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Update on Screening for Sight-Threatening Diabetic Retinopathy

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Abstract
Purpose: The aim of this article was to describe recent advances in the use of new technology in diabetic retinopathy screening by looking at studies that assessed the effectiveness and cost-effectiveness of these technologies. ***Methods:*** The author conducts an ongoing search for articles relating to screening or management of diabetic retinopathy utilising Zetoc with keywords and contents page lists from relevant journals. ***Results:*** The areas discussed in this article are reference standards, alternatives to digital photography, area of retina covered by the screening method, size of the device and hand-held cameras, mydriasis versus non-mydriasis or a combination, measurement of distance visual acuity, grading of images, use of automated grading analysis and cost-effectiveness of the new technologies. ***Conclusions:*** There have been many recent advances in technology that may be adopted in the future by screening programmes for sight-threatening diabetic retinopathy but each device will need to demonstrate effectiveness and cost-effectiveness before more widespread adoption.

Introduction

The Wilson and Junger criteria, which are the 1968 principles [1] applied by the World Health Organisation, have formed the basis of development of screening programmes and required an evidence base which I adapted [2] for sight-threatening diabetic retinopathy (STDR):

1. STDR is an important public health problem [3, 4]
2. The incidence of STDR is going to remain the same or become an even greater public health problem [5, 6]
3. STDR has a recognisable latent or early symptomatic stage [7–9]
4. Treatment for STDR is effective and agreed upon universally

Diabetic retinopathy (DR) can be prevented or the rate of deterioration reduced by improved control of blood glucose [10–12] and blood pressure [13, 14]. Laser treatment is effective [15, 16], and vascular endothelial growth factor inhibitors can improve the results of treatment in diabetic maculopathy [17, 18] and in some cases of proliferative DR [19, 20].

In this article I have concentrated on reviewing the updates in relation to the final two criteria:

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5. The test – a suitable and reliable screening test is available, acceptable to both health care professionals and (more importantly) to the public
6. Cost-effectiveness – the costs of screening and effective treatment of STDR are balanced economically in relation to total expenditure on health care – including the consequences of leaving the disease untreated

Methodology

The review of the literature relating to screening for DR has been ongoing since March 2000. The methodology involves a search technique for articles relating to screening or management of DR utilising Zetoc (http://zetoc.jisc.ac.uk/), which is a comprehensive research database, giving you access to over 34,500 journals and more than 55 million article citations and conference papers through the British Library's electronic table of contents covering 1993 to the present day and is updated daily.

Subject title keywords are searched daily using 21 different combinations (e.g., "retinopathy" or "digital" and "imaging" and "eye" in title), and contents page lists from 28 journals are reviewed monthly. Articles of interest identified with this search strategy were sourced from online electronic journal resources (e.g., Open Athens [21] or the Royal Society of Medicine [22]).

Results

The Test

Reference Standards for Digital Photographic and Other Screening Methods

There are two accepted reference standards to compare with any new screening methodology.

(a) 7-field (30-degree) stereo photography is considered the best reference standard.

The advantage of this reference standard is the area of retina covered and the detailed grading classification [23] which has been developed for this standard. The disadvantage is that the unassessable image rate is at 10% in one report from the Wisconsin Epidemiological Study of Diabetic Retinopathy [24] and, in many studies, not reported so is likely higher than that rate.

(b) Slit lamp biomicroscopy by an ophthalmologist is another accepted reference standard, although it is preferable with this methodology to use one or a small number of retinal specialists. The studies demonstrate significant variation compared to 7-field stereophotography with some studies in which the ophthalmologists performed poorly [25, 26], and others with better results [27, 28]. Gangaputra et al. [29] compared evaluation by clinical examination with image grading at a reading centre for the classification of DR and diabetic macular oedema and concluded that the results support the use of clinical information for defining broad severity categories but not for documenting small-to-moderate changes in DR over time.

Gangaputra et al. [30] also compared 35-mm film with digital photography and found that agreement between film and digital images was substantial to almost perfect for DR severity level and moderate to substantial for diabetic macular oedema and clinically significant macular oedema severity levels, respectively. The study concluded that replacement of film fundus images with digital images for DR severity level should not adversely affect clinical trial quality.

The "Exeter Standards," which were a consensus view formed at a meeting [31] in Exeter in the UK in 1988, formed the basis for a publication [32] for an acceptable method for use in a systematic screening programme for DR in the UK, which was adopted in the planning [33] of the English NHS Diabetic Eye Screening Programme. The Exeter Standards recommended that a screening test for STDR should achieve a minimum sensitivity of 80% and a minimum specificity of 95%.

A systematic review by Piyasena et al. [34] found that both mydriatic and non-mydriatic digital imaging methods generate a satisfactory level of sensitivity. The mean proportion of ungradable images in non-mydriatic methods was 18.4% (CI 13.6–23.3%) and for the mydriatic method 6.2% (CI 1.7–10.8%) and, once these were excluded from analysis:

(a) the 1-field non-mydriatic strategy gave summary estimates of sensitivity of 78% (CI 76–80%) and of specificity of 91% (CI 90–92%); the 2-field non-mydriatic strategy gave summary estimates of sensitivity of 91% (95% CI 90–93%) and of specificity of 94% (CI 93–95%);

(b) the 1-field mydriatic strategy gave summary estimates of sensitivity of 80% (CI 77–82%) and of specificity of 93% (CI 92–94%); the 2-field mydriatic strategy gave summary estimates of sensitivity of 85% (95% CI 84–87%) and of specificity of 82% (95% CI 81–83%).

The article concluded that, overall, there was no difference in sensitivity between non-mydriatic and mydriatic methods (86%, 95% CI 85–87%) after exclusion of ungradable images.

In the literature, studies vary as to whether they count ungradable images as test positive, and it is more likely that a study will achieve the 95% specificity if they do not count ungradable images as test positive.

Alternatives to Digital Photography

Goh et al. [35] produced a comprehensive review of retinal imaging techniques for DR screening. The most excit-

ing new technologies that may be used in screening in the future, providing they can be shown to be effective and cost-effective, are the scanning confocal ophthalmoscopes that use either laser light or light-emitting diodes (LED). Examples of 4 CE-marked scanning confocal ophthalmoscopes that are currently commercially available are discussed:

The Optos California which is described as ultrawide-field imaging incorporates low-powered laser wavelengths in red (635 nm), green (532 nm) and blue (488 nm) that scan simultaneously and produce a composite image that joins the 3 wavelengths of light into a false-colour image. In 2016, Silva et al. [36] compared the efficiency of non-mydriatic ultrawide-field imaging and non-mydriatic fundus photography in a DR ocular telehealth programme.

The Heidelberg Spectralis OCT2 with multicolour functionality also uses three laser wavelengths, blue (488 nm), green (515 nm) and infrared reflectance (820 nm), to simultaneously capture a composite false-colour image.

The Eidon confocal scanner (Centervue, Padova, Italy) combines confocal imaging with natural white-light illumination to provide a true-colour image using a white LED (440–650 nm).

The Zeiss Clarus 500 uses red (585–640 nm), green (500–585 nm) and blue (435–500 nm) LEDs to capture a composite image.

There have not yet been any major studies published using any of these imaging techniques in a DR screening setting.

The Area of Retina Covered by the Screening Method

The original 35-mm film fundus cameras that were used for 7-field stereophotography had 30-degree fields. In 1989, Moss et al. [24] demonstrated that for 8 retinopathy levels, the rate of agreement with 7 stereoscopic fields ranges from 80% for two 30-degree stereo fields to 91% for four 30-degree stereo fields.

The non-mydriatic digital fundus cameras that are widely used in screening programmes, whether or not the patient's eyes are dilated, usually have 45-degree fields. Population-based screening programmes that utilise non-mydriatic photography commonly capture a single 45-degree field centred on the fovea of each eye [37]. For many mydriatic schemes, two 45-degree fields are taken [38] – one centred on the fovea and one on the optic disc.

The Scanning Confocal Ophthalmoscopes have the fields of view shown below:

(a) *Heidelberg Spectralis OCT2 with multicolour functionality:* 1-field or 2-field non-mydriatic 55-degree image(s) per eye (when using supplementary lens)
(b) *Optos California:* 1-field non-mydriatic 200-degree image per eye
(c) *Zeiss Clarus 500:* 1-field non-mydriatic 130-degree image per eye
(d) *CentreVue Eidon:* 1- or 2-field non-mydriatic 60-degree image(s) per eye

Size of the Device and Hand-Held Cameras

There have been many claims for the use of smartphones in DR screening. There is an excellent review of potential devices by Bolster et al. [39]. Hand-held devices have historically performed poorly in DR screening [40] although a recent study suggested that they could be used for optic disc imaging [41] and another study suggested that a small device had been validated [42] for DR screening. The latter was an excellent study that compared the sensitivity and specificity of a "fundus on phone" camera, a smartphone-based retinal imaging system, as a screening tool for DR detection and DR severity in comparison with 7-standard field digital retinal photography. It was noteworthy that mydriasis was used and that the smartphone was fixed and the patient's head positioned using a slit lamp chin rest, overcoming many of the problems of movement of patient and operator that is associated with hand-held devices. It may be that the way forward with these small devices is to use an inexpensive device to fix them and a slit lamp chin rest for the patient.

Mydriasis versus Non-Mydriasis or a Combination of Both

A strong correlation has been reported [43] between older age and poor-quality image rate in non-mydriatic digital photography in DR screening. The main reason for this is higher rates of media opacity and smaller pupil sizes in older people. Scanlon et al. [44] reported an ungradable image rate for non-mydriatic photography of 19.7% (95% CI 18.4–21.0%), and Murgatroyd et al. [45] reported an ungradable image rate for non-mydriatic photography of 26%. The mean age of the patients in the study of Scanlon et al. [44] was 65 years, and in that of Murgatroyd et al. [45] the median age of the patients was 63.0 years (range 17–88 years, interquartile range 51.8–70.3 years). There is also an ethnicity component with some studies demonstrating poorer results for non-mydriatic digital photographic screening in eyes with more iris pigmentation [46]. Scotland introduced the concept of staged mydriasis into their screening programme, only dilating those who the technician taking the images determined had poor-quality images without mydriasis. As the age of the Scottish population has increased, the num-

bers needing dilation have risen to 34% [pers. commun. Mike Black, Scottish DRS Collaborative Coordinator].

Silva et al. [47] have demonstrated that the ungradable rate per patient for DR and diabetic macular oedema was significantly lower with non-mydriatic ultrawide-field imaging compared with non-mydriatic fundus photography (DR, 2.8 vs. 26.9%, $p < 0.0001$; diabetic macular oedema, 3.8 vs. 26.2%, $p < 0.0001$) in the Indian Health Service-JVN programme, which serves American Indian and Alaska Native communities.

Measurement of Distance Visual Acuity

Visual acuity is widely accepted as an adjunct to screening for diabetic maculopathy, but in isolation it is not sufficiently sensitive to be a screening tool [48, 49], and there is currently no study that supports the added benefit of visual acuity in screening. It is however, from the patient's perspective, probably the most important factor.

Grading the Images

In most screening programmes, trained graders grade the images, and the ones with the severer pathology are referred to ophthalmologists to decide on further management. Different grading criteria are used in different countries.

Use of Automated Analysis for Grading

Automated grading of images from DR screening has been pioneered in Scotland with the development of iGradingM (Scottish Health Innovations Ltd.) which has been used extensively as first level disease/no disease grader [50]. This includes an image quality assessment to reduce the workload of manual grading in the Scottish screening programme which takes 1-field non-mydriatic photographs.

Tufail et al. [51] reported on a study which included a total of 20,258 patients with 102,856 two-field per eye images. Three software products were tested, iGradingM (Scottish Health Innovations Ltd.), EyeArt (Eyenuk Inc., Woodland Hills, CA, USA) and Retmarker (Retmarker Ltd., Coimbra, Portugal), with the following sensitivities: EyeArt 94.7% (95% CI 94.2–95.2%) for any retinopathy (manual grades R1, U, M1, R2 and R3 as refined by arbitration), 93.8% (95% CI 92.9–94.6%) for referable retinopathy; corresponding sensitivities for Retmarker were 73.0% (95% CI 72.0–74.0%) for any retinopathy, 85.0% (95% CI 83.6–86.2%) for referable retinopathy. For manual grades R0 and no maculopathy (M0), specificity was 20% (95% CI 19–21%) for EyeArt and 53% (95% CI 52–54%) for Retmarker. In this study the version of iGradingM was unable to grade the nasal field.

The Iowa Detection Program (IDx-DR) is another software solution for automated grading that was tested [52] in the Hoorn Diabetes Care System in the Netherlands.

There are also a number of developing systems [53, 54] that are not yet commercially available.

Automated analysis of OCT images through use of deep learning is being explored in a collaborative project between Moorfields Eye Hospital and Google DeepMind [55] and in the Singapore Eye Research Centre [35].

A recent study [56] examined the variability in different methods of grading, definitions of reference standards, and their effects on building deep learning models for the detection of diabetic eye disease. The results from the studies are very dependent on the image sets that they are being tested upon.

Cost-Effectiveness

The cost-effectiveness of screening for STDR is dependent on the local health care system but there are various reports of screening being cost-effective in health care settings such as Singapore [57], Canada [58], South Africa [59] and India [60] with the proviso that low-risk groups can be identified and cost-effectiveness of screening for STDR can be improved in some settings by differential or individualised screening intervals for low- and high-risk groups [61–63]. Automated grading was shown to be cost-effective in the Scottish Screening Programme [64, 65], and the Tufail study [51] reported that two of the software packages that they tested (Retmarker and EyeArt) achieved acceptable sensitivity for referable retinopathy and false-positive rates (compared with human graders as reference standard) and appear to be cost-effective.

The use of OCT in screening has been considered but the cost of the equipment makes it more likely that this would only be useful as a second-line screening tool [66, 67] for those who are screen positive with 2-dimensional photographic markers for diabetic maculopathy.

With respect to the use of ultrawide-field imaging systems in DR screening programmes, a review by Fenner et al. [68] summed up the current situation that, despite the impressive outcomes in clinical trials, it remains unclear whether the cost savings of reduced inappropriate referrals are sufficient to justify the financial outlay.

Discussion/Conclusion

There have been many recent advances in technology that may be adopted by screening programmes for STDR in the future.

Most screening programmes currently use staged mydriasis with one 45-degree field non-mydriatic digital photography or two 45-degree field mydriatic digital photography. Advances in camera technology and in particular scanning confocal ophthalmoscopes with laser light or light-emitting diodes show good potential for non-mydriatic photography with wider fields. Each device will need to demonstrate effectiveness and cost-effectiveness before more widespread adoption. Automated reading of images is progressing, with Scotland having already introduced this into their national programmes and other countries likely to follow in the future.

Statement of Ethics

The author has no ethical conflicts to disclose.

Disclosure Statement

I have attended Advisory Boards for Pfizer, Allergan, Roche, Bayer and Boehringer.

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