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Ocular Complications in Children with Diabetes Mellitus

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Purpose: The effectiveness of annual eye examinations in diabetic children is unclear. We sought to determine the prevalence and onset of ocular pathology in children with diabetes mellitus (DM), identify risk factors for ocular disease, and recommend a screening regimen for asymptomatic children.

Design: Retrospective, consecutive cohort study.

Participants: Children aged less than 18 years with type 1 or 2 DM examined over a 4-year period.

Methods: All children underwent a complete eye examination, including dilated fundoscopy and cycloplegic refraction. A literature review was performed, identifying the youngest reported age and shortest reported duration of DM before the diagnosis of diabetic retinopathy (DR).

Main Outcome Measures: Prevalence of DR, cataract, high refractive error, and strabismus.

Results: A total of 370 children (mean age, 11.2 years; range, 1−17.5 years) had 693 examinations, with a mean DM duration of 5.2 years (range, 0.1−16.2 years) and a mean hemoglobin A_{1c} (HbA_{1c}) of 8.6 (range, 5−≥14). No children had DR. A total of 12 children had cataract; 5 required extraction but were identified by decreased vision, not diabetic screening. A total of 19 children had strabismus; only 1 was microvascular paralytic strabismus. A total of 41 children had high refractive error. There were no associations between these conditions and duration or control of DM. In the literature, the youngest age at diagnosis of severe DR was 15 years, and the shortest duration of disease was 5 years.

Conclusions: Diabetic retinopathy is rare in children regardless of duration and control of DM. On the basis of our study and literature review, screening examinations for type 1 diabetes could begin at age 15 years or at 5 years after the diagnosis of DM, whichever occurs later, unless the child is judged by the endocrinologist as being at unusually high risk. Other ocular complications are identifiable through existing amblyopia screening methods. *Ophthalmology 2015;122:2457-2464 © 2015 by the American Academy of Ophthalmology.*

Diabetes mellitus (DM) is a well-known cause of multiple ophthalmic problems in adults, including diabetic retinopathy (DR), macular edema, cataract, refractive change, and microvascular paralytic strabismus. Diabetic retinopathy and macular edema progress to the ultimate ocular complication of blindness in 12 000 to 24 000 new patients each year in the United States, making DM the leading cause of blindness among American adults aged 20 to 74 years.[1] The Early Treatment of Diabetic Retinopathy Study and the Diabetic Retinopathy Study demonstrated that early recognition and treatment of diabetic macular edema and proliferative DR (PDR) in patients with DM reduced the risk of moderate and severe vision loss.[2,3] Therefore, there has been a fervent public health effort to establish ophthalmic screening regimens for those with DM, beginning at an early age. For a screening program to be worthwhile, it must identify a disease that is asymptomatic and has a cost-effective treatment, conditions that generally are met by DR.

Current guidelines by the American Academy of Ophthalmology encourage annual screening examinations for all patients with type 1 DM to begin 5 years after diagnosis of DM.[4] However, the age at diagnosis and prevalence of DR among children are not well established, with varied reports in the literature, and there is a paucity of information about the onset and prevalence of other diabetic ocular complications among children because the majority of studies have focused on DR. Some data are available with regard to modifiable risk factors to prevent the development of ophthalmic complications of DM, but not particularly in the very young. Findings from the Diabetes Control and Complications Trial (DCCT) demonstrated that intensive glucose control in children aged 13 to 17 years with type 1 DM reduced the risk of development of DR by 53%.[5,6] The risk of DR seems to increase with increased duration of DM,[7−9] but 1 study of DM in young children suggested that development of type 1 DM at a very young age (i.e., <5 years) might protect against the development of DR.[10] Even less is known about DR risk and incidence among children with type 2 DM, which is an increasingly important population to study given the growing prevalence of children with this disease.

In light of our limited knowledge of the age at onset and prevalence of these ocular complications, the clinical effectiveness of annual diabetic eye examinations in children is unclear. We sought to determine the prevalence and onset of ocular pathology among children with DM, including DR, cataract, high refractive error, and strabismus.

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We also sought to identify potential risk factors for ocular disease and to recommend an updated ophthalmic screening regimen for asymptomatic children with DM on the basis of our study results and a review of the literature.

Methods

We conducted a retrospective consecutive cohort study of children aged less than 18 years with type 1 or 2 DM who underwent 1 or more complete dilated eye examinations at our institution over a 4-year period between 2009 and 2013. The study protocol was approved by the Institutional Review Board of The Children's Hospital of Philadelphia, conformed to the requirements of the US Health Insurance Portability and Accountability Act, and adhered to the tenets of the Declaration of Helsinki.

A search of the electronic medical record was performed to identify all children examined in the outpatient ophthalmology clinic meeting the inclusion criteria. Data collected included the gender, race, ethnicity, child's age at each eye examination, age at diagnosis of DM, presence and severity of DR, presence and severity of cataract, refractive error, presence and type of strabismus, and serum hemoglobin A_{1c} (HbA_{1c}) levels. Duration of DM was calculated on the basis of the age at diagnosis of DM and age at time of the eye examination. The HbA_{1c} recorded was the most recent HbA_{1c} measurement obtained before each particular visit date. If multiple ophthalmology examinations were available for 1 patient, an average (±standard deviation [SD]) of all prior HbA_{1c} measurements was calculated.

Retinopathy screening was conducted with dilated fundoscopic examinations performed by pediatric ophthalmologists. Refractive errors were obtained by cycloplegic refractions and classified by the amount of spherical equivalence (in diopters [D]) into the following categories: high myopia (≥4.0 D of myopia), myopia (0.25−3.75 D of myopia), hyperopia (plano to 2.75 D of hyperopia), and high hyperopia (≥3.0 D of hyperopia). High astigmatism was defined as ≥1.5 D cylindrical refractive error. "High refractive error" was a composite variable defined as the presence of 1 or more of high myopia, high hyperopia, and high astigmatism.

Statistical Analysis

Descriptive statistics (mean, SD, median, minimum, and maximum) were calculated for baseline characteristics of the subjects. The primary outcomes were the prevalence with 95% confidence interval of DR, cataract, strabismus, and high refractive error. Potential risk factors were categorized for analysis according to threshold values suggested in the literature. These factors included age at DM diagnosis (≤5, >5−<10, ≥10 years),[11−13] DM duration (≤5, >5−<10, ≥10 years), and mean HbA_{1c} (≤7.5, >7.5−<10, ≥10%).[14] The associations between ocular complications and age at DM diagnosis, duration of DM, and HbA_{1c} were analyzed in univariate analyses. The Fisher exact test was used to assess for statistical significance, which was defined as a P value less than 0.05. Kaplan−Meier survival curves were plotted to demonstrate the time to development of each ocular complication from the diagnosis of DM. All statistical analyses were performed using SAS for Windows version 9.4 (SAS Inc., Cary, NC).

Literature Search

Studies reporting the occurrence of DR and other ocular complications in children with DM were identified through the following methods. A PubMed search was performed for various combinations of the following terms: *diabetes mellitus*, *diabetic retinopathy*, *proliferative diabetic retinopathy*, *children*, *pediatric*, *complications*, *cataract*, *strabismus*, *cranial neuropathy*, *cranial nerve palsy*, *screening*, and *guidelines*. The American Academy of Pediatrics and American Academy of Ophthalmology guidelines were reviewed. The reference sections of relevant articles and guidelines were searched to identify additional potential studies.

Results

A total of 370 children underwent 693 diabetic screening examinations during the study period. Baseline characteristics of these subjects appear in Table 1. A total of 338 children had type 1 DM, and 32 children had type 2 DM. The mean age at first eye examination was 11.2 (SD, 3.7) years, ranging from 1 to 17.5 years. The mean age at DM diagnosis was 7.0 (SD, 4.1) years, ranging from 0.5 to 16.8 years. The mean DM duration at the time of examination was 5.2 (SD, 3.7) years, ranging from 0.1 to 16.2 years, with mean HbA_{1c} of 8.6 (SD, 1.9), ranging from 5 to ≥14 (values >14 were reported by the laboratory as "≥14" only). The ages at diagnosis of DM and the ages at last examination for each child are shown in Figure 1.

The prevalence of ocular complications is shown in Table 2. No children (0%; 95% confidence interval, 0−1) were found to have DR during any of the 693 examinations (Table 2). Eighteen eyes of 12 children (3.3%; 95% confidence interval, 1.5−5.1) were found to have cataracts (Table 3). The average age at cataract diagnosis was 13.6 years, at a mean of 5.3 years after DM diagnosis. The youngest age at cataract diagnosis in our study was 7.5 years, 4.5 years after DM diagnosis. No associations were found between cataract formation and age at diagnosis, duration, or control (as indicated by HbA_{1c}) of DM (Table 4). Not all of these cataracts were thought to be due to complications of DM (Table 3). Specifically, 1 child with a unilateral cataract had ipsilateral cytomegalovirus retinitis, which was the presumed cataract cause. Another child with bilateral cataracts had received whole-body irradiation for metastatic neuroblastoma several years before his cataract diagnosis, and the radiation may have been the more causative element. Nine eyes of 5 children required cataract extraction. In all 5 cases, the diagnosis of cataract was made after the children presented with symptoms of decreased vision; they were not diagnosed at the time of routine diabetic eye screening.

Nineteen patients (5.2%) were found to have strabismus. The average age at strabismus diagnosis was 11 years, 3.7 years after DM diagnosis. The youngest age at strabismus diagnosis was 2.7 years. Of these 19 children, only 1 patient was noted to have a paralytic strabismus from an abducens nerve palsy, which resolved spontaneously. This transient abducens nerve palsy was thought to be a microvascular neuropathy from DM after a thorough neurologic workup, which included brain computed tomography, brain magnetic resonance imaging, myasthenia gravis antibody panel, and lumbar puncture with cerebrospinal fluid studies and opening pressure, yielded normal results. This abducens neuropathy occurred at 12 years of age, which was 1.5 years after the diagnosis of DM; however, information on her HbA_{1c} was not available. The child with sixth nerve palsy was diagnosed after presenting with diplopia and not during a routine diabetic screening examination. No associations were found between strabismus and type, age at diagnosis, duration, or control of DM (Table 4).

Forty-one patients (11%) were found to have high refractive error, with 2.8% having high hyperopia, 2.8% having high myopia, and 7.2% having high astigmatism in at least 1 eye. The majority of children (55.8%) were found to have mild hyperopia (Table 2).

Table 1. Baseline Characteristics of Study Population

Characteristic	Diabetes		
	Type 1 (n = 338)	*Type 2 (n = 32)*	***Overall (N = 370)***
Gender – n (%)			
Male	183 (54)	12 (38)	195 (53)
Female	155 (46)	20 (62)	175 (47)
Ethnicity – n (%)			
Hispanic	24 (07)	0 (00)	24 (07)
Non-Hispanic	297 (88)	29 (91)	326 (88)
Unknown	17 (05)	3 (09)	20 (05)
Race – n (%)			
Asian	14 (04)	1 (03)	15 (04)
African American	75 (22)	27 (84)	102 (28)
White	225 (67)	4 (13)	229 (62)
>1 reported	1 (00)	0 (00)	1 (00)
Unknown	23 (07)	0 (00)	23 (06)
Age at diabetes onset (yrs)*			
Mean ± SD	6.6±4.0	11.8±2.7	7.0±4.1
Median (min, max)	6.0 (0.5, 16.8)	11.9 (5.8, 16.0)	6.5 (0.5, 16.8)
≤5	144 (43)	0 (00)	144 (39)
>5–<10	108 (32)	5 (16)	113 (31)
≥10	77 (23)	27 (84)	104 (28)
Missing	9 (03)	0 (00)	9 (02)
Duration of diabetes at last visit (yrs)†			
Mean ± SD	5.4±3.7	2.8±2.3	5.2±3.7
Median (min, max)	4.9 (0.1, 16.2)	2.0 (0.1, 10.1)	4.5 (0.1, 16.2)
≤5	168 (50)	27 (84)	195 (53)
>5–<10	111 (33)	2 (06)	113 (31)
≥10	41 (12)	1 (03)	42 (11)
Missing	18 (05)	2 (06)	20 (05)
Age at first examination (yrs)			
Mean ± SD	10.9±3.7	14.1±2.2	11.2±3.7
Median (min, max)	11.0 (0.66, 17.5)	14.4 (7.7, 17.2)	11.4 (0.66, 17.5)
≤10	143 (42)	2 (06)	145 (39)
>10–<15	133 (39)	17 (53)	150 (41)
≥15	53 (16)	11 (34)	64 (17)
Missing	9 (03)	2 (06)	11 (03)
Age at last examination (yrs)			
Mean ± SD	11.9±3.8	14.5±2.1	12.1±3.7
Median (min, max)	12.0 (1.2, 17.5)	14.9 (7.7, 17.2)	12.5 (1.2, 17.5)
≤10	112 (33)	1 (03)	113 (31)
>10–<15	131 (39)	15 (47)	146 (39)
≥15	86 (25)	14 (44)	100 (27)
Missing	9 (03)	2 (06)	11 (03)
Average $HgbA_{1c}$ during study period			
Mean ± SD	8.6±1.8	8.9 ±2.9	8.6±1.9
Median (min, max)	8.2 (5.0, 14.0)	8.2 (5.5, 14.0)	8.2 (5.0, 14.0)
≤7.5	98 (29)	14 (44)	112 (30)
>7.5–<10	164 (49)	3 (09)	167 (45)
≥10	62 (18)	14 (44)	76 (21)
Missing	14 (04)	1 (03)	15 (04)

Data are n (%) unless otherwise indicated.
$HgbA_{1c}$ = hemoglobin A_{1c}; SD = standard deviation.
*n=361: 9 subjects missing age at diabetes onset.
†n=350: 11 subjects missing with no eye examination information plus 9 subjects missing age at onset.

There was no significant relationship found between refractive errors and type, age at diagnosis, duration, or control of DM.

Discussion

We found no cases of DR among a large cohort of children with type 1 and 2 DM of duration up to 16 years and blood glucose control ranging from good to poor. Our cohort included children diagnosed at a very young age and followed through adolescence (Fig 1). Although other investigators have reported similar results,[15] we also reviewed the literature to identify studies reporting the occurrence of DR during childhood (Table 5). Among these studies, the prevalence of DR among children was reported to be between 9% and 28%.[7–9,16–23] One

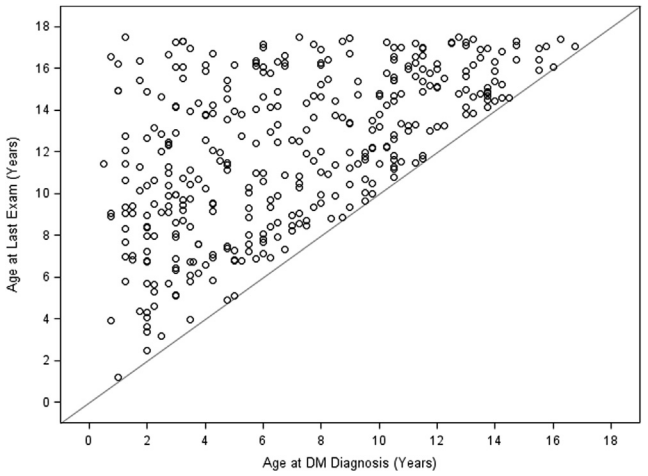

Figure 1. Age at last examination of all 370 children with diabetes mellitus (DM) in reference to age at diagnosis of DM.

possible reason for this wide range of prevalence estimates (0%–28%) might be differing baseline characteristics of the study samples, including different ages at examination or blood glucose control. Another reason might be different screening modalities. The use of fundus photography has been found to be more sensitive than fundoscopy for detecting mild retinopathy, particularly in children, who are more difficult to examine than adults.[8,21] Finally, improvements in the effectiveness of diabetes diagnosis and management over time may be resulting in a decrease in the incidence of DR.[23,24] Some of these studies present clinical data from as far back as 30 to 40 years ago, before publication of the major DR studies, such as the DCCT in 1993, which identified modifiable risk factors for DR and established glucose control goals.[5]

The majority of children with DR in prior studies had mild non-PDR, many of whom were found to have only a single microaneurysm or retinal hemorrhage unilaterally.[7,8,16,18,19] The youngest age at which a child was diagnosed with DR was 5.5 years, and this child had a single microaneurysm in 1 eye.[7] We think that the value of screening for such mild disease is questionable, considering the large number of normal examinations being performed. A more reasonable screening target may be identification of sight-threatening DR, which might be close to requiring treatment (Table 5). In our review of the literature, we could identify only 5 possible cases of children aged less than 18 years with sight-threatening DR.[7,9,22] Holl et al[7] reported 1 child who had received laser treatment before their study, but they did not report the age of the patient at treatment nor the duration of DM.[7] Minuto et al[22] reported 1 patient requiring laser treatment for "sight-threatening DR," but they did not provide the age at treatment; the authors report that among all patients with DR (n = 26), the median age was 26.5 years and the first quartile age was 19.8 years. Therefore, it is not clear that this patient was aged less than 18 years when treated for DR.[22] A minimum age for the group is not provided, and no duration of DM before treatment was reported.[22] Likewise, a more recent study of type 1 and type 2 DM in youth reported a single case of PDR in a child with type 2 DM, although the age of this child at diagnosis of PDR was not provided and could be in the third decade of life, based on the study methods described.[25] Three additional cases of PDR possibly diagnosed before age 18 years were reported in 1984 from the Wisconsin Epidemiologic Study of Diabetic Retinopathy, preceding the DCCT.[9] The ages of these patients are reported only as a range from 15 to 19 years.[9] The shortest duration of DM before the development of PDR was provided as 5 to 6 years.[9] On the basis of this review, the earliest documented age of severe DR is 15 years, conservatively assuming the lower end of the range noted earlier, and the shortest duration of DM before severe DR is 5 years. Of note, none of the studies

Table 2. Prevalence of Ocular Complications by Type of Diabetes Mellitus

Ocular Complication	Diabetes		
	Type 1 (n = 338)	*Type 2 (n = 32)*	***Overall (N = 370)***
Retinopathy – n (%, 95% CI)*	0 (0.0, 0.0–1.1)	0 (0.0, 0.0–10.7)	0 (0.0, 0.0–1.0)
Cataract – n (%, 95% CI)*	10 (3.0, 1.1–4.8)	2 (6.3, 0.0–14.6)	12 (3.3, 1.5–5.1)
Strabismus – n (%, 95% CI)*	16 (4.8, 2.5–7.0)	3 (9.4, 0.0–19.5)	19 (5.2, 2.9–7.4)
Refractive error at last visit†			
(min, max)	(−8.00, 7.00)	(−4.00, 4.25)	(−8.00, 7.00)
Refractive error categories – n (%, 95% CI)†			
High myopia: ≤−4.0 D	8 (02.7, 01.0–05.0)	1 (03.7, 00.0–10.8)	9 (02.8, 01.0–05.0)
Myopia: >−4.0 to ≤−0.25 D	110 (37.4–31.8, 43.0)	14 (51.9–33.0, 70.7)	124 (38.6, 33.3–44.0)
Hyperopia: >−0.25 to <3.0 D	169 (57.5, 51.8–63.1)	10 (37.0, 18.8–55.3)	179 (55.8, 50.3–61.2)
High hyperopia: ≥3.0 D	7 (02.4, 01.0–04.0)	2 (07.4, 00.0–17.3)	9 (02.8, 01.0–05.0)
Astigmatism: ≥1.5 D in either eye†,‡			
n (%, 95% CI)	19 (06.5, 03.7–09.3)	4 (14.8, 01.4–28.2)	23 (07.2–04.3, 10.0)

CI = confidence interval; D = diopter.
*n=368: 2 subjects missing outcome information.
†n=321: 49 subjects with no refractive error measurements.
‡Absolute value of cylinder ≥1.5 D in either eye.

Table 3. Demographics of 12 Pediatric Cataracts Associated with Diabetes Mellitus

Subject	Age at Cataract Diagnosis (Yrs)	DM Duration at Diagnosis (Yrs)	Cataract Morphology	Surgery	Age at Surgery (Yrs)	Mean (%) HbA_{1c}	Highest (%) HbA_{1c}
1	9	3.25	Peripheral cortical wedge (unilateral)	No	N/A	7.3	7.7
2*	7.5	3.75	1+ PSC (unilateral)	No	N/A	7.4	8.4
3	14	14	Dense, intumescent OU	Yes; OU	14	"High"	14
4	17	2.25	2+ PSC OU	No	N/A	N/A	N/A
5	13.5	0	Mature white OU	Yes; OU	13.5	"High"	14
6	15	0	1+ PSC OD, 3+ NSC OS	Yes; OU	15	9	13.6
7	14	0	Trace PSC (unilateral)	No	N/A	10.2	14
8	14	2.5	Trace PSC (unilateral)	No	N/A	9.9	14
9	11.5	6.5	Peripheral deposits OU, trace PSC (unilateral)	No	N/A	11	11.4
10	16	2	Trace PSC (unilateral)	No	N/A	11	14
11†	18	15	Dense PSC OU	Yes; OU	18	13	14
12	13.8	14	Dense PSC OU	Yes; OD	14	8.3	9.7
Mean (SD)	13.6 (3.0)	5.3 (5.8)			14.9 (1.8)	9.7 (1.9)	12.3 (2.5)

DM = diabetes mellitus; HbA_{1c} = hemoglobin A_{1c}; N/A = not available; NSC = nuclear sclerotic cataract; OD = right eye; OS = left eye; OU = both eyes; PSC = posterior subcapsular cataract; SD = standard deviation.
*Patient had ipsilateral cytomegalovirus retinitis.
†Patient received whole-body irradiation for metastatic neuroblastoma.

discussed earlier reported a case of clinically significant macular edema in a child.

The mean incidence of diabetic cataracts in children has been reported to be 0.7% to 3.4%.[26,27] In our study, we found a similar cataract incidence of 3.3% (12 children, 19 eyes). The youngest age at cataract diagnosis in our study was 7.5 years, 4.5 years after DM diagnosis, with an average age of 13.2 years, 4.4 years after DM diagnosis. These findings are similar to those of a recently published series of cataracts in patients with type 1 DM, in whom the mean age at cataract diagnosis was 11.4 years, 2.3 years after DM diagnosis, with the youngest cataract diagnosed at age 5 years.[28] Of note, 2 of their patients presented with cataracts before diagnosis of DM, and 5 cataracts were diagnosed at the time of DM diagnosis. In this report, Wilson et al[28] describe pediatric diabetic cataracts of varied morphology: posterior subcapsular, lamellar, flake-like, and dense milky-white cataracts. They propose the

Table 4. Ocular Complications and Potential Risk Factors

Characteristics	Patients* (n = 368)	Cataract (n = 12), n (%)	Strabismus (n = 19), n (%)	Any Ocular Complications† (n = 30), n (%)
Type of diabetes		$P = 0.28$‡	$P = 0.22$	$P = 0.30$
Type 1	336	10 (03.0)	16 (04.8)	25 (07.4)
Type 2	32	2 (06.3)	3 (09.4)	5 (15.6)
Age at diabetes onset (yrs)		$P = 0.01$	$P = 0.43$	$P = 0.04$
≤5	143	4 (02.8)	10 (7.0)	13 (09.0)
>5–<10	112	0 (00.0)	3 (02.7)	3 (02.7)
≥10	104	8 (07.7)	6 (05.8)	14 (46.7)
Missing	9	0 (00.0)	0 (00.0)	0 (00.0)
Duration of diabetes at last visit (yrs)		$P = 0.56$	$P = 0.19$	$P = 0.33$
≤5	195	8 (04.1)	10 (05.1)	18 (09.2)
>5–<10	111	2 (01.8)	4 (03.6)	6 (05.3)
≥10	42	1 (02.4)	5 (11.9)	5 (11.9)
Missing	20	1 (05.0)	0 (00.0)	1 (05.0)
Average HbA_{1c} during study period		$P = 0.37$	$P = 0.06$	$P = 0.09$
≤7.5	111	5 (04.5)	7 (06.3)	11 (09.8)
>7.5–<10	166	3 (01.8)	4 (02.4)	7 (04.2)
≥10	76	4 (05.3)	6 (07.9)	10 (13.1)
Missing	15	0 (0.00)	2 (13.3)	2 (13.3)

HbA_{1c} = hemoglobin A_{1c}.
*Two subjects missing outcome information.
†One subject with cataract and strabismus.
‡P values are from Fisher exact tests.

Table 5. Studies Reporting Occurrence of Diabetic Retinopathy in Children

Article	Youngest Age at Onset of Any DR (Yrs)	Shortest Duration of DM at Onset of Any DR (Yrs)	Youngest Age at Onset of Pre-PDR* or PDR (Yrs)	Shortest Duration of DM at Onset of Pre-PDR* or PDR (Yrs)
Kubin et al,[19] 2011	8	1.7	None	None
Kernell et al,[18] 1997	9.5	1.5	PDR at 21.5	PDR at 9.5
Palmberg et al,[8] 1981	>20	<1 yr (in a 29-year-old patient)	1 case of DR requiring laser after age 20 yrs	13
Donaghue et al,[16] 1997	8	1.2	None	None
Holl et al,[7] 1998	5.5	2.2	1 case of DR requiring laser, age not reported	Not reported
Kullberg et al,[20] 2002	>9	Not reported; range, 6–13 in study	>18 yrs	Not reported; range, 6–13
Minuto et al,[22] 2012	Not reported	Not reported	1 case of DR requiring laser, age not reported	Not reported
Maguire et al,[21] 2005	<11	Not reported	None	None
WESDR II (Klein et al,[9] 1984)	≤9	1	PDR 15–19	PDR at 5–6
WDRS (1990–2002) (Lecaire et al,[23] 2006)	≤9	≤4	Not reported	PDR at ≤7 yrs
Flack et al,[17] 1996	11.5	1.3	Severe NPDR 18.8; no PDR	Severe NPDR 5.5; no PDR
Mayer-Davis et al,[25] 2012	Not reported	Not reported	1 case of PDR in child with type 2 DM, age not reported	Not reported

DM = diabetes mellitus; DR = diabetic retinopathy; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; WDRS = Wisconsin Diabetes Registry Study; WESDR II = Wisconsin Epidemiologic Study of Diabetic Retinopathy II.
*Pre-PDR defined as severe non-PDR.

variation in cataract morphology in these children may be due to differences in age at DM diagnosis and severity of DM.[28] In our study, we also found varied cataract morphologies, including posterior subcapsular, posterior flecks, mature white, and intumescent cataracts. Nine eyes of 5 children in our cohort required cataract surgery. All of these children with visually significant cataracts presented symptomatically or were discovered during vision screening examinations.

The prevalence of high refractive errors and strabismus in our cohort was found to be similar to a nondiabetic pediatric population.[29,30] However, the case of a possible microvascular abducens neuropathy due to DM was an interesting finding and has not been reported in the literature in a child to our knowledge. However, subclinical peripheral neuropathy has been detected by nerve conduction studies in half of children with a type 1 DM duration of greater than 5 years[31]; therefore, a microvascular insult causing strabismus in children is biologically plausible. This particular patient had the majority of her DM care at another institution; therefore, little information regarding control of her DM or other comorbid conditions, including other microvascular insults, was available. She presented symptomatically with diplopia, rather than being diagnosed with esotropia during routine screening examination.

The American Academy of Ophthalmology guidelines recommend annual screenings for DR to begin 5 years after the diagnosis of DM, and the American Academy of Pediatrics guidelines suggest initiating annual examinations 3 to 5 years after DM diagnosis or after the age of 9 years, whichever occurs later.[4,32] On the basis of our study results and review of the literature, screening for ocular complications of DM could begin later than suggested by these guidelines. No children in our study were diagnosed with retinopathy. The earliest documented age of severe DR in the literature was 15 years, and the shortest duration of DM before the development of severe DR was 5 years. In our study, 121 children had DM for at least 5 years and an examination before age 15 years, and there were 213 examinations before age 15 years that involved children who had DM for at least 5 years. The children with visually significant cataracts were diagnosed when they presented for vision loss. Likewise, the 1 child with a diabetic sixth nerve palsy presented with diplopia. Finally, there are already established amblyopia and amblyopia risk factor screening programs in place in schools and pediatricians' offices that are effectively identifying strabismus and high refractive errors in school-aged children. The US Preventive Services Task Force currently recommends vision screening for all children at least once between the ages of 3 and 5 years to detect the presence of amblyopia or its risk factors.[30]

We suggest the collaborative consensus groups that publish recommendations for screening consider updating the current guidelines. On the basis of the available evidence, we believe that screening for DR may commence at 15 years of age or at 5 years after the diagnosis of DM, whichever occurs later. In addition, examinations could begin earlier in children considered to be at unusually high risk for systemic diabetic complications, as judged by the treating endocrinologist (e.g., children with chronically poorly controlled blood glucose concentrations or in the case of pregnancy). In addition, because only a small percentage of our sample had type 2 DM, and there is a paucity of information in the literature on the prevalence and incidence of DR in children with type 2 DM, this growing

population may need to be considered separately. Until additional data are available, children with type 2 DM could be considered within the high-risk category and begin DR screening upon DM diagnosis, as in adults with type 2 DM.

Study Limitations

Our study has limitations worth considering. We did not include fluorescein angiographic analysis to identify occult DR; however, fluorescein angiography is not routinely performed in children, is not widely available in pediatric ophthalmology offices, and is not recommended for routine DR screening in adults or children.[4] Furthermore, we did not perform ocular color fundus photography to screen for DR. Fundus photography has been found to be more sensitive than ophthalmoscopy in the diagnosis of mild DR.[8,21] However, we believe our methodology is more clinically relevant to the screening techniques used by most pediatric ophthalmologists, and the utility of identifying very mild background DR is questionable. The generalizability of our results to children in other geographic regions and of different ethnic backgrounds may be limited by the racial and ethnic profile of our study sample. However, the children in our study were referred by their endocrinologists or primary care pediatricians for DR screening, and our cohort is therefore representative of a typical population of children presenting for such screening. Results relating to blood glucose control in this study may be limited by the possibility that the collected HbA_{1c} values were not always representative of the patient's overall glucose control. We did not collect all available HbA_{1c} values (only the value preceding each examination) or information on HbA_{1c} variability, which has been found to be an independent risk factor for the development of DR in patients with type 1 DM.[10] However, each HbA_{1c} collected is a random spot sampling of each patient's glucose control and free from any potential bias of more frequent testing in an uncontrolled patient. Furthermore, our study does not include information on concurrent hypertension, maternal history of gestational diabetes, or other prenatal insults that have been suggested as potential risk factors for DR in children.[33] Finally, the successful implementation of a clinical guideline depends on its acceptance by clinicians, and some physicians may be uncomfortable with our screening recommendations. However, the recommendation to not examine children with DM until age 15 years is based on the current evidence available in the scientific literature.

Vision-threatening DR is extremely rare in children, regardless of the duration or control of DM. Current screening guidelines seem to create an unnecessary financial and logistic burden for families and unnecessary appropriation of resources of pediatric ophthalmologists and the health care system. On the basis of the available evidence, we believe that screening examinations for DR could begin at age 15 years or after 5 years of DM duration, whichever occurs later, with an exception made for high-risk children and type 2 diabetic children. Annual examinations could then continue into adulthood, when the risk of developing sight-threatening DR increases. A collaborative consensus group should consider revising the current DR screening guidelines.

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Abbreviations and Acronyms:
D = diopters; **DCCT** = Diabetes Control and Complications Trial; **DM** = diabetes mellitus; **DR** = diabetic retinopathy; **HbA_{1c}** = hemoglobin A_{1c}; **PDR** = proliferative diabetic retinopathy; **SD** = standard deviation.

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