	✓	✓	✓	V			✓	✓	II
Ryder, 1996 ²⁹		✓	✓	✓	✓	IV				✓	I
Taylor, 1998 ³¹	✓	✓	✓	✓	✓	V	✓		✓	✓	III
Gupta, 1996 ³³		✓	✓	✓	✓	IV				✓	I
Lindsay, 1998 ³⁴		✓	✓		✓	III			✓	✓	II
Gardner, 1996 ³⁵	✓	✓	✓	✓	✓	V	✓		✓		II
Sinclair, 1996 ³⁶	✓	✓	✓	✓		IV			✓	✓	II
Ege, 1997 ³⁷			✓	✓		II				✓	I
Ward, 1989 ³⁹	✓					II		✓	✓		II
Phillips, 1991, ⁴⁰ 1993 ⁴¹	✓	✓		✓	✓	IV	✓	✓	✓	✓	IV
Goldbaum, 1990 ⁴²	✓		✓	✓	✓	IV			✓		I
Kozousek, 1992 ⁴⁴	✓	✓	✓	✓	✓	V			✓		I
Daxer, 1993 ⁴⁷	✓	✓	✓	✓	✓	V	✓	✓	✓		III
Newsom, 1991 ⁵⁵		✓		✓	✓	III		✓	✓		II

spots among panretinal photocoagulation scars were misdiagnosed as laser burns. However, while accepting the limitation of their system operating at a pixel density of 768×512 , the digital camera shows promise as an additional tool in retinopathy management with the potential to improve its performance as technology advances.

Digital imaging versus Polaroid photography

A direct comparison of instant electronic imaging systems against Polaroid photography has been presented by Ryder and colleagues (*Table 24*).²⁹ After administration of mydriatics, 213 eyes were imaged. Diabetic retinopathy was found to be present in 58 eyes, and identifiable in 55 of the digital images but only 49 of the Polaroid photographs. Thirty-four eyes were deemed appropriate for referral to an ophthalmologist: evidence of retinopathy requiring referral was present in the digital images in all cases but only seen in 24 (71%) of the Polaroid photographs. In addition to the superiority of lesion detection demonstrated, the patients preferred the electronic imaging system as the less intense photographic flash was perceived to be more comfortable. This reflects the findings of Taylor and colleagues (*Table 24*), who found that 96% of patients surveyed following fundus photography found the electronic systems as comfortable or better (44%) than Polaroid photography.³⁰ From an educational aspect, 93% of patients agreed that the ability to view their own fundus images was important, with 91% also finding value in an immediate explanation of the images.

The same group have also performed an assessment of the effectiveness of digital imaging in comparison with Polaroid photography (*Table 24*).³¹ They demonstrated a sensitivity of 74% (Polaroid 72%) and a specificity of 96% (Polaroid 88%) for the detection of any retinopathy; the detection of retinopathy meriting referral to an ophthalmologist showed a sensitivity of 85% (Polaroid 90%) and a specificity of 98% (Polaroid 97%). These results were obtained with the use of seven-field stereo photography as a recognised gold standard. Therefore, while retaining the advantages of an instantly acquired image, it would appear that the potential for enhanced picture storage and manipulation from a digital system can be gained without any loss of picture quality.

St Thomas' Hospital, London has an established Diabetic Eye Complication Screening programme, allowing open access for GPs who manage their own diabetic clinics.³² Although photography was

traditionally performed using a non-mydratic Polaroid camera, this technique has recently been replaced by digital photography. The authors confirm that an on-going evaluation of their new system in comparison with conventional imaging is in progress but are unable to provide preliminary results at this stage.

Digital imaging versus retinal examination

In an evaluation of digital cameras in a clinical setting, images were directly acquired from 11 consecutive patients using three 30° fields of view (*Table 24*).³³ The results of image analysis and clinical examination by a retinal specialist showed agreement of classification in 19 of the 22 eyes. Of those where there was disagreement, one case of new vessels was determined by photography alone; one case of questionable new vessels on photography was clearly evident on examination; and in one eye, diabetic maculopathy was classified on photographic screening with background retinopathy only being present on examination. This latter finding may relate to the difficulty in determining the presence of macular oedema from non-stereoscopic images. The numbers reviewed in this presentation are small and the authors' claim that digital imaging will provide an efficient screening tool is premature without the benefit of a large-scale clinical trial. However, they do highlight the possibility of using the digital camera to acquire images at the place of delivery of diabetic care with subsequent electronic transmission elsewhere for further analysis.

With perhaps more relevance to the practical management of diabetic patients within a hospital setting in the UK, the detection rate of retinopathy was noted to be higher in consecutive patients attending a general diabetic clinic when digital imaging was added to routine screening by direct ophthalmoscopy (type 1 diabetes mellitus, prevalence of background retinopathy with digital imaging 42.6% versus 26.7% with routine screening only; type 2 diabetes mellitus, prevalence of background retinopathy with digital imaging 33.2% versus 20.3% with routine screening only) (*Table 24*).³⁴ It was assumed that the prevalence of retinopathy would be equal in both groups under study, although details of their randomisation protocol are not available. Although there was no significant difference in detection rates for other degrees of retinopathy, the data presented suggest that the use of digital photography can enhance the detection of mild retinopathy when early lesions may be difficult to detect with direct ophthalmoscopy alone.

Automated analysis of images

Detection of general retinopathy

Retinal microaneurysm counts have been shown to be a useful indirect marker for grading the severity of retinopathy. These correlate with the presence of both haemorrhages and cotton-wool spots and, to a lesser degree, with hard exudates and intraretinal microvascular abnormalities.⁶ In addition, based on a study monitoring the increase in total microaneurysm count over a 4-year period, it is suggested that this change from baseline may be used as a surrogate measure for identifying those patients likely to develop significant diabetic retinopathy in the future.⁵

This prompted Gardner and colleagues (*Table 24*) to apply automated computer analysis techniques to digitised colour slides for the detection of early retinopathy.³⁵ In a prospective study of 301 posterior pole fundal images from both diabetic patients with retinopathy and non-diabetic controls with healthy fundi, a neural network system was able to detect retinopathy with a sensitivity of 88.4% and a specificity of 83.5% in comparison with examination of the original fundus photographs by an experienced ophthalmologist. The ability to differentiate lesions from normal background retina was 73.8% for microaneurysms and haemorrhages and 93.0% for hard exudates. Adjustment of the sensitivity thresholds to 99% would allow all cases detected by the specialist to be identified by the system but would have led to a corresponding reduction in specificity to 69%. Their initial results are, however, comparable to those being achieved by optometrists and diabetologists using direct ophthalmoscopy and Polaroids from non-mydratric cameras (*Table 22*).

In practice, the application of widespread retinal photography on the scale required to undertake regular screening assessment of the diabetic population will be limited by the availability of trained photographic graders. Therefore, there is pressure to develop a fully automated screening programme, taking advantage of the potential for computer-aided analysis of digital images. Sinclair and colleagues (*Table 24*) are currently developing an automated diabetic retinopathy screener with early results being presented at the American Diabetic Association Meeting in June 1996.³⁶ From analysis of the images of 100 patients, using direct acquisition or secondary digitisation of colour slides in seven standard 35° fields, their findings appear encouraging. In comparison with an assessment of the original colour fundus

photographs by a retinal specialist, the computer showed a 99% specificity in detection of microaneurysms, blot and striate haemorrhages. Although the sensitivity was quoted to be better than that of the retinal specialist, exact values were not given. With regard to the detection of the more advanced lesions of nerve-fibre layer infarcts, exudates, intraretinal microvascular abnormalities and neovascularisation, the computer achieved a sensitivity of 93% and a specificity of 90%. Clearly, the need for validation of their program in a larger trial is recognised but these preliminary results suggest that automated systems may be able to play a role not only in the detection of retinopathy but also in monitoring patient progression to a stage where referral to an ophthalmologist is warranted.

Using a statistical approach to pattern recognition, Ege and colleagues (*Table 24*) report preliminary data on the ability of their automated system to analyse digital images taken as part of the routine monitoring of retinopathy in their clinic setting.³⁷ Based on analysis of 134 images, the optic disc and fovea were correctly identified in 78.4% of cases. Microaneurysms, haemorrhages, exudates and cotton-wool spots were detected with sensitivities of 66, 89, 97 and 63%, respectively. Problems were identified in the ability to differentiate microaneurysms and haemorrhages and to distinguish cotton-wool spots from hard exudates. The authors recognise that their system is at an early stage of development and further refinement is required before it may provide a clinically useful tool. However, their presentation underlines the need for the development of reliable automated screening programmes if digital photographic services are to be more widely offered as a routine part of diabetic care.

Detection of hard exudates

Hard exudates have been noted to be a consistent feature as retinopathy progresses, indicating areas of retinal vascular leakage.³⁸ As manual counting of exudates and calculation of their area is both time consuming and unsatisfactory, several authors have applied computer analysis to this problem area (*Table 24*).³⁹⁻⁴² As exudates reflect more light than the background retina, they are represented by pixels of a higher grey level value in digital images, that is, they appear 'whiter' than the surrounding retina. This property allows their identification by a process of thresholding, where pixels equal to or greater than a chosen grey level are selected by the computer. After a series of shade correction programs on secondary digitised images, both Ward and colleagues³⁹ and Phillips

and colleagues^{40,41} were able to apply this principle successfully in an effort to provide a quantitative method of detecting exudates. By monitoring both number and area, this could provide a method of determining response to treatment such as focal laser therapy.

Although the above techniques do not distinguish between other objects with a similar grey threshold such as cotton-wool spots or drusen, Goldbaum and colleagues (*Table 24*) have attempted discrimination of hard exudates from these lesions on the basis of colour alone.⁴² A training set of images was employed, where groups of pixels from representative lesions were selected manually and used to calculate colour estimates for each lesion type. Using this software program, the authors found a limited ability to discriminate between these lesions, although hard exudates were most likely to be correctly identified (hard exudate, sensitivity 70% and specificity 95%; cotton-wool spot, sensitivity 70% and specificity 65%; drusen, sensitivity 50% and specificity 85%). Further refinement of the technique has been proposed with the addition of measures of size, shape, edge sharpness and texture to improve accuracy.

Detection of venous beading

The relative importance of individual features of diabetic retinopathy for predicting future progression of disease has been determined by the ETDRS.⁷ In addition to the severity of intraretinal microvascular abnormalities and haemorrhages/microaneurysms, venous beading was noted to be a powerful predictor for the future development of proliferative retinopathy. Several authors have used a technique of Fourier analysis to determine variation in the diameter of blood vessels, developing a computer-assisted method of detection and quantification of venous beading.⁴³⁻⁴⁵ Kozousek and colleagues (*Table 24*) have compared their program with assessment of the original colour slides by professional photographic graders, using the Airlie House criteria for classification.⁴⁴ An exact agreement with photographic graders was achieved in 76% of the 51 digitised slides suitable for analysis. For the remainder, grading differed by one level of severity only, with seven out of 12 cases being in the 'questionable versus definite' category. The calculated venous beading index could be used to differentiate between gradings of severity and to distinguish normal vessels from both definite and advanced beading. Although the regions of interest were manually identified for computer analysis in this initial study, the authors suggested that the technique could prove a valuable addition

to future automated general retinopathy screening programmes.

Detection of neovascularisation

The ETDRS has indicated that patients who have progressed to the development of high-risk retinopathy should receive panretinal laser photocoagulation.⁸ They recommended that those with less severe retinopathy should have deferral of laser therapy and close monitoring of their progress. At this earlier stage, the adverse effects of laser radiation on visual field and central vision outweigh the benefit gained in reduced likelihood of future development of high-risk retinopathy. However, this strategy is dependent on the consistent recognition of advancing eye disease.

Therefore, there is clearly a need to develop techniques that will allow the detection of neovascularisation at the earliest possible stage for appropriate timing of laser therapy. In his overview of fractal analysis applied to the retinal vasculature, Mainster describes the application of a fractal dimension (FD) to describe the properties of a branching vessel pattern.⁴⁶ For example, a straight line is attributed an FD of 1, an area is given an FD of 2 and a structure filling three-dimensional space is given an FD of 3. Therefore, the FD of a branching structure lying flat on the retina will lie somewhere between 1 and 2. As it is an indirect measure of how completely a structure fills space, the relative value attributed to a branching structure will increase as its nature becomes more convoluted and it effectively covers a surface more completely, that is, the FD will become closer to 2.

Using this principle, Daxer (*Table 24*) has performed computer analysis of digitised images to determine if fractal properties can confirm the presence of neovascularisation.⁴⁷ In a comparison of images from 10 diabetic patients with proliferative retinopathy and 14 healthy controls, the FDs of the retinal vasculature were generally higher in the diabetic group. Using a threshold FD value of 1.8, Daxer was able to predict neovascularisation at the optic disc equivalent of the ETDRS grade 3 with a sensitivity of 90% and a specificity of 93%, using trained photographic graders as a reference standard. The original work required manual delineation of vessels patterns from colour slide photographs, which then underwent secondary digitisation for analysis. This process could be simplified significantly with direct acquisition of digital fundus images.

The technique used in this study was based on the evaluation of a low-angle 10° field centred on the optic disc and does not address the detection of peripheral new vessels elsewhere. However, as optic disc neovascularisation is recognised as the most high-risk form of proliferative retinopathy for subsequent retinal or vitreous haemorrhage, this novel technique remains promising for future detection of those most at need of urgent laser therapy. In subsequent research, Daxer has demonstrated that FD values could reflect the clinical evidence of development of new vessels in an adult with type 2 diabetes mellitus, and their regression following panretinal laser therapy.⁴⁸ Although preliminary results were confined to the study of a single patient, it is possible that this technique may also provide a quantitative measure of the effectiveness of laser photocoagulation.

Applications of digital photography in research

In 1986, Brinchmann-Hansen and Engvold⁴⁹ described a technique for the calculation of vessel diameter from digitised images, which has been applied as a research tool by several authors in the investigation of the pathogenesis of diabetic retinopathy (see *Table 26*).^{50–54} Together with the use of laser Doppler velocimetry, an indirect calculation of blood flow through the retinal circulation has been made possible. However, as the technique is dependent on the manual assessment of vessels' edges which may induce observer error, Newsom and colleagues (*Table 24*) have developed a semi-automated technique of image analysis.⁵⁵ Using digitised 35-mm retinal images, the vessel region of interest was identified by cursor and the computer calculated the average grey-level profile across the vessel from an average of 12 serial measurements. With the ability to perform automatic vessel edge detection, the computer-driven program showed a lower coefficient of variation than the observer-driven method (1.7–7.5% versus 6–34%). The standard deviation of variation from the mean was lower in the semi-automated analysis program at 4.2 μm (95% CI 3.2 to 6.0 μm) compared with 18.9 μm for the observer method (95% CI 14.6 to 27.1 μm), suggesting lower variability of the technique. Therefore, in summary, the authors propose that their computer-assisted analysis program will provide a useful research tool which is likely to be improved by the study of directly acquired digital images.

Other aspects of evaluation – telemedicine

The application of telemedicine to screening for

retinopathy has already been adopted in areas where, for economic or geographical reasons, access to ophthalmic services has been limited. There is an on-going collaboration between local physicians and the Ophthalmology Faculty at the University of Texas, San Antonio, TX, USA to improve the delivery of eye care in the community.⁵⁶ With funding from the South Texas/Border Health Initiative, a bus has been provided to allow a mobile ophthalmic evaluation service to operate. This includes digital fundus photography with direct transmission of images to a grading team at the San Antonio campus, who provide an immediate diagnosis for the examining doctor to discuss with the patient. Given the high prevalence of diabetes mellitus in the local Hispanic population, this strategy has the potential to revolutionise the delivery of diabetic eye screening although, at present, no formal evaluation of the success of this technique appears to have been carried out.

However, even at this early stage of development, digital technology has been adopted as a way forward in diabetes care in the USA, with several ophthalmic imaging networks already in place to provide central image interpretation for patients in locations as diverse as California and Puerto Rico.⁵⁷

In response to the St Vincent Declaration¹² and the low rate of retinopathy screening being achieved with traditional programmes in Germany, Mann and colleagues have presented early work outlining a central grading centre support for images transmitted from diabetes centres.⁵⁸ Although accepting that images are of lower resolution than 35-mm slides, this has not been deemed to obviate their use for population screening in the opinion of experienced ophthalmologists. At this stage, no data on a formal evaluation of the system are available.

Within the UK, a similar strategy has been employed to allow rural GPs in remote areas access to specialist ophthalmic services by the direct transmission of fundus images of their diabetic population for specialist grading. In Powys, Wales, GPs are linked to Telemed, described as Europe's most advanced medical telecommunications project.⁵⁹ This system allows integration of patients, primary care physicians and hospital specialists with applications not only in retinopathy screening but also extending to cover dermatology referrals and video-linked consultations for physiotherapy assessment and asthma care. In practice, the convenience of these

TABLE 26 Fundus photography – applications in research

Technique under review	Population studied	Study aim	Research technique	Results	Authors' conclusions	Reference
Secondary digitisation of conventional fundus photographs						
Digitisation of 30° red-free fundus photographs to determine vessel diameter in conjunction with laser Doppler velocimetry of the superior temporal vein to calculate flow rates	24 healthy volunteers and 76 patients, the latter attending retinopathy clinic (63 with type 1 DM, 13 with type 2 DM). Diabetic patients comprised 12 with no retinopathy; 27 with background retinopathy; 13 with pre-proliferative and 12 with proliferative retinopathy	Determination of rate of retinal blood flow in healthy and diabetic fundi	Technique of vessel diameter assessment validated elsewhere by Brinchmann-Hansen and Engvold. ⁴⁹ Average of three readings of diameter from three photographs, corrected for patient's refraction, gives coefficient of variation of 0.26%	Hyperperfusion of retinal circulation noted in all patients compared with normal; in comparison with patients with no retinopathy, retina flow was 33.2% higher with background, 69.4% with pre-proliferative and 50.1% with proliferative retinopathy. Panretinal photocoagulation led to a significant reduction in flow in comparison with all other groups (4.48 compared with 9.52 µl/min in non-diabetic controls)	Flow rates calculated to be independent of age, sex, BP, blood glucose concentration, HbA _{1c} , intraocular pressure and type and duration of diabetes. The authors propose that the increased shear stress induced by hyperperfusion is an important factor in the pathogenesis of DR	Patel, 1992 ⁵⁰
Digitisation of 30° monochromatic fundus photographs to determine vessel diameter in conjunction with laser Doppler velocimetry to calculate flow rates. Photography taken in mid-diastole to eliminate effect of pulsatility from cardiac cycle	10 normal volunteers; 12 type 1 DM – 10 studies performed with blood glucose maintained > 10 mmol/l and 10 studies with blood glucose < 10 mmol/l (i.e. 8 patients studied twice). All diabetics had mild NPDR. Elevation of MAP above baseline was achieved using a tyramine infusion	To investigate the effect of hypertension on retinal vascular autoregulation in diabetic and non-diabetic subjects via estimation of blood flow velocity	Techniques validated in earlier work by Brinchmann-Hansen and Engvold ⁴⁹	In non-diabetics, retinal blood flow showed significant increase only at MAP 40% above baseline ($p = 0.012$). In contrast, increased flow in diabetics with low glucose significant at both 30% and 40% elevation above MAP ($p < 0.05$). For diabetics with high blood glucose, only 15% elevation of MAP required to give significant increase in flow ($p < 0.03$)	By calculation of the coefficient of autoregulation, significant impairment of response to increased perfusion pressure was evident in all diabetics, most marked in those with elevated blood glucose > 10 mmol/l. The authors conclude that the resultant increase in flow rate will exacerbate endothelial damage, providing a potential mechanism for accelerating the progression of DR	Rassam, 1995 ⁵¹

continued

TABLE 26 Fundus photography – applications in research (cont'd)

Technique under review	Population studied	Study aim	Research technique	Results	Authors' conclusions	Reference
Secondary digitisation of 60° red-free negatives centred on the fovea	Retrospective analysis of images from 45 diabetic children with type I DM aged 9.4–18.4 years – images from 74 eyes studied	To evaluate the effect of long-term glucose control on retinal vessel diameter in children and young adults and to determine whether this may be a predictor of future retinopathy	Technique validated by earlier work by Brinchmann-Hansen and Engvold. ⁴⁹ Manual calculation of vessel width directly on monitor using mouse-controlled cursor (micrometry)	Coefficient of variation for repeated measurements 1.8–2.0% for veins and 1.8–2.1% for arteries using densitometry, cf. 3.0–3.1 and 3.6–4.1% respectively using micrometry. Linear regression analysis showed association between HbA _{1c} value on date of second photograph ($p = 0.049$) and average HbA _{1c} in year prior to photography ($p = 0.051$) with average increase in venous calibre. No association with changes in arterial calibre noted, although no correction possible to compensate for potential effect of perfusion pressure from cardiac cycle on overall appearance. No correlation found with sex, age, duration or age of onset of diabetes, stage of puberty or BP	Despite limitations of a retrospective study using small number of patients, the authors conclude that the observed increase in venous diameter in association with prolonged hyperglycaemia supports previous research into the hyperperfusion model of DR. Clinically visible venous congestion may herald the development of capillary changes in young diabetics. Improvements in digital image analysis may allow presented technique to gain application in clinical use for rapid evaluation of vessel diameter	Falck, 1995 ⁵²

continued

TABLE 26 Fundus photography – applications in research (cont'd)

Technique under review	Population studied	Study aim	Research technique	Results	Authors' conclusions	Reference
Digitisation of 30° monochromatic fundus photographs to determine vessel diameter in conjunction with laser Doppler velocimetry to calculate flow rates	4 groups of 15 patients studied: normotensive non-diabetics; normotensive diabetics (12 type 1 and 3 type 2); hypertensive non-diabetics; hypertensive diabetics (5 type 1; 10 type 2). Diabetics were studied under conditions of relative normoglycaemia (< 10 mmol/l) and hyperglycaemia (> 15 mmol/l); hypertensive patients were studied before and after control achieved. Diabetics had mild NPDR	To determine whether DM can alter the autoregulatory vasoconstrictive response to 60% oxygen breathing under hypertensive and hyperglycaemic conditions via measurement of retinal blood flow	Technique validated in previous work by Brinchmann-Hansen and Engvold ⁴⁹	Oxygen reactivity reduced in hypertensive and normotensive diabetics in hyperglycaemic conditions compared with normotensive volunteers ($p < 0.005$). Also reduced in controlled and uncontrolled hypertensive diabetics at hyperglycaemia compared with respective normoglycaemic group. No statistical difference between hyperglycaemic and normoglycaemic normotensive diabetics. For non-diabetics, oxygen reactivity reduced in hypertensive compared with normotensive volunteers (for controlled hypertension, $p = 0.026$; for uncontrolled hypertension, $p < 0.059$)	The authors conclude that retinal vascular reactivity to hyperoxygenation stimuli is significantly reduced in the hypertensive diabetic patient, regardless of blood glucose control. However, the deleterious effect of hyperglycaemia is thought to outweigh that of hypertension. The need for improved glycaemic control and control of hypertension to prevent accelerated progression of retinopathy is discussed	Patel, 1994 ⁵³

continued

TABLE 26 Fundus photography – applications in research (cont'd)

Technique under review	Population studied	Study aim	Research technique	Results	Authors' conclusions	Reference
Analysis of 30° red-free fundus photographs using a Context Vison GOP-302 digital image analysis system; laser Doppler velocimetry used to allow estimation of retinal blood flow rate	10 diabetic patients, both type 1 and 2, recruited from the diabetic retinopathy clinic with NDPR (1 patient ETDRS grade 20; 4 grade 30; 6 grade 41); 16 non-diabetic controls	To determine the effect of alcohol on retinal autoregulation in response to the vasoconstrictive challenge of 60% oxygen inhalation in diabetic and non-diabetic subjects	Technique validated in previous work by Brinchmann-Hansen and Engvold ⁴⁹	Both groups responded significantly to oxygen challenge before and after dosing with ethanol 0.5 g/kg, which was thought adequate to reflect social blood alcohol levels – reduced maximum red cell velocity, vessel diameter and retinal blood flow were demonstrated in each group in comparison with baseline measurements. No statistical difference was noted between diabetic subjects and non-diabetic subjects in their response	In the normotensive normoglycaemic diabetic patients with mild non-proliferative retinopathy under review, the autoregulatory response to hyperoxygenation was comparable to that of non-diabetic subjects. It remained unaffected by acute ethanol consumption in both groups, leading the author to suggest that the retinal circulation may be superior over other circulatory systems in its ability to autoregulate in the presence of ethanol. However, the limited number of patients under review and absence of more advanced grades of retinopathy suggest caution in interpretation of these findings	Dhasmana, 1994 ⁵⁴

BP, blood pressure; MAP, mean arterial pressure.

techniques for the patient are readily apparent although as yet no formal study of the efficacy or effectiveness of digital screening in diabetic retinopathy against formal clinical examination has been identified in this setting.

Digital angiography

Introduction

The use of a fluorescent emission from circulating dye to highlight features of the human retinal vasculature was initially described by Novotny and Alvis in 1961.⁶⁰ However, the technique was limited in practice owing to the need to capture images on ciné film, requiring subsequent development and projection for viewing. An advance on conventionally acquired serial photographic images was the introduction of the low-light TV camera in 1986 by Korber, which allowed results to be viewed immediately by the clinician.⁶¹ The data obtained could then be stored by use of a conventional video cassette recorder. The recording of real-time data allowed the author to develop a quantitative method of assessment of retinal blood flow by the examination of individual still pictures from a sequence using computer-controlled image analysis. This method of estimating arteriovenous passage time, arm-to-retina time and mean plasma flow velocity was subsequently adopted widely.^{62,63}

Using high-quality video recordings, which were then slowed to one-quarter of real-time speed for analysis courtesy of Scotland Yard, Jacobs and colleagues (see *Table 29*) were able to study the vascular origins of optic disc new vessels.⁶⁴ In a study involving 10 people, including seven diabetic patients with proliferative retinopathy, variable origin of new vessel filling was identified. Within the diabetic sub-group, three patients derived flow from the retinal venous circulation, three patients demonstrated filling of new vessels simultaneously with the central retinal artery and one patient with diabetes showed filling that appeared to derive from two cilioretinal arteries, suggesting a choroidal origin. Although the authors were unable to determine the clinical significance of their findings, their work illustrated the superiority of videofluoroscopy with an image capture rate of 25 frames per second over conventional fluorescein photography in dynamic investigation of neovascularisation.

The later development of PC-based video frame grabbers allowed conversion of analogue images to a digital format, permitting computerised

image analysis. In 1989, OIS and Topcon marketed the first commercially available system capable of direct acquisition of analogue-to-digital images within the camera control unit itself, designed specifically for use with fluorescein angiography.

Studies evaluating fluorescein angiography are summarised in *Table 27* and their study methodologies and results evaluated in *Table 28*.

Indirect digitisation of angiograms

An early comparative study to demonstrate that the conversion to digital format did not cause degradation of conventional fluorescein angiograms which would adversely affect clinical information was carried out by Seeley and colleagues in 1989 (*Table 27*).⁶⁵ Sixty-eight images were selected, giving a representative selection of common retinal pathologies (29 images included evidence of diabetic retinopathy) and an equal number of normal images. After conversion to a 512 × 480 pixel digital format, images were presented on a cathode-ray tube display. Clinical grading was compared with that obtained by examination of back-illuminated photographic transparencies, without projection. Using ROC curves for analysis, no appreciable difference between the information derived from the two sets of images was identified. The inter-observer differences in performance were attributed to varying clinical experience. Therefore, from their preliminary study, the authors supported the concept of development of a digitised angiogram facility, recognising the future potential for easier image storage and retrieval and image enhancement.

Other authors have applied indirect digitisation techniques to both conventionally acquired photographic angiogram sequences and videoangiograms in order to provide a more quantitative assessment of background diabetic retinopathy, as summarised in *Table 27*.

Digital image analysis

Automated assessment of microaneurysms

In response to the difficulty in achieving reliability and reproducibility in the manual counting of microaneurysms, Phillips and colleagues (*Table 27*) applied computerised image analysis to the assessment of digitised angiogram negatives.⁴⁰ Microaneurysms are visible as round hyperfluorescent objects, with a higher grey level than the background retina, providing a method of differentiation. However, as they are similar in threshold to neighbouring structures such as blood

TABLE 27 Evaluation of digital fluorescein angiography

Technique under review	Population studied	Study aim	Gold standard or comparative method	Results	Authors' conclusions	Reference	Methodology and results grading
Comparison of digitised angiograms with original 35-mm images							
68 conventional FA images selected for digitisation via video format camera and frame grab board to give 512 × 480 pixel images. Images viewed on CRT display	29 out of 36 patients under review had DR	To evaluate whether conversion of conventional photographic angiograms to digital images leads to loss of resolution causing failure in diagnosis of DR . Both sets of images assessed by 3 experts in retinal diagnosis	Gold standard Opinion of expert in retinal angiography responsible for selection of images	Using ROC curve analysis to evaluate diagnosis and certainty responses, no appreciable difference between the two types of images was noted. Observer 1, AUC for CRT 0.80 and for slides 0.79; observer 2, 0.87 and 0.86, respectively; observer 3, 0.91 and 0.91, respectively. Inter-observer differences attributed to past experience but did not reflect on methods under review	The chosen digital technique does not cause loss of diagnostic information. The perceived advantages of the digital system are ease of image archiving and retrieval; immediate review of examinations, and the potential for transmission of images to other centres while retaining the original on file	Seeley, 1989 ⁶⁵	Methodology Grade V Results Grade IV
Automated assessment of microaneurysms							
Indirect digitisation of 30° or 45° macular views from FA negatives performed by Panasonic WV-CD 20 CCD video camera, Data Translation DT-286 I frame grabber with IBM-compatible computer	Macular region of eight angiograms from diabetic patients assessed	Automated assessment of MA s	Gold standard Manual counting of MAs by a single observer using digitised angiographic frames under evaluation	MAs: sensitivity 82–93% in comparison with manual counting, with specificity of 93%. Coefficient of variation 7–14.5%	The authors conclude that their results for detection of MAs compare favourably with previously published work by other authors using automated methods	Phillips, 1991 ⁴⁰	Methodology Grade IV Results Grade IV

continued

TABLE 27 Evaluation of digital fluorescein angiography (cont'd)

Technique under review	Population studied	Study aim	Gold standard or comparative method	Results	Authors' conclusions	Reference	Methodology and results grading
Fluorescein angiograms converted to digitised 512 × 512 array using a monochrome CCD camera and Data Translation DT-2861 frame grabber linked to an IBM-compatible PC	Development of an automated method for the detection and quantification of MAs	Assessed against results obtained by manual counting by team of 5 experienced ophthalmologists working independently, and grading both analogue and digitised images	Gold standard Correct location of the lesions on analogue prints established by two of the authors	Using FROC curves to evaluate performance, there was no difference between computer and clinician on the analysis of digitised images. Significantly higher true-positive rate (sensitivity) was achieved by the clinicians using analogue images for any given false-positive rate	The authors suggest that direct on-line acquisition of digital images may reduce the effect of image degradation inherent in the secondary digitisation technique described. Increasing image resolution to the currently available 1024 × 1024 array will also improve sensitivity. With refinement, the automated technique may prove valuable in the detection and monitoring of DR	Spencer, 1992 ⁶⁷	Methodology Grade IV Results Grade IV
Fluorescein angiogram negatives were converted into digital format using a Kodak Megaplug CCD camera and Series-151 image-processing system, achieving images with a resolution of 1024 × 1024 pixels	13 images from diabetic patients reviewed, with 7 displaying evidence of MAs	An automated method for identification and quantification of MAs from digital images compared with manual assessment of MA counts from high-quality analogue prints of the original angiogram negatives made by 5 ophthalmologists (2 consultants and 3 registrars)	Gold standard Authors assessment of MA counts from the angiogram prints	Analysis performed using FROC curves, revealing that the computer's performance was satisfactory in comparison with that demonstrated by the clinicians. A maximum sensitivity of 82% was reached by the automated system, imposed by limitations of the present program in recognising lesions leaking fluorescein or conglomerations of MAs , calculated as too large for inclusion	Digital image processing can offer an objective and easily repeatable quantification of retinal MAs . The authors feel that the method has significant advantages over previously described techniques although no direct comparisons have been made	Spencer, 1996 ⁶⁸	Methodology Grade V Results Grade IV

continued

TABLE 27 Evaluation of digital fluorescein angiography (cont'd)

Technique under review	Population studied	Study aim	Gold standard or comparative method	Results	Authors' conclusions	Reference	Methodology and results grading
Indirect digitisation of standard 35° fluorescein angiogram negatives	Patients with evidence of DR (severity of retinopathy and number of patients not stated)	Development of a fully automated method of MA detection – comparison made with manual assessment of computerised images by clinicians	Gold standard Manual identification of MAs from test images by an experienced study ophthalmologist and medical physicist	The automated detector achieved 82% sensitivity with 5.7 false positives per image. Data presented as a FROC curve suggest the automated method is comparable in practice to results from clinicians	The authors outline a fully automated strategy, with image registration by computer allowing analysis of serial images from an individual. The system can be adjusted to allow greater sensitivity at the expense of specificity or vice versa depending on the characteristics of the population under study. In comparison with clinicians, the system appears robust enough for use in clinical practice	Cree, 1997 ⁶⁹	Methodology Grade IV Results Grade III
Conventional angiogram negatives digitised to give 25 overlapping fields for analysis, each comprising 256 × 256 pixels	25 angiograms chosen randomly from diabetic patients participating in a prospective trial of the effect of antiplatelet agents in micro-angiopathy (DAMAD study). Type 1 and 2 represented, with at least background retinopathy and ≥ 5 MAs in the posterior pole of the eye	Automated detection of MAs from fluorescein angiograms	Comparative study 1. Manual counting of MAs from projected negatives by ophthalmologists and a trained technician. Each angiogram assessed twice. 2. A second validation was done by technician marking digital image on screen directly with a light-pen to overcome influence of magnification on manual and automated methods	When computer assessment validated by the technician using method 2, the authors attribute the automated method with 70% sensitivity and a predictive value of 86%. The technique did not allow calculation of specificity	The authors conclude that the method of automated detection under review provides a method of MA detection comparable to that achieved by a trained technician, both in accuracy and performance time (30–40 minutes per angiogram)	Baudoin, 1984 ⁷⁰	Methodology Grade II Results Grade II

continued

TABLE 27 Evaluation of digital fluorescein angiography (cont'd)

Technique under review	Population studied	Study aim	Gold standard or comparative method	Results	Authors' conclusions	Reference	Methodology and results grading
Automated assessment of maculopathy							
Indirect digitisation of 30° or 45° macular views from fluorescein angiogram negatives performed by Panasonic WV-CD 20 CCD video camera, Data Translation DT-2861 frame grabber with IBM-compatible computer	10 angiograms analysed, of which 3 demonstrated diabetic retinopathy (1 central serous retinopathy; 1 age-related macular degeneration; 1 branch retinal vein occlusion; 4 normal controls). Comparison made of the intensity of fluorescence in early and late images to give an indication of the degree of vessel leakage	Automated method of performing an assessment of macular leakage – if this is present, the calculation of the area of an angiogram showing persistence or increase in fluorescence levels is under evaluation as an indirect method of quantitative assessment	Comparative study No definitive gold standard available. Threshold gradient value calculated using normal angiograms to minimise false-positive results. Assessments made of repeatability and robustness after calibration against test angiograms. Repeatability – same images digitised and assessed on 5 consecutive occasions. Robustness improved by analysing 3 early frames, counting only positive pixels appearing in 2 out of 3 images, against those from a single late image	High degree of repeatability and robustness for single and multiple areas of leakage > 1/5 of disc area (coefficient of variation 6%) and for single areas < 1/5 of disc area. System performed less well with multiple small areas with total area < 1/5 of disc area (coefficient of variation 27%)	The authors propose that their method provides a simple method of quantifying macular leakage which is superior to manual assessment (although results of direct comparison not quoted). This has implications for both diagnosis and monitoring response to treatment. At this stage in development, potentially misleading lesions such as drusen need to be excluded by prior clinical examination	Phillips, 1991 ^{40,66}	Methodology Grade III Results Grade III

continued

TABLE 27 Evaluation of digital fluorescein angiography (cont'd)

Technique under review	Population studied	Study aim	Gold standard or comparative method	Results	Authors' conclusions	Reference	Methodology and results grading
Assessment of perifoveal and macular microcirculation							
30° fluorescein angiograms centred on the macula obtained – digitised to 512 × 512 pixel resolution. Manual identification of the FAZ performed using a cursor and area and longest diameter calculated. Vitreous fluorophotometry also performed in diabetics as an indirect assessment of dye leakage	Prospective study of 18 diabetic patients with diabetes duration of ≥ 5 years and retinopathy <grade 2 of the modified Airlie House criteria; 12 healthy non-diabetic controls. Only one eye studied – for diabetics, selected as that with greater degree of retinopathy	Semi-automated analysis of the FAZ	Comparative study Comparison with manual calculation of FAZ from non-digitised images	A statistically significant correlation between the calculated FAZ by both semi-automated and manual methods found with the diabetic group ($r = 0.63$, $0.005 < p < 0.05$); not apparent in the normal control group ($r = 0.42$, $0.10 < p < 0.05$). Differences between the groups for individual variables studied in manual method not reflected by semi-automated method. Neither method revealed a significant correlation with vitreous fluorophotometric analysis, confirming the results earlier researchers	Semi-automated calculation of the FAZ will aid evaluation of capillary closure in DR. While noting close correlation with manual estimation in the retinopathy group, the authors are unable to explain the lack of discrimination between diabetics and normal volunteers using their computer-aided method. Clearly, further work is required to validate the technique as a potential screening tool	Leite, 1989 ⁷¹	Methodology Grade III Results Grade II

continued

TABLE 27 Evaluation of digital fluorescein angiography (cont'd)

Technique under review	Population studied	Study aim	Gold standard or comparative method	Results	Authors' conclusions	Reference	Methodology and results grading
Standard 30° fluorescein angiogram. Negatives digitised using the IS 2000 image analyser – clustering algorithm performed to identify regions of variable pixel intensity	Retrospective analysis of investigations of a 22 year old type I DM male with ischaemic diabetic maculopathy affecting the left eye	An automated method for quantification of diabetic macular circulation	Comparative study Intraphotographic reproducibility calculated by assessing same image 10 times; results obtained from image analysis compared with manual qualitative assessment of area of perfusion; trend to increased area of non-perfusion on second photographic series confirmed by clinical assessment of angiograms by five clinicians masked to the patient's history or sequence of imaging	MPI calculated as percentage of total area perfused; macular ischaemic index representing percentage of area under study which is non-perfused. Mean MPI reduced significantly over the study period (0.44 to 0.36) with calculations showing high reproducibility in serial analysis of same image (standard deviation 0.016 with coefficient of variability 3.5% for initial images)	While accepting that this is an indirect method of calculating perfusion and macular viability, it represents an advance over previous time consuming manual assessment and correlates with clinical evaluation of angiograms	Goldberg, 1989 ⁷²	Methodology Grade IV Results Grade III
<p>AUC, area under the curve; CRT, cathode-ray tube; FA, fluorescein angiography; FAZ, foveal avascular zone; FROC, 'free response' ROC; MA, microaneurysm; MPI, macular perfusion index.</p>							

TABLE 28 Assessment of study methodology and results – evaluation of digital fluorescein angiography techniques

Reference	Methodology						Results				
	Use gold standard	Independent assessment	Appropriate study population	No verification bias	Reproducible description	Grading	Correct sensitivity/specificity	Reproducibility calculated	Statistics appropriate	Data presented	Grading
Seeley, 1989 ⁶⁵	✓	✓	✓	✓	✓	V	✓	✓	✓	✓	IV
Phillips, 1991 ⁴⁰	✓	✓		✓	✓	IV	✓	✓	✓	✓	IV
Spencer, 1992 ⁶⁷	✓	✓		✓	✓	IV	✓	✓	✓	✓	IV
Spencer, 1996 ⁶⁸	✓	✓	✓	✓	✓	V	✓	✓	✓	✓	IV
Cree, 1997 ⁶⁹	✓	✓		✓	✓	IV	✓		✓	✓	III
Baudoin, 1984 ⁷⁰				✓	✓	II		✓		✓	II
Phillips, 1991 ⁶⁶			✓	✓	✓	III		✓	✓	✓	III
Leite, 1989 ⁷¹			✓	✓	✓	III			✓	✓	II
Goldberg, 1989 ⁷²	✓	✓		✓	✓	IV		✓	✓	✓	III

TABLE 29 Digital fluorescein angiography – application in research

Technique under review	Population studied	Study aim	Gold standard or comparative method	Results	Authors' conclusions	Reference
Acquisition of high quality retinal images via 590 Newvicon tube video camera, with resolution of 300 × 225 pixels after editing	Assessment of 10 patients with clinical evidence of new vessels at the disc, in 7 cases secondary to type I DM	Use of videofluoroscopic technique to evaluate the origin of new vessels	Confirmation of clinical examination findings	6 patients showed a retinal venous filling of new vessels; 3 patients showed filling from the retinal artery, which has not previously been reported; 1 patient showed new vessels originating from the choroidal circulation	Although the significance of these findings to clinical practice is not established, the paper demonstrates potential advantages of videofluoroscopic techniques with an image acquisition rate of 25 frames per second over conventional sequence photography	Jacobs, 1988 ⁶⁴

vessels, more sophisticated programs involving matched filter systems, which assume the shape and size of the object under study, and vessel masking were employed.

With serial analysis of 14 regions of interest on five occasions, the coefficient of variation for reproducibility of microaneurysm counts was between 7 and 14.5%. In comparison with a single experienced observer performing manual counts, a sensitivity of 82–93% was achieved with a specificity of 93%.

A comparable sensitivity was achieved by automated methods by Spencer and colleagues (*Table 27*) in comparison with manual assessment of the digitised images and the original angiogram analogue prints by experienced clinicians.^{67,68} Using free-response ROC curves, there was no statistically significant difference in performance of computer and clinicians when analysing digitised prints. However, the authors concluded that the improved number of true-positive responses (sensitivity) for any given number of false positives achieved by the clinicians' study of analogue prints could be attributed to a loss of resolution in a 512×512 pixel format. Certainly, enhancement of the digitised images to four times the original resolution gave rise to automated results similar to those of manual interpretation of the analogue images. As cameras are now commercially available which can capture images in a 1024×1024 pixel format, the authors suggest that their automated program is capable of producing results which are as good as observer analysis, unhindered by the effect of image degradation occurring from indirect digitisation procedures.

The programs devised by Spencer and colleagues have been modified by Cree and colleagues (*Table 27*) to allow the development of a fully automated system, where the region of interest is defined without operator intervention and image registration can be performed by computer to allow comparative analysis of serial images.⁶⁹ A rigorous set of test angiogram images from diabetic patients was chosen for digitisation, specifically including those with tigroid fundi and both minimal and severe retinopathy. Despite the challenging nature of the test set, which may not be representative of the population likely to be encountered in a general diabetic population, the automated system performed well, achieving microaneurysm detection with a sensitivity of 82% and a rate of 5.7 false positives per image. In practice, this was comparable to the results

achieved by clinicians' manual counting of microaneurysms from the digitised images. It would be possible to adjust the program to enhance sensitivity at the expense of specificity or vice versa, depending on the nature of the population under study, for example, high sensitivity in a screening programme. The authors suggest that the microaneurysm detector could be used with directly acquired digital images from currently available fundus cameras, greatly enhancing the speed of image analysis.

These results compared favourably with those of Baudoin and colleagues (*Table 27*), whose automated method was quoted as achieving a sensitivity of 70% and a predictive value of 86% for microaneurysm detection.⁷⁰ Each angiographic image was magnified 150 times prior to digitisation, requiring that the image be divided into 25 equal fields for computer analysis. The original gold standard of manual counting of microaneurysms by two consultant ophthalmologists and a trained technician was discontinued as the projected angiogram negatives had a magnification of only $\times 17.5$, which was not felt to provide a satisfactory comparison with computer analysis.

Instead, a semi-automated method was devised, using a trained technician, who superimposed his assessment of microaneurysms on to those detected by computer on a video terminal using a light-pen. As neither of these techniques could be classed as a recognised gold standard, this serves only to identify the number of lesions missed by each technique, rather than actual false-positive and false-negative rates. In addition, the technique was applied only to patients with established retinopathy without the use of normal controls.

Automated assessment of maculopathy

With regard to the development of diabetic maculopathy, it is recognised that the irregular shape and ill-defined margins of this condition make manual quantification difficult to achieve, with a tendency for high variability of inter- and intra-observer assessment. Two frames from a conventional angiogram sequence were selected by Phillips and colleagues (*Table 27*), corresponding to the completion of venous filling and a late-phase image, taken at 250–300 seconds, anticipating that this allowed sufficient time for any fluorescein leakage to have occurred.^{40,66} Knowing that the natural course of fluorescence during a normal angiogram examination is to reach a peak during the initial passage of dye

through the retinal circulation followed by a decrease with time, the investigators hoped to use the tendency for vessel leakage of dye in maculopathy to slow this decay or even result in relative hyperfluorescence. By comparing images, the difference in individual pixel grey-scale intensity, corresponding to the degree of fluorescence, was noted. A gradient of intensity was calculated, with all pixels demonstrating a gradient below a previously calculated threshold being classified as having retarded loss of fluorescence, or demonstrating vessel leakage.

Although a recognised gold standard for comparison does not exist, the automated assessment compared well with that performed manually by experienced ophthalmologists. A high degree of reproducibility was determined for single and multiple areas of leakage that covered an area equivalent to at least one-fifth of the optic disc area, with a coefficient of variation being calculated as less than 6%. With an image processing time of 5 minutes, the authors propose that this will prove to be a simple method of quantifying macular leakage, with relevance both to understanding the natural history of diabetic retinopathy and to monitoring the response to therapeutic intervention.

Assessment of perifoveal and macular microcirculation

Further investigative work in the macular region has been carried out by Leite and colleagues (Table 27).⁷¹ With progression of diabetes, there is a tendency for perifoveal capillary occlusion. This is evident as a reduction in the density of the capillary network demonstrated around the fovea on fluorescein angiography, described as 'capillary drop-out'. In the past, this has proven difficult to quantify manually, prompting the application of semi-automated analysis of digitised conventional angiogram photographs.

Once images had been digitised, the foveal avascular zone (FAZ) was delineated by the authors using a cursor, allowing subsequent computerised calculation of the area and longest diameter of the region of interest. These results were compared with the calculations made from direct manual assessment of the original images, using a previously agreed standard formula (equivalent area = longest diameter × longest perpendicular diameter).

The authors were able to demonstrate a clear statistically significant correlation between measurements derived by both methods in the

diabetic patient group ($r = 0.63$, $0.005 < p < 0.05$); this finding did not extend to the non-diabetic control group and remains unexplained. When comparing the measurements made in diabetic and non-diabetic patients, a significant difference was found with every non-digitised parameter studied; this was not evident on the comparison of semi-automated assessment of FAZ area.

Therefore, given the small numbers of patients recruited to the study (18 with diabetes and 12 without) and the equivocal outcomes reported, the authors admit that further work will be required to validate the use of image processing systems in this area. However, the development of a reliable semi-automated method of FAZ assessment would undoubtedly enhance the clinician's ability to detect and monitor the progression of diabetic maculopathy, although the need for fluorescein injection would prevent its widespread use as a screening tool.

Goldberg and colleagues (Table 27) have applied a different approach to the assessment of posterior pole ischaemia, demonstrated by application in the case of a single 22-year-old male with diabetes.⁷² After enhancement of indirectly digitised angiograms, areas of high-intensity pixels correlating with fluorescein passage were selected according to predetermined thresholds, and used to calculate the macular perfusion index (a percentage of the total area perfused). Conversely, those pixels below the threshold intensity were designated as indicating areas of non-perfusion, allowing the calculation of a macular ischaemic index. In serial analysis of images from a patient with clinical deterioration in visual acuity, the assessment of increased evidence of ischaemia by five clinicians masked to the patient's details and sequence of image acquisition reflected the findings of the automated assessment system. Between initial and subsequent angiograms, a significant reduction in macular perfusion index was evident ($p = 0.0005$).

Although we must accept that no attempt was made to differentiate between areas of ischaemia and infarction, and that the attempt to correlate findings with clinical interpretation has limitations, this paper indicates a potentially useful method of establishing quantifiable evidence of macular perfusion. The technique has also been applied to follow the case of a 26-year-old female with diabetes with a variable visual acuity of 20/50 initially, 20/40 at 2 months and 20/50 at 3 months.⁷³ The macular perfusion index was calculated as 76, 74 and 81%, respectively, occurring spontaneously without therapy.

Although caution must be exercised in the interpretation of these figures, given the limited information available on the accuracy of this novel technique, further work is certainly justified into investigation of the correlation between the calculated perfusion index and physiological alterations in perfusion resulting in altered macular function.

Conclusion

As digital technology becomes more commonplace in the clinical setting, the advantages of the speed of image acquisition and image manipulation to aid the diagnostic information available from fluorescein angiography are being widely accepted. The instant availability of images has the potential to revolutionise working practice in ophthalmology departments, allowing immediate intervention with laser therapy if appropriate without the inherent delays in diagnosis associated with film development. The early work on microaneurysm and maculopathy detection presented here provides a quantitative method of following the development of key features of retinopathy. Although, at present, no automated system has been adopted as a replacement to the clinical monitoring of retinopathy by experienced ophthalmologists, current research is likely to provide useful tools for future diabetic retinopathy management.

Scanning laser ophthalmoscope

Introduction

Following the translation of the principles of light amplification by stimulated emission of radiation (LASER) into a working device by Maiman in 1961,⁷⁴ the main application of this technology in ophthalmology has been directed towards providing a tool for therapeutic intervention. However, the introduction of the scanning laser ophthalmoscope has the potential for revolutionising our ability to view the retina for diagnostic purposes. Webb and colleagues were the first to describe a novel approach to fundus imaging in 1980 with adaptation of the 'flying spot' TV ophthalmoscope.⁷⁵ Instead of using cathode-ray tube illumination, the 'flying spot' was supplied by a focused laser light source moved by scanning mirrors, and later re-named the scanning laser ophthalmoscope (SLO).

Unlike conventional fundus imaging where the majority of the retina is illuminated at the same time, the SLO requires the use of a highly collimated light beam. This is passed over the retina in a raster fashion, building up a point-by-

point image based on a rectangular line grid pattern. Manivannan and colleagues have quoted an acquisition time of 40 ms for an 18° by 24° fundus view, which is sufficiently rapid to avoid any potential aberration induced by patient eye movement during the procedure.⁷⁶

As the proportion of the pupil aperture required by the incident light is significantly reduced, the area available for emergent light to leave the eye is enhanced. Therefore, the system can operate at a low light intensity level of 50 μ W, markedly lower than those required for conventional photography, improving patient comfort. In addition, the incident light beam occupies only 1% of the calculated area of the average 4 mm undilated pupil.⁷⁷ Therefore, the need for mydriasis to obtain adequate images may be avoided, particularly when operating with 40° field of view.⁷⁸

The wavelength of light being used in the SLO can be manipulated to allow selective imaging of different retinal structures. The infrared spectrum gives improved imaging of the choroid because of its ability to penetrate the retinal pigment epithelium;⁷⁹ the visible light spectrum appears more useful for examination of superficial structures such as blood vessels.

Initial prototypes of the system were dependent on on-line video acquisition of information, either viewed directly on a video monitor or taped on a cassette recorder, which could then be converted to a digital format for further computer-aided analysis. Manivannan and colleagues have improved on this process by the direct conversion of analogue signals from the photoreceptor to a digital format via the use of a frame grabber and IBM-compatible PC.⁸⁰ This reduces the likelihood of image degradation and is likely to aid both ease of image collection and storage.

Performance

Comparison of SLO with clinical examination

Wykes and colleagues (*Table 30*) have evaluated the SLO as an imaging tool against examination of the diabetic fundus by an experienced ophthalmologist.⁸¹ The methodology and results are evaluated in *Table 31*. Using 54 patients, agreement was reached in 92.7% of patients with background retinopathy and 31.3% of patients with pre-proliferative changes, classified by detection of individual features. Although poor at detection of cotton-wool spots and IRMA, the SLO clearly delineated venous beading, identifying this feature in two cases missed by clinical examination.

TABLE 30 Evaluation of the SLO

Technique under review	Population studied	Study aim	Gold standard or comparative method	Results	Authors' conclusions	Reference	Methodology and results grading
Comparison of SLO with clinical examination							
Examination of fundi through undilated pupils achieved by direct acquisition of digitised video image on SLO – images then graded by experienced ophthalmologist	54 patients from general population attending diabetic clinic	To evaluate the ability of SLO to record fundal changes of DR for assessment and grading by ophthalmologists	Comparative study Clinical examination after mydriasis by an experienced ophthalmologist	92.7% agreement for background retinopathy. Of the 5 cases missed by the SLO, 3 were of minimal grade. Agreement in 31.3% of pre-proliferative retinopathy achieved – clinical examination missed 2 cases of VB and 1 with CWS; SLO technique missed 5 cases of CWS and 3 of IRMA. Proliferative retinopathy – 3 out of 4 cases of 'missed' NVD by SLO technique were inactive vessels following laser therapy and the fourth had vitreous haemorrhage. In 2 cases SLO imaging proved superior over clinical examination, in part due to the presence of cataract-limiting clinical examination. 79.4% agreement achieved for maculopathy	Based on the findings of subsequent clinical examination, the decision to refer 18 patients from their SLO images was appropriate in each case. All patients requiring treatment were referred. Although a direct comparison has not been performed, the authors propose that the SLO has advantages over conventional non-mydriatic cameras, particularly owing to its greater depth of focus, allowing identification of new vessels growing into the vitreous and comparatively few unusable photographs due to technical difficulties (4.63% and 17–23%, respectively)	Wykes, 1994 ⁸¹	Methodology Grade IV Results Grade II
Rodenstock 101 laser ophthalmoscope used to acquire images of disc to macular regions, together with superior and inferior temporal and nasal retinal views	57 consecutive diabetic patients attending a routine retinal screening clinic based in an ophthalmology department	To determine quality of SLO acquired images for diagnosis of DR by manual grading by a single observer	Comparative study Clinical examination by direct ophthalmoscopy by medical staff (ophthalmic clinical assistant and diabetes senior registrar)	113 eyes analysed – discordant results in 35% with SLO grading severity greater in 90% (mainly background retinopathy compared with normal) and less in 10%. Each technique classed 3 fundi as normal where the alternative considered referral appropriate – authors do not clarify lesions meriting referral in all cases and do not provide a recognised gold standard review of patients to give definitive evaluation of techniques	The authors propose that SLO may provide a useful additional screening tool but will require further clinical comparison against non-mydriatic cameras to determine its future role	Pope, 1993 ⁸³	Methodology Grade IV Results Grade II

With regard to proliferative retinopathy, the four cases of neovascularisation missed by the SLO were identified as showing regression of new vessels following laser therapy or vitreous haemorrhage obscuring detail, the latter being a reason for referral in itself. No active new vessels were missed. When graded according to the need for referral for specialist advice, 14 out of 16 patients referred warranted laser therapy for either neovascularisation or exudative maculopathy. In contrast to the high proportion of ungradable photographs, quoted as between 17 and 26%, which have hampered some non-mydriatic retinal photography studies,⁸² only 4.6% of the SLO images were ungradable, in two patients owing to dense cataract in one and vitreous haemorrhage in the other.

As no patient requiring active intervention remained undetected, the authors concluded that the SLO could provide a safe means of screening and monitoring the diabetic population. As only patients with discordant results and those requiring specialist referral underwent further examination to clarify their retinopathy status, their argument is weakened by the lack of a recognised gold standard. This would have clarified the accuracy of assigning grades of retinopathy at the pre-proliferative level, necessary for monitoring patient progression. Given the small sample population under study, further evaluation of the SLO would seem warranted before endorsing its role in clinical practice.

Pope and colleagues (*Table 30*) have compared a commercial SLO against the results of direct ophthalmoscopy performed by medical staff (a diabetes senior registrar and an ophthalmic clinical assistant).⁸³ The methodology and results are evaluated in *Table 31*. In a series of 57 consecutive patients attending a retinal screening centre, agreement of retinopathy grading occurred in 65%, the majority of whom were graded as having mild or no retinopathy. The single case of sight-threatening retinopathy was detected by both techniques. Of the discordant results, the SLO gave a grading of greater severity in 90% of cases, usually mild rather than no retinopathy, and a lesser grading in 10%. No further examination procedure was performed to determine the validity of these results. Therefore, while accepting that the SLO examination was well tolerated by patients and rapidly performed by a trained operator, the role of the SLO as a screening tool remains unclear. The limitations of their pilot assessment of the technique are acknowledged by the authors, who intend to proceed to further evaluation against conventional photography.

Confocal imaging with the SLO

Further enhancement of the SLO performance can be achieved with the introduction of confocal imaging. If the emergent light is passed through an aperture conjugate to the laser focus prior to contact with the photodetector, this will allow light scattered by media opacities to be excluded from the final image, improving image contrast.⁸⁴ Image planes containing structures of particular interest can be studied with this technique as reflected light from areas outwith the chosen depth of field can be excluded by the confocal aperture, imparting a degree of axial resolution. Obviously, the ability to image a structure deep to the surface of the retina will depend on the degree to which the chosen light wavelength can penetrate overlying structures.

Woon and colleagues applied these principles to a group of 51 patients attending retinal and low-tension glaucoma clinics.⁷⁸ They confirmed that high-quality images of the lamina cribrosa deep to the retina could be obtained in all 10 patients with low-tension glaucoma; unfortunately, confocal imaging made retinal exudates more difficult to detect in the three patients studied, presumably owing to the light-scattering nature of these lesions. This contrasts with the ability of the SLO to image these lesions in its non-confocal modality, used by Leistriz and Schweitzer in their preliminary work on the development of an automated exudate detection program.⁸⁵ They suggest that by using a monochromatic light source, the absence of vignetting across the image which has hindered automated thresholding techniques in conventionally acquired photographic fundus images will prove to be of significant benefit to analysis.

Assessment of macular oedema

In their overview of the clinical use of the laser tomographic scanner, Bartsch and colleagues utilise the axial resolution properties of the confocal SLO to obtain 30- μm optical slices of the retina, parallel to the plane of the internal limiting membrane.⁸⁶ This allowed them to examine the topography of the macula and posterior pole by reconstruction of serial sections, building a height profile on macular lesions. A clinical evaluation of the technique was performed in a series of 42 patients with a variety of fundal pathology. The presence of macular oedema in four patients, as determined by clinical examination and stereoscopic fundus photography and angiography, could be confirmed by an elevation of the internal limiting membrane. With further research, this may provide a quantitative

TABLE 31 Assessment of study methodology and results – evaluation of SLO techniques

Reference	Methodology						Results				
	Use gold standard	Independent assessment	Appropriate study population	No verification bias	Reproducible description	Grading	Correct sensitivity/specificity	Reproducibility calculated	Statistics appropriate	Data presented	Grading
Wykes, 1994 ⁸¹		✓	✓	✓	✓	IV			✓	✓	II
Pope, 1993 ⁸³		✓	✓	✓	✓	IV			✓	✓	II

method of detecting the presence of macular oedema in diabetic patients and monitoring their response to therapeutic intervention.

Stereoscopic images from the SLO

An alternative approach to improving the diagnosis of macular pathology has been adopted by Frambach and colleagues, who have developed a technique of obtaining stereoscopic SLO images using the same principles as are applied in conventional photography.⁸⁷ By use of an Allen separator, the quality of stereoscopic images obtained is greater with the SLO. The authors attribute this to the narrower incident light beam, which allows maximum separation of right- and left-perspective images for a given degree of pupillary dilatation. Although their preliminary report on the technique did not refer specifically to diabetic patients, this technique could prove useful in the detection of macular oedema, particularly in those patients with a poor response to mydriatic therapy which limits the success of conventional photography.

Use of the SLO in patients with cataract

Two groups have investigated the unique properties of the SLO in patients where conventional photography is hampered by the presence of significant cataract causing increased intraocular light scattering.^{88,89} In both studies, the authors conclude that SLO imaging is significantly better than fundus photography in achieving adequate pre-operative retinal assessment, probably owing to the better penetration of the non-homogeneous lens by the narrow collimated light beam. The confocal mode was seen to enhance vessel contrast in some patients, although it did not invariably improve results. The small number of patients studied in each group (19 and 47, respectively) did not allow any conclusion to be reached regarding the effect of different types of cataract on overall outcome. However, there are obvious benefits to being able to visualise the retina adequately prior to cataract extraction, excluding underlying pathology such as age-related macular degeneration or diabetic maculopathy, which may limit the success of surgical intervention.

Taking this a stage further, Le Gargasson and colleagues have used the SLO to project a series of letters directly on to the retina of 47 patients, including those with diabetes, with a moderate lens opacity and co-existing macular disease.⁹⁰ Improved visual acuity scores were consistently achieved in patients used the SLO technique over

standard clinical visual acuity measurement. While accepting that it may be easier for the patient to discriminate information presented in a point-by-point manner rather than using a static chart presentation with associated visual background noise, the authors conclude that the ability of SLO to overcome the obstacle to assessment posed by cataract is significant. This is supported by the finding of comparable pre-operative SLO and post-operative clinical visual acuity in 77% of cases. Clearly, the use of this tool to make a functional assessment of underlying macular health may provide guidance when determining whether cataract extraction is appropriate and likely to yield further improvement in visual acuity.

Assessment of retinal microcirculation

Problems have been encountered in determining the effect of diabetes on retinal microcirculation, both haemodynamically and morphologically, owing to the limited speed of image acquisition in fluorescein angiography using conventional photography. In an attempt to find an alternative technique, previous work by Fallon and colleagues describes the measurement of retinal flow in diabetics by the blue light entoptic phenomenon.^{91,92} As patients look into a blue filtered light source of wavelength 430 nm, leucocytes become visible to the patient as they travel through their retinal circulation, moving in a pulsatile fashion with each cardiac cycle. Patients are asked to match the perceived speed of progression against that of 'simulated leucocytes' moving across a TV monitor, providing an indirect calculation of velocity that is hampered by its subjectivity and has not been widely adopted as a research tool.

In contrast, the application of the SLO to fluorescein angiography appears to be making a useful contribution to overcoming the problem of achieving a quantifiable assessment of blood velocity. Commercially available instruments have revolutionised this field, being capable of scanning up to 50 frames per second. Nasemann used this facility to follow the course of erythrocytes through retinal blood vessels in a frame-by-frame analysis.⁹³ He observed the presence of segments of hypofluorescence, which was suggested to represent the movement of erythrocytes in rouleaux formation through vessels, interspersed with the highly fluorescent segments of free plasma. Although this preliminary work was able to detect reduced retinal blood flow only in those patients with severely impaired retinal microcirculation, the technique has been refined for use by Wolf and colleagues⁹⁴ and employed by several of the authors whose work is presented in *Table 32*.

TABLE 32 Established SLO techniques in research

Technique under review	Population studied	Study aim	Gold standard or comparative method	Results	Authors' conclusions	Reference
Video images generated by the SLO converted to digital information for recording on an image sequence storage unit, allowing off-line evaluation of mean blood flow velocity; FAZ; mean perifoveal intercapillary area (PIA)	13 patients with type I diabetes with mild diabetic retinopathy; 21 healthy volunteers with no history of systemic disease	To determine the ability of the SLO to measure retinal capillary blood flow velocity	Technique validated in prior publication. ⁹⁴ 15 vessels of each patient examined, evaluating the transit time of high fluorescence segments within 10 regions of each vessel, i.e. each mean blood flow velocity was calculated from 150 individual measurements. Manual delineation of the FAZ and PIA was performed with a cursor on the digital images, allowing calculation of the respective areas ¹¹⁰	Mean capillary blood flow velocity in macular capillaries was significantly lower in diabetics (2.89 ± 0.57 mm/s) compared with healthy volunteers (3.28 ± 0.45 mm/s); $p < 0.05$; Mann–Whitney <i>U</i> -test. The area of PIA was more than doubled in the diabetic population ($p < 0.01$; Mann–Whitney <i>U</i> -test) There was no statistically significant difference in calculated FAZ between the groups	The ability of the SLO to acquire images at a rate of 50 per second allows movement of the retinal blood stream to be calculated. The authors have based their work on the assumption that measurement of segments of low and high fluorescence through a vessel may correspond to the passage of erythrocytes in rouleaux formation (low) through plasma (high), allowing indirect calculation of blood flow velocity. They suggest that the perceived reduction in blood flow velocity seen in the diabetic group may be due to endothelial change within the vessels or an alteration in rheological properties. The increase in calculated PIA reflects capillary drop-out, suggesting that evidence of macular ischaemia may occur at an earlier stage in the development of diabetic retinopathy than had been previously recognised	Wolf, 1991 ⁹⁵

continued

TABLE 32 Established SLO techniques in research (cont'd)

Technique under review	Population studied	Study aim	Gold standard or comparative method	Results	Authors' conclusions	Reference
Acquisition of scanning laser fluorescein angiograms subjected to digital processing for off-line analysis	33 type I patients with diabetes (8 with no retinopathy; 25 with mild retinopathy) and 24 healthy volunteers	Measurement of retinal micro- and macro-circulation with SLO in diabetic patients	Technique validated in prior publication. ⁹⁵ Microcirculation calculated as in Wolf and colleagues. ⁹⁶ Macrocirculation parameters defined as: (1) Arm-retina-time (ART) – period between dye injection into cubital vein and appearance in retinal arteries. (2) Arteriovenous passage time (AVP) – interval between first appearance in retinal artery and appearance in corresponding retinal vein, indicating circulation through the retinal microcirculation. (3) Mean dye velocity (MDV) – velocity of dye passing through a retinal artery	Both ART and AVP were significantly increased in the diabetic group compared with healthy volunteers ($p < 0.01$ and $p < 0.05$, respectively; <i>U</i> -test and <i>t</i> -test). The capillary blood flow velocity in the diabetic group was significantly reduced ($p < 0.01$; <i>U</i> -test and <i>t</i> -test). Mean calculated PIA was significantly enlarged in diabetics ($p < 0.01$; <i>U</i> -test and <i>t</i> -test).	Authors conclude that results on the effect of diabetes on the macrocirculation support the findings of Grunwald and colleagues ¹⁰⁸ using laser Doppler velocimetry; and those of Bertram and colleagues ¹¹¹ in analysis of patients with severe retinopathy. Results from analysis of the microcirculation support previous work by the authors. ⁹⁵ The study has highlighted significant alterations in retinal haemodynamics in diabetics which may be evident before the development of clinically apparent retinopathy	Wolf, 1992 ⁹⁶

continued

TABLE 32 Established SLO techniques in research (cont'd)

Technique under review	Population studied	Study aim	Gold standard or comparative method	Results	Authors' conclusions	Reference
Technique and methodology as described in Wolf and colleagues ⁹⁵	48 diabetic patients comprising 25 type 1 and 23 type 2; 21 healthy volunteers The diabetic group had 4 grades of retinopathy: 4 with no retinopathy; 17 with mild to moderate NPDR; 10 with pre-proliferative DR; 14 with proliferative DR	Evaluation of the perifoveal capillary network and the effect of diabetes mellitus on the dynamic and morphological properties of the retinal microcirculation	Technique validated in prior publication ^{94,95}	Findings are comparable to those in previous studies showing significantly reduced CBV in the diabetic group ($p < 0.01$; <i>U</i> -test); a doubling of the PIA ($P < 0.01$) and, in this study, a significant enlargement of the FAZ. CBV did not show a significant difference between grades of retinopathy; progressive enlargement of PIA and FAZ with increasing severity of retinopathy reached significance	Authors emphasise that the recorded reduction in CBV and observed increase in PIA is evident in diabetic patients with apparently normal fundi on clinical examination. Conclude that observed changes in retinal microcirculation may contribute to the development of retinal ischaemia, a recognised contributor in the pathogenesis of diabetic retinopathy	Arend, 1991 ⁹⁷
Technique and methodology as described in Wolf and colleagues ⁹⁵	46 patients with type 2 diabetes; 31 healthy volunteers The diabetic patients comprised 18 with either no, mild or moderate retinopathy; 18 with pre-proliferative retinopathy and 10 with evidence of proliferative retinopathy	An evaluation of the perifoveal circulation in type 2 diabetes	Technique validated in prior publication ⁹⁴	The authors found a significant reduction in capillary blood flow velocity at 2.33 ± 0.36 mm/s ($p < 0.01$) and significant increase in PIA and FAZ in the diabetic group. Both PIA and FAZ were found to increase progressively with worsening retinopathy, but no significant variation in blood flow velocity was noted	The increase in PIA is a reflection of the histological finding of capillary drop-out in diabetic retinopathy. This is evident even in diabetics who show no microaneurysm formation, aiding understanding of the sequence of progression of diabetic retinopathy. The authors conclude that the SLO may provide a quantitative method of following subclinical changes in diabetic fundi, although further research is required to determine the prognostic implications of these findings	Arend, 1994 ⁹⁸

continued

TABLE 32 Established SLO techniques in research (cont'd)

Technique under review	Population studied	Study aim	Gold standard or comparative method	Results	Authors' conclusions	Reference
Video fluorescein angiographic signal from SLO digitised, allowing offline evaluation of perifoveal CBV, the area of the FAZ and the mean PIA, characterising capillary density	23 diabetic patients with diffuse macular oedema, 23 diabetic patients without CMO (matched for age, sex and retinopathy grading) and 23 healthy volunteers	To use SLO to evaluate the macular microcirculation in diabetics and its effect on the development of CMO	Technique validated in prior publication ⁹⁴	Both diabetic groups showed significant reduction in CBV in comparison with healthy volunteers (CMO patients 26%, diabetics without CMO 18%; $p < 0.0001$). At least doubling of PIA occurred in both groups compared with healthy volunteers ($p < 0.0001$). FAZ significantly enlarged in patients with CMO (29%, $p < 0.05$) and almost doubled in diabetics without CMO ($p < 0.01$) compared with healthy volunteers	Although significant differences noted in comparison with healthy volunteers, both diabetic groups comparable. Suggests that chronic inner retinal ischaemia shown by increasing FAZ and PIA not a vital component in the development of cystoid formations in diabetic retinopathy	Arend, 1995 ⁹⁹
Video fluorescein angiograms performed using Rodenstock 101 SLO	23 diabetic patients with diffuse macular oedema – retinopathy classified using EDTRS protocol and ranging from mild to severe NPDR	To determine relationship between severity of cystoid macular change in DR and visual acuity	Technique for estimation of FAZ validated in previous research. ¹¹⁰ Macular cyst number and area manually identified by two independent observers (inter-observer agreement 96%) using cursor – area calculated from number of pixels contained within boundary	All patients found to have ≥ 1 cyst overlapping FAZ. Significant negative correlation between visual acuity and number ($r = -0.69$; $p < 0.01$) and area ($r = -0.78$; $p < 0.01$) of cysts. No significant correlation between VA and area of FAZ; age; stage of diabetic retinopathy; duration of diabetes or HbA1c. No correlation found between area of cysts and stage of retinopathy or type of diabetes	The present work introduces a quantitative measurement of cystoid component of macular oedema. The authors propose that this will provide an objective criterion for estimation of visual prognosis and evaluation of therapeutic intervention	Arend, 1995 ¹⁰⁰

CBV, capillary blood flow velocity; CMO, cystoid macular oedema.

A consistent finding in the examination of diabetic fundi is the reduction in capillary blood flow velocity, and a significant enlargement of both the perifoveal intercapillary area (PIA), indicating capillary drop-out, and the FAZ. These changes were noted to be present before retinopathy was clinically apparent. Therefore, the authors propose that the SLO could provide a tool for monitoring the early development of retinal ischaemia, enhancing our understanding of the pathogenesis of retinopathy and following the response to therapeutic intervention.

Cystoid macular oedema is a condition most commonly associated with cataract extraction, but it may also occur with retinal vascular disorders, including diabetic maculopathy. Arend and colleagues have used the SLO to demonstrate that although capillary blood flow velocity is generally reduced in patients with diabetes compared with healthy volunteers, there does not seem to be a correlation with the development of cystoid macular oedema.^{99,100} In addition, they have noted that there is no apparent association with cystoid macular oedema and the accompanying grade of retinopathy. However, in developing a quantitative system of analysing cyst size and area, they suggest that their system will aid further research into understanding the pathogenesis of this condition and the efficacy of pharmacological or laser therapy.

There is also interest in the potential role of leucocytes in the pathogenesis of diabetic retinopathy and Le Gargasson and colleagues are developing strategies for monitoring the progress of individual white cells and platelets within the retinal circulation.¹⁰¹ At present, their method of reintroduction of fluorescein-labelled autologous blood cells remains confined to animal models, although they suggest that their technique could be applied theoretically to human studies. However, they do not have any evidence to determine whether the process of cell labelling will in itself affect the rheological properties of cells and their interaction with endothelial surfaces. Therefore, it seems unlikely that this technique will be applied clinically in the near future.

Examination of the choroidal circulation

Our understanding of the choroidal circulation has been improved by the use of indocyanine green (ICG) dye, which will fluoresce under infrared lighting conditions.¹⁰² By injecting ICG and fluorescein dye together, Bischoff and colleagues attempted to examine both retinal and choroidal circulation in a single procedure.¹⁰³ The

SLO can allow simultaneous use of argon and infrared lasers, the latter allowing penetration through the retinal pigment epithelial layer, which has proven an obstacle to previous investigation of the choroidal circulation by other investigative techniques. It proved possible to view the acquired video images separately or combined by off-line digital analysis. The combination of 5 ml of 20% fluorescein and 1 ml (25 mg) of Cardiogreen was well tolerated, with no reported adverse events in a series of 340 patients. Assessment of the images obtained was compared with that of single-wavelength techniques by a team of 10 clinicians and photographers, and found to be comparable with the added benefit of increased time efficiency.

Although earlier work performed with both video angiography and the SLO using ICG suggested that there was evidence of choriocapillary damage in individuals with evidence of diabetic retinopathy,^{104–106} this has not been demonstrated by a pilot study presented by Gibson and colleagues using video angiography.¹⁰⁷ They did note that ICG dye enhanced the appearance of some microaneurysms and previous laser therapy scars. However, while ICG dye continues to be used more widely in the investigation of age-related macular degeneration, there is no evidence to support a contributing role in the current management of diabetic retinopathy.

Assessment of retinal blood velocity

The technique of laser Doppler velocimetry previously described by Grunwald and colleagues¹⁰⁸ can also be applied to use with the SLO. Michelson and colleagues have used this combination to both image the retina and quantify circulation times in a non-invasive manner.¹⁰⁹ Using the principle of the optical Doppler effect, the degree to which reflected laser light is scattered by its contact with blood flowing at variable velocities is detected by a photodetector. The SLO allows serial recordings to be made in an individual point-by-point manner in rapid succession. The data on retinal flow which are subsequently calculated allow the construction of a two-dimensional image, where areas of healthy blood flow are attributed the brightest pixel density. Occluded vessels will be attributed a low pixel density, and are indistinguishable from the background retina. In their examination of a 55-year-old with type 1 diabetes with proliferative retinopathy, the resolution was sufficient to allow 'visualisation' of a neovascular structure confirmed on ophthalmoscopy. Areas of impaired retinal perfusion were clearly delineated with evidence of

capillary drop-out. Despite the requirement of a 2-second acquisition time, which may hamper the quality of imaging in patients with poor fixation skills, the technique has shown impressive results in the small number of patients presented. The information has been obtained by a technique well tolerated by patients and without the need for fluorescein dye injection, which may make serial analysis of individuals more acceptable.

Conclusion

The SLO may prove to be a novel but effective additional diagnostic tool for diabetic retinopathy, providing high-contrast imaging with low-level illumination. Although much of the work presented in this review describes the experimental evolution of the technology, the potential benefits in terms of diagnostic imaging and functional assessment in the future management of diabetic patients are clearly evident. However, at this stage in its development, the technique is not suitable for use in diabetic retinopathy screening and is unlikely to be a replacement for fundus photography.

Discussion

Introduction

Digital imaging for monitoring diabetic retinal disease was identified as a priority within the NHS Health Technology Assessment programme in 1995. The commissioning brief called for a combination of two sorts of research, a systematic review of reported studies and further new data collection studies. This is the report of the first of these.

In the event, we found that research on digital imaging is still at a relatively early stage of development. While the review showed that the technology does have definite promise, there were very few studies that gave any indication of how it might perform within a clinical setting. The review therefore confirmed that further research is needed, but gave little scope for exploring the issues of most relevance to the Health Technology Assessment Programme, such as diagnostic performance in respect of key stages of diabetic retinopathy. The studies were too few and the technologies described too variable to allow quantitative synthesis of data. We also decided that the technology is at too early a stage for a meaningful incorporation of data on resources and costs, as originally envisaged in the application. Although the principal interest was in digital imaging in comparison with other methods

of screening, a decision was taken to extend the review to include two other potentially useful applications of digital techniques in diabetic retinopathy, digital fluorescein angiography and SLO.

Reviewing the literature

The review was performed systematically in the sense that explicit search strategies and explicit selection criteria for the studies considered were used. It would therefore be expected that repetition of what we did would be likely to lead to similar findings.

We aimed for a highly sensitive but relatively non-specific search strategy in an attempt to identify as complete a register of relevant studies as possible. As a result, approximately 2767 published abstracts were assessed to identify the 40 studies included in this review – a dividend of 14 relevant studies per 1000 abstracts. About 62% of relevant studies were identified from MEDLINE and this is consistent with experience in other fields.¹¹²

Despite the fact that a highly sensitive search strategy was applied, it is still possible that a few relevant studies have not been included as our search has not been exhaustive. Electronic bibliographic databases were searched up until December 1997, so any new relevant abstracts indexed since then will not have been picked up. Although we used a wide range of search terms describing digital imaging techniques, it is likely that new terminology will keep appearing as digital imaging is a developing technology. This should be taken into consideration if planning to run the search strategies at a later date. We have not searched non-English language databases or the 'grey literature', and the search carried out on the Internet was quite focused. In addition, handsearching was limited to three key journals and we did not receive any response from 17 of the 42 authors who were contacted either to clarify their study methodologies or identify other relevant studies.

Although the Internet did produce a number of potentially relevant hits, all of the published research identified in this way had already been picked up by searches on electronic databases. However, the Internet did provide information on two on-going studies which may publish relevant information in the near future. In addition, we found a number of sites describing the novel use of digital fundus photography in telemedicine applications.

For studies where digital technology was compared against other techniques of eye examination, an assessment was made of the methodology used and the authors' interpretation and presentation of results. A numerical grading system based on the criteria proposed by Caruthers and colleagues²³ was devised. Each of these criteria has been given the same weighting when determining the overall grading of a study. It is recognised that this arbitrary scoring system does not differentiate between the relative importance of each of the defined criteria. Therefore, the data have been presented in full in tabular form to allow the reader more information regarding the strengths and weaknesses of the publications included in this review.

As digital technology remains at an early stage of evaluation, information derived from poster presentations was included in this review to ensure that a complete overview of digital imaging was achieved. Attempts were made to contact authors for further clarification of techniques used and for validation of the results presented. If no additional information was provided, poster presentations were generally attributed a lower methodology and results grading. This does not imply that future publications based on these preliminary reports would be awarded a similar grading. However, until these publications are available, results derived from these sources should be treated with caution.

Digital fundus photography

In the absence of an ideal method of screening for diabetic retinopathy, the use of digital fundus photography shows a great deal of promise. Preliminary work in direct image acquisition indicates improved image storage and retrieval and patient acceptability of the system. An instantly available photograph has potential benefits for patient education. In comparison with both Polaroid and 35-mm colour slide photography, digital images appear comparable or superior in terms of lesion detection, although these studies are limited by the small patient populations studied.^{27,29,30} The introduction of digital photography to a general diabetic clinic has the potential to increase detection of early retinopathy when compared with routine ophthalmic screening performed by diabetologists using direct ophthalmoscopy alone.³⁴

Digital technology has already been used to offer retinal screening in areas previously disadvantaged by their limited access to specialist ophthalmic care by the application of telemedicine.⁵⁶⁻⁵⁸ Although these programmes offer to provide a

revolutionary method of eye care delivery, we have not identified any studies which directly compare the results of digital photography with previously established screening techniques provided in these areas, or which address the problem of potential image degradation from transmission of digital signals via telephone links.

If photography is to be offered as a nationwide screening method, there is an urgent need to address the problem of image grading. Existing photographic grading centres would be overwhelmed by the increased workload generated by this policy and, therefore, the development of computer-assisted analysis is very attractive. This has been addressed by several authors. They have focused on the detection of either an individual lesion or general retinopathy.

The assessment of hard exudates as evaluated by Phillips and colleagues appears reliable, with a sensitivity of 87% (CI 61-100%) and low coefficient of variation for reproducibility of 3% for confluent areas of exudate.⁴¹ While the problem of differentiation of exudates from drusen has not been addressed and may prove an obstacle to automated screening, the technique could provide a method of quantitative assessment of exudative retinopathy and its response to treatment. The automated detection of cotton-wool spots has proved unreliable from current work, with difficulty in differentiation from both drusen and hard exudates.^{37,42} However, the ability to classify moderate retinopathy on the presence of venous beading is more encouraging, although the technique presented requires initial identification of a region of interest by a trained observer.⁴⁴ With further development, it may be possible for this technique to be fully automated.

The application of fractal analysis has allowed Daxer to identify neovascularisation at the disc of \geq EDTRS grade 3 with a sensitivity of 90% compared with trained photographic graders.⁴⁷ Although this work was performed on manual tracing of vessel patterns from indirectly digitised images, it may be possible in future work to simplify this process with a direct-acquisition digital camera. The work has limitations in that the low-angle photography used encompasses a 10° field around the optic disc, and will not detect neovascularisation occurring more peripherally along the vessel arcades.

Sinclair and colleagues suggest the most promising results for a fully automated analysis program encompassing all of the characteristic

lesions of diabetic retinopathy.³⁶ However, the data available at the time of publication of this review are confined to a poster presentation at the American Diabetes Association 56th Annual Meeting and personal correspondence with the authors. The results are derived from a relatively small patient population and, in the absence of a reproducible description of their technique, should be interpreted with caution.

At present, no author has published evidence to support a clinically applicable automated method that has been validated in comparison with existing techniques in a prospective clinical study. Until a system has proven to be reliable under these conditions, it appears likely that those who are currently employed in providing diabetic eye screening will be expected to undertake the task of manual interpretation of fundus photographs when digital photography is added to existing protocols.

While development of computer-assisted image analysis is likely to remain of key interest over the coming years, it should be remembered that an automated system will report only that which it has been programmed to detect. At present, manual evaluation of the fundus by either funduscopy or grading of photographic images will detect incidental findings such as increased cup-disc ratios suggestive of glaucoma, or naevi which warrant follow-up. While retinopathy grading programs are a potentially valuable additional tool, these potential weaknesses in other areas should be borne in mind.

Digital angiography

As technology in this area has evolved, the advantages of direct digital image acquisition and enhanced storage and retrieval for this routinely used diagnostic test are evident. Investigators have effectively demonstrated the use of fully automated computer-assisted analysis to count microaneurysms with a sensitivity for microaneurysm detection comparable to that of ophthalmologists' manual assessment of fluorescein angiograms.⁶⁹ Although the use of fluorescein precludes this form of analysis as a screening tool, the quantitative assessment of both microaneurysm number and turnover rate may provide a tool for monitoring the rate of retinopathy progression and the response to therapeutic intervention.

Diagnosis of diabetic maculopathy has traditionally been dependent on the examination of a stereoscopic image of the retina, either by an

ophthalmologist employing slit-lamp examination or the use of specialised photographic techniques. An automated program for the detection of fluorescein leakage by comparison of early and late images from an angiogram series provides a relatively robust indirect measure of vessel leakage.⁶⁶ While accepting that the region of interest employed in this work is restricted to the macular area and unlikely to detect neovascularisation at either the disc or on the vessel arcades, the technique has potential to provide a method of quantifying macular leakage and the response to laser therapy. Although indirectly digitised images have been used to study the perifoveal and macular microcirculation,^{72,73} these methods of monitoring retinal ischaemia have yet to be validated in clinical practice.

Although these techniques may provide further insight into the pathogenesis and progression of retinopathy, there is no current automated alternative to serial examination by experienced ophthalmologists for those patients with maculopathy or retinopathy of at least moderate severity.

SLO

The SLO was also included in this review of digital technology in diabetic retinopathy as it has been suggested that this technique may prove a rival to the digital fundus camera in providing care for the diabetic patient. Certain advantages have been proposed by authors, including the low light levels required for operation and the avoidance of mydriatics. It is likely to be particularly useful for patients with cataract, where the fundus view is otherwise obscured.⁸⁸ Although accepting the advantages of this technique over conventional photography in pre-operative macular assessment, the technique has not been validated against the results of indirect ophthalmoscopy performed by experienced eye specialists, which may be the more realistic alternative in a clinical setting.

With regard to monitoring of the retinal microcirculation, there has been promising work into the development of a more reliable method of assessment of blood flow velocity using the SLO which will aid understanding of the pathogenesis of retinal ischaemia.⁹⁴⁻⁸⁶

However, the evidence of reliability of the SLO as a tool for screening for diabetic retinopathy has been confined to two small comparative studies.^{81,83} These are weakened by a lack of validation of the technique against a recognised gold standard and do not give sufficient evidence

to support the use of the SLO in this clinical setting. In addition, it is a novel approach to imaging which may not appeal to physicians who are more familiar with the results of colour retinal photography. Therefore, although colour SLO are now in development, the SLO is likely to remain a research tool in the field of diabetic retinopathy at present.

Implications for clinical practice and research

Even at this early stage of development, digital photography may provide a useful tool in the diagnosis and management of diabetic retinopathy. The following section highlights the most important implications for clinical practice and future research based on the evidence identified by this review.

Implications for clinical practice

- Digital photography offers a promising alternative to conventional photography. Its diagnostic performance is not impaired by the lower resolution of currently available systems.
- The technology has the potential to provide greatly enhanced image storage and retrieval facilities.
- Instant accessibility of images provides an opportunity for greater involvement of patients in their care owing to their improved understanding of retinopathy.
- Digital images can be analysed at a distance using telemedicine technology, providing retinal screening in areas previously disadvantaged by their limited access to specialist ophthalmic care.
- Current methods of screening are labour intensive. Automated analysis systems could potentially save human resources and thus could facilitate the introduction of widespread photographic screening. In principle, these systems might improve diagnostic performance by increasing the objectivity of assessment. In practice, it will prove technically very difficult to develop a program that can identify the range of lesions seen by a trained observer using ophthalmoscopy. This review has not identified any computer-assisted system likely to offer a clinical solution in the near future.
- It is likely that those currently involved in providing retinal screening will be required to undertake the manual evaluation of digital images produced by a widespread photographic screening programme in the foreseeable future.

Implications for research

- Further studies are required to compare digital photography with conventional photography, when both sets of images are manually assessed by trained observers. In addition, digital photography should be assessed against the performance of those currently providing retinopathy screening by direct ophthalmoscopy.
- Screening which is dependent on the manual assessment of digital images will have significant human resource implications for the health service. Priority should be given to developing computer-assisted methods for automated interpretation of digital photographs.
- This review has shown that, worldwide, a number of research groups are developing methods for computer-assisted interpretation of digital images. At present, the emphasis appears to be on the development of programs aimed at identifying individual lesions. However, the diagnosis of retinopathy is dependent on detecting the presence or absence of multiple characteristic features. The development of a strategy to detect general diabetic retinopathy may benefit from collaboration between existing research groups. Clinician involvement will also be required to ensure that the techniques developed are appropriate for clinical practice.
- As methods for computer-assisted assessment are developed, their diagnostic performance should be assessed in a range of patient groups, such as those being screened for retinopathy and those already known to have retinopathy. These studies should incorporate comparison with conventional manual interpretation, validated against a 'gold standard'. Studies should be large enough to give estimates of diagnostic performance which are sufficiently precise to be clinically useful.
- Demonstration of adequate diagnostic performance is not a sufficient basis for introduction into the health service; this requires formal evaluation in clinical settings in respect of benefits, adverse effects, costs and resource use. A screening programme based on digital imaging should ideally be compared with current programmes before formal implementation.
- Digital fluorescein angiography has the potential to revolutionise practice within the ophthalmology clinic owing to the speed of image acquisition. Further research is needed to clarify the role of automated analysis of digital fluorescein angiograms in monitoring the progression of retinopathy. This review has not

identified a substitute for continued monitoring of patients with advanced retinopathy by ophthalmologists.

- SLO is a promising adjunct to other methods with potential application in the detection of macular oedema. It may have an application where cataract formation hinders photography. Further research is required to define its role in routine clinical practice.

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Search strategies

Search strategies used in main electronic databases

The following general search strategies for identification of studies reporting the use of either direct or indirect digital imaging techniques in the field of diabetic retinopathy were used.

MEDLINE

MEDLINE (National Library of Medicine, electronic version of Index Medicus, USA) on OVID, CD PLUS was searched from January 1980 to December 1997 using the following strategy:

- 01 retinopath\$.tw.
- 02 retinal hemorrhage/
- 03 retinal neovascularization/
- 04 microaneurysm\$.tw.
- 05 cotton wool spot\$.tw.
- 06 (exudate\$ adj2 (hard or retina\$ or soft or circinate)).tw.
- 07 (diabet\$ adj2 iridopath\$.tw).
- 08 diabetes mellitus/
- 09 diabetes mellitus, experimental/
- 10 diabetes mellitus, insulin-dependent/
- 11 wolfram syndrome/
- 12 diabetes mellitus, lipoatrophic/
- 13 diabetes mellitus, non-insulin-dependent/
- 14 diabetic angiopathies/
- 15 diabetic retinopathy/
- 16 diabetic ketoacidosis/
- 17 obesity in diabetes/
- 18 prediabetic state/
- 19 pregnancy in diabetes/
- 20 diabetes, gestational/
- 21 (neovascular\$ adj25 (retina\$ or optic)).tw.
- 22 (venous adj5 bead\$.tw.
- 23 (rubeosis adj2 (iris\$ or irid\$)).tw.
- 24 (macul\$ adj25 diabet\$.tw.
- 25 (diabet\$ adj25 (retina\$ or fundus or fundi or fundal)).tw.
- 26 vitreoretinopath\$.tw.
- 27 (retina\$ adj2 (perme\$ or leak\$)).tw.
- 28 ((epiretina\$ or subretina\$ or preretina\$ or posterio retina\$ or intraretina\$ or dot or flame or retina\$ or fundus or fundi or fundal) adj2 (haemorrhag\$ or hemorrhag\$)).tw.
- 29 or/ 1-28
- 30 "retinopathy of prematurity"/
- 31 29 not 30
- 32 (animal not human).sh.
- 33 31 not 32
- 34 lasers/
- 35 ophthalmoscopy/
- 36 34 and 35
- 37 (laser\$ adj25 ophthalmoscop\$.tw.
- 38 image interpretation, computer-assisted/
- 39 exp cineradiography/
- 40 radiographic image enhancement/
- 41 radiography, dual-energy scanned projection/
- 42 angiography, digital subtraction/
- 43 radiographic image interpretation, computer-assisted/
- 44 cineangiography/

- 45 fluorophotometry/
- 46 image enhancement/
- 47 subtraction technique/
- 48 image processing, computer-assisted/
- 49 diagnosis, computer-assisted/
- 50 imagenet.tw.
- 51 oculab.tw.
- 52 megavision.tw.
- 53 ((digit\$ or computer\$) adj25 (camera\$ or imag\$ or technolog\$ or subtract\$)).tw.
- 54 ((retina\$ or fundus or fundi or fundal) adj25 (digit\$ or computer\$)).tw.
- 55 (tomogr\$ adj25 (retina\$ or fundus or fundi or fundal)).tw.
- 56 ((MRI or resonance) adj25 (retina\$ or fundus or fundi or fundal)).tw.
- 57 quantnet.tw.
- 58 topcon.tw.
- 59 confocal.tw.
- 60 ((digit\$ or computer\$) adj25 (camera\$ or imag\$ or technolog\$ or record\$)).tw.
- 61 ((digit\$ or computer\$) adj25 record\$.tw.
- 62 (automat\$ adj25 (camera\$ or imag\$)).tw.
- 63 ((digit\$ or automat\$ or computer\$) adj25 photogr\$.tw.
- 64 exp "tape recording"/
- 65 exp optical storage devices/
- 66 microscopy, video/
- 67 microscopy, confocal/
- 68 video\$.tw.
- 69 (tape\$ adj2 record\$.tw.
- 70 (automat\$ adj25 (detect\$ or quantifi\$)).tw.
- 71 ((laser\$ or digit\$ or computer\$) adj2 angiograph\$.tw.
- 72 or/36-71
- 73 microradiography/
- 74 fluorescein angiography/
- 75 radionuclide angiography/
- 76 radionuclide imaging/
- 77 cineangiograph\$.tw.
- 78 fluorophotometr\$.tw.
- 79 or/ 73-78
- 80 53 or 54
- 81 79 and 80
- 82 72 or 81
- 83 33 and 82

Key: / = MeSH (Medical Subject Heading) term; exp = exploded MeSH term; \$ = wildcard; adj n = adjacent, within n words either side of the other term; tw = searches in title and abstract.

EMBASE

EMBASE (BIDS, OVID interface) (Elsevier Science Publishers, electronic version of Excerpta Medica, Amsterdam) was searched from January 1993 to October 1997 using the following search terms:

- 01 exp diabetes mellitus/
- 02 explode retinopathy/
- 03 exp retinopathy/
- 04 (retinopath\$ or retina or fundus or fundi or fundal).ti,ab,hw,tn,mf.
- 05 1 or 3 or 4
- 06 (topcon or quantnet or imagenet).ti,ab,hw,tn,mf.
- 07 (laser\$ adj25 ophthalmoscop\$).ti,ab,hw,tn,mf.
- 08 ((laser\$ or digit\$ or computer\$) and angiograph\$).ti,ab,hw,tn,rnf.
- 09 (automat\$ adj25 (detect\$ or quantif\$)).ti,ab,hw,tn,mf.
- 10 ((laser\$ or digit\$ or computer\$) adj25 angiograph\$).ti,ab,hw,tn,mf.
- 11 ((digit\$ or automat\$ or computer\$) adj25 (photogr\$ or camera\$ or imag\$ or technolog\$)) ti,ab,hw,tn,rnf.
- 12 (automat\$ adj25 (camera\$ or imag\$)) ti,ab,hw,tn,mf.
- 13 or/6-12
- 14 5 and 13

Key: / = EMTREE term; exp = exploded EMTREE term; \$ = wildcard; adj n = adjacent, within n words either side of the other term; ti,ab,hw,tn,rnf = searches in title, abstract, subject heading word, trade name and manufacturer name.

Science Citation Index

Science Citation Index (electronic version, paper version of same name, produced by ISI, Institute for Scientific Information, Philadelphia, PA, USA) on BIDS was searched from January 1994 to 25 November 1997 using the following search terms:

- 01 ((digit*, computer*) + technolog*)@TKA.
- 02 (automat* + technol*)@TKA
- 03 ((camera*, imag*) + automat*)@TKA.
- 04 ((digit*, automat*, computer*) + photogr*)@TKA
- 05 ((detect*, quantif*) + automat*)@TKA
- 06 (digit* + camera*)@TKA.
- 07 (topcon, quantnet, imagenet)@TKA
- 08 ((laser*, digit*, computer*) + angiograph*)@TKA.
- 09 (laser* + ophthalmoscop*)@TKA,
- 10 12,3,4,5,6,7,8,9
- 11 (diabet*, retinopath*, retina, fundus, fundal, fundi)@TKA
- 12 10+11

Key: TKA = title, abstract, keyword; * = wildcard.

Ei Compendex Plus

Ei Compendex Plus (Computerized Engineering

Index, electronic version of The Engineering Index, produced by Engineering Information, Hoboken, NJ, USA) on BIDS was searched from January 1994 to 25 November 1997 using the following search terms:

- 01 ((digit*, computer*) + technolog*)@TI,AB,EI,FL
- 02 (automat* + technol*)@TI,AB,EI,FL
- 03 ((camera*, imag*) + automat*)@TI,AB,EI,FL
- 04 ((digit*, automat*, computer*) + photogr*)@TI,AB,EI,FL
- 05 ((detect*, quantif*) + automat*)@TI,AB,EI,FL
- 06 (digit* + camera*)@TI,AB,EI,FL
- 07 ((laser*, digit*, computer*) + angiograph*)@TI,AB,EI,FL
- 08 (laser* + ophthalmoscop*)@TI,AB,EI,FL
- 09 (topcon, quantnet, imagenet)@TI,AB,EI,FL
- 10 1,2,3,4,5,6,7,8,9
- 11 (diabet*)@TI,AB,EI,FL
- 12 (retinopath*, retina, fundus, fundi, fundal)@TI,AB,EI,FL
- 13 11,12
- 14 10+13

Key: TI,AB,EI,FL = searches in title, abstract, descriptors and identifiers; * = wildcard.

Cochrane Library

Cochrane Library: The Cochrane Library (database on disk and CDROM). The Cochrane Collaboration; 1997, Issue 3. Oxford: Update Software; 1997. Updated quarterly (searched on 15 October 1997).

The following databases, available through the Cochrane Library were systematically searched:

- The Cochrane Database of Systematic Reviews
- Database of Abstracts of Reviews of Effectiveness (DARE)
- The Cochrane Controlled Trials Register

The following search terms were used:

- 01 = LASERS
- 02 = OPHTHALMOSCOPY
- 03 = #1 and #3
- 04 = IMAGE INTERPRETATION COMPUTER ASSISTED
- 05 = * CINERADIOGRAPHY
- 06 = RADIOGRAPHIC IMAGE ENHANCEMENT
- 07 = RADIOGRAPHY DUAL ENERGY SCANNED PROJECTION

08 = ANGIOGRAPHY DIGITAL SUBTRACTION
 09 = RADIOGRAPHIC IMAGE
 INTERPRETATION COMPUTER
 ASSISTED
 10 = CINEANGIOGRAPHY
 11 = FLUOROPHOTOMETRY
 12 = IMAGE ENHANCEMENT
 13 = SUBTRACTION TECHNIQUE
 14 = IMAGE PROCESSING COMPUTER
 ASSISTED
 15 = DIAGNOSIS COMPUTER ASSISTED
 16 = MICRORADIOGRAPHY
 17 = FLUORESC EIN ANGIOGRAPHY
 18 = RADIONUCLIDE ANGIOGRAPHY
 19 = RADIONUCLIDE IMAGING
 20 =* TAPE RECORDING
 21 =* OPTICAL STORAGE DEVICES
 22 = MICROSCOPY VIDEO
 23 = MICROSCOPY CONFOCAL
 24 = #1 or #2 or #3 or #4 or #5 or #6 or #7 or
 #8 or #9 or #10 or #11 or #12 or #13 or
 #14 or #15 or #16 or #17 or #18 or #19
 or #20 or #21 or #22 or #23
 25 = RETINAL HEMORRHAGE
 26 = RETINAL NEOVASCULARIZATION
 27 = * DIABETES MELLITUS
 28 = DIABETES MELLITUS EXPERIMENTAL
 29 = DIABETES MELLITUS INSULIN
 DEPENDENT
 30 = WOLFRAM SYNDROME
 31 = DIABETES MELLITUS LIPOATROPHIC
 32 = DIABETES MELLITUS NON INSULIN
 DEPENDENT
 33 =* DIABETIC ANGIOPATHIES
 34 = DIABETIC KETOACIDOSIS
 35 = OBESITY IN DIABETES
 36 = PREDIABETIC STATE
 37 = * PREGNANCY IN DIABETES
 38 = #25 or #26 or #27 or #28 or #29 or #30
 or #31 or #32 or #33 or #34 or #35 or
 #36 or #37

39 = RETINOPATH* or RETINA* or FUNDUS
 or FUNDAL or FUNDI
 40 = #38 or #39
 41 = DIGIT* or COMPUTER* or AUTOMAT*
 42 = CAMERA* or IMAG* or TECHNOLOG* or
 PHOTOGR*
 43 = #41 and #42
 44 = TOPCON or QUANTNET and IMAGENET
 45 = LASER* near OPI-ITHALMOSCO*
 46 = (LASER* or DIGIT* or COMPUTER*) and
 ANGIOGRAPH*
 47 = AUTOMAT* and (DETECT* or
 QUANTIF*)
 48 = #24 or #43 or #44 or #45 or #46 or #47
 49 = #40 and #48

Lines 1–37 (inclusive) are MeSH terms. Lines
 39–47 are searches in title and abstract.

Key: * (at end of term) = wildcard; * (at start of
 term) = exploded MeSH search (do not use this
 symbol directly on the search line, at the present
 time can only explode a search by using the on-
 screen ‘explode search’ key).

Other strategies

NRR

NRR (National Research Register) on Idealist
 (14th consolidation, September 1996).

Search terms used:

diabetic retinopathy diabet* and (digit* or
 comput*) retina* and (imag* or automat* or
 digit* or camera* or comput*)

Key: * = indicates words starting with these
 letters.

Letter and forms sent to authors

Director
Adrian Grant
Programme Directors
Jeremy Grimshaw
Simon Naji

HEALTH SERVICES RESEARCH UNIT
DEPARTMENT OF PUBLIC HEALTH
DREW KAY WING POLWARTH BUILDING FORESTERHILL
ABERDEEN AB25 2ZD
Fax 01224-663087 Telephone 01224-681818 Ext 43307
e-mail: m.odonnell@abdn.ac.uk

6 August 1997

Name of author/s

Dear

Digital Imaging in Diabetic Retinopathy

We are undertaking a systematic literature review to evaluate the current role of digital imaging techniques in the field of diabetic retinopathy, investigating both the clinical applications of screening and experimental techniques of studying disease pathogenesis. Although our primary review will focus on the use of fundal photography, encompassing direct acquisition of digital images and indirect digitisation of conventional photography, we are extending our search to include other relevant techniques.

One of your studies (detailed below) has been identified as relevant to our review:
"Insert name of study"

We would be grateful if you would provide us with information on any additional research, unpublished or on-going, that you may know of relating to digital imaging techniques in diabetic retinopathy. You can contact us via fax or email (see above) or by filling in the enclosed forms and returning them to us in the accompanying envelope.

Yours sincerely

Dr Fiona Strachan
Clinical Research Fellow in
Diabetes and Ophthalmology

Maire O'Donnell
Health Services Research Unit
University of Aberdeen

DIABETIC RETINOPATHY

DIGITAL IMAGING TECHNIQUES

Question 1

Do you have any additional publications or on-going research relating to the use of **digital fundus photography** (either direct acquisition or indirect digitisation of conventional photography)?

Yes

No

If **Yes**, could you please give further details by filling in the enclosed **yellow Studies Form**



Question 2

Are you aware of **any other studies**, unpublished or ongoing, relating to the use of **digital fundus photography** (either direct acquisition or indirect digitisation of conventional photography)?

Yes

No

If **Yes**, could you please give further details by filling in the enclosed **yellow Studies Form**



Question 3

Are you aware of **any other studies**, unpublished or ongoing, using **other digital imaging techniques** (either direct acquisition or indirect digitisation)?

Yes

No

If **Yes**, could you please give further details by filling in the enclosed **yellow Studies Form**

DIABETIC RETINOPATHY AND DIGITAL IMAGING TECHNIQUES

OTHER STUDIES

If you know of any other studies please fill in available details below:

Title	
Authors	
Department and Address of Institution	
Published or presented	Yes/No (please circle one)
Journal or Conference	
Volume/Number/Pages	

Title	
Authors	
Department and Address of Institution	
Published or presented	Yes/No (please circle one)
Journal or Conference	
Volume/Number/Pages	

DATA FORM

Individual Features of Retinopathy

Study Title:

Population understudy:

'Gold Standard' used for comparison:

Key Feature	Criteria for test positive	Sensitivity (%)	Confidence interval 95%	Specificity (%)	Confidence interval 95%
Microaneurysm					
Blot/dot haemorrhage					
Hard exudate					
Cotton-wool spot (soft exudate)					
Venous beading					
Intra-retinal microvascular abnormalities					
Neovascularisation					
– general					
– new vessels disc					
– new vessels elsewhere					
Pre-retinal haemorrhage					
Vitreous haemorrhage					
Macular oedema/retinal thickening					
Other – please specify					

Appendix 2

Consent form, letter of invitation and patient information sheet

CONSENT FORM

CONSENT BY PATIENT/VOLUNTEER TO PARTICIPATE IN:-

..... DIGITAL IMAGING IN DIABETIC RETINOPATHY STUDY

Name of Patient/Volunteer:

Name of Study.

Principal Investigator: Prof P Sharp/Prof JV Forrester

I have read the patient/volunteer information sheet on the above study and have had the opportunity to discuss the details with Dr F Strachan and ask questions. The doctor has explained to me the nature of the tests to be undertaken. I understand fully what is proposed to be done.

I have agreed to take part in the study as it has been outlined to me, but I understand that I am completely free to withdraw from the study or any part of the study at any time I wish and that this will not affect my continuing medical treatment in any way.

I understand that these trials are part of a research project designed to promote medical knowledge, which has been approved by the Joint Ethical Committee, and may be of no benefit to me personally.

I also understand that, where appropriate, my General Practitioner will be informed that I have taken part in this study.

I hereby fully and freely consent to participate in the study which has been fully explained to me.

Signature of Patient/Volunteer:

Date:

I confirm that I have explained to the patient/volunteer named above the nature and purpose of the tests to be undertaken.

Signature of Investigator:

Aberdeen Royal Hospitals

Ophthalmology Out-Patient Department
Aberdeen Royal Hospital NHS Trust
Foresterhill
Aberdeen

04/11/97

Dear Mr/Mrs/Ms XXXXX

Digital Imaging In Diabetic Retinopathy Study

Following our recent conversation about the above research project at the Woolmanhill Diabetic Clinic, I am writing to inform you of the proposed appointments arranged for yourself at both the ophthalmology and optician clinics. **Please remember that at both appointments we will be required to administer eye-drops to allow thorough examination.**

Ophthalmology Clinic 07/11/97 at 02.00pm

The Ophthalmology Out-patient Department is situated opposite the A&E Department on the Foresterhill site, overlooking Westburn Road. This appointment will last approximately one and a half hours.

Optician Appointment 20/11/97 in the afternoon

Participating Optician Ms C Keith
Douglas Straine – Opticians
49 Rose Street
Aberdeen
Tel 01224 624103

For convenience, please contact our study optician to arrange a mutually convenient appointment time on the date given above.

If you have difficulty in keeping either of these appointments or wish to discuss any aspect of the project, please do not hesitate to contact me on 0802 816833. Alternatively, a message can be left at the Ophthalmology Out-patient Department on 01224 681818 Extension 51150.

Yours sincerely,

Fiona Strachan
Research Registrar

Patient Information Sheet

Digital Imaging In Diabetic Retinopathy

Diabetic retinopathy, or diabetic eye disease, is a condition that may affect 1 in 3 people with diabetes and is seen more commonly the longer you have had diabetes. Sight-threatening changes occurring before vision is actually affected occur in 1 in 100 people with diabetes every year. It is at this stage that laser treatment is most effective in saving sight. People with diabetes therefore need to have their eyes checked with drops at least once a year.

At present the best way of picking up these sight-threatening changes is not known. Over 7000 people are known to have diabetes in Grampian and nationally 1 to 2% of the population is believed to be affected. It is obviously a huge problem for the NHS. In Aberdeen, the University Departments of Biomedical Physics and Ophthalmology and the Diabetic Clinic, Woolmanhill have worked closely to develop computer programs that can detect and measure diabetic eye changes from computerised photographs. We have been given a grant from the NHS to compare this method with existing methods including screening by conventional photography, optometrists and ophthalmologists. If this proves successful, it may become the national way of screening for diabetic eye disease.

What does it involve?

Your eyes will be examined in the usual way at the diabetic clinic with dilating drops.

Group 1

If you have no or mild diabetic eye disease, you will be invited to attend the eye clinic at Foresterhill where your pupils will be dilated again, photographs will be taken and you will be examined by an ophthalmologist. A separate examination will also be arranged with an optometrist (optician). These examinations will be repeated again in one year.

Group 2

If you have moderate or severe diabetic eye disease you will need to attend the eye clinic anyway and as well as the above tests, a fluorescein angiogram would be required routinely. This involves the injection of a small amount of dye into a vein in the arm that travels to the vessels at the back of the eye to allow more accurate diagnosis. This would be repeated at 6 months and a year.

A small number of patients from Group 1 will also be invited to participate in this part of the project.

If you are found to have changes requiring laser treatment, this will be carried out in the usual manner and this study will not interfere with your routine care.

Thank you for your attention.

Fiona Strachan



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Aberdeen

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We look forward to hearing from you.