

## **When should screening for diabetic retinopathy begin for children with type 1 diabetes?**

### **Treatment of diabetic retinopathy**

Visual impairment and blindness as a result of diabetic retinopathy (DR) is amongst the most feared complication of diabetes. However, the prevalence of sight threatening diabetic retinopathy (STDR) has been slowly decreasing [1-4]. Recently it has been reported that diabetes is no longer the leading cause of blindness in the working age population in the UK [5]. These observations may reflect the cumulative impact of better management of diabetes, the introduction of screening programmes aiming to identify STDR and more active and effective ophthalmologic management. Good glycaemic and blood pressure control are pivotal in the primary prevention of DR with some evidence of direct benefit from fibrates when used in those with dyslipidaemia [6, 7]. The introduction of intensive insulin therapy to optimise glycaemic control in children with type 1 diabetes aged 13-17 years was seen to reduce the risk of developing DR by 53% [8]. The benefit of such intensive management in the adolescent years remained evident many years later (legacy effect) even when HbA<sub>1c</sub> values were similar for the intensively treated and control groups [9]. Currently treatment for STDR, which encompasses proliferative DR (PDR) and selected cases of severe non-proliferative DR (pre-proliferative DR, (PPDR) and maculopathy, is primarily by laser photocoagulation and more recently in conjunction with intra-vitreous injections of inhibitors of vascular endothelial growth factors (anti-VEGF). The relatively recent addition of anti-VEGF treatment has improved visual outcomes in those with PDR and clinically significant macular oedema (CSMO) [10]. If these measures are deemed inadequate then vitrectomy may be required. It is generally acknowledged that diabetic retinopathy remains asymptomatic until it reaches an advanced stage (STDR) and that the benefit from treatment with laser photocoagulation is best achieved the earlier the diagnosis and treatment is delivered. This is the basis for the introduction of screening for DR which has also been shown to be cost-effective especially in comparison to the societal cost of blindness [11]. The detection of any DR will help to prompt the need for improving and maintaining good glycaemic control to prevent progression to STDR. In the context of this review glycaemic control is usually worse in adolescents compared with younger age children [12]

### **Guidelines for diabetic retinopathy screening in children and young persons with diabetes**

DR screening programmes have been instituted in several countries over the last 20 years, aiming for the early detection and close monitoring of retinal changes related to diabetes in an attempt to prevent loss of vision or blindness as the primary goal and secondarily, to instigate interventions to prevent the progression of non-sight threatening DR. National structured and community based DR screening programmes for diabetic retinopathy have been operational in the UK since 2003. Currently screening is offered to all persons with diabetes from the age of 12 years, and carried out on an annual basis as recommended by the Royal College of Ophthalmologists [13]. However, the question remains unresolved as to when is the most appropriate age to begin screening for DR in persons with type 1 diabetes. Recommendations vary between programmes/countries either based on duration of diabetes or age of the children (Table 1). The American Academy of ophthalmology currently recommends annual screening for all with a duration of diabetes of more than 5 years, whilst the American Academy of Paediatrics recommends an initial screening 3-5 years after diagnosis of diabetes if over age 9 and annually thereafter and the American Diabetes Association also recommends screening begins 3-5 years after diagnosis of diabetes and once the child is 10

years old. However in Europe, the International Society for Pediatric and Adolescent Diabetes (2011) recommends screening for DR from the age of 11 years after 2 years of diabetes and from the age of 9 years for those with diabetes of 5 years or more. The Retinopathy working party recommends screening from the onset of puberty [14]. In Scandinavia, Finland begin DR screening when patients enter puberty [15], and Sweden commence DR screening from the age of 10 years [16].

### **Prevalence of diabetic retinopathy in children**

The evidence indicates that the prevalence of diabetic retinopathy in children is low and is extremely rare prior to puberty [17, 18]. The prevalence of DR has been found in children and young persons with diabetes ranges between 10.5% and 57.6% depending on the inclusion age and duration of diabetes at the time of screening and adopted methods of screening for DR (Table 1) [18-31].

The youngest age at which DR has been observed was 5 years [28] and the youngest age at which sight-threatening DR was reported was 15 years with the shortest duration of diabetes being 5 years [32] with only 5 cases of sight-threatening DR in children <18 years [28, 32]. However, in a recent study of 370 children with diabetes aged <18 years no cases of DR were found [25] prompting the suggestion that screening for DR be delayed to the age of 15 years or once duration of diabetes is 5 years whichever comes later and also on the basis that few require treatment for sight-threatening DR at an earlier age. Some clinicians have also suggested that screening for DR at such a young age may theoretically have a psychosocial impact creating stress and anxiety, which is an area that requires further examination.

In our experience involving 1,770 children and young people with diabetes aged 12 to 18 years with type 1 diabetes undergoing screening for the first time in the Diabetic Retinopathy Screening Service for Wales (DRSSW) the prevalence of DR was 17.4%, consisting of 17.1% non-sight-threatening DR and 0.3% sight-threatening DR [33]. Of those with sight-threatening DR 1 person was found to have PPDR, 4 had maculopathy and none had PDR. The youngest with sight-threatening DR was aged 14 years. Eleven point nine percent presented with non-sight-threatening DR aged 12-13 years. Adjusting for gender and duration of diabetes those aged 14-16 years and  $\geq 17$  years were 2.8 fold and 2.9 fold respectively more likely to develop DR compared to those aged  $\leq 13$  years. Diagnosing non-sight threatening DR at this early stage allows appropriate enhancement of diabetes management in an attempt to near-normalise metabolic control to avoid any further deterioration of the DR [8].

### **Recommendations**

It is imperative to assess the positive and negative impact of screening for DR on children and young persons with type 1 diabetes. In general, screening programmes have the potential to generate anxiety. Further investigation should be undertaken to fully evaluate the early introduction of screening in this population. Whilst it is recognised that few type 1 subjects require laser photocoagulation for STDR before mid-teens, the earlier detection of DR affords an opportunity to improve glycaemic control and the other putative risk factors including BP to prevent progression to STDR. However, what benefits accrue in clinical practice remains unclear. Further debate is now required to review in detail the available evidence, together with input from patients, parents/guardians, paediatric diabetologists and ophthalmologists to reach a consensus as to what

age DR screening should commence in children and young persons with type 1 diabetes. Until such time delaying starting DR screening beyond the age of 12 years cannot be justified.

### Financial and competing interests disclosure

None

### References

1. Hovind, P., et al., *Decreasing incidence of severe diabetic microangiopathy in type 1 diabetes*. Diabetes Care, 2003. **26**(4): p. 1258-64.
2. Klein, R., et al., *Changes in visual impairment prevalence by period of diagnosis of diabetes: the Wisconsin Epidemiologic Study of Diabetic Retinopathy*. Ophthalmology, 2009. **116**(10): p. 1937-42.
3. Wong, T.Y., et al., *Rates of progression in diabetic retinopathy during different time periods: a systematic review and meta-analysis*. Diabetes Care, 2009. **32**(12): p. 2307-13.
4. Romero-Aroca, P., et al., *Changes in the diabetic retinopathy epidemiology after 14 years in a population of Type 1 and 2 diabetic patients after the new diabetes mellitus diagnosis criteria and a more strict control of the patients*. Journal of Diabetes and its Complications, 2009. **23**(4): p. 229-38.
5. Liew, G., M. Michaelides, and C. Bunce, *A comparison of the causes of blindness certifications in England and Wales in working age adults (16-64 years), 1999-2000 with 2009-2010*. BMJ open, 2014. **4**(e004015).
6. Mohamed, Q., M.C. Gillies, and T.Y. Wong, *Management of diabetic retinopathy: a systematic review*. JAMA 2007. **298**(8): p. 902-16.
7. Morgan, C.L., et al., *Primary prevention of diabetic retinopathy with fibrates: a retrospective, matched cohort study*. BMJ open, 2013. **3**: p. e004025.
8. The Diabetes Control and Complications Trial Research Group, *The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus*. New England Journal of Medicine, 1993. **329**: p. 977-986.
9. White N H, et al., *Beneficial effects of intensive therapy of diabetes during adolescence: outcomes after the conclusion of the diabetes control and complications trial (DCCT)*. Journal of Pediatrics, 2001. **139**: p. 804-812.
10. Cho, W.B., et al., *Panretinal photocoagulation combined with intravitreal bevacizumab in high-risk proliferative diabetic retinopathy*. Retina, 2009. **29**(4): p. 516-22.
11. Javitt, J.C. and L.P. Aiello, *Cost-effectiveness of detecting and treating diabetic retinopathy*. Annals of Internal Medicine, 1996. **124**(1 Pt 2): p. 164-9.

12. O'Hagan, M. and J.N. Harvey, *Glycaemic control in children with Type 1 diabetes in Wales: the influence of the paediatric diabetes specialist nurse*. *Diabetes Care*, 2010. **33**: p. 1724-6.
13. The Royal College of Ophthalmologists, *Diabetic Retinopathy Guidelines*, 2012: London.
14. The Retinopathy Working Party, *A protocol for screening for diabetic retinopathy in Europe*. *Retinopathy Working Party*. *Diabetic Med*, 1991. **8**(3): p. 263-7.
15. Karma, A., et al., *Diabeettinen retinopatia: seuranta hoito ja nakovammautuneen diabeetikon kuntoutus*. *Suomen Laakarilehti*, 1992. **24**: p. 2199-2211.
16. Swedish National Board of Health and Welfare, *National guidelines for treatment of diabetes mellitus*. 1999.
17. Klein, R., et al., *Retinopathy in young-onset diabetic patients*. *Diabetes Care*, 1985. **8**(4): p. 311-5.
18. Kernell, A., et al., *Prevalence of diabetic retinopathy in children and adolescents with IDDM. A population-based multicentre study*. *Diabetologia*, 1997. **40**(3): p. 307-10.
19. Kubin, M., et al., *Prevalence of retinopathy in Finnish children and adolescents with type 1 diabetes: a cross-sectional population-based retrospective study*. *Archives of disease in childhood*, 2011.
20. Donaghue, K.C., et al., *Diabetes microvascular complications in prepubertal children*. *Journal of pediatric endocrinology & metabolism : JPEM*, 1997. **10**(6): p. 579-85.
21. Kullberg, C.E., et al., *Prevalence of retinopathy differs with age at onset of diabetes in a population of patients with Type 1 diabetes*. *Diabetic medicine : a journal of the British Diabetic Association*, 2002. **19**(11): p. 924-31.
22. Maguire A, et al., *The case for biennial retinopathy screening in children and adolescents*. *Diabetes Care*, 2005. **28**(3): p. 509-513.
23. LeCaire T, et al., *Lower than expected prevalence and severity of retinopathy in an incident cohort followed during the first 4-14 years of type 1 diabetes: the Wisconsin Diabetes Registry Study*. *Am J Epidemiol*, 2006. **164**: p. 143-150.
24. Flack, A., M.L. Kaar, and L. Laatikainen, *A prospective, longitudinal study examining the development of retinopathy in children with diabetes*. *Acta paediatrica*, 1996. **85**(3): p. 313-9.
25. Geloneck, M.M., et al., *Ocular complications in children with diabetes mellitus*. *Ophthalmology*, 2015. **In Press**.
26. Cahill, M., et al., *Detection and prevalence of early diabetic retinopathy in juvenile diabetics with diabetes for 10 years or more*. *Eye*, 2000. **14**(Pt 6): p. 847-50.

27. Florkowski, C.M., et al., *Age at diagnosis, glycaemic control and the development of retinopathy in a population-based cohort of Type 1 diabetic subjects in Canterbury, New Zealand*. Diabetes Research and Clinical Practice, 2001. **52**(2): p. 125-31.
28. Holl, R.W., et al., *Diabetic retinopathy in pediatric patients with type-1 diabetes: effect of diabetes duration, prepubertal and pubertal onset of diabetes, and metabolic control*. The Journal of pediatrics, 1998. **132**(5): p. 790-4.
29. Olsen, B.S., et al., *The significance of the prepubertal diabetes duration for the development of retinopathy and nephropathy in patients with type 1 diabetes*. Journal of Diabetes and its Complications, 2004. **18**(3): p. 160-4.
30. Dujic, M.P. and Z. Ignjatovic, *Juvenile diabetes eye complications and treatment*. Vojnosanit Pregl, 2009. **66**: p. 729-732.
31. Demirel, F., et al., *Microvascular complications in adolescents with type 1 diabetes mellitus*. J Clin Res Pediatr Endocrinol, 2013. **5**: p. 145-149.
32. Klein, R., et al., *The Wisconsin epidemiologic study of diabetic retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years*. Arch Ophthalmol, 1984. **102**(4): p. 520-6.
33. Thomas, R.L., et al., *Prevalence of diabetic retinopathy in persons with type 1 diabetes aged 12 to 18 years in the Diabetic Retinopathy Screening Service for Wales, 2015*: International Diabetes Federation, World Diabetes Congress.