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Diabetic retinopathy

A clinical update

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Abstract. Easy observation of the fundus oculi makes retinopathy the most frequently reported chronic complication of diabetes and, consequently, the one we know best in terms of epidemiology and natural history. Achieving near-normal levels of blood glucose and blood pressure provides empirical though powerful tools for clinicians to delay the onset and progression of diabetic retinopathy. Even when these measures have failed and retinopathy becomes sight-threatening, laser photocoagulation has proven remarkably effective. Nonetheless, retinopathy remains a leading cause of blindness and there is little evidence that diabetes-related visual loss is decreasing in industrialized countries. This may result from the mixed blessing of prolonged survival of patients who had become diabetic when metabolic control was pursued less fastidiously than today. Screening for sight-threatening retinopathy is the most cost-effective medical procedure known and should help optimise the use of diagnostic and therapeutic resources, but its widest deployment still meets with inertia and lack of interest within most health care systems. Improving clinical skills and technology, however, allow us to take a more optimistic look at the future, as pathogenesis-targeted forms of treatment are being developed and tested through appropriately powered clinical trials. [Diabetologia (2002) 45:1617–1634]

Keywords Diabetes, diabetic retinopathy, metabolic control, blood glucose, blood pressure, laser photocoagulation, blindness.

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Abbreviations: CSME, Clinically significant macular edema; DAMAD, Dipyridamole and Aspirin MicroAngiopathy of Diabetes study; DCCT, Diabetes Control and Complications study; DR, diabetic retinopathy; ETDRS, Early Treatment of Diabetic Retinopathy Study; EUCLID, EURODIAB Controlled trial of Lisinopril in Insulin Dependent diabetes mellitus; FAG, fluorescein angiography; GH, growth hormone; IGF-I, insulin-like growth factor-I; NPDR, non-proliferative diabetic retinopathy; NVD, new vessels on optic disc; NVE, new vessels elsewhere; OCT, optical coherence tomography; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation; QALY, quality-adjusted life years; STDR, sight threatening diabetic retinopathy; TIMAD, Ticlopidine MicroAngiopathy of Diabetes study; UKPDS, United Kingdom Prospective Diabetes Study; VEGF/VPF, vascular endothelial growth factor/vascular permeability factor; WESDR, Wisconsin Epidemiology Study of Diabetic Retinopathy.

Introduction

Diabetic retinopathy (DR) is the leading cause of visual impairment among people of working age and has social consequences beyond sight loss. Employed men with younger-onset diabetes and proliferative DR (PDR) are at an increased risk of being unemployed within 4 years [1]. This worsens their disadvantage, as it may be more difficult for young diabetic people to find a job in the first place [2]. Younger-onset, married diabetic women with visual impairment have an increased risk of being divorced 4 years later [1].

The burden of DR is unacceptably high for society, as well. In the United States, in the early 1990's, a blind diabetic adult cost 12 769 US dollars per year if younger than 65, and 823 US dollars per year if older, not including reduced productivity, output loss, societal burdens of rehabilitation and other local expenses. The annual cost of blindness secondary to diabetes in the United States was estimated at about 500 million US dollars. Early detection and timely laser treatment

of DR could save more than 400 million US dollars [3].

Such calculations may apply to all industrialized countries and there is no indication that the situation has improved over the last decade. Given the predicted world-wide rise in the prevalence of diabetes [4], the consequences of DR could become even more burdensome for developing countries and their citizens. Since much sight loss is avoidable, it is paramount that physicians, nursing personnel and patients learn to play an active role in prevention.

Prevalence and risk factors

The Wisconsin Epidemiology Study of Diabetic Retinopathy (WESDR) is probably the widest and most prolonged survey of DR, its prevalence, incidence and related risk factors completed so far. In the initial cross-sectional approach on 2366 patients done in 1980 to 1982 [5], the prevalence of DR was 71% among people with diabetes onset at a younger age than 30 (roughly corresponding to Type I diabetes mellitus) and 39% among older-onset subjects (roughly Type II diabetes mellitus). Sight-threatening retinopathy (STDR), such as PDR and clinically significant macular edema (CSME), were observed in 23% and 14% of younger-onset patients, respectively. Prevalence increased with diabetes duration, virtually all patients having developed some DR within 20 years of diagnosis, and almost half had PDR. EURODIAB, a cross-sectional study of 3250 patients with Type I diabetes in 31 clinics across Europe, reported lower prevalences at the beginning of the 1990's [6]: 35.9% for non-proliferative DR (NPDR) and 10.3% for PDR. Prevalence of NPDR was 82% among patients with 20 or more years duration Type I diabetes, while PDR reached 37% after 30 years.

Although not normally present during the first 5 years of Type I diabetes [7], STDR may rarely develop in pre-pubertal patients if they are extremely poorly controlled [8]. PDR is not likely to develop within the first 10 years of diabetes but its incidence reaches about 30 out of 1000 patients per year rapidly afterwards [9, 10]. Type II diabetes mellitus can remain unrecognized for years, and this could be why from 7% to as many as 38% of patients already have DR, sometimes STDR, when diabetes is finally diagnosed [11, 12]. CSME is a major cause of visual impairment in these patients [13]. The incidence of macular edema, however, can become as high in younger-onset as in older-onset diabetic patients after 10 years duration [14].

The major determinants for onset and progression of DR are diabetes duration and the degree of metabolic control maintained over the years [5, 6, 12, 15]. Additional factors independently associated with presence and severity of DR include microalbuminuria [16] and ocular perfusion pressure [17]. Predictors of future progression include microaneurysm count [18], and such features of the insulin-resistance syndrome as waist-to-hip ratio and serum triglyceride [19]. Serum triglyceride and cholesterol concentrations were associated with faster development of hard exudates and moderate visual loss in a subanalysis of the ETDRS [20]. Moderate alcohol consumption [21] and smoking [22] do not appear to influence the course of DR. If anything, smoking was associated with reduced progression in the UKPDS cohort [23]. According to the EURODIAB-PCS follow-up study of the original EURODIAB cohort, onset of diabetes before puberty could be independently associated with later progression to PDR [24]. Observational studies have failed to show consistent associations between systolic or diastolic blood pressure at baseline and incidence or progression of DR [19, 24, 25, 26].

The importance of individual variability has long been appreciated by clinicians and confirmed in a recent reassessment of DCCT data, showing that about 10% of patients in the lowest HbA_{1c} quintile developed DR, whereas 43% in the worst quintile remained lesion-free [27].

Diabetes-related blindness

Severe visual loss is due to DR in 86% of patients with Type I diabetes, but only 33% of older-onset groups, as other eye diseases take an increasing toll with age [5]. Cataract, corneal erosions and optic neuritis are more prevalent in diabetes. All together, diabetes is responsible for 5 000 newly registered blind persons every year in the United States [28, 29]. In the WESDR cohort the cumulative 14-year incidences of doubling of the visual angle and blindness (defined as visual acuity ≤20/200 from the best eye) were 14.2% and 2.4%, respectively [30].

In the west of Scotland DR was the fourth cause of blindness (8.5% of total) in 1980, and the most common cause in working age (20–64 years) [31]. In County Avon, in 1984 to 1986, DR came third (6.0%) and again the main cause among 30 to 69 year olds [32]. In Denmark, 13 to 23% of newly registered blind subjects are diabetic [33]. In the Turin province, Northern Italy, DR accounted for 13.1% of registered blindness in 1967 to 1991 and its incidence is increasing steadily over the years [34]. Again, DR was the main cause in the 40 to 70 age group. In Württemberg-Hohenzollern, Germany, incidence of diabetes-related blindness is approximately 2 out of 100 000 of the general population per year and is not decreasing, even when allowing for rising diabetes in the population [35].

Although at least 250 000 patients are estimated to develop STDR every year in the United States [36], until recently one-third of persons with diabetes had

Table 1. Abbreviated summary of the ETDRS severity scale for individual eyes used in the DCCT

Level	Severity	Lesions
10	DR absent	
14–15	DR questionable	
20	Very mild DR	MA only
35	Mild non-proliferative DR	MA plus HE, CWS and/or mild RH
43	Moderate non-proliferative DR	MA plus mild IRMA or moderate RH
47	Moderate non-proliferative DR	More extensive IRMA, severe RH or VB in 1 quadrant only
53	Severe non-proliferative DR	Severe RH in 4 quadrants, or VB in at least 2 quadrants, or moderately severe IRMA in at least 1 quadrant (4-2-1 rule)
61	Mild PDR	NVE<0.5 disc area in 1 or more quadrants
65	Moderate PDR	NVE≥0.5 disc area in 1 or more quadrants or NVD <0.25–0.33 disc area
71–75	High-risk PDR	– Either NVD <0.25–0.33 disc area or NVE <0.5 disc area, and VH – NVD ≥ 0.25–0.33 disc area (with or without VH) – NVE >1 disc area (with or without VH)
81–85	Advanced PDR	Traction, retinal detachment, rubeosis iridis, fundus partially obscured
90	Cannot grade	

CWS, Cotton wool spots; HE, hard exudates; IRMA, intra retinal microvascular abnormalities; MA, microaneurysms; NVD, new vessels on disc; NVE, new vessels elsewhere; PDR, proliferative diabetic retinopathy; RH, retinal haemorrhage; VB, venous beading; VH, vitreous haemorrhage. (Modified from [126] with permission)

never had a dilated eye examination and about one-half did not have one over the previous 2 years [37]. Although the best chances of preventing visual loss are when DR is treated before symptoms occur, about 1 in 5 patients are referred late to specialists [38]. Poor education and lower socio-economic status are strongly associated with PDR and visual loss, both in the United States [39] and Europe [40].

Classification

The Airlie House classification [41], proposed in the late 1960's and still used by clinicians world-wide, distinguishes two patterns of retinopathy, NPDR (or background retinopathy) and PDR. This classification remains successful because it is simple, easy to use in clinical practice, based on pathology, and informative for prognostic purposes.

Abnormalities in NPDR are confined within the retina, and consist in microaneurysms, dot and blot haemorrhages, edema, hard exudates and capillary occlusions. In PDR, newly formed fibrovascular tissue grows from the retinal surface into the vitreous cavity.

The definition of preproliferative retinopathy was adopted when the Diabetic Retinopathy Study (DRS) began, in the early 1970's, to describe a stage of NPDR which progresses more rapidly to proliferation [42]. Preproliferative retinopathy is now called severe NPDR. The Early Treatment of Diabetic Retinopathy Study (ETDRS) modification of the Airlie House classification [43], today differentiates DR in stages (Fig. 1) characterised by the lesions detailed in Table 1.

Severe NPDR is identified by at least one of the following: extensive intra-retinal microaneursyms and large haemorrhages in four quadrants; venous calibre abnormalities in two quadrants; or intra-retinal microvascular abnormalities (IRMA) in one quadrant (4-2-1 rule). Very severe NPDR shows at least two features of the 4-2-1 rule. The progression rates of severe and very severe NPDR to high-risk PDR are, respectively, 15% and 45% after 1 year and 56% and 71% after 5 years [44].

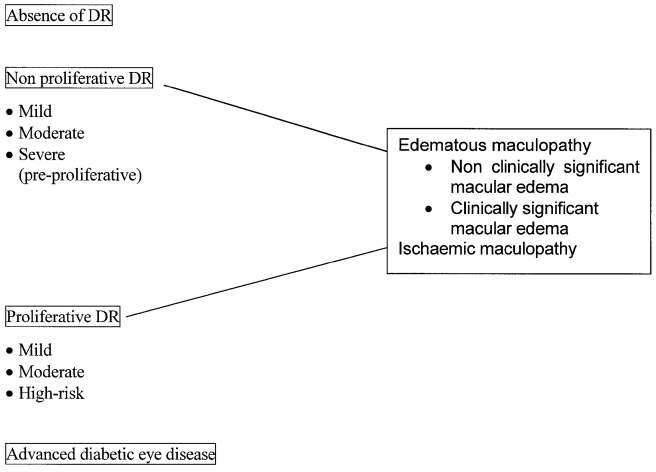

Fig. 1. Classification of diabetic retinopathy

PDR is defined by new vessels, originating from normal vessels of the retina or the optic disc and accompanied by a fibro-glial scaffolding. Extra-retinal fibrovascular proliferation is considered a response to widespread intra-retinal capillary obliteration and resulting ischaemia, with release of angiogenic factors [26]. New vessels, classified by their dimensions, codify different levels of PDR (Table 1).

When retinal ischaemia is very extensive, new vessels can reach the iris surface and anterior chamber

angle. Outflow of aqueous humour is impeded and neovascular glaucoma ensues. Secondary retinal detachment may follow contraction of fibrovascular tissue and be associated with retinal tears. These final stages are defined as advanced diabetic eye disease.

Edema is identified by thickening of the retina, visible on slit-lamp examination. The ETDRS classified diabetic macular edema as non-clinically significant and clinically significant (CSME), the latter defined as [43]: (i) retinal thickening at or within 500 μm of the center of the macula; (ii) hard exudates at or within 500 μm of the center, if associated with thickening of the adjacent retina; (iii) an area of thickening larger than one disc area, if located within one disc diameter of the center.

Florid PDR

In young patients, mainly females, with long-standing Type I diabetes, PDR can develop rapidly, devastatingly towards neovascular glaucoma and secondary retinal detachment. This presentation, known as florid DR, is characterised by huge new vessels, wide areas of retinal ischaemia and marked breakdown of the blood-retinal barrier. Although improving, the prognosis remains worrying. Treatment is by aggressive panretinal photocoagulation (PRP), if necessary, associated with early surgery [45].

Diabetic papillopathy

Diabetic papillopathy, characterised by transient edema of the optic disc, can appear in patients with long-standing Type I diabetes [46]. Its pathogenesis is not completely understood but its development is usually benign and specific treatment is not required.

Diagnosis is based on a thorough examination and fluorescein angiography (FAG). Dilated vessels are perfused early by fluorescein, maintain their usual shape and do not leak profusely. In late phase frames, hyperfluorescence tends to mimic the distribution pattern of the third retinal peripapillary capillary layer. Cotton wool spots and flame-shaped retinal haemorrhages are often present [47]. On visual field assessment, an enlarged central blind spot is the only functional abnormality found.

Diagnosis

After pupil dilatation, the fundus can be observed by direct and indirect ophthalmoscopy but retinal details are best visualised by slit-lamp biomicroscopy with a contact three-mirror lens. This also permits to assess the anatomical relationships between the posterior hyaloid and the retinal surface. Areas of retinal ischaemia are difficult to recognise by biomicroscopy alone. They generally show a pale colour, are crossed by whitish vessels and are located in the mid-periphery. FAG highlights hypofluorescent areas of capillary drop-out and tufts of new vessels, showing early perfusion and leakage on later frames. The wall of new vessels, formed by basement membrane tubes lined by endothelial cells without tight junctions, is easily crossed by fluorescein.

Fluid accumulation inside the central retinal tissue causes macular edema. Patients report decreased central visual acuity, possibly associated with metamorphopsia. Diagnosis is based on slit-lamp examination with either non-contact (Volk) or contact lenses (Mainster, three-mirror). FAG, with either diffuse or circumscribed pooling of fluorescein inside intraretinal spaces, allows detailed definition of macular edema. Retinal thickening can also be documented by stereoscopic fundus photography.

Though not necessary for diagnosis, FAG identifies leaky vascular abnormalities responsible for fluid accumulation. Different angiographic patterns identify progressively worsening prognoses for macular edema [48]: (i) a well preserved capillary network with areas of focal leakage, with or without hard exudates, generally carries a better prognosis; (ii) a diffuse pattern of edema with numerous vascular abnormalities, possibly associated with hard exudates, carries a less favourable prognosis; (iii) prognosis is worse when cystoid changes are identified, whether or not associated to a central cavity (complete or incomplete cystoid macular edema); (iv) prognosis is at its worst when edema is associated with ischaemic damage of the capillary bed. Ischaemic maculopathy is defined by at least doubling of the foveal avascular zone.

Ophthalmic coherence tomography (OCT) [49] is an important ancillary test to quantify fluid accumulation and define different edema patterns and morphologies within the retina. OCT also allows to recognise tractional edema by visualising the relationships between retina and posterior hyaloid.

Biomicroscopic examination for identifying iris new vessels should be done before pupil dilation. In case of doubt, examination of the anterior chamber angle and FAG of the iris vessels can help, as sensitivity and specificity of the latter are higher than those of biomicroscopy [50]. Iris angiography is also helpful when cataract or vitreous haemorrhage prevent retinal examination because, if iris new vessels are detected, PDR is highly likely to co-exist.

Diabetic retinopathy and nephropathy

DR and nephropathy are closely related from epidemiological, pathogenetic and clinical points of view. The notion of a diabetic “triopathy”, including retinal, renal and peripheral nerve complications has been pro-

posed [51]. However, metabolic mechanisms can play a bigger role in neuropathy and severe retinopathy does not necessarily imply kidney involvement.

The prevalence of DR increases progressively with duration of diabetes, so that within 15 to 30 years it involves nearly all patients, whereas overt nephropathy increases within 5 to 15 years but declines later on, so that only about one-third of all patients with Type I diabetes ever develop the complication [52]. Analogies could be closer between PDR and nephropathy, as the two share similarities in prevalence and cumulative incidence. In a Joslin Clinic series [9], 80% of patients with persistent proteinuria had PDR, as opposed to 25% of those without proteinuria. Incidence of new PDR is less than 1% per year among patients without proteinuria but rises to 10 to 15% if they have proteinuria. Interestingly, incidence rates begin to increase 3 to 4 years before the onset of nephropathy and retinal lesions tend to deteriorate more rapidly.

The EURODIAB study [53] introduced elements of further complexity as the correlation between increasing blood pressure and albumin excretion rate was only confirmed in patients who also had retinopathy, independently of glycaemic control or diabetes duration, suggesting that DR in association with increased blood pressure is an important independent risk factor for the progression of nephropathy (Fig. 2).

Virtually all patients with nephropathy also have retinopathy [54, 55], often PDR, whereas about one-third of patients with PDR do not have microalbuminuria [56]. DR is found in 85 to 99% of patients with Type I diabetes and persistent proteinuria but only in 47 to 63% of people with Type II diabetes [57, 58], suggesting that about 30% of proteinuria in the latter might not be due to diabetic nephropathy. As a clinically relevant consequence, further diagnostic procedures are indicated in confirmed proteinuria if DR is absent, as kidney lesions can have a non-diabetic origin.

Patients with overt diabetic nephropathy are almost certain to have DR and are very likely to develop STDR. Hence, their fundus should be examined frequently. Since fluorescein is excreted by the kidneys, FAG should not be used routinely and reduced amounts of fluorescein should be administered if necessary.

Blindness due to PDR and CSME is frequent among patients with end-stage renal disease. In 1985, 35% of diabetic people on renal replacement therapy in the United Kingdom were blind [59]. Progress in laser therapy and vitreo-retinal surgery have presumably helped, particularly by minimizing the risk of vitreous haemorrhage secondary to heparin use during haemodialysis.

Diabetic retinopathy in pregnancy

Pregnancy is frequently associated with worsening of DR, generally after the 16th week [60]. If absent at conception, DR has a 25% chance of developing during pregnancy. The incidence of PDR increases if moderate to severe NPDR is present at the start. Other risk factors for PDR are poor metabolic control and its rapid improvement during the first trimester, diabetes duration and hypertension [61]. Worsening of DR during pregnancy is usually transient and, if not reaching sight-threatening characteristics, does not affect long-term visual prognosis [62].

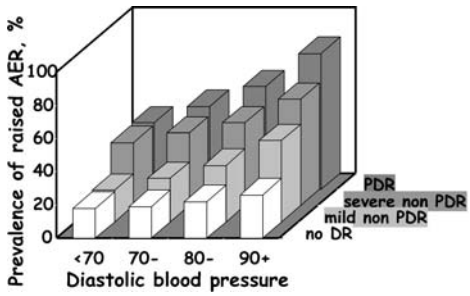

Fig. 2. The prevalence of microalbuminuria increases with diastolic blood pressure only in patients with diabetic retinopathy. Modified from Stephenson et al. [53] with permission

In patients with severe NPDR, early PRP could be considered when planning pregnancy or as soon as possible afterwards. Regular and frequent examination is mandatory over the first and second trimester, monthly during the third trimester. If high-risk lesions develop, photocoagulation must be carried out immediately. Onset of macular edema during the third trimester, followed by spontaneous remission after delivery, has been reported on an anecdotal basis. Laser treatment is not normally required.

Although FAG is not associated with increased risk of foetal or maternal complications, adequate assessment of DR is best achieved by biomicroscopy and colour photography.

Screening for sight-threatening diabetic retinopathy

Procedures

Since optimization of metabolic and blood pressure control delays but does not completely prevent retinopathy [12, 27] and since photocoagulation should be applied before symptoms arise, screening aimed at early diagnosis of STDR is the best option to prevent blindness.

Programs for the prevention of diabetes-related blindness have been developed world-wide, including North-America [29] and Europe [63]. The European Field Guide-Book to screening [63] has been independently validated [64]. Its protocol includes collection of basic clinical history (visual symptoms, use of eye-drops suggestive of glaucoma, hypertension, smoking habits and intercurrent illnesses), measurement of visual acuity, pupil dilation and fundus examination.

Appropriate tests and trained operators are paramount for screening programmes. Simulation models suggest that substantial savings, both monetary and in sight-years, are reached with an overall sensitivity of 60%, as the cost-benefit curves drop steeply for lower sensitivities and plateau for better performances [65]. Since average sensitivity and specificity for trained operators and dedicated equipment range from 80 to 90% [66], available methodologies could be deployed with very good prospects of success. A recent systematic review concluded that mydriatic retinal photography, associated with direct and/or indirect ophthalmoscopy if the pictures are ungradable, remains the most reliable screening test. [66]. FAG should not be used to screen.

Digital imaging could prove superior to photographic film, although definition of small detail remains poorer, because it allows immediate checking of image quality, practical data storage and retrieval and easier training of operators. Since digital cameras are more sensitive than film, less light is necessary to obtain retinal images of sufficient quality for grading [67]. Further possibilities offered by digital imaging include stereo imaging [67] and telemedicine [68]. Algorithms for automated photographic reading could possibly reach acceptable sensitivity (78–88%) and specificity (84–100%) in detecting different lesions of retinopathy, as compared to an ophthalmologist [69, 70], opening the way to computer-assisted grading. As a main problem with medical image interpretation is the rapid deterioration of graders' concentration with increasing workloads, this prospect will become a viable option in mass screening for STDR.

All diabetic people should have their eyes examined at diagnosis. If they have Type I diabetes, this will convey the message that screening is important. If they have Type II diabetes, STDR could be already present [11, 12]. After puberty, all patients wih Type I diabetes and Type II diabetes should be screened at least every other year, if no retinopathy is present at the last visit. After DR is recognized, and in the case of nephropathy, major surgery or other intercurrent illnesses, retinal examination should be done as frequently as deemed necessary by an experienced observer (e.g. 3–6 month or more frequent intervals). In pregnancy, fundus examination should be carried out at the time of planning, if possible, at confirmation and then at least three times monthly until delivery.

Impact of screening

Where implemented, screening has delivered. In Iceland, where most patients with Type I diabetes have been screened by a central Unit since 1980, only one has been registered blind over the last few years [71]. Encouraging results are reported also for Icelanders with Type II diabetes. Implementation of the European guidelines in the Stockholm region could have been instrumental in reducing referrals to a low-vision unit, taken as proxy for new blindness, by more than one third over 5 years [72]. Unfortunately, diabetic patients can still go blind after STDR is successfully detected and treated. Progression of the underlying disease, CSME, ischaemic maculopathy and age-related macular degeneration are the main untreatable causes of residual blindness [25, 30, 73].

Cost-effectiveness of screening

Screening makes financial sense. Econometric simulations suggest that preventing blindness is much cheaper than subsidising it, from both monetary [65] and quality of life points of view [74]. Costs in the Turin area are about 25.00 EUR per patient screened and about 550 EUR per patient subjected to photocoagulation as a result of screening, independently of the procedure adopted [75]. Blindness benefits vary in different countries but are definitely much higher than that. Indeed, screening for STDR, and treating it as required, is the most cost-effective medical procedure known today, with 3190 US dollars per Quality-Adjusted Life Years (QALY) of sight saved. This compares favourably with 7650 US dollars per QALY gained when screening for neonatal hypothyroidism, or 5100 US dollars per QALY from coronary by-pass surgery [74]. Health economists suggest that medical procedures costing less than 20 000 US dollars per QALY are definitely worth implementing [76].

Screening in the patients' perspective

An important but so far neglected aspect is awareness of DR in the general public and among diabetic patients. As mentioned above, poor schooling and lower socio-economic status are associated with diabetes-related visual loss [39, 40] and more should be done to encourage patients' active participation in optimizing their blood glucose and pressure and having regular eye checks. Educational methodologies should start with structured studies of patients and their beliefs and attitudes. A survey run jointly in DR screening clinics of Turin and South Wales suggests that many patients are not aware that diabetes can damage their eyes, that something can be done to prevent the damage and that they could actually help in the process [77]. An important portion of patients did not even realize they were being screened for diabetic eye disease, let alone why. The same study showed that patients involved in a programme of permanent health education [78] had developed more correct health beliefs and had adopted preventative activities. More recent data suggest that implementing this management model could even prevent deterioration of retinopathy [79]. Having a specific

knowledge of the retina or DR did not appear to influence awareness of the threat to eyesight or attitudes to prevention, suggesting that patient education should focus more on correct health conducts than on technicalities of diabetes complications [77].

Medical treatment of diabetic retinopathy

Medical prevention and treatment of DR today is based on optimised control of blood glucose and blood pressure, but not on DR-specific pharmacologic drugs. Hypotheses on pathogenesis and pathogenesis-based treatments have been reviewed recently [80, 81] and new approaches are under evaluation by randomized controlled clinical studies of renin-angiotensin system blockade, inhibition of specific protein kinase C (PKC) isoforms and long-acting somatostatin analogues.

The role of metabolic control

Hyperglycaemia is necessary though not sufficient for DR to develop. The notion that higher chronic blood concentrations of glucose result in more frequent and severe microvascular damage is perhaps intuitive and was supported by prospective observational studies [51, 82] and small intervention trials [83, 84, 85, 86]. However, the role played by other factors could not be put into perspective until two major long-term intervention trials were published.

The DCCT [15] included 1441 patients with Type I diabetes, 726 without DR and 715 with mild DR, to establish what effect the best achievable blood glucose control would have on the onset of new retinopathy ("primary" prevention) and the progression of existing DR ("secondary" prevention). Patients were past puberty (13–39 years old) at recruitment, non hypertensive or hypercholesterolaemic and not prone to severe hypoglycaemia. Intensive insulin treatment meant at least 3 daily injections or continuous subcutaneous infusion wth dosages adjusted according to minimum 4-daily self-monitoring, monthly visits in clinic and continuously available medical, dietary, educational and psychological support. The goals were fasting blood glucose between 70 to 120 mg/dl (3.9–6.7 mmol/l), postprandial below 180 mg/dl (10 mmol/l) and HbA_{1c} within the reference range (<6.05%). Conventional therapy involved 1 to 2 daily injections without dosage adjustments, blood or urine self-monitoring, 3-monthly appointments and generic education on treatment, diet and exercise. The targets were remaining ketonuria-free and symptom-free and maintaining stable growth and body weight.

The primary endpoint was a sustained three-step worsening of DR. Onset of severe NPDR, PDR and the need for photocoagulation were additional outcomes.

After an average 6.5 years follow-up, patients on intensive treatment maintained an HbA_{1c} of 7.2%, versus 9.1% for conventional therapy. Intensified treatment reduced onset of new retinopathy by 76%, risk of existing DR worsening by 54%, progression to severe NPDR by 47% and necessity of photocoagulation by 56%. Extrapolations of these results suggest that, over lifetime, intensive treatment can buy patients 14.7 more years free from PDR, 8.2 free from CSME and 7.7 free from blindness [87]. Four years later, when all DCCT patients had returned to their habitual care, differences in metabolic control were abolished but those who had been on intensive treatment had maintained their advantage in terms of reduced risks of worsening of DR and need of photocoagulation [88].

Intensified insulin treatment caused three times as many severe hypoglycaemic episodes, and a 33% increased risk of becoming overweight. Maintaining optimised control with the DCCT approach cost about 20 000 US dollars per QALY (in 1996 dollars) [87], approximately the line above which medical intervention is no longer considered to be cost-effective [76].

The UKPDS [12] enrolled 3867 newly diagnosed Type II diabetic patients aged 48 to 60 who, after 3 months on diet only, were randomised either to intensive treatment with sulphonylureas or insulin, the target being a fasting blood glucose of less than 6 mol/l (108 mg/dl), or conventional policy, i.e. the best fasting blood glucose achievable by diet alone, with drugs added only if concentrations went above 15 mmol/l (270 mg/dl) or symptoms were present. DR-relevant end-points included: blindness (visal acuity <6/60) in one eye, two-step worsening of DR, 3-line worsening of visual acuity on the logMAR chart (doubling of the visual angle), and an aggregate microvascular end-point including onset of vitreous haemorrhage, need for photocoagulation and cataract extraction.

Maintaining a difference of 0.9% HbA_{1c} over 12 years reduced the risk of DR worsening by 21%, photocoagulation by 29%, and cataract extraction by 24%. Non-significant reductions were observed for vitreous haemorrhages and blindness in one eye. Also in the UKPDS intensified treatment caused weight gain (on average 3.1 kg) and increased risk for hypoglycaemia.

Early worsening of diabetic retinopathy

An unexpected side-effect of rapidly improving metabolic control is transient worsening of DR. This phenomenon was reported in some early intervention studies of intensified insulin treatment [83, 84, 85], confirmed by the DCCT [89] and also described in patients with Type II diabetes after starting insulin to improve control [90]. Early worsening was observed in

moderate to severe NPDR within 6 to 12 months of rapidly improving control but appeared to be self-limiting. Within 2 years into the trials, DR had progressed more among patients on conventional treatment.

The mechanisms are not clear. That early worsening occurs when some retinal ischaemia is already established suggests that lowering blood glucose might reduce retinal blood flow and further impair perfusion. However, a study in which retinal blood flow was measured before and after rapid improvement of control showed that blood flow increased, rather than decrease, in the patients who developed early worsening [91], suggesting a pathogenic role for increased shear stress on the capillary wall. Others have suggested that increased insulin concentrations augment hepatic synthesis and release of insulin-like growth factor I (IGF-I), which could be involved in fibro-vascular proliferation [92], and retinal expression of VEGF [93].

Clinicians need to worry about early worsening when they consider intensified treatment in poorly controlled patients with moderate to severe retinopathy. There is no experimental evidence to support more or less rapid lowering of HbA_{1c}. The best advice is to check the fundus before starting and, if DR is present, keep checking the retina every 3 to 4 months. Patients should be informed that improving control could lead to temporary worsening of retinopathy and that photocoagulation might even become necessary.

Treatment of hypertension and diabetic retinopathy

Observational surveys did not fully reveal the importance of hypertension on the course of DR [19, 24, 25, 26, 82]. It took a substudy of the UKPDS [94], to clearly show that lowering blood pressure substantially reduces the risks of DR progression and visual loss in diabetic patients who are also hypertensive.

This substudy [94] was carried out in 1148 patients with Type II diabetes and hypertension, to establish whether: (i) more tight blood pressure control would reduce morbidity and mortality, and (ii) an ACE-inhibitor, captopril, or a β-blocker, atenolol, would show specific advantages in reducing the risk of vascular complications. The patients were randomized to either "less tight" treatment (goal: blood pressure below 180/105 mmHg) or "more tight" control, with a 150/85 mmHg target. In total, 400 patients were randomised to "more tight" control with captopril plus any other agent required, except β-blockers, 358 to "tight control" with atenolol plus any others except ACE-inhibitors, and 390 acted as control subjects on "less tight" treatment with any class of drugs but those under study. Over 9 years of follow-up, "more tight" patients maintained an average 144/82 mmHg, "less tight" ones remained at 154/87. Captopril and atenolol were almost equally effective, 144/83 and 143/81 mmHg respectively, although diastolic blood pressure was lower with the β-blocker.

The risk of two-step worsening of DR was reduced by 24% after 6 years and by 34% after 9 years. The effect on visual acuity was even more pronounced, with a 47% reduced risk of doubling of the visual angle. Captopril and atenolol reduced the cumulative risk of microvascular end-points to the same extent, suggesting an effect related to blood pressure lowering rather than properties intrinsic to the agents. Mechanisms proposed for hypertension-induced worsening of DR include endothelial shear stress and stretch-related release of VEGF from the vessel wall [95], consequent to impaired autoregulation of retinal blood flow with increasing perfusion pressures [9].

Other options for the medical treatment of DR

The EUCLID trial suggested that ACE-inhibition *per se* might be beneficial in DR [97], as lowering systolic blood pressure by 3 mmHg with lisinopril, against placebo, reduced the risks of DR progression by 50% and PDR development by 80%.The therapeutic targets were 75 to 90 mmHg diastolic pressure and less than 155 systolic. However, DR was not a primary outcome of EUCLID, the sample was undersized, there were confounding factors, and other trials such as HOPE [98] and ABCD [99] which also included DR among their secondary end-points, do not support the notion that ACE-inhibitors have specific effects on the course of retinopathy.

Nevertheless, the regulatory authorities of Canada, Italy, New Zealand and Portugal have included medical treatment of DR among the indications of lisinopril, creating situations in which local doctors could feel compelled to prescribe this agent to patients with DR, if anything for medical-legal reasons. Consequently, also based on in vitro evidence that angiotensin II increases glucose uptake by retinal pericytes [100], induces release of VEGF by retinal endothelial cells [101], and that blockade of the renin-angiotensin system could prevent new vessel growth in a transgenic animal model of retinopathy of prematurity [102], an angiotensin-receptor blocker is undergoing a clinical trial appropriately targeted and powered to test its possible role in the primary and secondary prevention of DR.

Poulsen's seminal observation [103] of spontaneous regression of severe PDR in a woman with postpartum pituitary apoplexy stimulated extensive research into the role of growth hormone (GH) in DR. Patients with DR secrete GH with more frequent and larger spikes than control subjects [104]. GH might act directly or via IGF-I. However, concentrations of IGF-I may be depressed in poorly controlled diabetes [105] and a protective rather than permissive role has been proposed for this growth factor in the pathogene-

sis of DR [106]. Pituitary ablation was a last-resource treatment for patients with PDR before photocoagulation became available and a retrospective survey showed that, in spite of its severe and sometimes fatal complications, it effectively stopped the progression of retinopathy and nephropathy [107]. Pharmacological GH suppression by long-acting somatostatin analogues, was reported to reduce progression of early and severe PDR [108, 109]. One such analogue is currently undergoing a randomized controlled clinical trial in patients with severe NPDR. In this context, however, one has to keep in mind that patients with acromegaly and diabetes do not carry an increased risk of retinopathy.

Protein kinase C (PKC) is a family of intracellular transmitters that modulate protein synthesis and release and cell proliferation [110]. Two isoforms, $PKC_{\beta 1}$ and $PKC_{\beta 2}$, are activated and translocated to the cell membrane by high glucose and, in turn, can promote release of VEGF with its permeabilizing and angiogenic effects [111]. A specific PKC_{β} inhibitor is undergoing clinical trials in patients with macular edema and/or early PDR.

Other agents underwent clinical trials to test their use in DR. The aldose-reductase inhibitor Sorbinil was not effective [112]. Platelet anti-aggregating agents, aspirin alone or with dipyridamole and ticlopidine, slowed down the appearance of new microaeurysms in early retinopathy [113, 114]. In STDR, aspirin neither influences progression nor increases the risk of bleeding from new vessels [115]. Hence, PDR is not a contra-indication to anti-aggregating treatment for the prevention of cardio-vascular events. Studies of aminoguanidine [116, 117], soluble anti-VEGF receptors and anti-oxidants or free-radical scavengers are at present preliminary in nature and/or confined to animal models of retinopathy.

Interpreting results of clinical trials on diabetic retinopathy

DR is probably the field to which the principles of evidence-based medicine were applied earlier and more extensively. Large, randomized controlled clinical studies, such as the DRS [118] and ETDRS [119], were started in the 1970's and 1980's to objectively evaluate the effects of light photocoagulation and were followed by the DCCT [15] and UKPDS [12] which established the influence of medical intervention on retinopathy. Detailed knowledge of the natural history of DR has helped in the design of such investigations. Nevertheless, retinopathy poses problems related to its slow, unpredictable course in individual patients. The challenges facing clinical studies on DR include how to detect DR and measure its severity, how to select the stage(s) of intervention and outcome(s) to be measured, the lenght of observation, and sample size.

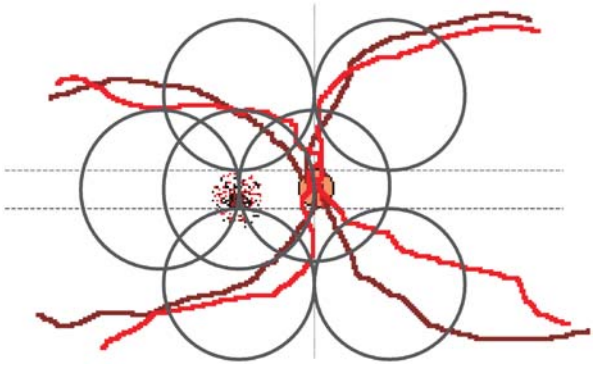

Fig. 3. Standard seven fields graded with the ETDRS classification

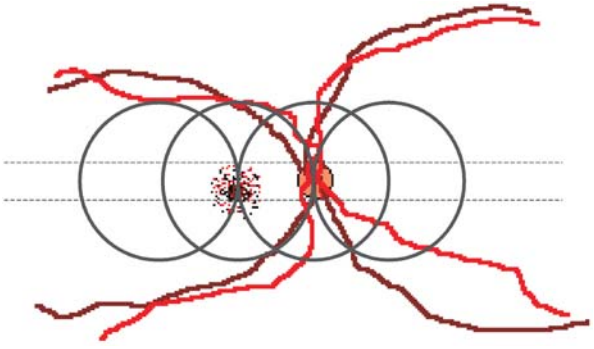

Fig. 4. Diagram of the four fields graded in the UKPDS

Although the lesions of DR are relatively easy to observe and photograph, it is difficult to derive objective, quantitative and repeatible measurements. Ophthalmoscopy and slit-lamp biomicroscopy, depend on patient collaboration and observer performance and do not leave permanent records. FAG provides detailed, objective imaging and was used in some studies [113, 114], to assess microaneurysm turnover (Table 2), but is no longer used in clinical trials, partly for its possible side-effects and partly because of the potential for false positives [120].

Colour photography is the accepted procedure to date. The reference method for semi-quantitative assessment of DR is grading of seven 30° stereoscopic images of the retina, according to the ETDRS protocol [121] and further modifications (Fig. 3). The stereo effect is obtained by photographing each field from slightly different angles. By observing the pairs with appropriate goggles, retinal thickening and lesion depth can be appreciated. The UKPDS adopted a simplified procedure [12] on four stereo fields (disc, macular and temporal of the ETDRS plus a nasal field) (Fig. 4). The UKPDS procedure can miss lesions above or below the fields photographed but, conversely, the seven-field protocol can miss ischaemic lesions which are often nasally located in early severe NPDR. Finally, the EURODIAB [122] procedure, adopted for the EURODIAB [6] and EURODIAB PCS [19, 24] surveys and the EUCLID study [97] includes two 45°, non-stereoscopic fields (Fig. 5).

Table 2. Main intervention trials on diabetic retinopathy

Trial	Agent	Detection	Quantification	DR at start	End-point	Length (years)	Sample size
DAMAD [113]	Aspirin, aspirin + dipyridamole	FAG	MA count	>5 MA	New MA/year	3	475 (T1DM and T2DM)
TIMAD [114]	Ticlopidine	FAG	MA count	>5 MA	New MA/year	3	435
Sorbinil Trial [112]	Sorbinil	7-field	ETDRS	<5 MA	2-step change	2.5	497 (T1DM)
ETDRS [119]	Early photo coagulation	7-field	ETDRS	Severe	VA <5/200	5	3,711 (T1DM and T2DM)
DCCT [15]	Metabolic control	7-field	ETDRS	No/mild	Sustained 3-step change	6.5 (3–9)	1,441 (T1DM)
UKPDS [12]	Blood glucose control	4-field	ETDRS	Any	VA <6/60, 2-step change	11	3,867 (T2DM)
UKPDS [94]	Blood pressure control	4-field	ETDRS	Any	2-step change, doubling of visual angle	9	1,148 (T2DM)
EUCLID [97]	Lisinopril	2-field	EURODIAB	Any	1-step change, progression to PDR	2	354 (T1DM)

T1DM, Type I diabetes mellitus; T2DM, Type II diabetes mellitus; FAG, fluorescein angiography; DAMAD, Dipyridamole and Aspirin Microangiopathy of Diabetes study; TIMAD, Ticlopidine Microangiopathy of Diabetes study; ETDRS, Early Treatment of Diabetic Retinopathy Study; DCCT, Diabetes Control and Complications Study; UKPDS, United Kingdom Prospective Diabetes Study; EUCLID, EURODIAB Controlled trial of Lisinopril in Insulin Dependent diabetes mellitus; VA, visual acuity

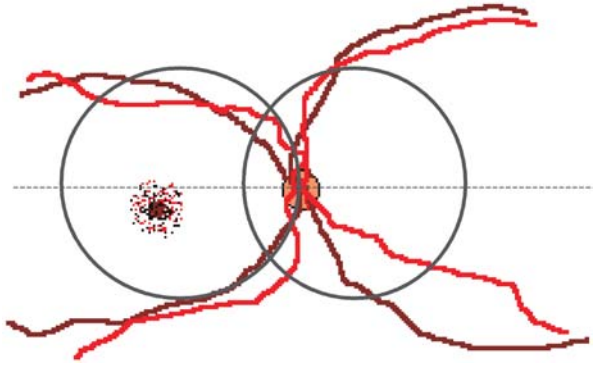

Fig. 5. Diagram of the two fields graded in the EURODIAB system

Grading DR is the next step. In the ETDRS method, each of 7 standard fields, and any others showing clinically important lesions, are first assessed for quality and then compared with sets of standard photographs to derive a measure of severity for each lesion. A score is assigned to each eye, ranging from 10 (no DR) to 85 (advanced PDR) (Table 1). The EURODIAB scale has fewer steps (Table 3) and may be less sensitive to small changes of DR.

After both eyes are graded, they are pooled together in a scale of "steps" (Table 4). Progression of DR in the UKPDS was defined as a difference of at least two steps on this scale. In the DCCT, "sustained" progres-

Table 3. EURODIAB severity scale for individual eyes

EURODIAB level	Retinopathy	Corresponding ETDRS level
0	Absent/questionable	10–15
1	Mild NPDR	20–35
2–3	Moderate/severe NPDR	43–53
4–5	Proliferative/photocoagulated	61–85
Unassessable	Cannot grade	90

(Reprinted with permission [122])

Table 4. Abbreviated final version of the ETDRS scale of DR severity for persons

Step	Level
1	10/10 (absent)
2	20/<20 (Very mild DR)
3	20/20
4	35/<35 (Mild DR)
5	35/35
6	43/<43 (Moderate DR)
7	43/43
8	47/<47
9	47/47
10	53/<53 (Severe non PDR)
11	53/53
12–13	≥61/<61 (PDR)

DR, Diabetic retinopathy; PDR, proliferative diabetic retinopathy. (Reprinted with permission [126])

sion was defined as at least three steps worsening over baseline, maintained over two consecutive observations 6 months apart. Worsening in EUCLID was one step along the EURODIAB scale.

The stage of DR at recruitment is chosen according to the hypothesized outcome, i.e. no clinical DR in primary prevention studies, whereas trials of treatments aimed at more advanced stages will recruit patients with specific clinical presentations. In the UKPDS, patients with Type II diabetes were recruited at diagnosis, irrespective of the presence and severity of DR. In EUCLID, DR was not a primary endpoint. Neither study, therefore, considered populations that were homogeneous for severity of DR at enrolment.

The choice of suitable end-points is possibly even more important. Hard end-points, such as legal blindness or doubling of the visual angle, are relatively rare events in a study population. Consequently, most studies after the ETDRS have adopted surrogate end-points, such as two or three-step worsening of DR or changes in microaneurysm counts. The UKPDS [12, 94] used both hard (doubling of the visual angle) and surrogate end-points, such as two-step worsening.

The length of observation is another challenge, considering the slow progression of DR. There is no fixed rule but 5 years is arguably a safe window to assess treatment effects in a selected population. No clinical studies should be run for less than 3 years, unless dealing with very specific outcomes in selected subpopulations.

Sample sizing, of course, is not specific to trials on DR. In general, calculations must consider the statistical approach with which the results will be analysed, the expected incidence of events in the control arm, the expected reduction of events brought about by the treatment being tested, an "inflation" factor for patient drop-out, and the α and 1-β statistical power necessary to avoid detecting effects that are not there (type I errors) or, respectively, missing effects that do exist. In the UKPDS control of hypertension substudy [94], the expected two-step worsening of DR over the observation period was 40%. To detect an estimated 30 to 40% effect of "more tight" control of blood pressure with power α=0.01 and 1-β=90%, some 312 to 544 patients had to be studied, active and placebo included. Since more tight blood pressure control reduced by 34% the 33% incidence of events observed among the control subjects, a sample of 1148 patients was adequately sized. With the end-point "doubling of visual angle", instead, even reducing the 1-β power to 80%, the number of patients was just enough.

Photocoagulation

Laser treatment of diabetic macular edema

The ETDRS criteria for laser treatment of diabetic macular edema include [123]: (i) areas of focal leakage, responsible for hard exudate formation, located at more than 500 μm from the centre of the foveal avascular zone; (ii) diffuse areas of leakage; (iii) small areas of capillary drop-out.

FAG is used to preliminarily identify treatable lesions and to evaluate the outcome of photocoagulation and possible indications for further treatment [119]. It also helps to define other clinical conditions which cannot be treated by laser, such as: (i) lack of angiographic correlation between vascular abnormalities and macular edema [124]; (ii) ischaemic maculopathy, defined as an area of non perfusion at least twice as large as the physiological foveal avascular zone. Grid laser treatment of edema in ischaemic maculopathy is associated with a high rate of visual loss after 2 years of follow-up [125]; (iii) macular edema secondary to contraction of the posterior hyaloid. In these cases early angiographic phases show a round hypofluorescence pattern, followed in later phases by hyperfluorescence. Typically, there is no relation between vascular abnormaities and fluorescein leakage.

Photocoagulation heats the retinal and choroidal tissues, causing coagulative necrosis and scars. The pigments involved in absorbing laser light are Xantophil (plexiform layers), melanin (retinal pigment epithelium and choroidal melanocytes) and haemoglobin (blood retinal and choroidal vessels).

Focal treatment. The aim of focal treatment is to stop or at least reduce fluid leakage from vascular abnormalities, allowing reabsorption of edema and exudates. Microaneurysms, capillary abnormalities and areas of focal leakage are treated directly by laser spots of small size (100–250 μm) with relatively long exposure. Laser pulses should induce whitening of the microvascular abnormalities targeted using the lowest energy sufficient, as retinal scars tend to enlarge with time and spots applied near the fovea, years later, can result in atrophy of the macular centre [119, 127].

Grid treatment. Diffuse macular edema, sometimes with a cystoid component, is treated with a grid of non-confluent laser impacts over the whole area of fluorescein leakage. Usually this presentation is not associated with hard exudates or microaneurysms, and the extension and amount of edema are variable.

Laser spots are generally 150 to 200 μm in diameter, with one spot diameter left between each other. The power is lower than for focal treatment. Direct treatment of intra-retinal haemorrhages is avoided because energy absorption in the inner retinal layers can seriously damage the internal limiting membrane and the nerve fibre layer.

In everyday practice, the presentation is usually one of mixed focal and diffuse leakage patterns. In these cases a modified grid treatment is carried out, consisting in the focal treatment of well-defined leaky lesions combined with a lighter grid on the more diffuse thickened areas. The efficacy of this approach was shown to compare well with the results reported by the ETDRS [128].

Complications of laser treatment for macular edema. Most possible complications of laser treatment were reported by the ETDRS. Para-central scotomas after focal treatment close to the fovea can result from confluent spots. A most serious complication is accidental photocoagulation of the fovea. Choroidal neovascularization can originate from laser scars 2 weeks to 5 months after treatment [129], and visual acuity remains poor even if further photocoagulation is applied. Laser scar enlargement can occur months to years after grid treatment [127]. Both neovascularization and scar enlargement can be prevented by lowering the power of the photocoagulator.

Another potentially severe complication is subretinal fibrosis in the macular region, resulting from ruptures of Bruch's membrane due to excessively intense laser energy [130, 131]. Subretinal fibrosis is associated with the presence of extensive hard exudates, especially after re-absorption of macular edema [132].

Laser treatment of proliferative retinopathy

In PDR, the aims of photocoagulation are regression of existing new vessels and preventing the onset of newly formed ones. The DRS [118] had demonstrated that PRP reduces by 50% the onset of severe visual loss in patients with high-risk PDR, defined as: (i) NVD greater than 1/3 of an optic disc area, independently of pre-retinal or vitreous haemorrhages; (ii) presence of pre-retinal or vitreous haemorrhages with any NVD or with NVE larger than 1/2 disc area.

The ETDRS showed that high-risk clinical characteristics develop within 1 year in 50% of eyes with either initial PDR or very severe NPDR [119]. This suggests that PRP could be indicated in these conditions, even if initially producing mild visual loss, because it could prevent more severe visual loss or vitrectomy later on. Altogether, the ETDRS showed that early photocoagulation of PRP reduces legal blindness at 5 years by more than 90% [119].

The ETDRS results on visual acuity [119] are not as clear-cut and do not support the need for urgent PRP in severe NPDR. Associated risk factors, systemic and ocular, can be predictive of rapid worsening of DR and justify preventive treatment. Systemic factors include poor metabolic control, nephropathy, hypertension and pregnancy [26]. Ocular factors include developing cataract, which would hinder fundus examination and retinal photocoagulation, PDR or severe NPDR in the fellow eye, a blind fellow eye, rapidly progressing DR, rubeosis iridis secondary to associated ocular ischaemic syndrome, and inability to carry out periodic follow-ups at regular intervals.

Immediate PRP is mandatory if iris neovascularization is observed, even in the absence of retinal new vessels, to prevent the progression to neovascular glaucoma.

When performing PRP, extensive photocoagulation of the retinal mid-periphery is essential because ischaemia in this area is probably the main culprit for new vessel growth. Treatment can sometimes involve small peripheral new vessels, provided no vitreous traction is present. Direct treatment of NVE, apart from the risk of worsening vitreous traction, can produce large scars with disturbing visual field defects. NVD and NVE raised by vitreous tractions or close to the posterior pole should never be treated directly.

In general, 1600 to 2000 spots, 500 μm diameter and spaced 1/2 spot diameter from each other, are applied from the posterior pole vascular arcades to the periphery, divided over two or more sessions. Compared with macular edema, the spots used in PRP are more visible because of their higher power. In severe or florid PDR, 2000 to 3000 or more spots may be required to obtain regression or stabilization of new vessels. Dividing PRP in sessions of 6 to 800 spots spaced 1 to 3 weeks apart helps to minimize temporary short-term complications such as pain, iritis, choroidal detachment with possible angle closure and exudative retinal detachment. PRP can be done in a single session in patients with rubeosis iridis or very severe PDR. Such one-session treatments could have similar efficacy and long-term complications as those fractioned over more sessions [133].

Often regression of new vessels is partial. Complete regression after 1 year was observed in only 21% of eyes treated in the DRS [118], although 72% of eyes with high-risk characteristics have less severe lesions 3 weeks after treatment [134]. Of the eyes that do not respond, 64% maintain high-risk characteristics after 6 months but 50% of those with severe PDR can still improve by increasing the total number of spots to 7500 [135]. Additional PRP is done by applying more spots in between existing ones and to less heavily treated areas. Although 50 to 70% of eyes that do not respond to PRP improve after additional treatment, some will still require surgery. Even in these cases the long-term prognosis after surgery will be better if PRP is completed in advance.

The mechanism of action of PRP is still not known. As widespread capillary occlusion leads to insufficient oxygen supply to the peripheral neuroretina, which then releases angiogenic factors in an inappropriate attempt to revascularize, ablation of ischaeic tissue may allow sufficient perfusion to the remaining tissue to remove the stimulus for angiogenesis and cause new

vessels to regress [136]. An alternative hypothesis is that PRP, besides destroying the highly oxygen-requiring photoreceptor-pigment epithelium complex, could let oxygen diffuse from the choroid to the inner retina [137]. Indeed, the diameter of retinal vessels is reduced after PRP, possibly as a consequence of increased oxygen availability. A third possibility is that photocoagulation results in the release of anti-angiogenic factors from the pigment epithelium [138, 139].

Complications of PRP

The most frequent and important complications of PRP are loss of visual acuity and narrowing of the visual field.

The main cause for visual loss is onset or exacerbation of macular edema. In the DRS [140] 10% of treated patients experienced loss of two or more lines, which was more pronounced after xenon arc than with argon laser. Increased macular edema was reported in 43% of treated eyes 6 to 10 weeks after PRP [141]. Of these, 27% developed persistent edema with loss of more than two lines in 33%.

If edema and PDR are both present, the macula should be treated first and progression of retinopathy closely monitored. If PRP cannot be postponed, the nasal and inferior quadrants should be photocoagulated first and the spots placed more peripherally, especially in patients older than 50 years [119]. The macula can be reassessed for further treatment 3 to 4 months later. Improved visual acuity and macular edema were reported after PRP, if the latter is done peripherally and divided over several sessions in eyes with good macular perfusion [142].

Less frequent causes of visual loss associated with PRP are accidental foveal photocoagulation and macular detachment. The former, a rare but dramatic event, is usually due to a sudden eye movement during treatment but could also be caused by improper use of the Goldmann's lens trapezoidal mirror. Macular tractional detachment is generally due to intensive treatment in eyes that had evolved to high-risk PDR after previous inadequate photocoagulation [143].

Narrowing of the visual field [144] and reduced dark adaptation [145] are common and predictable, though rarely seriously invalidating, complications of PRP. Reduction of peripheral light sensitivity correlates with the localization and extension of photocoagulation.

Surgery

In spite of PRP, some patients can develop severe PDR complicated by traction retinal detachment. In these cases, and when extensive new vessels or vitreous haemorrhage preclude fundus visualization and photocoagulation, pars-plana vitrectomy becomes the only possible approach to prevent permanent visual loss. Over the last 25 years indications to vitreo-retinal surgery have extended to earlier stages of DR, while surgical techniques and instrumentation have considerably improved.

The Diabetic Retinopathy Vitrectomy Study (DVRS) [146] compared the visual prognosis of diabetic patients with severe vitreous haemorrhage and visual acuity worse than 1/40 operated of early (within 1–6 months) versus late vitrectomy (after 1 year). The major benefits of early vitrectomy were obtained in patients with Type I diabetes of less than 20 years duration. Patients with longer duration, whether Type I or II, did not seem to benefit from surgery.

Current indications to pars-plana vitrectomy include opacities of ocular media, vitreo-retinal traction with or without macular involvement and macular edema.

Eye opacities

When a vitreous haemorrhage occurs, it is reasonable to wait up to 6 months before considering vitrectomy. If the vitreous clears spontaneously, new vessels are treated by PRP and surgical risks are avoided. Whereas waiting is justified in patients with Type II diabetes, vitrectomy should be carried out within a few months in Type I diabetic patients when severe vitreous haemorrhages do not reabsorb [147]. Rubeosis iridis, especially if PRP was never done, and large retro-hyaloid haemorrhages obscuring the macula strengthen the need for surgery.

Prognosis is good in vitreous haemorrhage without retinal detachment. Visual acuity improves in more than 80% of eyes, along with anatomic stabilization, being 1/40 or better in 76% of cases. The DVRS [148] showed that, in Type I diabetic patients, early vitrectomy (carried out within 1–4 months of severe vitreous haemorrhage) preserves 5/10 visual acuity or better after 2 years in 36% of eyes, versus 12% if surgery is delayed 6 months or more. However, these conclusions are debatable because the DVRS protocol did not include PRP or endolaser treatment for control eyes allocated to late vitrectomy.

Vitreo-retinal tractions

Removal of retinal and epiretinal tractions remains the most common indication to vitrectomy in DR. Peripheral and mid-peripheral tractional detachments, if not involving the fovea, can stabilize and simply require regular follow-up. Vitrectomy should be done within 6 months if the macula is involved or threatened. Surgery becomes mandatory when traction causes a retinal tear (tractional-rhegmatogenous detachment).

In tractional retinal detachment with macular involvement, vitrectomy is generally followed by anatomical improvement in 65 to 80% of eyes and visual acuity improvement in 26 to 70% [149]. Functional results are influenced by age, duration of macular traction, extension of capillary non-perfusion, vitreous haemorrhages, rubeosis iridis and previous laser treatment. Combined tractional-rhegmatogenous detachments are less responsive to surgery. About 50% of treated eyes improve, and 60% reach 1/40 or more [150].

Macular edema

In about 5% of cases macular edema is generated and/or sustained by traction exerted by a thickened and taut posterior hyaloid firmly attached to the internal limiting membrane [151, 152]. The diagnosis is suggested by the FAG pattern, and OCT helps to identify the tractions. Photocoagulation is ineffective, if not contraindicated, in this situation. During surgery, posterior vitreous detachment is induced and the internal limiting membrane is peeled off the retina. Because of its rarity and difficult diagnosis, most studies on this condition are limited to small series. Some authors [153, 154, 155, 156] reported positive outcomes in up to 90% of eyes, with visual acuity improving to 5/10 or more in almost 30%. However, the benefits seem to be short-lived, as acuity can drop again in the medium-long term and the indications for surgery in diabetic macular edema have yet to be established more firmly.

Sources. The review is based on the relevant literature published in the English language during 1990 to 2001 and seminal prior contributions. The sources available to the authors were integrated with sources identified through PubMed searches for “diabetic retinopathy”.

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