Improving the economic value of photographic screening for optical coherence tomography-detectable macular oedema: a prospective, multicentre, UK study

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Scientific summary

The economic value of photographic screening for optical coherence tomography

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Scientific summary

Background

Compared with more established screening programmes, such as cervical and breast screening, diabetic retinopathy screening is still in its infancy: national screening programmes for diabetic retinopathy have been running throughout the UK for less than a decade.

The risk of retinopathy increases with disease duration. Type 2 diabetes is often diagnosed several years after onset (almost 40% of people with type 2 diabetes are found to have retinopathy at diagnosis). This is potentially sight-threatening in between 4% and 8% of cases. Sixty per cent of people with type 2 diabetes will have retinopathy 20 years from onset.

There are two main mechanisms responsible for visual loss from diabetic retinopathy. The first of these is proliferative retinopathy and the development of new blood vessels. The second is macular oedema (MO), the build-up of fluid involving the area of the retina associated with best vision, the macula. Although proliferative disease is most likely to lead to serious vision loss, MO is more common and is the leading cause of moderate visual loss in people with diabetes. However, laser treatment is only moderately effective, at best, for MO.

At the time of the introduction of national programmes for screening for diabetic retinopathy in the UK, screening for diabetic MO was not deemed to meet strict World Health Organization guidelines for screening. Diabetic retinopathy at the macula (maculopathy) is more common than proliferative diabetic retinopathy so retinal screening programmes have had to develop pathways to address this, although it is acknowledged that the evidence base for doing so is limited.

The current recommended method of retinal screening for diabetic retinopathy is digital fundus photography, a two-dimensional technology which cannot detect MO directly. Current photographic grading schemes rely on a combination of surrogate photographic markers, chosen by expert consensus, to infer the presence of MO. These manual grading schemes use combinations of features of retinopathy including microaneurysms/dot haemorrhages (M/DHs), blot haemorrhages (BHs), exudates and also visual acuity. At present, there is no consensus among the four nations as to which, and how many, features should be used to infer the presence of diabetic MO.

Clinical experience from the Grampian Retinal Screening Programme and Liverpool Screening Programme suggests that only 12–14% of these patients have evidence of MO, when examined by ophthalmologists using slit-lamp biomicroscopy.

Optical coherence tomography (OCT) is now recognised as the reference standard for measuring MO. It is an optical analogue of ultrasound imaging. The test is rapid, non-invasive and well tolerated by subjects. By acquiring a series of cross-sections it is possible to generate a thickness map of the macula. However, the equipment is still expensive.

Retinal ischaemia acts as a stimulus for the production of vascular endothelial growth factor. Vascular endothelial growth factor has very potent permeability-inducing properties, as well as stimulating angiogenesis. Currently there is a great deal of interest in the use of a range of treatments to counteract the action of vascular endothelial growth factor. Trials show, for the first time, that visual loss in people with diabetic MO can be reversed by intravitreal antivascular growth factor injection in approximately half of all treated patients, introducing a new paradigm in the treatment of diabetic MO and also now screening. It is probable that with these new treatments, screening for diabetic MO will meet the

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World Health Organization's criteria. Identifying patients, who will benefit most from these new therapies, is now an important issue for all diabetic retinopathy-screening programmes.

Objectives

The primary aim of the study was to determine the best photographic surrogate markers for detecting potentially sight-threatening diabetic MO, within English and Scottish national screening programmes. Specifically we wished to:

(a) investigate whether or not particular distributions and combinations of lesions (M/DHs, BHs and exudates), assessed manually or automatically, were more specific photographic surrogate markers of MO than current practice, using OCT as the reference standard
(b) assess the costs and consequences of using alternative distributions and combinations of these lesions to screen for MO, using either automated or manual detection of lesions
(c) model the long-term cost and quality-of-life implications of using alternative distributions and combinations of surrogate markers to screen for MO.

Once the study was under way, several screening programmes were found to be using OCT as part of the screening process to reduce false-positive referrals to the hospital eye service. Consequently, we added a further aim to assess the costs and consequences of using OCT within retinal screening programmes in addition to photographic surrogate markers, as this would affect how photographic markers would be used in future.

Methods

A total of 3540 patients with photographic signs of diabetic retinopathy visible within the macular region [exudates within two disc diameter radius (DD), M/DHs, BHs within one DD] were recruited from seven study centres at Aberdeen, Birmingham, Dundee, Dunfermline, Edinburgh, Liverpool and Oxford. Each subject had retinal photography and OCT on both eyes where possible.

Software was developed to assist the research nurse in the manual annotation of potential surrogate markers for MO (M/DHs, BHs and exudates), visible in the colour photographs.

Separate software was developed to analyse the distribution of retinal lesions, either annotated manually or automatically, to investigate whether or not particular distributions and combinations of lesions (M/DHs, BHs and exudates) within one or two DD from the centre of the fovea are more specific photographic surrogate markers of MO than current grading practice, using OCT as the reference standard.

The OCT images were analysed both quantitatively and qualitatively by the research nurse.

Statistical modelling was carried out to see if any of the manual grading schemes in England and Scotland included everything that might be considered important if starting from de novo. This information was used to inform the inclusion of various eye and subject characteristics within computer-assisted manual grading strategies and full automated grading strategies for detecting MO.

The grading strategies utilising photographic surrogate markers for detecting MO can be categorised as:

- *Manual grading strategies* These use photographic features in a binary fashion, similar to existing national criteria, which can be determined by visual inspection of retinal photographs by trained graders.

- *Computer-assisted manual annotation grading strategies* These use more detailed features obtained by manual annotation of retinal photographs which are then combined by a software classifier to determine a likelihood that MO is present.
- *Fully automated annotation grading strategies where no human intervention is required* These use features automatically annotated by image analysis software. As with computer-assisted manual annotation grading strategies, these are combined by a software classifier to determine a likelihood that MO is present.

A study was then carried out to assess the cost-effectiveness of alternative pathways for screening for MO using various combinations of photographic grading strategies, automation, visual acuity and OCT. An initial analysis focussed on the cost per true case of MO appropriately detected and referred. However, in most instances improvements in the sensitivity of the referral process come at the expense of decreased specificity. Thus, a secondary analysis assessed whether or not the increased costs associated with more sensitive screening strategies, resulting from more referrals to ophthalmology clinics (appropriate and inappropriate), are worth incurring given the potential health benefits. A Markov microsimulation model was developed for this purpose.

Results

The statistical analysis showed that the detection of MO in corresponding optical coherence tomograms was strongly related to the presence of retinal lesions in retinal photographs, being roughly five times more detectable among subjects with an exudate, a BH, or a M/DH present within one DD compared with the same lesion being absent. Having more than two M/DHs within one DD in an eye was of particular importance.

Subjects with worse visual acuity were about five times as likely to have MO in the relevant eye as those with better visual acuity.

The best-performing photographic grading strategy was a computer-assisted manual annotation grading strategy. This uses the results of manual annotation of the individual lesions in each image. Computer-assisted manual annotation is, however, a time-consuming procedure and so is unlikely to be considered for routine screening practice. Therefore, this strategy was not taken forward for economic analysis. Grading strategies relying on the manual annotation of retinal images without computer assistance of all retinal images were similarly not included.

The manual grading strategies chosen for comparison in the economic analysis included the current English grading scheme (manual grading strategy 1) and the current Scottish grading scheme (manual grading strategy 2). Manual grading strategy 2 is one of the higher-specificity, simple, manual grading strategies (59.5% sensitivity; 79% specificity) whereas manual grading strategy 1 represents a moderate-sensitivity, moderate-specificity, manual grading strategy (72.6% sensitivity; 66.8% specificity). A further manual grading strategy (strategy 16) was also included as a potential alternative to grading strategy 1 (having similar sensitivity, 73.3%, and higher specificity, 70.9%). Furthermore, consideration was given to the potential cost-effectiveness of utilising a fully automated annotation grading strategy which also utilised visual acuity (denoted FA2), with slightly higher sensitivity (75.9%) and better specificity (73.7%) than manual grading strategy 16. In addition, consideration was given to a grading strategy (grading strategy 8) that had 100% sensitivity, albeit with only 1.7% specificity, coupled with OCT prior to referral.

The impact of a screening pathway combining the selected grading strategies with OCT (within the screening programme prior to referral) to minimise false-positive referrals to eye clinics was also assessed.

The incremental costs per extra case of MO detected vary by grading strategy. Considering the more sensitive grading strategy 16 compared with grading strategy 2, the additional cost per extra case detected

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ranges from £1579 (English costs) to £985 (Scottish costs). When the grading strategies are coupled with OCT, in the screening pathway, these incremental costs fall to £636 and £528, respectively. Although the fully automated annotation grading strategy dominates manual grading strategies 1 and 16 under the base-case assumption of zero net increase in grading costs, it costs £897 per additional case detected and referred in comparison with manual grading strategy 2 (applying English screening and referral costs). This incremental screening cost drops to £405 when the grading strategies are coupled with OCT prior to referral. The 100% sensitive screening strategy 8 costs an additional £1510 per extra case detected in comparison with the most specific screening strategy (strategy 2 + OCT) when applying English referral costs, and £1360 per extra case detected when applying Scottish referral costs. In comparison with manual grading strategy 16 plus OCT, screening strategy 8 costs £1955 and £1784 per extra case detected and referred when applying English and Scottish referral costs, respectively.

The longer-term cost-effectiveness results mirror the pattern observed in the short term, in that the addition of OCT to the screening pathway results in cost-savings without reducing the health benefits. As with the short-term results, the fully automated annotation grading strategy also dominates manual grading strategies 1 and 16, under the assumption of zero net increase in grading costs associated with the introduction of automated grading. Furthermore, manual grading strategy 16 remains essentially dominant over, or very cost-effective in comparison with, strategy 1.

Conclusions

Compared with all current manual grading schemes, for the same sensitivity, a fully automated annotation grading strategy, using the automated detection of patterns of photographic surrogate markers, achieves a higher specificity for detecting OCT detectable MO in people with diabetes, especially if visual acuity is included in the automated strategy.

Overall costs to the health service are likely to increase if more sensitive referral strategies are adopted over more specific screening strategies for MO, for only very small gains in quality-adjusted life-years.

The addition of OCT to each grading strategy, as part of the screening pathway prior to referral, results in a reduction in costs to the health service with no decrement in the number of MO cases detected.

Study registration

This study has been registered as REC/IRAS 07/S0801/107, UKCRN ID 9063 and NIHR HTA 06/402/49.

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