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Risks and Prevalence of Diabetic Retinopathy in Children and Young People with Type 1 Diabetes Mellitus

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Abstract

Diabetic retinopathy is a progressive ophthalmic microvascular complication of diabetes and is one of the commonest complications of Type 1 diabetes (T1D). The prevalence of diabetic eye disease varies within different population and age groups, and many risk factors are associated with the development and progression of diabetic retinopathy in T1D. This review discusses the current prevalence of diabetic retinopathy in children and young people (0-18 years) with T1D and the risk factors associated with the presence of diabetic eye disease in this population.

Keywords: Type 1 diabetes, poor glycaemic control, high blood pressure

Introduction

Type 1 diabetes (T1D) is associated with microvascular and macrovascular complications [1].

Duration of diabetes, poor glycaemic control, high blood pressure and proteinuria are reported risk factors contributing to the development of diabetes related complications [1-3]. Diabetic retinopathy (DR) is a progressive, potentially sight threatening disease of the retinal neuro-vasculature associated with diabetes. Diabetic retinopathy develops due to chronic hyperglycaemia which causes damage to the retinal capillaries, leading to capillary blockage and leakage. Diabetic retinopathy is asymptomatic until the advanced stages and if undiagnosed and remains untreated, can progress to severe visual loss. Globally it is the leading cause of blindness among the working age population (aged 16-64 years) and the commonest complication of T1D [4]. However, in the UK diabetic retinopathy has been overtaken by hereditary retinal disease as the leading cause of blindness [5,6]. This is largely due to the introduction of screening for diabetic retinopathy and improvement in the management of diabetes, and more effective ophthalmological management. Early complications of DR have been reported in adolescents with T1D between 2 to 5 years diabetes duration despite more intensive management [7].

Comparative Data and Prevalence

Prevalence of DR is variable as reported in several studies. This variability is due to differences in study populations such as age, type of diabetes, and location i.e. community or hospital setting, methods of detecting diabetic retinopathy fundoscopy, digital photography and slit lamp examination and grading protocols used. The global prevalence of DR was 34.6% from a pooled analysis of 22,896 individuals with diabetes [8], this was updated in the International Diabetes Federation (IDF) atlas 9th edition with any DR reported to be 27.0%, non-proliferative DR 25.2%, proliferative DR 1.4% and DME 4.6% between 2015 and 2019 [9]. The lowest prevalence of any DR was reported in South East Asia at 12.5% and highest in the Western Pacific at 36.3%. The prevalence of DR in children and young people with diabetes has been

reported to range between 2.3% and 57.6% [10-25]. In Wales between 2003 and 2018 in 4,172 people diagnosed with T1D up to the age of 18 years eligible for screening (in those with T1D from 12 years) with gradable retinal photographs, the prevalence of background DR was 26.7%, referable DR 10.7% and proliferative DR 4.1% [26].

In the recent National Paediatric Diabetes Audit (NPDA) 2018/19 report for the United Kingdom, there were 28,597 (52% male) children and young people with T1D [27]. The NPDA only records eye screening as normal and abnormal with the majority of the abnormal results being due to background DR. There were 11,431 aged 12 years or older with a valid eye screening examination. DR was found in 13.1% of young people (0-18 years old) with T1D in England and Wales with variation between country (13.4% England and 7.6% Wales) and regions (7.8% West Midlands and 17.5% East Midlands). The prevalence of abnormal DR in the current NPDA 2018/19 report was higher compared to the previously published 2017/18 report when it was 12.8% but lower than the 2016/17 and 2015/16 reports at 14.8 and 15.3% respectively.

Prevalence of DR has been shown to be rare in young people <10 years but increases with increasing age. The Wisconsin study (WESDR) [4] which was the landmark study of DR reported the prevalence of DR in people diagnosed with T1D before the age of 30 years. WESDR found the prevalence of DR in those aged 10-14 years was 2% and in those aged 15-19 years was 10%. The youngest age at which DR has been observed was 5 years, [20] and the youngest age at which sight threatening DR reported was 15 years, [4] with only five cases of sight threatening DR reported in children <18 years [4,20]. However, in a study of 370 children with diabetes aged <18 years, no cases of DR were found [23]. In the NPDA, the risk of DR increased with age and was highest amongst adolescent females with 6.2% of boys and 5.6% of girls aged 12 years rising to 21.7% and 30.4% of boys and girls respectively aged 18 years having abnormal screening results [27].

Risk Factors for DR

There are many risk factors that have been shown to be associated with the development and progression of DR; duration of diabetes, hyperglycaemia, hypertension, ethnicity, dyslipidaemia, puberty, pregnancy, proteinuria, genetics, obesity, alcohol consumption, inflammation and endothelial dysfunction. However, the evidence is inconsistent, and the mechanism of action is less well known [28]. Some of these risk factors are further discussed here.

Duration of diabetes has been shown in many studies to be a risk factor for the development of DR, with the early Wisconsin study showing that 2% of those with a duration of diabetes <2 years had DR increasing to 98% after 15 years and 25% having proliferative DR [4]. A few other studies have also reported DR in those with a duration of T1D <2 years [29-32]. This was also seen in Wales where 10% of those with a duration of diabetes of 2 years had DR. However, other studies have shown no DR below a duration of diabetes of 5 years [26]. In the NPDA 4.7% of those with T1D for less than 1 year had abnormal screenings increasing to 14.7% at 5-9 years and 33.5% after 15 years or longer [27].

Hyperglycaemia has long been associated with an increased risk of developing DR as seen in the landmark DCCT study as well as many other studies in the UK [33,34], Europe [35,36] and the US [37,38]. The age standardised prevalence of DR in the global meta-analysis increased with increasing HbA_{1c} from 17.9% at ≤ 53mmol/mol to 51.2% at HbA_{1c} >75mmol/mol [8]. In the NPDA young people with T1D and higher HbA_{1c} had an increased risk of abnormal eye screening [27]. In those with a HbA_{1c} ≥ 69 mmol abnormal screening was seen in >50%, compared to >35% with a normal screening. In those with abnormal screening 30.1% had HbA_{1c} levels above 80 mmol/mol compared to 16.4% of those with normal screening. The introduction of intensive insulin therapy to optimise glycaemic management in children has been observed to have a beneficial effect on DR in multiple studies [3,39,40]. In Australia [3], comparing the prevalence of DR between 1990-1994 and 2005-2009 and Wisconsin[41] comparing 20 year DR rates have both observed a decrease in DR overtime, which has been attributed in part to the intensification of diabetes insulin regimens. The benefit of such intensive management in the adolescent years remains evident many 44 years later (legacy effect) even when HbA_{1c} values deteriorate, becoming similar to those undergoing conventional insulin therapy [40].

Hypertension has also been shown to be a risk factor for DR. The age standardised prevalence of DR in the global meta-analysis increased with increasing blood pressure from 30.8% at blood pressure of ≤ 140/90 mmHg to 39.6% at blood pressure of >140/90 [8]. The relationship in children is more complicated as hypertension is relatively uncommon and so absolute cut offs can't be used. Instead hypertension is defined with reference to percentiles taking into account age. In the NPDA amongst the cohort of young people aged 12 years and above with T1D and an abnormal eye screening result, 61.5% had above average systolic blood pressure, and 93.7% had above average diastolic blood pressure [27]. The NPDA also showed that all four risk factors – high blood pressure (above 98 centile), high cholesterol (above 5mmol/mol), high HbA_{1c} and obesity were more prevalent in people with abnormal DR screening compared to those without.

Studies have shown that those of African American, Hispanic and South Asian origin have an increased risk of DR compared to Caucasians [42,43]. The effect of dyslipidaemia on DR has been less consistent with the DCCT study showing the severity of retinopathy was associated with increasing triglycerides and inversely associated with HDL cholesterol [44]. However, in the in the global meta-analysis by Yau et al. showed higher cholesterol levels were associated with a higher prevalence of diabetic macular oedema but not diabetic retinopathy [8]. The use of fenofibrate has been shown in studies to reduce the need for laser therapy however, its affects appear to be due to mechanisms other than its lipid lowering effects [45,46].

The effect of puberty on DR is difficult to study as it is not well recorded and so normally chronological age has been used which is a poor marker for puberty. In addition, duration of diabetes needs to taken into consideration. WESDR used the onset of menarche as the marker for puberty and found that duration of diabetes after menarche was associated with 30% excess risk of DR compared with duration of diabetes before menarche [47].

DR has been shown in studies to progress rapidly during pregnancy. This may be due to rapid reductions in HbA1c levels during pregnancy known as the early worsening phenomenon or the release of pregnancy hormones [48, 49]. Therefore, more frequent screening is recommended for women with diabetes who become pregnant depending on the level of DR seen [50].

Screening Recommendations

Current recommendations relating to screening for DR vary considerably. The National Institute for Clinical Excellence (NICE) guideline for diagnosis and management of T1D in Children and young people (NG18) suggests monitoring for DR from 12 years onwards and annually thereafter [11]. There are several guidelines in the US which have slightly different recommendations for when DR monitoring should begin. The American Academy of Ophthalmology currently recommends annual screening for all with a duration of diabetes of more than 5 years [51]. The American Academy of Paediatrics recommends an initial screening 3–5 years after diagnosis of diabetes if over age 9 and annually thereafter [52]. Whereas the American Diabetes Association recommends that screening begins 3–5 years after diagnosis of diabetes and once the child is 10 years old [53]. The Canadian Diabetes Association recommends screening begins 5 years after diagnosis in all from the age of 15 years [54]. Whilst, in Europe, the International Society for Paediatric and Adolescent Diabetes (ISPAD 2018) recommends screening for DR from the age of 11[55]. The Retinopathy Working Party recommends screening from the onset of puberty [56]. In Scandinavia, Finland begin DR screening when patients enter puberty [57], and Sweden commence DR screening from the age of 10 years [58]. All these recommendations are more consensus than evidence based.

Evidence has also been building since screening began for the extension of screening intervals from annual to biennial and recently supporting the implementation of risk based screening for DR [59-64]. In 2016, the UK National Screening Committee (UK NSC) recommended biennial screening for those considered to be at low risk of progression to sight-threatening DR [65]. The American Diabetes Association in 2017, also recommended screening to be conducted every 2 years conditional on there being no evidence of DR on one or more prior annual screening events, with glycaemia well managed and with robust information technology systems and support to ensure future re-call for screening [66]. However, a recent study assessing the cost-effectiveness of extending annual screening intervals to biennial in people at low risk of developing sight-threatening DR found that for those with T1D it was only cost-effective in those with a HbA_{1c} <48mmol/mol or a duration of diabetes <5 years [67]. When considering the extension of screening intervals, the risk of non-attendance at screening needs to be understood. In a study of people attending diabetic eye screening Wales (DESW) those with diabetes aged 17-32 were least likely to attend with uptake rates falling below the 75% acceptable level.

With evidence from UK screening programmes suggesting DR is rare before a duration of diabetes of 5 years and the prevalence of DR is approximately 10% in those aged 12 at first screening [68,69] in addition to the extension of screening recommendations, a review of screening recommendations for children and young people with T1D may be required.

Conclusions

Prevalence of DR in children screened is substantially higher than that previously reported and remains a significant concern in T1D. It is essential to identify DR early on so that steps could be taken to slow the progression and or treat it early. Good glycaemic and blood pressure management are the cornerstones of both the prevention of onset and progression of DR.

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