Effective and accurate screening for diabetic retinopathy using a 60° mydriatic fundus camera

T R Carmichael, G I Carp, N D Welsh, W J Kalk

Objectives. To establish whether an experienced endocrinologist could screen accurately for diabetic retinopathy using mydriatic 60° fundus photographs compared with a reference standard, viz. the combined highest scores of two experienced ophthalmologists.

Design. Retrospective review of 60° colour transparency photographs taken over a 6-year period. Retinopathy was graded in a standardised way.

Setting. Patients attending the diabetic clinic at Johannesburg Hospital, South Africa.

Subjects. Fifteen hundred and seventeen patients (2 446 eyes) formed the basis for the study. Patients were included if there was more than 50% readability of the fundus photographs.

Outcome measures. Outcome measures were prevalence of any retinopathy and presence of referable (severe) retinopathy. Inter-observer agreement was measured using the kappa statistic, and sensitivity and specificity of the screener were evaluated.

Results. The prevalence of retinopathy at the clinic was approximately 30%, but only about 12% was severe enough to warrant referral to the ophthalmology outpatient department. The endocrinologist was very accurate in determining cases requiring referral; there was 97% agreement with the reference standard, viz. the combined highest score of two experienced ophthalmologists (gold standard). Correlation on the determination of any retinopathy was less accurate (80% agreement), mostly owing to the endocrinologist reporting more isolated microaneurysms than the ophthalmologists. The screening method used gave a sensitivity of 83% and specificity of 99% which are within recommended standards.

Conclusions. The screening strategy using a mydriatic fundus camera at the diabetic clinic was found to be effective and accurate and greatly reduced the number of possible referrals to the ophthalmology outpatient department.

S Afr Med J 2005; **95:** 57-61.

Diabetic retinopathy is a leading cause of blindness in people in the working age group in developing and developed countries, and screening for retinopathy forms part of the strategy to reduce the morbidity associated with diabetes mellitus.[1]

Within the African context, shortages of medical personnel, funding and facilities make it imperative that these scarce resources are utilised optimally. Screening for diabetic retinopathy has been performed by several different kinds of health care personnel, including general practitioners and optometrists,[1] and dilated mydriatic colour fundus photography is currently regarded as the most effective screening strategy.[2] Screening using direct ophthalmoscopy has been shown to have low sensitivity (65%) compared with photography (89%).[3]

Fundus photographs have the advantage that a trained technician can do the screening and the photographs can later be viewed and graded by a medically trained person or else adequately graded by a technician.[4] The patient's photographs can be compared with standard fundus photographs, such as the Wisconsin set of standard photographs (**http://eyephoto.ophth.wisc.edu/**).

Complex and precise methods of grading retinopathy[4] may be required for research, but simpler classifications can facilitate rapid screening. A recent attempt to achieve consensus on common terminology also tried to produce a practicable method for clinical assessment.[5] The authors suggested three degrees of non-proliferative retinopathy, viz. mild, moderate and severe, as well as proliferative retinopathy. Maculopathy was graded separately but can simply be classified as present or absent if the severity of the maculopathy cannot be judged by the screening person. Once common terminology has been established, agreement might then be reached between screener and referral ophthalmologist on what grades of retinopathy require referral for treatment.

In South Africa, mydriatic fundus photography was found to be superior to both photography without mydriasis and direct ophthalmoscopy.[6] At the diabetic clinic at Johannesburg Hospital, 60° fundus photography was shown to compare well with one or two overlapping 45° field assessments and also with

Division of Ophthalmology, Department of Neurosciences, University of the Witwatersrand, Johannesburg

T R Carmichael, MB BCh, FCOphth (SA), PhD (Med)
G I Carp, MB BCh, FCOphth (SA)
N D Welsh, MB ChB, FCOphth (SA) MMed (Ophth)

Division of Endocrinology and Metabolism, Department of Medicine, University of the Witwatersrand, Johannesburg

W J Kalk, MB BCh, FRCP (Lond)

Corresponding author: *T R Carmichael (carmichaeltr@medicine.wits.ac.za)*

ophthalmologist screening.[7] Some associations with diabetic retinopathy at this clinic were later reported.[8] Severe diabetic retinopathy was found to be associated with African race group, and this group showed poorer glycaemic control and more systolic hypertension.

During the present study we tested the accuracy of the referral system and in particular established whether the endocrinologist missed cases warranting ophthalmological assessment. In this way it was hoped that the referral system might be improved to prevent avoidable vision loss.

Materials and methods

Diabetic patients attending the specialist diabetic clinic at Johannesburg Hospital had either one or both pupils dilated (tropicamide or cyclopentolate) during a routine clinic visit. A Canon CF-60 UV 60° fundus camera (35 mm colour transparency film) was used to perform mydriatic fundus colour photography centred on the macula.

Of the 1 595 patients screened, acceptable photographs of at least one eye were obtained for 1 517 patients (95.1%). In some patients insufficiently dilated pupils, cataracts or poor patient co-operation resulted in suboptimal photographic quality, which was not acceptable for screening purposes (more than 50% of the field was unreadable).

Each fundus photograph was scored according to a modification of the method of Davis *et al*.[9] (Table I) by an experienced endocrinologist/specialist physician (WJK). Three levels of retinopathy were defined: none (level 10), mild to moderate non-proliferative retinopathy (levels 20 and 30), and severe retinopathy (retinal score of 35 or higher). Patients with severe retinopathy were judged to warrant referral to the ophthalmology outpatient department for further assessment and possible treatment. The group included severe non-proliferative retinopathy, preproliferative and proliferative retinopathy, and maculopathy recognised as hard exudates within two disc diameters of the centre of the fovea.

During the present study, fundus photographs were reviewed over a 5-day period by two experienced consultant ophthalmologists (TRC and NDW) who viewed and scored the photographs independently of each other using the same criteria used by the endocrinologist. The slides were reviewed in a darkened room and projected to a size of about 2 m. Comparisons between the scores of the endocrinologist and the ophthalmologists were then made using the kappa statistic of agreement. For this statistic, 0.0 is poor agreement, 0 - 0.2 is slight, 0.21 - 0.4 is fair, 0.41 - 0.6 is moderate, 0.61 - 0.8 is substantial and 0.81 - 1.0 is almost perfect agreement.[10] Statistical analysis was performed using Stata version 8 software, Stata Corporation (College Station, Texas, USA). Where appropriate, a combined score of the highest score for the patient or eye by either ophthalmologist (gold standard) was used in the analysis to try to ascertain the 'true' retinal score for each eye or patient. This gold standard reference was used to reflect the worst possible score that the eye or patient might have had to give a combination of the gradings by the two ophthalmologists. Sensitivity and specificity were calculated according to the method described by Altman and Bland.[11] Demographic data and data pertaining to duration of diabetes (at the time of presentation to the clinic) and age of onset of diabetes were recorded and are reported, although they did not influence the main objective of the study which was to ascertain whether an experienced endocrinologist could use the fundus photographs to screen accurately for diabetic retinopathy.

Table I. Classification of diabetic retinopathy for retinal photographs

Score	Level of retinopathy
10	No retinopathy
20	Microaneurysms only (less than 20)
30	Microaneurysms 50 or less, haemorrhages 10 or less, hard exudates 5 or less and small, not near macula, questionable soft exudates, questionable IRMAs, questionable venous beading, definite venous loops
35	Hard exudates, 5 or less and small, within 2 disc diameters of macular centre
40	Microaneurysms > 50, haemorrhages > 10, hard exudates not near macula, definite soft exudates, definite IRMAs, definite venous beading
45	Hard exudates > 5 and/or larger, within 2 disc diameters of macular centre
50	As for score 40 but more severe and including at least 3 of: (*i*) microaneurysms 10 - 20 and haemorrhages 5 - 10; (*ii*) soft exudates > 2; (*iii*) definite IRMAs > 4 small areas or > 2 large areas; and (*iv*) venous beading > 2 veins
60	Neovascularisation, laser burns, score > level 50, may include macular oedema

IRMAs = intra-retinal microvascular abnormalities.

Results

Fifteen hundred and seventeen patients were included in the study. There were 2 446 eyes, of which 1 122 were right eyes and 1 324 left eyes. Nine hundred and twenty-nine patients (61.2%) had acceptable photographs of both eyes while 588 patients had acceptable photographs of only one eye.

The prevalence of any retinopathy as determined by the endocrinologist was 33.4% (507 patients). This was in comparison to 26.5% (402 patients), the highest score given to patients by the ophthalmologists. The prevalence of severe retinopathy was 11.7% (177 patients, endocrinologist) and 12.6% (191 patients, gold standard). The endocrinologist reported significantly more retinopathy than the combined ophthalmologists (two-sample test of proportion, $p = 0.0000$). However,

the difference between endocrinologist and ophthalmologists on severe retinopathy showed no significant difference. The difference in diagnosis of any retinopathy was due to an additional 99 patients with isolated microaneurysms (score 20) diagnosed by the endocrinologist but not seen/agreed on by the ophthalmologists.

As differences in prevalence have been reported for patients from different ethnic groups,[8] patients were stratified ethnically for comparison of demographic data (Table II).

The proportion of males was significantly different for the ethnic groups. There were significantly fewer black men at the clinic compared with whites. There were 44.6% men in the black group versus 57.8% in the white group ($p = 0.0000$, two-sample test of proportion). The proportion of men was not different for Indians (50.1%) versus whites ($p = 0.0829$) or for blacks versus Indians ($p = 0.1612$).

There were significant age differences between ethnic groups in the clinic, with the mean age for black patients of 45.8 years being lower than that for Indians (mean 48.4, $p = 0.0055$, Student's *t*-test) and whites (mean 48.5, $p = 0.0004$, Student's *t*-test). There was no significant difference between the ages of whites and Indians.

Age at diagnosis of diabetes was significantly higher for blacks (mean age 41.9 years, confidence interval (CI): 41.0 - 42.9) than for whites (mean 38.8 years, CI: 37.6 - 40.1) using the Student's *t*-test ($p = 0.0003$). There was no significant difference between the age of Indians (mean 40.9 years, CI: 39.08 - 42.75) and that of either blacks or whites.

The reported duration of diabetes differed by ethnic group, with the shortest duration in blacks (mean 4.2 years). This was significantly less ($p = 0.0000$, Student's *t*-test) than the duration in whites (mean 9.6 years) and Indians (mean 7.5 years). There was also a significant difference between duration in white and Indian patients ($p = 0.0115$, Student's *t*-test).

Compared with whites and Indians, blacks had significantly less retinopathy as scored by the endocrinologist (24.3%) and the combination of the highest scores given by either ophthalmologist (gold standard) viz. 20.1%. These differences were significant for the assessments by the endocrinologist using two-sample proportion tests of blacks versus whites ($p = 0.0000$) and blacks versus Indians ($p = 0.0004$). There was no significant difference between Indians and whites. Using the proportions scored on the gold standard there was again significantly less retinopathy in blacks than whites ($p = 0.0000$) and Indians ($p = 0.0193$).

From Table II it can be seen that the proportions of each ethnic group with severe retinopathy was about 12% with no significant differences between groups.

Among patients with any retinopathy, severe retinopathy was commonest in black patients, with 58.6% of patients needing referral (Table III). This figure was significantly higher than for whites (two-sample test of proportions, $p = 0.0050$), 42.3% of whom needed referral. Indian patients, with 54.4% severity, did not differ from either whites or blacks. Generally the proportion of patients with severe retinopathy increased with increasing duration of diabetes.

Patients were either referred or not referred based on the retinal score for one or two eyes. When the patient score for the endocrinologist was compared with the highest patient score for either ophthalmologist, this showed an agreement of 80.1%, with a kappa score of 0.59 showing moderate agreement. When the patients referred by the endocrinologist fell into the severe group, agreement between the endocrinologist and ophthalmologists was 'almost perfect' (agreement 96.6% with a kappa value of 0.84).

The endocrinologist referred 177/1 517 (11.7%) of the patients evaluated (Table IV). One or both ophthalmologists determined that 191 patients needed referral (12.6%).

There was a false-positive rate of 1.25% (19/1 517 patients). Neither ophthalmologist thought referral of these 19 patients

Table II. Characteristics of diabetic clinic patients by ethnic group

	Black	White	Indian
Number of patients (%)	588 (39)	739 (49)	180 (12)
Percentage of males in the group*	44.6	57.8	50.1
Mean age in years (CI)*	45.8 (44.9 - 46.7)	48.5 (47.3 - 49.6)	48.4 (46.7 - 50.1)
Mean age (years) at diagnosis (CI)*	41.91 (40.9 - 42.9)	38.80 (37.6 - 40.1)	40.91 (39.1 - 42.8)
Mean duration (years) of diabetes (CI)*	4.19 (3.5 - 4.8)	9.64 (8.9 - 10.4)	7.47 (6.2 - 8.8)
Prevalence of any retinopathy (%)			
CE*	24.3	39.4	37.8
Gold standard*	20.1	30.7	28.3
Severe retinopathy (score > 30) (%)			
CE	11.4	12.0	11.7
Gold standard	11.4	13.0	15.0

*Statistically significant difference.
CE = consultant endocrinologist; gold standard = the highest score given by either ophthalmologist.

Table III. Number of patients with diabetic retinopathy and severe retinopathy by ethnic origin and duration of diabetes (years)

Duration of diabetes (yrs)	Black			White			Indian		
	Retinopathy*	Severe (as a % of retinopathy)		Retinopathy*	Severe (as a % of retinopathy)		Retinopathy*	Severe (as a % of retinopathy)	
< 1	16	8	50.0	7	1	14.3	6	2	33.3
1 - 4	38	20	52.6	22	5	22.7	8	1	12.5
5 - 8	21	11	52.4	29	12	41.4	5	2	40
9 - 12	11	9	81.8	43	13	30.2	6	5	83.3
13 - 20	20	13	65.0	60	32	53.3	10	5	50
> 20	5	4	80.0	61	31	50.8	11	10	90.9
Total	111	65 (58.6)		222	94 (42.3)		46	25 (54.4)	

*Any diabetic retinopathy.

Table IV. Patients assessed as requiring referral by the highest rating from the consultant endocrinologist (CE) and consultant ophthalmologists (gold standard)

	Referral (gold standard)	No referral (gold standard)	
Referral (CE)	158	19†	177
No referral (CE)	33*	1 307	1 340
	191	1 326	1 517

*False-negative cases.
†False-positive cases.

was necessary. Of more concern was the 2.2% false-negative rate (33/1 517 patients) where at least one of the ophthalmologists thought the case should have been referred. In 8 cases, both ophthalmologists thought a referral was necessary. There was therefore also a difference of opinion between ophthalmologists on referral in 25 of the cases.

This gave a sensitivity for screening by the endocrinologist of 83%, so some cases were not referred which were thought to require referral, and a specificity of 99% (if the endocrinologist did not refer, the ophthalmologists almost always agreed).

Of the 33 false-negative cases that were not referred, 24 (73%) had exudates in the macula and a further 7 (21%) had either new vessels or laser burns.

Discussion

The prevalence of retinopathy in the diabetic clinic was approximately 30%, but only about 12% of patients screened were of a severity requiring referral.

There was excellent agreement between the endocrinologist and the ophthalmologists on which cases required referral. This was measured at 97% agreement (kappa value of 0.84). The agreement between screener and reviewers with regard to presence or absence of any retinopathy was less impressive (80% agreement, kappa value of 0.59). The difference was mostly in patients where microaneurysms only were present, with the screener tending to 'overdiagnose' isolated microaneurysms. This effect might have resulted from differences in viewing methods as the reviewers viewed the slides projected onto a screen at a rate of about 500 slides per day. Ophthalmologists screening a large number of slides over a short time period might be more inclined to scan quickly for pathology and in this way 'underreport' isolated microaneurysms. Since these cases were not referable, it was not an important difference.

The baseline level of diabetic retinopathy has been found to predict the prognosis and those with certain high-risk features are at very high risk of blindness.[12,13] In the Early Treatment Diabetic Retinopathy Study,[12] intraretinal microvascular abnormalities (IRMAs), haemorrhages and microaneurysms, and venous beading were found to be the most important predictors of progression to proliferative retinopathy. Severe vision loss (or vitrectomy) was found to follow the development of high-risk proliferative retinopathy,[13] as might be expected. For type 2 diabetics, if the patient had retinopathy restricted to microaneurysms, only 2 - 3% progressed to laser treatment within 9 years.[14] The authors found that if there was more than microaneurysms only, about one-third progress to require laser treatment by 12 years. Provided that they are referred, most patients with early retinopathy can be followed up annually should any sign of severity develop.

Within the clinic the race groups differed somewhat, with significantly more females among black patients. Black patients were significantly younger than the Indian and white patients. Some of these differences might be caused by socio-economic factors and might also reflect historical use of the clinic mainly by white patients in years gone by. The younger working black male might still have to access health care closer to his place of work, causing a difference in clinic distribution.

Age at diagnosis was significantly higher for black patients; this might reflect late diagnosis in this group or a greater proportion of type 2 diabetes. The duration of diabetes was shorter in black patients and this might also support late diagnosis in this group. The lower prevalence of retinopathy in blacks does not correlate with the more severe retinopathy seen

in most age groups in blacks when compared with the two other ethnic groups. This could be owing to a lower rate of isolated microaneurysm detection because of the darker pigmented fundus in the black subgroup, which may make it more difficult to identify microaneurysms in these patients.

Despite these differences, the screening method described gave a sensitivity of 83% and a specificity of 99%. This satisfies the British Diabetic Association standards of at least 80% sensitivity and 95% specificity for screening methods.[15]

This study confirms the accuracy of the screening method used at Johannesburg Hospital. Fundus photographs proved a sensitive method of screening and most patients requiring referral were accurately referred. There was a problem with the interpretation of maculopathy. Health care personnel should be aware of the need to refer patients with hard exudates near the fovea as this might require laser treatment to prevent vision loss. The results of this study support continued annual screening with mydriatic fundus photographs to determine which patients require referral to the ophthalmology clinic.

A similar strategy might be applicable in other areas of the country and could be applied by a range of suitable health care personnel, including adequately trained nursing staff, optometrists and general practitioners. If the referral base for diabetic patients is extended, preventable blindness might be avoided by early referral of patients requiring treatment.

References

1. Garvican L, Clowes J, Gillow T. Preservation of sight in diabetes: developing a national risk reduction programme. *Diabet Med* 2000; **17:** 627-634.
2. Richter B, Kohner E. Medical interventions for diabetic retinopathy. In: Wormald R, Smeeth L, Henshaw K, eds. *Evidence-based Ophthalmology*. London: BMJ Books, 2004: 331-338.
3. Harding SP, Broadbent DM, Neoh C, White MC, Vora J. Sensitivity and specificity of photography and direct ophthalmoscopy in screening for sight threatening eye disease: the Liverpool diabetic eye study. *BMJ* 1995; **311:** 1131-1135.
4. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs — an extension of the modified Airlie House classification. ETDRS report number 10. *Ophthalmology* 1991; **98:** 786-806.
5. Wilkinson CP, Ferris FL III, Klein RE, *et al*. representing the Global Diabetic Retinopathy Project Group. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology* 2003; **110:** 1677-1682.
6. Mollentze WF, Stulting AA, Steyn AF. Ophthalmoscopy versus non-mydriatic fundus photography in the detection of diabetic retinopathy in black patients. *S Afr Med J* 1990: **78:** 248-250.
7. Joannou J, Kalk WJ, Mahomed I, *et al*. Screening for diabetic retinopathy in South Africa with 60 retinal colour photography. *J Intern Med* 1996; **239:** 43-47.
8. Kalk WJ, Joannou J, Ntsepo S, Mahomed I, Mahanlal P, Becker PJ. Ethnic differences in the clinical and laboratory associations with retinopathy in adult onset diabetes: studies in patients of African, European and Indian origins. *J Intern Med* 1997; **241:** 31-37.
9. Davis MD, Hubbard LD, Trautman J, Klein R for the KROC collaborative study group. Studies of retinopathy. Methodology for assessment and classification with fundus photographs. *Diabetes* 1985; **34:** (Suppl. 3), 42-49.
10. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977; **33:** 159-174.
11. Altman DG, Bland JM. Diagnostic tests 1: sensitivity and specificity. *BMJ* 1994; **308:** 1552.
12. Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS report number 12. *Ophthalmology* 1991; **98:** Suppl., 823-833.
13. Davis MD, Fisher MR, Gangnon RE, *et al*. for the Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for high-risk proliferative diabetic retinopathy and severe visual loss: Early Treatment Diabetic Retinopathy Study Report #18. *Invest Ophthalmol Vis Sci* 1998; **39:** 233-252.
14. Kohner EM, Stratton IM, Aldington SJ, Holman RR, Matthews DR; UK Prospective Diabetes Study (UKPDS) Group. Relationship between the severity of retinopathy and progression to photocoagulation in patients with type 2 diabetes mellitus in the UKPDS (UKPDS 52). *Diabet Med* 2001; **18:** 178-184.
15. British Diabetic Association. *Retinal Photography Screening for Diabetic Eye Disease. A British Diabetic Association Report*. London: British Diabetic Association, 1997.

Accepted 23 August 2003.