Screening for retinopathy in children with type 1 diabetes in Denmark

Herskin, Camilla W; Olsen, Birthe S; Madsen, Mette; Kjærsgaard-Andersen, Per; Fredheim, Siri; Johansen, Anders; Kristensen, Kurt; Birkebaek, Niels H; Svensson, Jannet; Pilgaard, Kasper A; Johannesen, Jesper

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Authors:

Camilla Winther Herskin[1], Birthe Susanne Olsen[1], Mette Madsen[3], Per Kjærsgaard[4], Siri Fredheim[1], Anders Johansen[5], Kurt Kristensen[5], Niels Holtum Birkebæk[5], Jannet Svensson[1], Kasper Ascanius Pilgaard[2], Jesper Johannesen[1]

Affiliations:

1: Department of Paediatrics, Herlev University Hospital

2: Pediatric and Adolescent Department, Nordsjællands Hospital

3: Department of Paediatrics, Aalborg University Hospital

4: Department of Paediatrics, Herning Hospital

5: Department of Growth and Reproduction, Rigshospitalet

6: Steno Diabetes Center Aarhus, Aarhus University Hospital

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Abstract

Background: Children with type 1 diabetes (T1D) are screened regularly for retinopathy with fundus photography to prevent visual impairment. According to Danish national guidelines, screening should take place at age 12, 15 and 18 years after minimum 3 years of diabetes. As glycemic control has improved, prevalence of retinopathy is expected to be decreased.

Objective: The aim of this study is to investigate the prevalence, degree and progression of retinopathy in children with T1D and to explore if screening at 12 years is currently indicated in Denmark.

Subjects and methods: Data on all Danish children with onset of T1D from 2003-2013 (n=2943) were collected from the "DanDiabKids" registry. For children with registered screenings (n=2382), prevalence of retinopathy at 12, 15 and 18 years was determined. In children with retinopathy, subsequent screenings were studied to reveal if retinopathy was persistent or temporary.

Results: Prevalence of retinopathy at 12, 15 and 18 years was 0.9 %, 2.3 % and 3.1 %, respectively. Minimal background retinopathy was seen in over 90 % and 100 % at 12 years. In available re-screenings, retinopathy resolved spontaneously in 87.5 % of all cases and 100 % of cases at 12 years.

Conclusions: The prevalence of retinopathy in Danish children with T1D was low. At 12 years, prevalence was 0.9 % and exclusively minimal background retinopathy with 100 % remission in re-screenings. Thus, screening at this age does not seem to have significant clinical relevance. We propose more individualized screening selection before the age of 15.

Keywords:

Retinopathy, diabetes, children, adolescents

Introduction

People living with type 1 diabetes (T1D) are at risk for micro- and macrovascular complications, of which retinopathy is the most prevalent microvascular complication. Vascular changes in the retina lead to microaneurysms, hard exudates, hemorrhages, cotton wool spots (CWS) and ultimately neovascularization. Retinopathy is subdivided into non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR), depending on occurrence of neovascularization.[1,2] In the macula, exudates and edema can threaten central vision when occurring at the fovea, in the condition called maculopathy. Without early detection and treatment, both maculopathy, PDR and severe NPDR can cause visual impairment and ultimately blindness, which is a significant burden for the individual and for society.[2,3] Retinal changes is commonly diagnosed and graded by use of fundus photography. The mildest type of retinopathy, called minimal background retinopathy, does not cause visual impairment or require treatment, but can develop into more severe retinopathy. [2,4]

Children and adolescents with T1D are offered regular eye screenings with fundus photography at fixed intervals to reduce risk of blindness. International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends screening for retinopathy from 11 years of age, at onset of puberty if this is earlier, or after 2-5 years of diabetes duration.[5] According to Danish national guidelines, screening for retinopathy should take place at the age of 12, 15 and 18 years after at least 3 years of diabetes.[6]

Many factors are associated with development of retinopathy in children and adolescents, and some of the most well-known are duration of diabetes and glycated hemoglobin (HbA1c) levels.[7,8] Accordingly, improved glycemic control evaluated by decreasing HbA1c is associated with reduced prevalence of retinopathy among adolescents.[7] However, even with modern intensive therapy and improved glycemic control, PDR is estimated to be present in 20 % of patients with T1D after 30 years diabetes duration.[9] Among Swedish teenagers with T1D and HbA1c below 57 mmol/mol, retinopathy was present in more than 29 % and in more than half when HbA1c was higher.[10] Attention to this diabetic complication is therefore still highly relevant in today's diabetes care.

In Denmark, results from the mid 1990s showed retinopathy in 17.7 % of children aged 12-15 years with T1D.[8] Glycemic control among children with T1D has improved in Denmark since then, [11] and there is a common understanding among clinicians, that retinopathy in children with type 1 diabetes is rare in Denmark. Hence, our hypothesis is that the prevalence of retinopathy among Danish children with T1D has decreased.

The aim of this study is to investigate the prevalence, degree and progression of retinopathy in children with T1D and to explore if screening at 12 years of age is currently indicated in Denmark.

Methods

The Danish national diabetes registry for children, "DanDiabKids", which aims to contain information on all children diagnosed with T1D in Denmark, provided data for the study.[12] The registry contains data from onset of diabetes to transition to an adult outpatient diabetes clinic, which usually happens at 18 years of age. Registered data comprise basic clinical data including annual HbA1c measurements and retinopathy status. HbA1c measurements recorded in the registry are measured once a year in a central laboratory using a high-pressure liquid chromatographic method (RTosoh). The HbA1c values are validated twice monthly by the European Reference Laboratory and are aligned with the Diabetes Control and Complications Trial (DCCT) values. Screenings for retinopathy and maculopathy are performed locally by fundus photography and reviewed by a trained ophthalmologist to determine presence and extent of pathology. Fundus photography is performed according to Danish national guidelines and international standards using digital stereoscopic images, with at least two fields, in mydriatic conditions.[13] The severity of retinopathy is graded as recommended by Danish Endocrine Society on a scale from 1 (minimal background retinopathy, less than 4 microaneurysms or hemorrhages) to 5 (proliferative retinopathy).[14] Screening completeness show variation across regions with 80% completeness at the national level.[12] Screening and monitoring according to the national guidelines are initiated at 12 years of age and repeated at 15 years and 18 years of age. The data regarding screenings are entered in the registry by the local outpatient clinics.

Data on all Danish children with onset of T1D in the period from 2003-2013 (n=2943) were collected from the registry in January 2018 and thus contained information on each child from onset on diabetes to this time. For children with available screenings in the registry (n=2382), screenings at 12, 15 and 18 years were studied. Some children were screened when younger than 12 years and these screenings were studied additionally.

For those with pathological findings, results from subsequent screenings were studied to investigate if changes regressed, persisted or progressed.

Statistical analyses were performed in IBM SPSS Statistics 22. Prevalences at age 12, 15 and 18 were calculated by dividing number of individuals with retinopathy in the screening outcome with the total number of individuals with available screening results in the specific age group. Means of duration of diabetes and HbA1c at time of screening were compared using unpaired t-tests. Levene's test was performed to test equality of variances and when significant, p-values of t-tests were adjusted accordingly. A p-value of <0.05 was considered significant. Results are given as mean ± standard deviation for continuous variables and % (n) for categorical variables.

Results

Background data

In total, 2943 children and adolescents in the registry were diagnosed with T1D in the years from 2003-2013 in Denmark. Age of onset ranged from 0-18 years with a mean of 10.0 ± 3.7 years. The majority (91.5 %) were of Danish ethnicity and 52 % were boys. Of the whole group, 2382 children had at least one screening recorded in the registry.

Prevalence and characteristics of retinopathy according to age

Of 1273 children screened at age 12 years, retinopathy was found in 0.9 % (11) (table 1). Duration of diabetes and HbA1c were comparable regardless of screening outcome (table 1). None had maculopathy (table 2).

At age 15, prevalence of retinopathy was 2.3 %. Children with retinopathy had significantly longer duration of diabetes (6.3 ±3.3 vs. 4.8 ± 3.0 years, $p < 0.01$) (table 1). Two of the children with retinopathy had additional maculopathy (table 2).

At age 18, retinopathy was found in 3.1 % (table 1). Higher HbA1c at time of screening (82.6 ± 19.5 vs. 68.3 ± 16.6 mmol/mol (9.7 ± 3.9 vs. 8.4 ± 3.7 %), $p < 0.01$) and longer duration of diabetes (7.8 ± 2.9 vs. 6.1 ± 2.8 years, $p < 0.001$) was observed in children with retinopathy compared to those without retinopathy (table 1). Maculopathy was seen in three cases (table 2).

Among children screened when younger than 12 years (n=337), no retinopathy or maculopathy was found.

Most cases of retinopathy comprised minimal background retinopathy and unilateral changes (table 2).

Maculopathy

Prevalence of maculopathy at 12, 15 and 18 years were 0.0 %, 0.1 % and 0.4 %, respectively. Totally, five cases of diabetic maculopathy were found, and they were all found simultaneously with retinopathy at 15 or 18 years (table 2). Mean HbA1c at time of screening among the five cases with diabetic maculopathy was 89.8 ± 8.5 mmol/mol (10.4 ± 2.9 %) (data not shown).

Re-screenings

Of the total 72 children and adolescents with retinopathy, 32 children underwent one or more subsequent screenings and 40 children remained without registered re-screenings. Among these, 19 adolescents were 17 years or older and had likely been referred to adult diabetes care before their next screening. Individuals not re-screened had higher HbA1c at time of screening than those who were re-screened, both at age 15 (75.0 ± 16.7 vs. 62.2 ± 14.4 mmol/mol (9.0 ± 3.7 vs. 7.8 ± 3.5), $p < 0.05$) and age 18 (87.2 ± 18.3 vs. 63.5 ± 12.1 mmol/mol (10.1 ± 3.8 vs. 8.0 ± 3.3), $p < 0.05$). Among those re-screened, complete remission of retinopathy was seen in 87.5 % (28) when looking at retinopathy discovered at any age. One of these children received laser treatment. In the four cases where remission was not observed in re-screenings, only minimal background retinopathy

was present and no progression in degree was observed. For children with retinopathy at 12 years, 10 out of 11 were re-screened and all exhibited complete regression of retinopathy (table 2).

Among the five cases with maculopathy, no re-screenings were registered.

Discussion

The prevalence of diabetic eye disease in Danish children with T1D is low. At ages 12, 15 and 18 years, the prevalence of retinopathy was 0.9 %, 2.3 % and 3.1 %, respectively. Maculopathy was very rare and not found in children younger than 15 years. In children with registered re-screenings, complete remission rate of retinopathy was 87.5 % for all ages and 100 % for retinopathy discovered at 12 years of age.

The prevalence of retinopathy in our cohort of children with diabetes onset in the period 2003-2013 is radically reduced compared to a Danish cohort of children with diabetes onset before 1989, [8] as would be expected with the improved glycemic control over the years. Results from other industrialized countries are difficult to compare directly, as age, diabetes duration and HbA1c levels differ between study populations. In some cohorts, prevalence is similar to what we found, for example in a centre based Australian cohort, where retinopathy was found in 2.3 % of a group of children aged 14.5 ± 2.8 years and slightly longer diabetes duration than in the present study.[15] In results from the United States, a prevalence of 5.6 % was found, in a group of subjects age-adjusted to 21 years and with slightly higher HbA1c levels, which probably influence the outcome.[16]

Some studies present even lower prevalence than in our cohort, however methods differ significantly.[17,18] A cohort of American children in aged 1-17.5 years, with mean HbA1c of 70 mmol/mol (8.6 %) and diabetes duration of 5 years had no cases of retinopathy, however children with type 2 diabetes were also included, which makes the study group difficult to compare with ours.[17] Furthermore, sample size was only 370, which causes statistical uncertainty when studying rare outcomes. A large German study of more than 1700 children with over 10 years diabetes duration found retinopathy in only 1.4 %, however results were based on questionnaires filled out by patients and parents and not clinically retrieved.[18] The low prevalence could be due to recall bias and outcomes are therefore not comparable to ours. Higher prevalence around 20 % was found in

two cohorts from United Kingdom and Australia, however both HbA1c levels and diabetes duration were slightly higher than for our cohort in both studies, and children were not divided according to age.[19,20]

Over all, data of this type will often to some degree underestimate prevalence, however it seems that the prevalence in Denmark is probably on the same level as other countries with well-established complication assessment services.

Higher HbA1c and longer duration of diabetes are known as important risk factors for retinopathy in children.[19,21] This corresponds well to our findings among children aged 15 and 18 years, where we found longer duration of diabetes for those with retinopathy. Additionally, higher HbA1c was seen in children with retinopathy at 18 years. Recent data suggest that not only higher HbA1c values, but also HbA1c variability could be an independent risk factor for diabetic retinopathy in children.[22] We have not been able to investigate HbA1c variability in the current cohort, since HbA1c was only registered once every year.

In the present study, spontaneous remission of retinopathy was common. It is known from the literature, that diabetic retinopathy in type 1 and 2 diabetes can be transient and regress spontaneously without specific intraocular treatment in cases both with and without proliferative changes.[23-27] The pathophysiology behind spontaneous regression has not been explained completely, but observations have shown that background retinopathy is a dynamic process, where formation of new microaneurysms occur simultaneously with disappearance of others, perhaps due to thrombosis of the microaneurysm.[28,29] The total number of microaneurysms is thus determined by the balance between disappearance and formation rate, which might be sensitive to glucose levels.[28] Use of renin-angiotensin system inhibitors has also been linked with regression of retinopathy, [4] but since children are rarely treated with antihypertensives, this does not explain the high rates of regression of retinopathy in our cohort. Few other studies report remission rates in children and adolescents. One study found spontaneous remission of background retinopathy in 33.3 % of cases after two years in children aged 7-18 years with duration of diabetes between 0-14 years.[19] Another study reported partial or complete regression in retinopathy in 80 % of cases in

children under 11 years and in 36 % of cases in children older than 11 years.[30] This corresponds with our findings, where majority of retinopathy changes and all at age 12 years resolved spontaneously. No progression in degree of retinopathy was seen. Thus, it seems, that background retinopathy is a very dynamic process in children, but it is unknown if transient retinal changes compose a risk factor for future persistent retinopathy. However, number of retinal microaneurysms has been shown to predict progression of retinopathy.[4] It is reassuring that more than 94 % of changes found in our cohort was of minimal background retinopathy type with 4 or less microaneurysms.

Some limitations do apply when using data from a registry. Unfortunately, data from the registry do not provide any insight of the psychological aspect of screening or how the children are followed up after the screening result. Furthermore, missing data from the local out-patient clinics could be a reason for the unsatisfying number of registered re-screenings in addition to the actual cases where follow up is never achieved. Higher re-screening rates and ensuring that all re-screenings are entered in the registry would give a more precise picture of the natural development of retinopathy, as individuals without registered re-screenings had higher HbA1c levels. This likely leads to overestimating the spontaneous remission rate. However, we still believe that remission is common among children based on our results. Since HbA1c level is only registered once every year, and not always in relation to other screenings and tests, it is unsuitable to investigate any changes in glycemic control in the months before and after screenings. However, the strengths are also comprehensive, as we were able to study a complete cohort of children diagnosed with diabetes in Denmark and assess their screenings over several years. Accordingly, our sample size is larger than most when researching diabetes in children, which is beneficial when studying relatively rare outcomes. All pediatric diabetes out-patient clinics in Denmark report to the registry and data thus represent all areas and socioeconomic groups of the country, which make the results ideal for evaluating national guidelines.

In conclusion, the prevalence of retinopathy in Danish children with type 1 diabetes is low and most cases exhibit minimal background retinopathy. The majority of changes were transient and resolved spontaneously. The prevalence is lowest among children at 12 years and increase with age, diabetes

duration and increasing HbA1c. For retinopathy discovered at 12 years, only minimal background retinopathy was demonstrated, and spontaneous remission rate was 100 %. Thus, the screening for retinopathy within this young age group does not seem to have significant clinical relevance and we propose an individual screening selection for this age group. Follow up studies on children diagnosed with transient retinopathy in childhood are warranted to reveal if these findings affect future development of diabetic eye disease.

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Tables

Table 1 – Prevalence of retinopathy and comparison of diabetes duration and HbA1c according to screening outcome at age 12, 15 and 18 years

	No retinopathy	**Retinopathy**
12 years (N=1273)		
Prevalence, % (n)	99.1 % (n=1262)	0.9 % (n=11)
Duration of diabetes, years, mean ± SD	4.2 ± 2.8	3.9 ± 2.8
HbA1c at screening¶, mean ± SD	63.2 ± 12.0 (7.9 ± 3.2)	66.5 ± 10.0 (8.2 ± 3.1)
15 years (N=1642)		
Prevalence, % (n)	97.7 % (n=1605)	2.3 % (n=37)
Duration of diabetes, years, mean ± SD	4.8 ± 3.0	6.3 ± 3.3**
HbA1c at screening¶, mean ± SD	66.1 ± 14.9 (8.2 ± 3.5)	68.4 ± 16.6 (8.4 ± 3.7)
18 years (N=846)		
Prevalence, % (n)	96.9 % (820)	3.1 % (26)
Duration of diabetes, years, mean ± SD	6.1 ± 2.8	7.8 ± 2.9**
HbA1c at screening¶, mean ± SD	68.3 ± 16.6 (8.4 ± 3.7)	82.6 ± 19.5*** (9.7 ± 3.9)

¶ HbA1c values are indicated in mmol/mol (%). ** $p < 0.01$ (unpaired t-test) when comparing diabetes duration according to screening outcome at age 15 and 18 years. *** $p < 0.001$ (unpaired t-test) when comparing HbA1c according to screening outcome at age 18 years.

Table 2 – Characteristics of diabetic eye disease found at 12, 15 and 18 years

	12 years	**15 years**	**18 years**
Patients with retinopathy in screening, n	11	37	26
Bilateral affection, % (n)	27.3 % (3)	18.9 % (7)	38.5 % (10)
Minimal background retinopathy, % (n)	100 % (11)	91.9 % (34)	96.2 % (25)
Simultaneous maculopathy, % (n)	0 % (0)	5.4 % (2)	11.5 % (3)
Spontaneous remission in available re-screenings, % (n/n with available re-screenings)	100.0 % (10/10)	83.3 % (15/18)	40.0 % (2/5)