Targeted mydriasis strategies for diabetic retinopathy screening clinics

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CLINICAL STUDY

Abstract

Purpose To examine factors necessitating pupil dilation to achieve gradable diabetic screening photographs using a digital non-mydriatic camera and to establish techniques to predict the need for dilation and to validate them.

Methods Prospective clinic-based cross-sectional study with follow-up validation study. The participants' involved consecutive patients attending the diabetic retinopathy screening clinic at a University Hospital. Best corrected visual acuity, age, sex, pupil size, mean spherical equivalent, cataract grade and the requirement for dilation to achieve gradable photographs in 90 patients were recorded. Data analysis using principal component analysis and multivariate analysis of variance derived a set of equations to predict the requirement for dilation. The predictive powers of these equations were validated in an independent group of 51 patients.

Results Smaller pupil size, denser nuclear colour, older age, poorer best-corrected visual acuity, cortical lens opacity and posterior subcapsular lens opacity were associated with the need for dilation ($P < 0.001$ in all). Single variables used in isolation had a poorer predictive value than combining variables. Dilating patients with either a pupil size > 3.75 mm or age > 59 years correctly allocates 83 and 78% of patients, respectively to dilation or not. Combining pupil size with age produces a decision table that improves the predictive value to 84%. In the validation study this table had a predictive value of 80%.

Conclusion We have produced and validated criteria based on a range of clinical variables for application in a clinical setting that allows for the development of targeted mydriasis.

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Introduction

Diabetic retinopathy (DR) remains the leading cause of blindness in the Western world in the 20- to 60-year-old age group.¹ Visual loss from DR is largely preventable with proper screening and timely application of photocoagulation therapy.^{2,3} Over the next decade the incidence and prevalence of diabetes has been projected to increase, primarily due to changes in lifestyle and increasing survival placing a larger demand on already overburdened screening services.⁴ Thus, any technique that increases the efficiency and patient acceptance of screening is desirable.

Digital 45-degree non-mydriatic cameras have been advocated as an effective method of screening for sight-threatening diabetic retinopathy.^{5,6} Two approaches have been advocated for such screening, either attempting non-mydriatic photography and using mydriasis after a screening failure or routinely using mydriasis in all patients. In 'staged mydriasis' drops are only given when there is an inadequate non-mydriatic photograph.⁷ This removes the need for mydriasis for many patients but significantly increases visit duration for those requiring dilation and increases the number of photographs required. Others recommend the routine use of mydriasis on the premise that there is a reduced technical failure rate and improved sensitivity and specificity for the detection of diabetic retinopathy and for the ease of organisation.⁸ However, the use of mydriasis may have a negative impact on the patient. Mydriasis using tropicamide 1% can interfere with the patient's lifestyle by reducing visual acuity and decreasing their amplitude of accommodation, restricting driving and the return to

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employment.^{9–12} This may discourage attendance for the screening visit particularly in the younger age group who are more at risk for non-attendance.¹³ A recent study found that many return to work and drive immediately after the appointment and the introduction of the routine use of drops may discourage attendance.¹⁴ Developing rules to predict the requirement for pupil dilation offers a compromise between these two models that captures the benefits of both. A set of rules that allows the targeting of mydriasis to those that require it has a range of potential benefits including: minimising patient time in the clinic, decreasing the number of photographs required, improving screening efficiency and acceptability to patients. To be clinically useful and to prevent adding another administrative burden to the screening process this tool must need to be simple, quick and easy to use.

The aim of our study was to examine which factors are associated with the need for pupil dilation to achieve gradable diabetic screening photographs. Using these data, a secondary aim was to establish rules that predict the need for dilation and to validate these rules prospectively in an independent group of patients.

Methods

Patients

Patients were recruited consecutively from the diabetic eye-screening clinic of the Mater Misericordiae University Hospital, Dublin. Patients who were under 18 years of age, pseudophakic or pregnant were not included in the study as they attend the ophthalmology clinic. The study was conducted in accordance with the tenets of the Declaration of Helsinki and informed patient consent was obtained before study inclusion.

Initial cross sectional study

Informed consent was obtained from all 90 patients who were approached. The patients' age, mean spherical equivalent, best-corrected visual acuity (BCVA), pupil diameter, and cataract density was measured and documented by an ophthalmologist (POB). The BCVA was measured using a Snellen chart at 6 m and was converted into decimal form. Similar to a method used by Starck *et al*,¹⁵ each patient's pupil diameter was estimated in a darkened room using the height of the slit lamp's vertical slit-beam. The nurse photographer in another darkened room took two non-mydriatic photographs (45 degree) of both the right and left eyes using a Topcon TRC-NW100 non-mydriatic digital fundus camera (Topcon Medical Systems, Paramus, NJ, USA). One image was centred on the macula and the second on the optic

disc. The right eye was photographed first, after 5 min of adaptation to the dark. Each patient then had 1% tropicamide drops instilled into both eyes and waited for 15 min, before re-examination at the slit lamp by the ophthalmologist. Their cataract density was measured according to the LOCS III grading scale.¹⁶ If the initial photographs were not gradable, repeat mydriatic photographs were performed. Similar to the system used by Murgatroyd *et al*,¹⁷ images were determined to be gradable if the small vessels were defined, more than 3/4 of the image was viewable and the fovea was visible on the macula centred view.

These data were divided into two groups based on the patient requiring dilation or not to achieve gradable photographs. Each of the measured variables and linear combinations of the variables were analysed (by principal component analysis) to determine their predictive value in determining the need for pupil dilation.

Statistical methods

Data was analysed using an Excel (Microsoft Inc.) database and Matlab (Mathworks Inc. Version 6.5 Release 13.0.1). In the initial cross-sectional study the right eye of each patient was used for statistical analysis to derive the weighting for each factor to prevent second eye bias. In comparing individual factors (age, visual acuity, etc) unpaired Student's *t*-tests was used when these data were normally distributed and the Mann-Whitney test for data with non-normal distribution. *P*-values less than 0.05 were deemed to be significant.

Principal component analysis was used to transform the number of correlated variables (eg, age and cataract) into a smaller number of derived variables, each a linear combination of two or more variables in the original data. These derived variables generally have better predictive capabilities than any individual variable. This was performed using Matlab MANOVA1 function. The parameters lead to the creation of equations that generate a result that is either positive or negative in value. In this case a negative value indicated that the patient should be dilated and positive that no dilation was required. Using this approach a number of equations were created that gave the maximal predictive accuracy for each combination of variables.

Validation study

A further study was undertaken to test the reproducibility of the equations generated from the initial cross-sectional study on an independent group of patients. Informed consent was obtained from all 51 patients approached. Patients had their BCVA, pupil size

and age documented in a similar manner to the previous study by a different ophthalmologist (ED). The nuclear colour was measured through an undilated pupil at the slit lamp using a beam angled at 45 degrees to the eye. The data for both eyes of each patient were then entered into the equations generated in the first study. In applying these predictive equations both eyes were assessed as the worst eye determines the need for dilation and parameters such as cataract grading and pupil size are not necessarily symmetrical. The result was based on the eye with the lowest score and compared with the success of non-mydriatic photography. The nurse photographer performed non-mydriatic fundal photography. If ungradable photographs were obtained mydriatic photographs were taken. The photographer was masked to the results of the predictions regarding need for dilation.

Results

Initial cross-sectional study

The mean age was 61 ± 15.7 years (range 22–88 years) with 51% female. Forty-six (51%) required dilating drops to achieve gradable photographs. The mydriatic photographs of one patient were ungradable (1.1%) due to cataract.

Smaller pupil size, denser nuclear colour, older age, poorer BCVA, cortical lens opacity, posterior subcapsular lens opacity, and hypermetropic refraction are associated with the need for mydriasis (Table 1).

Pupil size, nuclear colour and age in order of importance had the greatest weighting in predicting the

requirement for mydriasis on univariate analysis (Table 2).

The best single variable cutoff point that predicts the requirement for mydriasis is dilating patients with a pupil size <3.75 mm. This correctly allocated 83% to dilation or not. Other cutoff points of age ≥ 60 years or nuclear colour ≥ 1.3 or BCVA $\leq 6/6$ had predictive values of 77, 74, and 74% respectively.

The best combination of variables to predict the requirement for mydriasis is pupil size/nuclear colour/age and BCVA correctly allocating 86% of patients.

Similar results are seen with combinations of pupil size/BCVA/age and pupil size/BCVA. There was only a small loss in discrimination by using pupil size/age, pupil size/nuclear colour, pupil size/age/nuclear colour, and pupil size/nuclear colour/BCVA correctly allocating 84%. The equations for each combination of variables and their ability to predict the need for dilation in both the initial and validation study is detailed in Supplementary Table 1.

Table 2 Results of the univariate analysis of variance

Variables	F Ratio	P-value
Pupil size (mm)	64.374	<0.001
Nuclear colour	39.838	<0.001
Age	34.176	<0.001
Decimal BCVA	16.811	<0.001
Cortical cataract	11.196	0.001
Refraction	5.828	0.018
Posterior subcapsular cataract	5.267	0.024

Table 1 Comparison of the variables measured between the group that requires dilation to achieve gradable digital non-mydriatic fundal photographs (dilation group) and the group that does not (no dilation group)

Study	Variable	No dilation group mean (range)	Dilation group mean (range)	P-value
Initial cross sectional study	Age (years)	52.6 (22–88)	69.1 (35–88)	0.0001 ^a
	Pupil size (mm)	4.31 (3.1–5.7)	3.14 (2.0–4.2)	$<0.0001^a$
	BCVA	1.07 (0.17–1.6)	0.74 (0.17–1.6)	$<0.0001^b$
	Nuclear colour	1.12 (0.1–3.5)	2.42 (0.2–5.0)	$<0.0001^b$
	Cortical opacity	0.40 (0.1–2.0)	1.05 (0.1–5.5)	0.0005 ^b
	PSCO	0.21 (0.1–2.5)	0.58 (0.1–5.9)	0.0001 ^b
	Female	57% (25/44)	43% (19/44)	0.3018 ^c
Validation study	Age	51.1 (19–76)	68.8 (45–81)	$<0.0001^a$
	Right pupil size	4.52 (3.5–5.5)	3.23 (2.0–4.2)	$<0.001^a$
	Left pupil size	4.39 (3.0–6.0)	3.17 (2.0–4.0)	$<0.0001^a$
	Right BCVA	0.98 (0.01–1.5)	0.97 (0.3–1.5)	0.91 ^b
	Left BCVA	0.98 (0.16–1.5)	0.95 (0.2–1.5)	0.71 ^b
	Right NC	1.06 (0.1–3.0)	2.39 (0.1–4.7)	$<0.0001^b$
	Left NC	1.17 (0.1–4.0)	2.51 (0.1–4.5)	$<0.0001^b$

BCVA, best-corrected visual acuity; PSCO, posterior subcapsular opacity; NC, nuclear colour

^aUnpaired Student's *t*-test;

^bMann–Whitney test;

^cFisher's exact test (two-sided).

Validation study

The mean age of the patients was 60 ± 16 years (range 19–80 years) with 55% female. To achieve gradable photographs, 26 (51%) did not require dilation. There were no ungradable photographs.

Similar to the initial study patients who had gradable non-mydriatic photographs were younger, had a lower nuclear colour score and had a larger pupil size. However, there was no significant difference in mean BCVA between the groups (Table 1).

The predictive value of the devised single variable cutoffs and the equations for the combination of variables from the initial study were similar with only a small loss in discrimination. The same cutoff values for pupil size, age, nuclear colour, and BCVA generated in the initial study had predictive values of 77, 75, 78, and 53%, respectively.

As in the initial study the best combination of variables to predict the requirement for mydriasis was pupil size/nuclear colour/age, and BCVA, which correctly allocated 90% of patients. There was only a small loss in discrimination by using pupil size/nuclear colour (88% correct), pupil size/nuclear colour/age (86% correct), and pupil size/BCVA/nuclear colour (86% correct) (Supplementary Table 1).

The most clinically useful combination balancing ease of measurement and predictability is age and pupil size. The equation, $(\text{pupil (mm)} \times 1.401) - (\text{age (years)} \times 0.021) - 3.967$, correctly allocates 84.4% patients to mydriasis in the initial study and 80.4% in the validation study. Any patient with a negative value from the results of either eye requires dilation while those with a positive value in both eyes do not. The results of this equation for each patient of both studies are seen in Figure 1. Based on this equation we have designed a simple table that can be used in clinics that defines an age cutoff for dilation for a given pupil size (Table 3).

Discussion

Consistent with previous studies we have found that older age; smaller pupil size; cataract and poorer visual acuity are associated with ungradable non-mydriatic digital photographs.^{6,18–20} Using these data we have produced a simple decision table based on pupil size and age that provides a basis for implementing a strategy of targeted mydriasis.

In developing a clinical tool that predicts the requirement for mydriasis a balance between the maximal statistical performance and practicality must be made. Combining four variables (pupil size/nuclear colour/age, and BCVA) gave the best predictive result for individual patients (87%). A slit lamp is required to

Figure 1 Results of the equation combining age and pupil size to predict the need for dilation to achieve gradable fundal photographs using a non-mydriatic digital fundal camera in a diabetic retinopathy screening clinic. The equation was generated using principal component analysis and multivariate analysis of variance. Each point (a box or triangle) represents the result for one patient. Any point on or above the zero axis represents a patient allocated not to receive dilation and below the zero axis represents a patient allocated to receive dilation. The initial study involved the analysis of the factors that influence the need for mydriasis and generation of the equation. The validation study tested the reproducibility of the equation generated on an independent group of patients.

Table 3 A decision table that designates a cutoff for dilation to achieve gradable non-mydriatic fundal photographs based on the patient's pupil size and age

Smallest pupil size of the two eyes (mm)	Dilate patient if age greater than (years)
<3	All patients
3.25	27
3.5	44
3.75	61
4	77
4.25	94
4.5	No patients

measure nuclear colour. BCVA can be affected by other ocular pathology including of course diabetic retinopathy that may have no role on image quality. This is likely the cause of the non-association of BCVA with ungradable non-mydriatic photographs in the validation study. These factors and the time taken to enter the results into the equation make it impractical to include these variables in a targeted mydriasis strategy. The simplest method would be to use an age cutoff, which has been successfully used in some screening projects.²¹ However, combining pupil size with age

improves both the predictive capacity and robustness. Although, we used a slit lamp-based method of scotopic pupil measurement pupil size, it can be measured simply and accurately with a pupil card.²² Also, using just two variables allows the preparation of a simple decision table which obviates the need to enter the variables into an equation. Combining these two best addresses the balance between maximal statistical performance and practicality correctly allocating 85% of patients to dilation or not.

The national screening committee (NSC) recommends dilating all patients on the basis of the ease of organisation and improved image quality.⁸ A number of factors need to be taken into consideration before incorporating the table into the guidelines. Pupil size measured by any of the valid clinically accurate ways depend on the method and in particular the illumination in the clinic. As the level of illumination encountered and the method of measurement of pupil size in screening clinics may vary, the table may need to be modified based on the environment of that clinic. Furthermore, exact pupil cutoff for adequate image quality in a non-mydratic camera is likely to be machine dependent. The use of the table may generate efficiencies in the workflow of the clinic and cost savings. However, this would need to be confirmed by further research before implementation within the NSC guidelines.

Published rates for the proportion of ungradable photographs obtained without mydriasis using the digital 45-degree non-mydratic camera range from 6 to 49% depending on the criteria used.^{5,6,17,23,24} The differences in the rates can be explained in large part by the age of the population studied. We found that 50% of our patients had ungradable photographs. Those with a similar mean-aged population (60 years) as our study reported a poor/ungradable image rate for non-mydratic photos of approximately 50%.^{5,23}

In the validation study, we tested the reproducibility of the equations generated in the initial study to predict the requirement for dilation to achieve gradable photographs. This required grading the nuclear colour through an undilated pupil. Dilation is required to reliably estimate the degree of posterior subcapsular and cortical lens opacity, but neither of these variables was tested for in the validation study. We felt that it was possible to accurately assess nuclear colour through an undilated pupil. The results from the two studies in relation to nuclear sclerosis were similar supporting this approach.

In conclusion, we have found that pupil size, nuclear colour, and age are the strongest predictors for the requirement of dilation to achieve gradable photographs. Combining age and pupil size to predict the requirement for dilation allows the development of 'targeted

mydriasis'. This may lead to a more efficient and patient friendly photographic diabetic screening in both optometry and hospital-based settings by reducing both the proportion of patients dilated and the need for repeat photography.

Summary

What was known before

- Older age, smaller pupil size, cataract, longer duration of diabetes, and poorer visual acuity is associated with ungradable non-mydratic digital diabetic screening photographs. The use of mydriasis interferes with patients' visual acuity and can discourage attendance for screening.

What this study adds

- A comprehensive evaluation of a range of clinical variables that provides a basis for implementing a strategy of targeted mydriasis to those that require it to achieve gradable photographs. A validated simple decision table based on age and pupil size that can effectively predict those that require dilation to achieve gradable photographs.

Conflict of interest

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on Eye website (<http://www.nature.com/eye>)