Clinical characteristics influence screening intervals for diabetic retinopathy.

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CLINICAL CHARACTERISTICS INFLUENCE SCREENING INTERVALS FOR DIABETIC RETINOPATHY.

Running head: Screening intervals in diabetic retinopathy

[1]Massimo Porta, [1]Mauro [1]Maurino, [1]Sara Severini, [1]Elena Lamarmora, [1]Marina Trento, [1]Elena Sitia, [1]Eleonora Coppo, [1]Alessandro Raviolo, [1]Stefania Carbonari, [1]Marcello Montanaro, [1]Lorenza Palanza, [2]Paola Dalmasso, [2]Franco Cavallo

[1]Diabetic Retinopathy Centre, Department of Medical Sciences,
and
[2]Department of Public Health and Paediatrics, University of Turin, Italy

Corresponding Author:
Prof. Massimo Porta, MD PhD
Department of Medical Sciences
University of Turin
Corso AM Dogliotti 14
10126 Torino
Italy

Tel. +39-011-6632354
Fax +39-011-6334515
e-mail: massimo.porta@unito.it

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ABSTRACT

Aims/hypothesis: Most guidelines recommend annual screening for diabetic retinopathy (DR) but resource limitations and the slow progression of DR suggest that longer recall intervals should be considered if patients have no detectable lesions. This study aimed at identifying the cumulative incidence and time of development of referable DR in patients with no DR at baseline, classified by clinical characteristics.

Methods: Analysis of data collected prospectively over 20 years in a teaching hospital-based screening clinic according to a consensus protocol. The cumulative incidence, time of development and relative risk of developing referable retinopathy over 6 years following a negative screening for DR were calculated in 4320 patients, stratified according to age at onset of diabetes <30 or ≥30, being on insulin treatment at the time of screening, and known duration of diabetes <10 or ≥10yrs.

Results: The 6-year cumulative incidence of referable retinopathy was 10.5% (95% CI: 9.4%, 11.8%). Retinopathy progressed within 3 years to referable severity in 6.9% (95% CI: 4.3%,11.0%) of patients with age at onset ≥30, on insulin treatment and 10 years or longer known disease duration. The other patients, especially those with age at onset <30, on insulin and <10 year duration, progressed more slowly.

Conclusions/Interpretation: screening can be repeated safely at 2-year intervals in any patient without retinopathy. Longer intervals may be practicable, provided all efforts are made to ensure adherence to standards in procedures and to trace and recall non attenders.

Key words: Diabetic retinopathy, screening, retinal screening, blindness prevention, type 2 diabetes, type 1 diabetes.

ABBREVIATIONS

DR, Diabetic Retinopathy

ETDRS, Early Treatment of Diabetic Retinopathy Study

OO-IT, Older-Onset Insulin Treated

OO-NIT, Older-Onset Non Insulin Treated

YO-IT, Younger-Onset Insulin Treated

YO-NIT, Younger-Onset Non Insulin Treated

INTRODUCTION

Unless treated before the appearance of symptoms, diabetic retinopathy (DR) may lead to severe visual loss (1). Consequently, recommendations to screen for asymptomatic sight-threatening DR have been issued in many countries (2-5). Most guidelines recommend that retinal examination is performed annually in people with diabetes (2,3) but resources for repeated yearly checks are in short supply and the progression of DR may be slow enough to consider longer intervals when patients have no detectable lesions. A cohort study in Liverpool suggested that patients with type 2 diabetes and no retinopathy may be safely seen every 3 to 5 years (6) and an econometric simulation based upon U.S. data concluded that screening may not be cost-effective unless performed every 2-3 years in type 2 patients without DR and at low risk of developing any (7). Another study suggested that also adolescents with type 1 diabetes may be screened every other year (8). More recent studies support the notion that 2-3 years between screenings are safe in patients without retinopathy (9-12).

This paper reports on an analysis of screening data collected over 20 years in a teaching hospital-based diabetes clinic according to the European Working Party protocol to Screen for DR (4) and its implementation document, the Field Guide-Book (5). The European protocol had been validated by independent investigators (13,14) and reported to reduce referrals to a low-vision clinic by one-third over 5 years (15). The specific aims were to evaluate the cumulative incidence and time of development of referable DR in patients with negative screening and different clinical characteristics.

METHODS

The Diabetic Retinopathy Centre is a facility dedicated to screening for DR within the outpatient diabetes clinic of Turin main teaching hospital. It offers screening to patients from inside and outside the clinic. Since its staff includes retinal specialists, it also functions as tertiary referral centre, though patients with sight-threatening DR are normally seen by the specialists without going through a formal screening procedure.

Data of 35,545 screening episodes [19,864 (55.88%) males; 15,861 (44.12%) females] performed in 12,074 patients [6,751 (55.91%) males and 5,323 (44.09%) females] between 1/1/1991 and 31/12/2010 were analysed. The individuals subjected to screening were almost totally Caucasians, with few patients of African, Asian or South American origin included in the latest years. Data were collected prospectively using a dedicated software, SEE (Save Eyes in Europe), which had been

specifically designed to record episodes according to the European screening protocol (16). All study participants gave their informed consent and the investigations were carried out in accordance with the Declaration of Helsinki as revised in 2000 (http://www.wma.net/e/policy/b3.htm). Until May 2000 screening was by direct and indirect ophthalmoscopy performed by diabetes specialists and colour photography on 35 mm slide film (Kodak Elite 200 ASA) using Kowa Pro-I and Kowa Pro-II funduscameras (2,237 patients, 5,328 episodes). From June 2000, patients were screened by non-mydriatic digital fundus photography (Canon NM45CR) and the images processed by the EyeCap software (Haag-Streit, Koeniz, Switzerland) (9,837 patients, 30,217 episodes). Photographs were taken by trained medical or nursing personnel. Grading was performed by diabetes specialists, after specific training, according to the European Working Party recommendations (4,5). Patients were assessed at retinal photography and formally graded later. Feed-back on referrals was by direct discussion with the consultant ophthalmologists working in the DR Centre. Doubtful cases were discussed on pictures alone and patients not requiring referrals re-graded accordingly.

Patients with mild non proliferative retinopathy not requiring referral (microaneurysms only, isolated larger haemorrhages and/or isolated cotton wool spots), equivalent to ETDRS level ≤35 (17), were given re-screening appointments. Those with moderate non proliferative retinopathy requiring referral (association of the above lesions in higher number and/or within one disc diameter of the centre of the fovea) or worse (pre-proliferative, proliferative, photocoagulated DR, advanced diabetic eye disease with or without macular involvement), equivalent to ETDRS level >35 (17), were referred to an ophthalmologist for further assessment and treatment, as required. For patient classification, DR severity in the worst eye was considered.

Yearly follow-ups in the same patients were calculated as screening episodes within multiples of 12±6 months after the first visit. Hence, follow-up screening episodes were considered to be at 1 year if they fell within 7-18 months of the first visit, 2 years if within 19-30 months, and so forth.

Comparison of ophthalmoscopy + 35mm photography and digital photography.
Since no formal trial was run to compare ophthalmoscopy + 35 mm photography versus non-mydriatic digital photography, the detection rates of DR using these two methods were assessed by two independent approaches:
1. the prevalence of all gradings in patients consecutively screened for the first time 9 months before 22 May 2000 (n=544) was compared with that of all patients first screened over the 9 months after changeover (n=622), assuming that there was no change in the prevalence

grades of DR over time. There was no difference in the distributions of DR [No DR: 321 (59.01%) vs 347 (55.79%); mild DR: 78 (14.34%) vs 95 (15.27%); referable DR: 134 (24.63%) vs 169 (27.17%); non gradable: 11 (2.02%) vs 11 (1.77%)] (p= 0.68 - Chi-square)..

2. the diagnoses of 317 patients who were screened with both methods, first within 9 months before May 2000 and then re-screened over the 9 months following changeover were compared, the assumption being that very little progression of DR would occur in this group. There was a minor trend to more DR over the second examination but no significant differences were observed between the distributions of DR detected by the two methods in the same population (p = 0.14) (chi-square). Kappa-statistics showed an agreement index K=0.75 (p<0.001) when comparing absence of DR [n=150 (49.02%) before and 141 (46.08%) after changeover] vs any DR [n=156 (50.98%) and 165 (53.92%), respectively], and a weighted K=0.81 (p<0.001) when comparing absence of DR vs mild [n=68 (22.2%) before and 71 (23.2%) after changeover] vs any other more severe (referral-requiring) DR [n=88 (28.76%) and 94 (30.72%), respectively]. Pictures of 4 (1.26%) and, respectively, 9 (2.84%) patients were ungradable before and after changeover.

Quality assessment of digital photographs.

Digital photographs of macular and nasal fields were assessed for quality and judged Good, Sufficient for grading if not worse than Standard 14 of the ETDRS protocol (17) or Insufficient. Photographic fields were judged Centred, Partially Centred if the disc was within one disc diameter of the desired position, or Non-Centred. Out of 11,359 eyes thus assessed, 80.2% macular fields and 77.9% nasal fields were of good quality, 16.7% and 19.4% were sufficient for grading, respectively, and only 3.1% and 2.7% were unreadable. More than 99% photographic fields were at least partially centred. Quality of images was influenced by lens opacities and pharmacologic mydriasis, though not by centring (data not shown).

Patient classification

At the time of first screening, the patients were divided into younger-onset (YO), if age at diagnosis of diabetes was <30, and older-onset (OO) if it was ≥30 and further stratified into insulin-treated (IT), either alone or with oral agents, and non insulin treated (NIT), i.e. on diet only or diet and tablets. Data from all patients so stratified who were screened at baseline and at least once within the following 6 years were analysed. In total, follow-up was available for 4320 patients with no detectable DR at first visit.

Of these, 2934 (67.9%) were OO-NIT (1712 males, 58.4%, age 62.1±9.7, known duration of diabetes 5.9±6.6), 689 (16%) were OO-IT (373 males, 54.1%, age 58.4±12.9, duration 8.5±8.1), 671 (15.5%) were YO-IT (347 males, 51.7%, age 22.2±11.7, duration 8.8±8.1) and 26 (0.6%) were YO-NIT (13 males (50.0%), age 39.0±15.4, duration 16.1±13.1).

Because of limited numbers, the YO-NIT group was not further considered for this work. The other 3 groups were further subdivided into patients with <10 or ≥10 years known duration of diabetes. In total, 2247 OO-NIT<10yrs, 687 OO-NIT≥10yrs, 426 OO-IT<10yrs, 263 OO-IT≥10yrs, 432 YO-IT<10yrs and 239 YO-IT ≥10yrs without retinopathy at their initial screening were included.

Statistics

Clinical and demographic differences at baseline were assessed with the χ^2 test or ANOVA, as appropriate. Cumulative and incidence rates of DR were calculated using the product limit method, with standard error (SE) according to Greenwood and 95% confidence interval (CI) computed as ± 1.96 x SE. Patients who had not developed DR contributed to person-years of follow-up until their last screening visit. Difference among subgroups was tested using the log-rank or Wilcoxon (Breslow) statistic. An interval censoring Weibull regression model was used to estimate hazard ratios (HR) and corresponding 95% CI according to the potential prognostic variables (subgroup and known duration of diabetes).Due to a partial violation of Cox's model basic assumption, we chose the Weibull model as it showed to be the best fitting one using Akaike Information Criterion (AIC) for comparison with the other parametric models (Gompertz and exponential). Statistical significance level was set at 0.05. Statistical analyses were performed using STATA 12.1.

RESULTS

Over the 6 years following the first screening episode, the incidence rate of referable DR was higher among the OO-IT (2.74 cases per 100 person/year, 95%CI: 2.23,3.37) than the OO-NIT (1.64, 95%CI: 1.45,1.85) or the YO-IT (1.90, 95%CI: 1.50,2.41).

Table 1 shows the cumulative incidence of referable or worse DR over the 6 years following a first screening in which patients had no detectable retinopathy, divided by subgroups. Being on insulin treatment and having been diagnosed 10 years earlier or more were both associated with higher incidence of referable DR (p<0.001).

The average times and 95% CI needed for 5% of the patients in the different subgroups to develop referable retinopathy were 56 months (95%CI 49,64) for OO-NIT with <10 years known duration, 33 (95%CI 23,51) for OO-NIT with ≥10 years known duration, 41 (95%CI 24,57) for OO-IT with <10 years known duration, 27 (95%CI 15,38) for OO-IT ≥10 years known duration, 60 (45,79) for YO-IT <10 years duration, and 39 (22,51) for YO-IT ≥10 years duration.

None of the subgroups reached 5% cumulative incidence of referable retinopathy within 2 years of a negative screening, whereas the OO-NIT≥10 years and OO-IT≥10 years did so within 3 years. Consequently, the relative risk of developing referable retinopathy within 3 years of a first screening was calculated for all subgroups. Table 2 shows that, compared to the OO-NIT<10 years duration group, taken as reference, both OO-NIT and OO-IT with 10 or more years known duration had more than twice the risk of developing referable retinopathy. In contrast, the YO-IT with less than 10 years duration had a 72% reduced risk of developing referable retinopathy within the same time frame.

DISCUSSION

To evaluate the potential for sight-threatening DR to develop in a real-life screening scenario, all records collected with tight observance of the 1990 European Working Party recommendations were analysed to find out the cumulative incidence and risk of developing referable DR over the 6 years following a screening episode in which no DR had been detected. Patients without retinopathy at first screening appeared to carry a negligible risk of developing lesions requiring referral over the following year, but 2.1% developed them within 2 years, and 3.2% after 3 years. The 6-year cumulative incidence of referable or worse DR was 10.5%. In the UKPDS, 17.5% of T2DM patients with no DR at first examination reached an ETDRS level of <35/35 or worse after 6 years (18). However, not all patients with this grading on the ETDRS scale would have been defined as requiring referral in our screening context, where they might simply be re-screened at shorter intervals. In addition, all UKPDS patients had newly-diagnosed type 2 diabetes at baseline and 4-field 30° stereoscopic retinal photography was used. For reasons of costs and practicality, stereo retinograpy is not recommended for screening purposes and our photographic protocol is based upon the EURODIAB procedure, which had been previously validated and found to perform as well as the ETDRS in detecting both mild and more severe DR (19).

The goal of screening is to identify eyes with sight-threatening DR before symptoms occur, so that photocoagulation or other treatments can be applied timely and appropriately (20). Data from Sweden (14) and Iceland (20) show that while very few people with type 1 diabetes progress to blindness if properly screened, patients with type 2 diabetes may still develop severe visual impairment, mostly due to macular disease (21). Both the American Diabetes Association (2) and NICE (3), among others, recommend that all diabetic patients are screened yearly. The 1990 European Working Party had recommended to "*Examine at diagnosis and at least two-yearly thereafter, at least annually if DR appears*" (4,5). However, the desirability of frequent controls has to be balanced against the high patient throughput and limited facilities available in most clinics.

A prospective study of 20,570 systematic screening episodes in Liverpool (6), suggested that patients with T2DM and no retinopathy can be re-screened every 5 years, and those with mild DR every year, to retain a 95% chance of remaining free of sight-threatening DR. However, those authors conceded that 3-year intervals may be more viable in real life. In that study, 3-field 50° photography and a somewhat different DR classification but a statistical approach similar to this study were used, though considering different variables. The cumulative incidence of sight-threatening DR in individuals with no retinopathy at baseline after 5 years follow-up was 3.9%. Such figures are lower than those reported in this paper but the definition used in Liverpool for sight-threatening DR (6 or more cotton-wool spots, venous changes, IRMAs) was more severe than our definition of referable DR.

The econometric simulation published by Vijan et al (7) considered intervals of 1 to 5 years in a sample model older than 40, as defined from data from the NHANES-III (22) population study and, for progression of retinopathy, from the UKPDS (18), DRS (23) and ETDRS (24) and suggested that screening may not be cost-effective unless carried out every 2 or even 3 years in DR-free patients who are older and in fairly good metabolic control. However, some of the assumptions made in that study, e.g. the population base and screening performed by ophthalmologists, may not apply to the settings tested in Liverpool or Turin.

More recently, Agardh et al (9) recommended 3 year screening intervals based on their case series in which only 1 out of 1,322 patients with type 2 diabetes without DR at baseline had developed a condition (macular oedema) requiring laser treatment within that time frame. Their patients had an average known duration of type 2 diabetes of 6 years, were mostly on diet or oral agents and in good glycaemic control (HbA1c 6.4±1.4%). Chalk et al (11) developed a simulation model based upon a National Health Service series in the UK and concluded that 2 years would be a safe re-screening interval. Thomas et al. (12), in South Wales, analysed nearly 50.000 patients with no DR

at first screening and at least 1 further screening within the following 4 years. Similarly to this paper, they subdivided patients with type 2 diabetes into those on insulin treatment or not and with less or more than 10 years known duration. Although reporting a higher cumulative incidence of referable retinopathy than in our population, they also concluded for screening intervals longer than one year, with the possible exception of patients on insulin treatment and with ≥10 years duration. The stages of DR defined as referable in their paper (preproliferative or worse) were more advanced than ours, which does not help to explain their higher incidence rate, and, similarly to us, they did not collect data on glycated haemoglobin or blood pressure. Finally, Aspelund et al (10) proposed a fully personalised algorithm which, applied to a population of 5,199 Danish patients followed for 20 years, suggested a mean screening interval of 29 months, although that included patients with DR at baseline. The algorithm takes into account not only duration and type of diabetes but also HbA1c, blood pressure and presence of retinopathy at previous visit, which commands shorter intervals. With reference to type 1 diabetes, one study suggested that 2-yearly screening may be safe also in DR-free adolescents with reasonable metabolic control, due to their rare progression to sight-threatening forms (8). Absence/presence of mild retinopathy in one or both eyes at two consecutive screening episodes has also been proposed as a risk indicator to develop sight-threatening DR in a UK based population in which no stratification was made for type of diabetes or current tratment (25).

Strengths of this study are its large real-world population base, the strictness with which data were prospectively collected and retinopathy consistently graded according to a validated consensus procedure developed more than 20 years ago, and the long follow-up. Internal procedures assured uniformity of the grading process through training of the operators and their continuous feed-back with the senior diabetes (MP) and ophthalmic (MM) specialists, who worked in the programme for the entire 20-year period. Overall quality of retinal photographs was satisfactory, with low rates of ungradable pictures, in which case the patients underwent full eye examination.
Possible problems are selection bias, the switch-over of screening methods in 2000 without a formal assessment of their sensitivity and specificity, and the lack of data on metabolic and blood pressure control in the patients screened. The Diabetic Retinopathy Centre offers screening to diabetic patients from inside and outside the hospital where it is based. Although it also functions as tertiary referral centre, patients with sight-threatening DR are not subjected to formal screening and would not have been included in this analysis of people without DR at first examination. The indirect comparisons described in Research Design and Methods suggest that the two approaches yielded equivalent results and disprove the possibility that the combined use of ophthalmoscopy and 35 mm

colour photography may lead to higher detection rate of minimal, non referable, retinopathy than digital photography alone (26). In addition, onset of referable DR was the outcome of this study, and its lesions arguably pose even less problems in detection than those of mild retinopathy. As also pointed out in the Liverpool Study (6), data on HbA1c and blood pressure, although major determinants of DR progression, are not usually collected in a general screening setting like ours, which provides a service to different diabetes units and general practitioners. HbA1c results were from different laboratories, not standardised, and blood pressure could not be measured consistently, due to time, personnel and space constraints.

In conclusion, although risk charts may result in a more personalised approach to screening intervals by taking multiple variables into account (10), knowledge of diabetes duration and type of glucose-lowering treatment is easily obtainable information that may suffice to provide useful guidance when planning re-screening appointments. In particular, this paper confirms that screening can be repeated safely at 2-year intervals in any patient with type 1 or 2 diabetes and no retinopathy, giving a 95% probability of remaining free of referable lesions according to the same standard adopted by previous reports (6, 12). It also shows that DR progresses more rapidly to referable severity in patients with type 2 diabetes on insulin treatment and 10 years or longer known disease duration. On the other hand, patients with shorter duration can potentially be seen even less frequently, eg at 3 years intervals, though prudence is always of the essence, considering that information on duration of type 2 diabetes is often imprecise. In addition, one word of caution refers to the sensitivity of most screening programmes, which is around 80-90% (26), meaning that 1 out of 5-10 diagnoses of no DR may be false negatives and the patients be given hazardously delayed appointments as a result. Thirdly, programming checks at excessively delayed intervals may convey to patients the impression that retinopathy is unimportant, and recalling people who do not attend appointments given 3 or more years earlier may be problematic.
Since no standardized procedure exists for grading digital retinal photographs, this same exercise should be carried out in any other programme where extended screening intervals are proposed and careful quality assurance needs to be carried out to ensure that there is no drift in grading or there are not one or two poor graders. All efforts should be made to ensure the highest adherence to standards and to put effective methods in place for tracing and recalling patients who do not attend re-screening appointments.

DUALITY OF INTEREST

The authors have no conflict of interest to declare.

CONTRIBUTION STATEMENT

MP Planned the study, researched the data and wrote the manuscript; MMa collaborated in the acquisition, analysis and interpretation of the data and revised the manuscript; SS, EL, MT, ES, EC, AR, SC, MMo and LP collected and researched the data and revised the manuscript; PD and FC analysed the data, contributed to their interpretation and reviewed the manuscript. All authors approved the final version of the manuscript.

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Table 1 - Cumulative incidence and 95% Confidence Interval (percent) of referable DR observed in patients with no DR at baseline, according to baseline characteristics

Time from first screening (years)	1	2	3	4	5	6
OO- NIT<10 yrs (95 CI%) (Numbers at risk)	0.72 (0.44,1.17) (2247)	1.59 (1.14,-2.22) (2162)	2.49 (1.89,3.28) (1866)	3.68 (2.89,4.67) (1531)	5.54 (4.51,6.81) (1281)	7.77 (6.45,9.34) (1061)
OO-IT <10 yrs (95 CI%) (Numbers at risk)	0.96 (0.36,2.53) (426)	2.64 (1.42,4.85) (403)	3.61 (2.11,6.17) (321)	6.37 (4.12,9.80) (263)	8.32 (5.57,12.32) (219)	15.13 (10.97,20.69) (174)
OO-NIT≥10 yrs (95 CI%) (Numbers at risk)	2.06 (1.23,3.46) (687)	3.50 (2.34,5.22) (648)	5.12 (3.64,7.18) (572)	6.25 (4.55,8.56) (476)	8.95 (6.73,11.86) (390)	11.86 (9.12,15.34) (308)
OO-IT ≥10 yrs (95 CI%) (Numbers at risk)	1.91 (0.80,4.54) (263)	3.59 (1.88,6.79) (249)	6.87 (4.25,11.00) (219)	11.48 (7.79,16.75) (173)	14.23 (9.95,20.13) (141)	21.13 (15.43,28.57) (112)
YO-IT <10 yrs (95 CI%) (Numbers at risk)	0.23 (0.03,1.64) (432)	0.47 (0.12,1.87) (422)	0.75 (0.24,2.33) (378)	3.28 (1.76,6.07) (319)	5.47 (3.30,9.01) (257)	7.77 (4.94,12.12) (195)
YO-IT ≥10 yrs (95 CI%) (Numbers at risk)	1.27 (0.41,3.87) (239)	2.61 (1.18,5.73) (233)	4.04 (2.12,7.63) (214)	6.16 (3.61,10.41) (194)	11.48 (7.67,16.99) (165)	17.18 (12.23,23.84) (142)

Table 2 - Risk of developing referable diabetic retinopathy 3 years after a negative screening test.

	Hazard Ratio	p	95% CI	
OO-NIT<10	Reference			
OO-NIT≥10	2.22	0.001	1.42	3.45
OO-IT<10	1.41	0.273	0.76	2.59
OO-IT≥10	2.75	0.001	1.57	4.83
YO-IT<10	0.28	0.032	0.09	0.90
YO-IT≥10	1.74	0.110	0.88	3.43