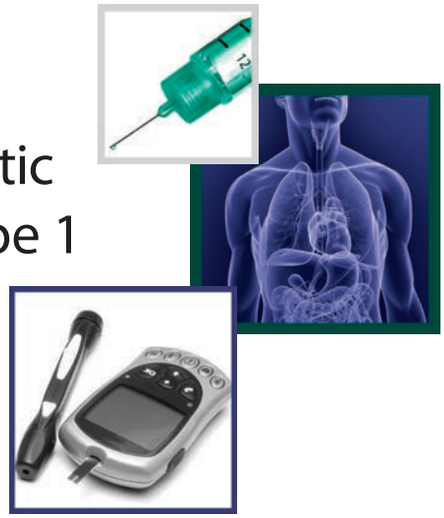
REVIEW

Prevention and management of diabetic retinopathy in young persons with Type 1 diabetes



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Practice Points

- Young people with Type 1 diabetes have a significant lifetime risk of visual impairment from diabetic retinopathy. This risk can be reduced by optimizing metabolic control, addressing modifiable risk factors and adequate eye screening.
- A multidisciplinary approach with input from medical specialists, dietitians, nurse educators and psychologists or social workers is important in optimizing outcomes.
- Glycemic control: in children aim for HbA1c ≤7.5% (58 mmol/mol) without severe hypoglycemia; and ≤7.0% (53 mmol/mol) for adults.
- Blood pressure (BP): maintain at <90th percentile for age, sex and height. If BP is between the 90–95th percentile initial intervention should include diet modification and exercise. Angiotensin-converting enzyme inhibitors are recommended if BP >95th percentile.
- Lipids: aim for low-density lipoprotein cholesterol <2.6 mmol/l and high-density lipoprotein cholesterol >1.5 mmol/l. Use dietary and lifestyle interventions to optimize glycemic control. Consider statins if abnormal lipid profile persists; however, long-term safety in children has not been established.
- BMI: <95th percentile for age, sex and height. Management should include a review of insulin requirements, as well as diet and lifestyle interventions.
- Smoking: counsel against smoking and offer smoking cessation assistance if required.
- Eye examinations: an initial examination should be arranged soon after diabetes diagnosis to screen for pre-existing eye conditions. Regular screening should commence according to national guidelines or at age 11 years after 2 years diabetes duration or age 9 years after 5 years duration (International Society for Pediatric and Adolesent Diabetes [ISPAD]). In England, annual screening for diabetic retinopathy is recommended for children aged 12 years and older.

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SUMMARY Young persons with Type 1 diabetes have a significant lifetime risk of visual impairment due to diabetic retinopathy (DR). Adequate medical management can significantly reduce the risk of DR. Recent advances in the treatment of DR have further reduced the risk of vision loss if implemented in a timely manner. This paper provides an overview of the pathophysiology, risk factors and current recommendations for screening and management of DR focusing on young persons with Type 1 diabetes.

Diabetic retinopathy (DR) is a sight-threatening microvascular complication of diabetes mellitus. Improvements in metabolic control and advances in treatment of retinopathy have made it possible to reduce the risk of vision loss in diabetes over recent decades. This article discusses the optimization of medical management, appropriate screening and treatment of DR with a focus on children and adolescents with Type 1 diabetes (T1D).

Definition & pathophysiology

DR refers to the appearance of characteristic retinal microvascular lesions detected on clinical examination in a person with diabetes. The changes themselves are nonspecific and can occur in conditions other than diabetes, such as vascular or hematological disorders. The lesions reflect underlying damage to the retinal microvasculature.

DR progresses through several nonproliferative (NPDR) stages before proliferative (PDR) disease appears **(Table 1 & Figure 1)** [1]:

- Early NPDR: microaneurysms are detected;
- Moderate NPDR: as retinopathy progresses intraretinal hemorrhages, cotton-wool spots and hard exudates (Hex) may appear;
- Severe NPDR or 'preproliferative' DR: extensive intraretinal hemorrhages, venous beading and/or intraretinal microvascular abnormalities are present;
- PDR: refers to the appearance of abnormal vessels on the optic disc or retina.

The pathogenesis of DR is multifactorial and the risk is modified by environmental and genetic factors [2]. Hyperglycemia leads to the uncoupling of the mitochondrial respiratory chain resulting in superoxide formation and a cascade of events involving multiple metabolic pathways including the increased activation of PKC [3,4], increased flux through the aldose reductase pathway [5,6], hexosamine pathway [7] and abnormal protein glycation [8]. The net result is an ischemic, inflammatory and procoagulant state with aberrant intra- and inter-cellular interactions. Retinal ischemia exacerbates the inflammatory state and leads to increased production of angiogenic factors including VEGF [9]. VEGF, in turn, stimulates the formation of friable and abnormal blood vessels.

Vision loss can occur at the PDR stage due to hemorrhage from fragile vessels or from tractional retinal detachment as the neovascular membranes organize and contract. In some cases, the anterior segment of the eye can also be affected with neovascularization across the trabecular meshwork leading to neovascular glaucoma.

Diabetic maculopathy is another important cause of vision loss in diabetes [10]. It runs a clinical course independent to the surrounding DR and is assessed and staged separately. Inflammatory cytokines, vasodilatory prostaglandins and VEGF increase vascular permeability and play an important role in the development of diabetic macular edema. Hex are due to leakage and precipitation of lipid material from nearby damaged retinal capillaries. Vision loss can occur due to macular edema or macular ischemia:

- Diabetic macular edema (DME) results in thickening of the retina and can be visualized using either stereoscopic fundus examination or more recently using optical coherence tomography. Hex is often present. Clinically significant macular edema (CSME) is a subclassification used in clinical trials and describes DME that is threatening the fovea and central vision [11];
- Macular ischemia requires a fluorescein angiogram for diagnosis. Shutdown of capillary networks in the central macular region is seen with an enlargement of the 'foveal avascular zone' [12]. It is relatively uncommon and is usually a late feature in the course of DR [13].

The term 'vision threatening' DR is usually used to describe the presence of severe NPDR or PDR, and/or CSME.

Table 1. Stages of diabetic retinopathy and suggested management.

Stage	Diagnostic features	Management
No retinopathy	No microvascular lesions	1–2 yearly review
Mild NPDR	Ma only	Yearly review
Moderate NPDR	Ma, CWS, Hex, intraretinal HA but not severe NPDR	3–6 monthly review Ophthalmologist referral
Severe NPDR	>20 intraretinal HA over all quadrants; or two quadrants with VB; or one quadrant with IRMA	3–6 monthly review Ophthalmologist referral
PDR	NVD or NVE Pre-retinal or vitreous hemorrhage	Indication for PRP as per ophthalmologist
Clinically significant macular edema	Macular thickening close to or within the central macula. May or may not be associated with Hex	Indication for focal/grid laser as per ophthalmologist

CWS: Cotton wool spot; HA: Hemorrhage; Hex: Hard exudate; IRMA: Intraretinal microvascular abnormality; Ma: Microaneurysm; NPDR: Nonproliferative diabetic retinopathy; NVD: Neovascularization of the optic disc; NVE: Neovascularization elsewhere; PDR: Proliferative diabetic retinopathy; PRP: Panretinal laser photocoagulation; VB: Venous beading.

Epidemiology

DR is the leading cause of vision loss in working age persons in the western world and the fifth most common cause of blindness globally [14–16]. In England and Wales, DR is responsible for approximately 6% of cases of registered blindness and visual impairment [17].

DR staging, progression and treatment is the same regardless of the type of diabetes; however, the epidemiology and relative risk factors may vary. T1D accounts for the majority of cases of diabetes in children and adolescence [101]; however, Type 2 diabetes (T2D) is becoming more common.

Pooled data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WI, USA) and New Jersey 725 study (NJ, USA) estimated the prevalence of DR in adults with T1D (defined as age <30 years at diagnosis and using insulin) to be approximately 75%, with vision threatening retinopathy in 30% [18]. The risk of DR is strongly associated with duration of diabetes. Virtually all (97%) persons with T1D developed retinopathy after 25 years of follow-up. During this period 42% developed PDR and 17% developed CSME [19,20]. The cumulative incidence of severe visual impairment was 3% [21].

Recent studies in younger cohorts have found lower rates of DR. An Italian study of childhood-onset T1D found 55% of patients developed some retinopathy and approximately 6% severe or proliferative retinopathy after 20 years duration [22]. In an Australian cohort of children with T1D, 24% had signs of retinopathy 6 years after diagnosis [23]. The lower rates compared with previous studies are partly due to younger patient populations and may also reflect improvements in metabolic control. A general trend of decreasing DR rates and severity over recent decades has been supported by several studies [19,20,24–27].

There is concern that young persons with T2D may be at higher risk of complications, although data is still relatively sparse. The SEARCH study in the USA found that amongst youth with T1D and T2D, the prevalence of DR was 17 and 42%, respectively. Both groups had similar diabetes duration (6.8 vs 7.2 years) but those with T1D

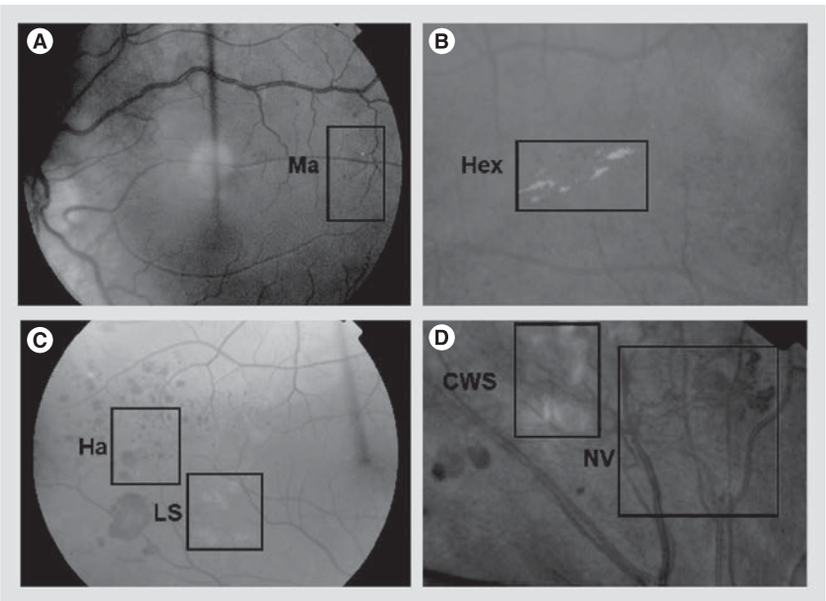

Figure 1. Typical fundus changes in diabetic retinopathy. (A) Ma, **(B)** Hex, **(C)** retinal Ha and LS, and **(D)** CWS and NV elsewhere.
CWS: Cotton wool spot; Ha: Dot/blot hemorrhage; Hex: Hard exudate; LS: Laser scar; Ma: Microaneurysm; NV: New vessel formation.

were younger (16.0 vs 21.1 years) [28]. In a study of young people (<30 years of age) with T2D from Japan, 9.3% had DR at diagnosis and 12.7% developed PDR by the age of 35 years [29]. T2D was previously considered rare amongst children and adolescents; however, rates have increased in recent decades, largely linked to lifestyle changes and growing rates of childhood obesity.

DME is uncommon amongst children and adolescents with diabetes. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy the prevalence of DME amongst T1D with less than 5 years duration was 0% compared with 29% amongst those with 20 years duration. Overall, T1D appears to have a lower rate of DME compared with T2D [30].

Risk factors & management

Modifiable and nonmodifiable risk factors influence the likelihood of developing DR and are discussed below **(Box 1)**. A summary of established modifiable risk factors and current recommendations for clinical management can be found in the 'Practice points' at the beginning of this article and in **Table 2**.

■ Modifiable risk factors

Glycemic control

The Diabetes Control and Complications Trial (DCCT) results, published in 1993, provided conclusive evidence that improved glycemic control reduced the risk of DR [31]. Each 1% reduction in HbA1c (e.g., from 9 to 8%) lowered the risk of DR by 30–40% [32]. Amongst the adolescent subjects (aged 13–17 years at entry), intensive control reduced the onset of retinopathy by 53% and progression by 70% [33]. Similarly, a Swedish study of 94 children diagnosed with T1D between the ages of 0–14 years found a 1% increase in HbA1c correlated with a 43% increase in the risk of developing DR over a mean duration of 11.8 years [34].

After the closure of the DCCT, all participants were placed on intensive therapy and followed in the Epidemiology of Diabetes Interventions and Complications study. Despite equalization of HbA1c the benefits of early glycemic control endured for the period of Epidemiology of Diabetes Interventions and Complications follow-up – a phenomenon dubbed 'metabolic memory' [35]. Furthermore, results from the 10-year follow-up demonstrated that benefits of early intensive therapy wane over time if HbA1c levels are not maintained [36]. Thus, achieving optimal glycemic control as early as possible and maintaining optimal control over time should be the goal of management.

Intensification of glycemic control can be associated with some negative effects for the patient. The DCCT demonstrated a small risk of transient worsening of DR in the first year of treatment; however, the long-term benefits outweigh this risk [37]. The risk is greater in patients with long-standing poor control, so early referral for DR screening is important in these cases. There was roughly a threefold increase in the risk of severe hypoglycemia in the intensive control group. Intensive treatment was also associated with increased weight gain [31,33].

The current recommended HbA1c targets for children and adolescents are ≤7.5% or 58 mmol/mol. Hypoglycemia is more common in adolescents and children and may be difficult to detect in the very young [38]. Management should be individualized to the patient to help them achieve these goals while minimizing the risk of hypoglycemia.

Box 1. Risk factors for diabetic retinopathy.

Modifiable
- Glycemic control
- Blood pressure
- Lipid levels
- Weight/obesity
- Smoking

Non-modifiable
- Duration of disease
- Puberty
- Pregnancy
- Genetic factors

Blood pressure & the rennin–angiotensin system

Both systolic and diastolic blood pressure (BP) are predictors of retinopathy in young patients with T1D [39]. In a large cohort of adults with T1D, each 10 mmHg increase in systolic BP was associated with approximately 10% excess risk of early DR and a 15% excess risk of PDR or DME [19,20,40]. A similar effect was found in an Australian study of adolescents with childhood-onset T1D [39].

In the UK Prospective Diabetes Study, lowering of BP in hypertensive T2D patients reduced the rate of DR progression by 34% over 9 years [41]. Renin–angiotensin system blockade may have beneficial effects on DR aside from any BP lowering effect. The EURODIAB Controlled Trial of

Table 2. Management targets and suggested interventions (adapted from International Society for Pediatric and Adolesent Diabetes [ISPAD] guidelines 2009).

Risk factor/activity	Target	Possible intervention
Glycemic control	HbA1c ≤7.5% (58 mmol/mol) without severe hypoglycemia for children ≤7.0% (53 mmol/mol) for adults	Optimize glycemic control
BP	<90th percentile for age, sex and height or <120/80 for young adults	Lifestyle intervention Consider ACE inhibitor if BP >90th percentile despite lifestyle intervention ACE inhibitor if BP >95th percentile
Lipids	LDL cholesterol <2.6 mmol/l HDL cholesterol >1.5 mmol/l	Optimize glycemic control Dietary intervention Statins
BMI	<95th percentile for age, sex and height or nonobese	Review insulin requirements Lifestyle intervention Dietary intervention
Smoking	No smoking	Counsel not to start Assist with cessation
Eye examinations	Eye examination soon after diagnosis Regular screening to commence according to national guidelines, or at 11 years of age after 2 years of diabetes duration or at 9 years of age after 5 years of duration (ISPAD)	Treat any pre-existing eye conditions Optimize metabolic control if early retinopathy detected Refer to ophthalmologist for possible intervention

ACE: Angiotensin-converting enzyme; BP: Blood pressure; HDL: High-density lipoprotein; ISPAD: International Society for Pediatric and Adolesent Diabetes; LDL: Low-density lipoprotein.

Lisinopril in Insulin-Dependent Diabetes Mellitus (EUCLID) showed that lisinopril reduced the risk of DR progression by 50% over 2 years in normotensive adults with T1D [42]. There was a modest, but nonstatistically significant, effect in reducing DR incidence. By contrast, the subsequent Diabetic Retinopathy Candesartan Trials (DIRECT)found that candesartan reduced incidence but not progression of DR [43]. The renin–angiotensin system study in normotensive, normoalbuminuric T1D patients found that enalapril or losartan reduced the risk of DR progression by 65 and 70%, respectively, independent of BP [44].

Hypertension in children with diabetes is rare and current available data come from adult study populations. As the exacerbating effect of hypertension on other vascular complications of diabetes is well known, maintaining optimal BP is a standard goal of management. BP values should be maintained at less than the 95th percentile for age or 130/80 for young adults. If hypertensive, angiotensin-converting enzyme (ACE) inhibitors are the recommended treatment and have been effective and safe in children in short-term studies, but are not safe during pregnancy [45,102].

Lipids

There is good evidence that serum lipids contribute to DME and retinal Hex formation [46]. By contrast, the presence and progression of DR (NPDR and PDR) have not shown a conclusive association with serum cholesterol and triglyceride levels. Other lipid biomarkers, such as apoproteins A and B, may provide better indicators of retinopathy risk than traditional measures [47].

Interestingly, interventional studies have demonstrated that lipid lowering agents can reduce the incidence and progression of both DME and DR [47]. In the case of statins alone, small case series have shown a beneficial effect in reduction of Hex; however, larger studies did not demonstrate any significant effect on DME, DR or the need for laser [47]. Fibrates, another class of lipid lowering agent, have shown more promise. Recent studies in adults with T2D found that fenofibrate lowered the risk of progression of both DR and DME and reduced the need for laser treatment [48,49].

No trials of lipid lowering therapy in pediatric populations with diabetes have been completed to date. The Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial is the first multicenter, multinational intervention study looking at the effect of ACE inhibitors and statins in adolescents with T1D and will provide much needed evidence in this area [50].

Smoking

The relationship between DR and smoking is less well established. The Europe and Diabetes

IDDM Complications (EURODIAB) study suggested that smoking was associated with higher rates of DR [51]; however, not all studies have shown a convincing association [52]. Smoking is known to increase the risk of other micro- and macro-vascular complications. Therefore, children and adolescents with diabetes should be advised not to smoke and assisted in efforts of smoking cessation.

Weight & obesity

Data from the several prospective studies suggest that greater BMI [39,53,54] and waist-to-hip ratio [55] increase the risk of DR. The aim should be to maintain BMI <95th percentile (nonobese) [45].

■ Non-modifiable risk factors

Diabetes duration is the most influential nonmodifiable risk factor for DR (see the 'Epidemiology' section above).

Puberty

The onset of puberty has a strong influence on the development of DR. The risk of retinopathy is low during early childhood; however, it increases dramatically at the onset of puberty and throughout adolescence, probably due to hormonal influences accelerating damage to the microvasculature [56]. The age at which T1D is diagnosed can influence how rapidly retinopathy develops. In a cohort of children with T1D in Australia, those diagnosed before the age of 5 years had a longer retinopathy-free period than those diagnosed between 5 and 15 years [56]. Similarly, a retrospective study of T1D in Finland found those diagnosed between 5 and 15 years had the most rapid progression to PDR, compared with both older and younger onset groups [57]. This suggests that diagnosis around the age of puberty may carry a higher risk of complications.

While duration of diabetes is the strongest risk factor for DR, there is evidence that the prepubertal years contribute slightly less to the risk of later complications. However, the contribution is still significant and owing to the very early age of onset, the overall lifetime risk of complications is very high. Therefore, optimal glycemic control should be the goal of management, even in very young patients [56,58,59].

Pregnancy

DR onset and progression is known to accelerate during pregnancy and the early postpartum period in both T1D and T2D [60]. Rapid progression to sight-threatening DR can occur. Risk factors include duration of diabetes, poor glycemic control, hypertension and nephropathy [61]. Careful metabolic control and more frequent screening are necessary to limit the risk of vision loss. DR stabilizes and usually regresses following delivery but monitoring during the postpartum period is still required [61,62]. Unless the DR progresses to sight-threatening levels, most women suffer no long-term effect from pregnancy [62].

Ethnicity & genetics

Ethnicity is a known risk factor for both T1D and T2D and may influence an individual's risk of developing DR. In the UK, no significant difference in retinopathy rates was found between racial groups with T1D. By contrast, individuals with T2D of south Asian or African–Caribbean background had higher rates of retinopathy than Caucasians [63]. Differences in lifestyle and access to healthcare may contribute to these results.

Genetic susceptibility may also play a role. The risk and severity of DR is increased among family members and siblings [64,65] and analysis of familial clusters of PDR indicate a heritable component is likely [2]. Numerous genes and variants have been studied in a range of cohorts and several have shown an association with risk of DR. The aldose reductase gene had the largest number of polymorphisms significantly associated with DR in both T1D and T2D. Variants protective against DR have also been demonstrated [66,67].

Multidisciplinary care & support

In all published trials, optimal glycemic control was achieved within the context of a multidisciplinary team with psychological, nutritional, educational and medical support to the patient and family [68]. These factors should not be ignored and indeed appear to be integral to the overall success of medical management. The frequency of visits to a multidisciplinary team has been shown to improve HbA1c levels, with quarterly visits recommended [69]. An Australian study of 209 children with T1D found that initial management at a teaching hospital or early contact with a multidisciplinary team was associated with a reduced rate of DR 6 years after diagnosis, independent of HbA1c levels [23].

Management of retinopathy

For patients with early-to-moderate retinopathy, observation with careful attention to systemic

risk factors is appropriate. The frequency of screening increases with progressive severity of retinopathy. Once retinopathy or maculopathy reach threshold or 'vision threatening' levels, targeted therapy is recommended in order to reduce the risk of vision loss [1,70].

The majority of children and adolescents who develop DR will only have early changes and progression to treatment thresholds before adulthood is rare. A brief summary of the current treatments for DR and DME is described below.

Laser

Laser photocoagulation has been the mainstay of therapy for PDR and DME for several decades. Panretinal laser photocoagulation (PRP) in patients with PDR reduces the risk of severe visual loss by approximately 50% over 5 years [71]. PRP is a destructive treatment that involves placing laser burns across the peripheral retina, sparing the macula and central field of vision. Destruction of retinal tissue reduces metabolic demands, which lessens the ischemic drive. This leads to a reduction in the release of angiogenic factors, such as VEGF, with gradual regression of abnormal vessels over 2–3 months. Side effects from PRP treatment include peripheral field loss, night blindness, mild reduction in visual acuity, as well as worsening of DME.

In the Early Treatment of Diabetic Retinopathy Study, low energy focal or grid laser for CSME reduced the risk of vision loss by 50% (from 24 to 12%) over 3 years; however, only a small number experienced a significant gain in vision (<3%) [72].

Surgery

Surgical vitrectomy may be required in selected patients with PDR where laser application is impeded by vitreous hemorrhage. The vitreous and blood are removed and laser is performed intraoperatively. In advanced PDR with tractional retinal detachment, vitrectomy may be recommended together with division of neovascular and fibrotic membranes. Laser and insertion of dense silicone oil may succeed in reattaching the retina, although prognosis is guarded at this stage and redetachment is common [70].

A number of trials have demonstrated a beneficial effect of vitrectomy for DME; however, the results have not been consistent. The greatest benefit is found if DME is associated with epi-retinal membrane or vitreomacular traction [73].

Anti-VEGF agents

Intravitreal injections of anti-VEGF have demonstrated a superior effect on DME and vision compared with laser; however, currently only short-term (1–2 year) follow-up data are available [74,75]. Bevacizumab and ranibizumab are both anti-VEGF agents; however, only ranibizumab is licensed for intraocular use while bevacizumab is far more economical. Ranibizumab has been demonstrated in one model to be a cost-effective treatment for DME despite its expense [10]. Gaining approval for government funding may present a challenge in many countries.

Anti-VEGF agents have found some use in selected cases of PDR. The main indications for anti-VEGF agents in PDR are to stabilize patients with neovascular disease while awaiting photocoagulation or surgery, or in cases with co-existing DME [76]. Blockade of VEGF activity leads to rapid regression of abnormal vessels within days to weeks; however, their use is limited by short-lived effects and a lack of established protocols.

Intravitreal steroids

Intravitreal steroid injections have been shown to provide transient improvement of DME and visual acuity [15]. The need for repeated injections, and the frequent side effects of cataract formation and elevated intraocular pressure would make them relatively unsuitable for use in younger patients where other modalities would be more appropriate.

Screening

DR can reach sight-threatening levels without any visual symptoms. Screening is essential to detect retinopathy at early stages so that systemic management can be improved, as well as at treatment threshold stages so that specific retinal therapy can be commenced to prevent serious visual complications.

Early retinopathy is commonly seen in children and adolescents within a few years of diabetes onset. Severe or sight-threatening retinopathy is rare but has been reported during puberty. The youngest reported cases of PDR were in two 13-year-old children (male and female) [77] and a case of severe NPDR was reported in an 11.8-year-old boy [78].

ISPAD recommends annual screening from the age of 11 years after 2 years diabetes duration, or from 9 years of age with 5 years duration [45]. The English National DR Screening Program

recommends annual screening from the age of 12 years [79]. These recommendations should successfully detect sight-threatening retinopathy in time to offer treatment, although later entry into screening may miss the opportunity of early identification of those most at risk.

All children with diabetes should be referred for vision screening and eye examination soon after diagnosis (within 3 months) to ensure they do not have any other conditions that could lead to visual impairment [102]. In children with T2D, retinopathy can be present at diagnosis so early referral for a full eye examination is recommended.

The frequency of screening has also been debated, with evidence that second yearly screening of those without retinopathy is safe and cost effective [80–82]. However, in practice there is a tendency for screening intervals to stretch beyond what is recommended so this may need to be taken into account. ISPAD currently recommends annual screening and practitioners should consult their own national guidelines. More frequent examinations may be required if retinopathy is detected.

During pregnancy DR can progress rapidly. The International Diabetes Federation recommends dilated fundus examination at the first antenatal visit and then once per trimester. The NICE guidelines recommend review at the first antenatal visit and once more at 28 weeks gestation. If any retinopathy is detected, patients need to be screened more frequently and monitoring needs to continue for at least 6 months postpartum [83,102].

Stereoscopic seven-field fundus photography by a trained grader is the gold-standard for detecting DR. It is primarily a research tool and rarely performed in routine clinical practice. Screening can also be performed by ophthalmologists or optometrists using dilated slit lamp biomicroscopy. This has the advantage of good sensitivity for detecting macular edema that can be difficult to visualize on photographs; however, the demand on specialist resources is high.

Mydriatic two-field fundus photography has good sensitivity and specificity if grading is performed by adequately qualified graders (up to 95 and 99%, respectively) [84,85] and is presently the recommended screening method in England. Future prospects for screening include automated DR grading technology, which has shown good levels of accuracy in pilot studies [86,87]. Their use could significantly reduce workforce requirements and may improve access to DR screening in remote locations. Early changes in retinal vascular geometry have been shown to predict incident DR and may be a useful indicator of risk in patients in whom signs of DR are not yet present [88].

Conclusion

Improved medical management of young persons with diabetes can significantly reduce the risk of DR; however, even with optimal control some patients will progress to sight-threatening disease. Modern techniques for treatment of DR can reduce the risk of vision loss if implemented in a timely manner. Regular retinal screening is essential to detect DR before serious vision-threatening complications occur.

Future perspective

Advances in understanding of the pathophysiology of DR will, in time, lead to the development of further novel treatments, as we have seen with anti-VEGF therapy in recent years. The use of anti-VEGF has proven, dramatic effects but is limited by the need for repeat injections. The development of slow-release devices or long-acting agents is currently underway and could dramatically alter treatment of DME and DR.

The benefits of ACE inhibitors and lipid-lowering therapies seen in adult populations will be investigated further in the Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial to determine whether the beneficial effects extend to adolescents with T1D. Although this trial is primarily designed to study cardiac and renal disease, retinopathy will be measured as a secondary outcome.

Implementation of screening programs present logistical challenges to even the most developed countries. Advances in image capture devices and DR grading technology may make screening easier and more accessible; however, the challenges in covering large patient populations and managing high volumes of data will remain.

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References

Papers of special note have been highlighted as:

- ■ of interest

1 ETDRS group. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Early Treatment Diabetic Retinopathy Study Research Group. *Ophthalmology* 98(Suppl. 5), S766–S785 (1991).

2 Hietala K, Forsblom C, Summanen P, Groop PH. Heritability of proliferative diabetic retinopathy. *Diabetes* 57(8), 2176–2180 (2008).

3 Koya D, King GL. Protein kinase C activation and the development of diabetic complications. *Diabetes* 47(6), 859–866 (1998).

4 Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes* 54(6), 1615–1625 (2005).

5 Lee AY, Chung SS. Contributions of polyol pathway to oxidative stress in diabetic cataract. *FASEB J.* 13(1), 23–30 (1999).

6 Gugliucci A. Glycation as the glucose link to diabetic complications. *J. Am. Osteopath. Assoc.* 100(10), 621–634 (2000).

7 Du XL, Edelstein D, Rossetti L *et al.* Hyperglycemia-induced mitochondrial superoxide overproduction activates the hexosamine pathway and induces plasminogen activator inhibitor-1 expression by increasing Sp1 glycosylation. *Proc. Natl Acad. Sci. USA* 97(22), 12222–12226 (2000).

8 Ahmed N, Thornalley PJ. Advanced glycation endproducts: what is their relevance to diabetic complications? *Diabetes Obes. Metab.* 9(3), 233–245 (2007).

9 Funatsu H, Yamashita H, Nakanishi Y, Hori S. Angiotensin II and vascular endothelial growth factor in the vitreous fluid of patients with proliferative diabetic retinopathy. *Br. J. Ophthalmol.* 86(3), 311–315 (2002).

10 Mitchell P, Annemans L, Gallagher M *et al.* Cost–effectiveness of ranibizumab in treatment of diabetic macular oedema (DME) causing visual impairment: evidence from the RESTORE trial. *Br. J. Ophthalmol.* 96(5), 688–693 (2012).

11 ETDRS group. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report Number 2. Early Treatment Diabetic Retinopathy Study Research Group. *Ophthalmology* 94(7), 761–774 (1987).

12 ETDRS group. Classification of diabetic retinopathy from fluorescein angiograms. ETDRS report number 11. Early Treatment Diabetic Retinopathy Study Research Group. *Ophthalmology* 98(Suppl. 5), S807–S822 (1991).

13 Fong DS, Ferris FL III, Davis MD, Chew EY. Causes of severe visual loss in the early treatment diabetic retinopathy study: ETDRS report no. 24. Early Treatment Diabetic Retinopathy Study Research Group. *Am. J. Ophthalmol.* 127(2), 137–141 (1999).

14 Kocur I, Resnikoff S. Visual impairment and blindness in Europe and their prevention. *Br. J. Ophthalmol.* 86(7), 716–722 (2002).

15 Mohamed Q, Gillies MC, Wong TY. Management of diabetic retinopathy: a systematic review. *JAMA* 298(8), 902–916 (2007).

16 Resnikoff S, Pascolini D, Etya'ale D *et al.* Global data on visual impairment in the year 2002. *Bull. World Health Organ.* 82(11), 844–851 (2004).

17 Bunce C, Xing W, Wormald R. Causes of blind and partial sight certifications in England and Wales: April 2007–March 2008. *Eye (Lond.)* 24(11), 1692–1699 (2010).

18 Roy MS, Klein R, O'Colmain BJ, Klein BE, Moss SE, Kempen JH. The prevalence of diabetic retinopathy among adult Type 1 diabetic persons in the United States. *Arch. Ophthalmol.* 122(4), 546–551 (2004).

19 Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BE. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XXII the twenty-five-year progression of retinopathy in persons with Type 1 diabetes. *Ophthalmology* 115(11), 1859–1868 (2008).

20 Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BE. The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXIII: the twenty-five-year incidence of macular edema in persons with Type 1 diabetes. *Ophthalmology* 116(3), 497–503 (2009).

21 Klein R, Lee KE, Gangnon RE, Klein BE. The 25-year incidence of visual impairment in Type 1 diabetes mellitus the wisconsin epidemiologic study of diabetic retinopathy. *Ophthalmology* 117(1), 63–70 (2010).

22 Salardi S, Porta M, Maltoni G *et al.* Infant and toddler Type 1 diabetes: complications after 20 years' duration. *Diabetes Care* 35(4), 829–833 (2012).

23 Donaghue KC, Craig ME, Chan AK *et al.* Prevalence of diabetes complications 6 years after diagnosis in an incident cohort of childhood diabetes.*Diabet. Med. J. Br. Diabetic Assoc.* 22(6), 711–718 (2005).

24 Klein R, Lee KE, Knudtson MD, Gangnon RE, Klein BE. Changes in visual impairment prevalence by period of diagnosis of diabetes: the Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Ophthalmology* 116(10), 1937–1942 (2009).

25 Nathan DM, Zinman B, Cleary PA *et al.* Modern-day clinical course of Type 1 diabetes mellitus after 30 years' duration: the diabetes control and complications trial/epidemiology of diabetes interventions and complications and Pittsburgh epidemiology of diabetes complications experience (1983–2005). *Arch. Inter. Med.* 169(14), 1307–1316 (2009).

26 Cho YH, Craig ME, Hing S *et al.* Microvascular complications assessment in adolescents with 2- to 5-yr duration of Type 1 diabetes from 1990 to 2006. *Pediatr. Diabetes* 12(8), 682–689 (2011).

27 Sivaprasad S, Gupta B, Crosby-Nwaobi R, Evans J. Prevalence of diabetic retinopathy in various ethnic groups: a worldwide perspective. *Surv. Ophthalmol.* 57(4), 347–370 (2012).

28 Mayer-Davis EJ, Davis C, Saadine J *et al.* Diabetic retinopathy in the SEARCH for diabetes in youth cohort: a pilot study. *Diabet. Med.* 29(9), 1148–1152 (2012).

29 Pinhas-Hamiel O, Zeitler P. Acute and chronic complications of Type 2 diabetes mellitus in children and adolescents. *Lancet* 369(9575), 1823–1831 (2007).

30 Williams R, Airey M, Baxter H, Forrester J, Kennedy-Martin T, Girach A. Epidemiology of diabetic retinopathy and macular oedema: a systematic review. *Eye (Lond.)* 18(10), 963–983 (2004).

31 The DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N. Engl. J. Med.* 329(14), 977–986 (1993).

32 The DCCT Research Group. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. *Diabetes* 44(8), 968–983 (1995).

33 The DCCT Research Group. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. Diabetes Control and Complications Trial Research Group. *J. Pediatr.* 125(2), 177–188 (1994).

34 Svensson M, Eriksson JW, Dahlquist G. Early glycemic control, age at onset, and development of microvascular complications in childhood-onset Type 1 diabetes: a population-based study in northern Sweden. *Diabetes Care* 27(4), 955–962 (2004).

35 The DCCT and EDIC Research Group: Effect of intensive therapy on the microvascular complications of Type 1 diabetes mellitus. *JAMA* 287(19), 2563– 2569 (2002).

36 White NH, Sun W, Cleary PA *et al.* Effect of prior intensive therapy in Type 1 diabetes on 10-year progression of retinopathy in the DCCT/EDIC: comparison of adults and adolescents. *Diabetes* 59(5), 1244–1253 (2010).

■ **Presents data from 10 years of follow-up after the Diabetes Control and Complications Trial (DCCT). Early HbA1c levels have a significant, long-lasting effect on the long-term risk of complications in both adults and adolescents.**

37 The effect of intensive diabetes treatment on the progression of diabetic retinopathy in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial. *Arch. Ophthalmol.* 113(1), 36–51 (1995).

38 Jones TW, Davis EA. Hypoglycemia in children with Type 1 diabetes: current issues and controversies. *Pediatr. Diabetes* 4(3), 143–150 (2003).

39 Gallego PH, Craig ME, Hing S, Donaghue KC. Role of blood pressure in development of early retinopathy in adolescents with Type 1 diabetes: prospective cohort study. *BMJ* 337, a918 (2008).

40 Ding J, Wong TY. Current epidemiology of diabetic retinopathy and diabetic macular edema. *Curr. Diabetes Rep.* 12(4), 346–354 (2012).

41 UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in Type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ* 317(7160), 703–713 (1998).

42 Chaturvedi N, Sjolie AK, Stephenson JM *et al.* Effect of lisinopril on progression of retinopathy in normotensive people with Type 1 diabetes. The EUCLID Study Group. EURODIAB controlled trial of lisinopril in insulin-dependent diabetes mellitus. *Lancet* 351(9095), 28–31 (1998).

43 Chaturvedi N, Porta M, Klein R *et al.* Effect of candesartan on prevention (DIRECT-Prevent 1) and progression (DIRECT-Protect 1) of retinopathy in Type 1 diabetes: randomised, placebo-controlled trials. *Lancet* 372(9647), 1394–1402 (2008).

44 Mauer M, Zinman B, Gardiner R *et al.* Renal and retinal effects of enalapril and losartan in Type 1 diabetes. *N. Engl. J. Med.* 361(1), 40–51 (2009).

45 Donaghue KC, Chiarelli F, Trotta D, Allgrove J, Dahl-Jorgensen K. Microvascular and macrovascular complications associated with diabetes in children and adolescents. *Pediatr. Diabetes* 10(Suppl. 12), S195–S203 (2009).

■ **Part of the International Society for Pediatric and Adolesent Diabetes (ISPAD) clinical practice consensus guidelines 2009. A summary of the evidence on interventions to prevent and manage microvascular complications (including nephropathy and retinopathy) with a consensus on best practice guidelines.**

46 Miljanovic B, Glynn RJ, Nathan DM, Manson JE, Schaumberg DA. A prospective study of serum lipids and risk of diabetic macular edema in Type 1 diabetes. *Diabetes* 53(11), 2883–2892 (2004).

47 Lim LS, Wong TY. Lipids and diabetic retinopathy. *Expert Opin. Biol. Ther.* 12(1), 93–105 (2012).

48 Keech AC, Mitchell P, Summanen PA *et al.* Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. *Lancet* 370(9600), 1687–1697 (2007).

49 Ismail-Beigi F, Craven T, Banerji MA *et al.* Effect of intensive treatment of hyperglycaemia on microvascular outcomes in Type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet* 376(9739), 419–430 (2010).

50 AdDIT Research Group. Adolescent Type 1 Diabetes Cardio-renal Intervention Trial (AdDIT). *BMC Pediatr.* 9, 79 (2009).

■ **Background literature review and study protocol for AdDIT. The study was primarily designed to investigate the effect of angiotenosin-converting enzyme inhibitor and statin therapy on renal and cardiac outcomes in adolescents with Type 1 diabetes; however, retinopathy will be a secondary outcome measure.**

51 Chaturvedi N, Stephenson JM, Fuller JH. The relationship between smoking and microvascular complications in the EURODIAB IDDM Complications Study. *Diabetes Care* 18(6), 785–792 (1995).

52 Moss SE, Klein R, Klein BE. Cigarette smoking and ten-year progression of diabetic retinopathy. *Ophthalmology* 103(9), 1438–1442 (1996).

53 Zhang L, Krzentowski G, Albert A, Lefebvre PJ. Risk of developing retinopathy in Diabetes Control and Complications Trial Type 1 diabetic patients with good or poor metabolic control. *Diabetes Care* 24(7), 1275–1279 (2001).

54 Henricsson M, Nyström L, Blohmé G *et al.* The incidence of retinopathy 10 years after diagnosis in young adult people with diabetes: results from the nationwide population-based Diabetes Incidence Study in Sweden (DISS). *Diabetes Care* 26(2), 349–354 (2003).

55 Chaturvedi N, Sjoelie AK, Porta M *et al.* Markers of insulin resistance are strong risk factors for retinopathy incidence in Type 1 diabetes. *Diabetes Care* 24(2), 284–289 (2001).

56 Donaghue KC, Fairchild JM, Craig ME *et al.* Do all prepubertal years of diabetes duration contribute equally to diabetes complications? *Diabetes Care* 26(4), 1224–1229 (2003).

57 Hietala K, Harjutsalo V, Forsblom C, Summanen P, Groop PH. Age at onset and the risk of proliferative retinopathy in Type 1 diabetes. *Diabetes Care* 33(6), 1315–1319 (2010).

58 Donaghue KC, Fung AT, Hing S *et al.* The effect of prepubertal diabetes duration on diabetes. Microvascular complications in early and late adolescence. *Diabetes Care* 20(1), 77–80 (1997).

59 Holl RW, Lang GE, Grabert M, Heinze E, Lang GK, Debatin KM. Diabetic retinopathy in pediatric patients with Type-1 diabetes: effect of diabetes duration, prepubertal and pubertal onset of diabetes, and metabolic control. *J. Pediatr.* 132(5), 790–794 (1998).

60 Klein BE, Moss SE, Klein R. Effect of pregnancy on progression of diabetic retinopathy. *Diabetes Care* 13(1), 34–40 (1990).

61 Rosenn B, Miodovnik M, Kranias G *et al.* Progression of diabetic retinopathy in pregnancy: association with hypertension in pregnancy. *Am. J. Obstet. Gynecol.* 166(4), 1214–1218 (1992).

62 Kaaja R, Loukovaara S. Progression of retinopathy in Type 1 diabetic women during pregnancy. *Curr. Diabetes Rev.* 3(2), 85–93 (2007).

63 Sivaprasad S, Gupta B, Gulliford MC *et al.* Ethnic variations in the prevalence of diabetic retinopathy in people with diabetes attending screening in the United Kingdom (DRIVE UK). *PLoS One* 7(3), e32182 (2012).

64 Liew G, Klein R, Wong TY. The role of genetics in susceptibility to diabetic retinopathy. *Int. Ophthalmol. Clin.* 49(2), 35–52 (2009).

65 Arar NH, Freedman BI, Adler SG *et al.* Heritability of the severity of diabetic retinopathy: the FIND-Eye study. *Investig. Ophthalmol. Visual Sci.* 49(9), 3839–3845 (2008).

66 Abhary S, Hewitt AW, Burdon KP, Craig JE. A systematic meta-analysis of genetic association studies for diabetic retinopathy. *Diabetes* 58(9), 2137–2147 (2009).

67 Donaghue KC, Margan SH, Chan AK *et al.* The association of aldose reductase gene (AKR1B1) polymorphisms with diabetic neuropathy in adolescents. *Diabet. Med. J. Br. Diabetic Assoc.* 22(10), 1315–1320 (2005).

68 Brink SJ. How to apply the experience from the diabetes control and complications trial to children and adolescents? *Ann. Med.* 29(5), 425–438 (1997).

- **Highlights the important lessons learnt from the DCCT and how they should be applied in models of clinical care.**

69 Kaufman FR, Halvorson M, Carpenter S. Association between diabetes control and visits to a multidisciplinary pediatric diabetes clinic. *Pediatrics* 103(5 Pt 1), 948–951 (1999).

70 Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. *Lancet* 376(9735), 124–136 (2010).

- **Comprehensive update on the epidemiology, pathophysiology and management of diabetic retinopathy.**

71 The DRS Research Group. Indications for photocoagulation treatment of diabetic retinopathy: Diabetic Retinopathy Study Report no. 14. The Diabetic Retinopathy Study Research Group. *Int. Ophthalmol. Clin.* 27(4), 239–253 (1987).

72 ETDRS group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. *Arch. Ophthalmol.* 103(12), 1796–1806 (1985).

73 Laidlaw DA. Vitrectomy for diabetic macular oedema. *Eye (Lond.)* 22(10), 1337–1341 (2008).

74 Mitchell P, Bandello F, Schmidt-Erfurth U *et al.* The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology* 118(4), 615–625 (2011).

75 Rajendram R, Fraser-Bell S, Kaines A *et al.* A 2-year prospective randomized controlled trial of intravitreal bevacizumab or laser therapy (BOLT) in the management of diabetic macular edema: 24-month data: report 3. *Arch. Ophthalmol.* doi:10.1001/archophthalmol.2012.393 (2012) (Epub ahead of print).

76 Salam A, Mathew R, Sivaprasad S. Treatment of proliferative diabetic retinopathy with anti-VEGF agents. *Acta Ophthalmol.* 89(5), 405–411 (2011).

77 Kimmel AS, Magargal LE, Annesley WH Jr, Donoso LA. Diabetic retinopathy under age 20. A review of 71 cases. *Ophthalmology* 92(8), 1047–1050 (1985).

78 Kernell A, Dedorsson I, Johansson B *et al.* Prevalence of diabetic retinopathy in children and adolescents with IDDM. A population-based multicentre study. *Diabetologia* 40(3), 307–310 (1997).

79 Scanlon PH. The English national screening programme for sight-threatening diabetic retinopathy. *J. Med. Screening* 15(1), 1–4 (2008).

80 Maguire A, Chan A, Cusumano J *et al.* The case for biennial retinopathy screening in children and adolescents. *Diabetes Care* 28(3), 509–513 (2005).

81 Vijan S, Hofer TP, Hayward RA. Cost-utility analysis of screening intervals for diabetic retinopathy in patients with Type 2 diabetes mellitus. *JAMA* 283(7), 889–896 (2000).

82 Stefansson E. The case for biennial retinopathy screening in children and adolescents: response to Maguire *et al.* *Diabetes Care* 29(1), 178; author reply 178–179 (2006).

83 Walker JD. NICE guidance on diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period. NICE clinical guideline 63. London, March 2008. *Diabet. Med. J. Br. Diabetic Assoc.* 25(9), 1025–1027 (2008).

84 Baeza M, Orozco-Beltran D, Gil-Guillen VF *et al.* Screening for sight threatening diabetic retinopathy using non-mydriatic retinal camera in a primary care setting: to dilate or not to dilate? *Int. J. Clin. Pract.* 63(3), 433–438 (2009).

85 Scanlon PH, Malhotra R, Greenwood RH *et al.* Comparison of two reference standards in validating two field mydriatic digital photography as a method of screening for diabetic retinopathy. *Br. J. Ophthalmol.* 87(10), 1258–1263 (2003).

86 Fleming AD, Goatman KA, Philip S, Prescott GJ, Sharp PF, Olson JA. Automated grading for diabetic retinopathy: a large-scale audit using arbitration by clinical experts. *Br. J. Ophthalmol.* 94(12), 1606–1610 (2010).

87 Fleming AD, Philip S, Goatman KA, Prescott GJ, Sharp PF, Olson JA. The evidence for automated grading in diabetic retinopathy screening. *Curr. Diabetes Rev.* 7(4), 246–252 (2011).

88 Benitez-Aguirre P, Craig ME, Sasongko MB *et al.* Retinal vascular geometry predicts incident retinopathy in young people with Type 1 diabetes: a prospective cohort study from adolescence. *Diabetes Care* 34(7), 1622–1627 (2011).

Websites

101 IDF. Diabetes in the young. In: *International Diabetes Federation (IDF) Diabetes Atlas (5th Edition)* (2011). www.idf.org/diabetesatlas/5e/diabetes-in-the-young

102 IDF. Global IDF/ISPAD guideline for diabetes in childhood and adolescence (2011). www.idf.org/global-idfispad-guideline-diabetes-childhood-and-adolescence