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Prevalence of diabetic retinopathy in children and adolescents at an urban tertiary eye care center

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Abstract

Background: Diabetic retinopathy (DR) is a serious complication that can progress to sight-threatening disease. The prevalence of DR in youth with diabetes has been reported to be 3.8% to 20%.

Objective: We aimed to evaluate the prevalence of DR among youth with diabetes at a large ophthalmologic referral center. Secondary goals were to determine the risk factors for DR and severity of disease.

Methods: Retrospective chart review of 343 patients with diabetes, <21 years of age, seen at a tertiary referral eye care center from 2013 to 2018.

Results: The study included 343 patients, of which 293 had type 1 diabetes (T1D) and 50 had type 2 diabetes (T2D). Thirteen of 343 patients had DR, with an overall incidence of 3.8% (3.4% in T1D and 6% T2D). DR severity included nine with mild non-proliferative, three moderate non-proliferative, and one with proliferative DR. Patients with hemoglobin A1c (HbA1c) > 8% had a higher risk of DR ($P = .049$). In this cohort, none of the patients with an HbA1c <8% had DR. In the multivariate analysis, a higher systolic blood pressure was marginally associated with risk for DR ($P = .07$).

Conclusions: We found lower prevalence of DR in youth with diabetes than previously reported. The incidence of DR was higher among patients with T2D and occurred with a shorter duration of disease, as compared with T1D. While the incidence of DR in youth with T1D is low, with the

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AUTHOR CONTRIBUTIONS

Roomasa Channa, Risa M. Wolf, and T. Y. Alvin Liu designed the research study. Mark Porter, Jessica Wagner, Laura Prichett, and Risa M. Wolf performed the research and extracted the data. Jessica Wagner and Laura Prichett analyzed the data. Mark Porter, Risa M. Wolf, and Roomasa Channa wrote the paper. Mark Porter, Roomasa Channa, Jessica Wagner, Laura Prichett, T. Y. Alvin Liu, and Risa M. Wolf have all read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

increasing incidence of T2D in adolescents and early risk for DR, early screening must be emphasized.

Keywords

diabetes complications; diabetic retinopathy; pediatric diabetes; retinopathy screening; risk factors

1 | INTRODUCTION

Type 1 diabetes (T1D) is one of the most common chronic childhood diseases,[1] with a 21% increase over the last decade, and current prevalence of 2/1000.[2] The incidence of type 2 diabetes (T2D) has also increased by 30% over the last decade, concurrent with the obesity epidemic.[1,3,4] Children with diabetes are at risk for developing complications of diabetes including macrovascular (stroke, myocardial infarction, and peripheral vascular disease) and microvascular (diabetic retinopathy [DR], neuropathy, nephropathy) complications.[5] The implementation of intensive insulin therapy following the Diabetes Control and Complications Trial (DCCT) in the mid-1990s aimed to decrease the development and progression of diabetes complications.[6]

DR is a serious complication of diabetes that can lead to blindness.[7,8] DR is present in almost all patients living with T1D for more than 20 years and is the cause of legal blindness in up to 8% of patients with diabetes.[9] The American Diabetes Association (ADA) guidelines recommend an initial dilated eye examination in patients with T1D at 3 to 5 years after diagnosis, and at diagnosis in patients with T2D, with follow-up exams every 1 to 2 years depending on glucose control.[10] However, screening rates are suboptimal, as demonstrated by a managed care network study finding that by 8 years after diagnosis, 30% of T1D patients and 50% of T2D patients had never had a diabetic eye examination.[11] Further, the eye examination rates were lower among families with lower household incomes as well as black and Hispanic patients.[11] The SEARCH for Diabetes in Youth Registry reported the prevalence of DR in children and adolescents with T1D and T2D as 5.6% and 9.1%, respectively,[2] while other studies reported the prevalence ranging from 3.8% to 20%.[12–17] Reported DR risk factors include elevated hemoglobin HbA1c, duration of diabetes, elevated cholesterol, and elevated blood pressure.[18–24] Puberty is also reported to be a risk factor for the development of DR due to a combination of poorer glycemic control in this age group and concurrent hormonal changes.[21,25] This study aimed to determine the prevalence and the risk factors of DR among adolescents and young adults with diabetes, who were seen at an urban, tertiary referral eye care center at a major academic institution.

2 | METHODS

2.1 | Data source and extraction

Retrospective chart review of 343 patients with diabetes <21 years of age undergoing DR exam, seen at a tertiary referral eye care center from January 2013 to September 2018. The Johns Hopkins Medicine Institutional Review Board approved this study in adherence to the Declaration of Helsinki. This project was supported by the Johns Hopkins School of Medicine Biostatistics, Epidemiology, and Data Management (BEAD) Core. Data were

collected from the electronic medical record (EMR), database (Epic), and through manual chart review. A trained Epic analyst extracted the EMR data including participant demographics, medications, and laboratory data.

2.2 | Inclusion and exclusion criteria

Children and adolescents with T1D and T2D under 21 years of age who were seen at the Wilmer Eye Institute for eye exams that obtained DR screening were included in this study. Diabetes diagnosis was determined from the problem list and encounter diagnosis and included ICD10 codes for T1D (E10), T2D (E11), or unspecified diabetes (E8, E13). Patients with diabetes due to underlying conditions or gestational diabetes were excluded. DR was identified by a modifier added to the diabetes code to indicate presence of retinopathy (E8.35, E10.32, E10.33, E10.34, E10.35, E11.32, E11.33, E11.34, E11.35, E13.31, E13.32, E13.33, E13.35), or unspecified retinopathy (H35). DR codes were selected to be as broad as possible to reduce the risk of missing DR cases. All codes indicating DR were verified by reviewing the medical chart, and documented eye exams were reviewed to ensure the diagnostic code was correct.

2.3 | Outcome measures

The duration of diabetes was calculated as years between the date of diabetes diagnosis and the date of Wilmer encounter. Age at diagnosis was calculated using the date of diabetes diagnosis and the date of birth. All body mass index (BMI) values for patients were extracted from the EMR. For patients without DR, the BMI measured on the date closest to the eye exam encounter date was used. For patients with DR, the BMI measured on the closest date prior to DR diagnosis date was used. BP measurements were similarly extracted. Participants were included only once, even if they had multiple eye examinations. To provide an estimate of the current glycemic control, all documented HbA1c values within 2 years of the most recent encounter date or first date of retinopathy diagnosis were extracted and averaged for a mean HbA1c value. Data related to insulin pump and continuous glucose monitor use could not be extracted due to limited documentation within Epic (the EMR).

2.4 | Retinopathy assessment

Retinal exams were graded based on the Early Treatment Diabetic Retinopathy study criteria as no DR, mild non-proliferative DR, moderate non-proliferative DR, severe non-proliferative DR, and proliferative DR.[26,27] The grading of non-proliferative DR accounts for the degree of microaneurysm and/or hemorrhage and/or retinal vessel morphology, such as venous beading. Proliferative DR was defined as the finding of abnormal new blood vessels originating from the retinal vasculature. Based on the clinical exam findings, each patient was assigned a retinopathy diagnosis based on the worse eye.

2.5 | Statistical analysis

Differences in groups were compared using a series of *t* tests for continuous variables and Fisher's exact test for categorical variables. Univariate and multivariate logistic regression analysis were used to explore predictors of developing DR for T1D, T2D, and all diabetes types combined. Potential predictors included demographic characteristics, time since

diabetes diagnosis, BMI, mean HbA1c, blood pressure measures, and insurance type. Predictive factors determined to have a statistically significant relationship with the outcome, DR at a level of $P < .05$ was included in the multivariate logistic regression model.

3 | RESULTS

3.1 | Clinical demographics

The study cohort included 343 patients (152 [44.3%] males and 191 females) with a mean age of 16.1 ± 4.0 years. Of the 343 patients included in the analysis, 293 (85.5%) had T1D (mean age of onset 11.5 ± 4.5 years) with a mean duration of diabetes of 4.1 years (range 0–20 years), and 50 (14.5%) had T2D (mean age of onset 17 ± 2.6 years), with mean duration of diabetes of 1.1 years (range 0–5 years). The cohort consisted of 185 non-Hispanic white (54.7%), 105 non-Hispanic black (31.1%), and 20 (5.9%) Hispanic youth. A minority of patients (31.2%) were residents of Baltimore city, whereas the majority (67%) came from outside the city limits. Patients with T1D had a higher mean HbA1c than patients with T2D, but this was only marginally significant (9.2% vs 8.1%, $P = .05$). Patients with T2D had higher BMI ($P < .001$), were older at diagnosis ($P < .001$), had a shorter duration of diabetes ($P < .001$), and had higher blood pressure ($P < .01$) compared with patients with T1D as presented in Table 1. Patients with T2D were also more likely to be black or Hispanic ($P < .001$). Among all patients, there was a significantly higher HbA1c among non-Hispanic black patients compared with non-Hispanic white patients (9.7% vs 8.5%, $P = .0002$). Similarly, non-Hispanic black patients had significantly higher HbA1c than Hispanic patients (9.7% vs 8.3%, $P = .03$).

3.2 | Prevalence of DR

In this cohort, 13 out of 343 patients had DR, for an overall incidence of 3.8%. Among patients with T1D, 3.4% had DR (10/293) with a mean duration of diabetes 10.4 ± 3.8 years (range 6–17 years), and in patients with T2D, 6% had DR (3/50) with a mean duration of diabetes of 2.7 ± 2.5 years (range 0–5 years). The grading of DR by severity is demonstrated in Table 2, where 9 out of 13 (69%) had a mild non-proliferative DR, 3 (23%) had moderate non-proliferative DR, and one (8%) had proliferative DR. The three patients with T1D and moderate non-proliferative DR had a mean duration of diabetes 10.4 ± 3.8 years (range 6–17 years). Patients with T1D who had DR (n = 10) were older than patients without DR (17.7 ± 2.3 vs 15.7 ± 4.1 years, $P = .024$), with a trend toward a higher HbA1c (9.8% ± 2.4% vs 9.1% ± 2.2%, $P = .405$) and higher mean arterial pressure (90 vs 84 mmHg, $P = .148$). Patients with T2D and DR (n = 3) were more likely to have a lower diastolic pressure (65.5 ± 2.1 vs 73.9 ± 11.3 mmHg, $P = .012$) and thus a wider pulse pressure (82 vs 48.8 mmHg) than T2D patients without DR. In patients with DR, there was a higher HbA1c in blacks compared with whites (11.5% vs 8.3%, $P = .007$), and while the prevalence of DR appears to be higher among blacks than among whites, this did not reach statistical significance (5.5% vs 3.7%, $P = .55$).

3.3 | Risk factors for DR

In the univariate analysis presented in Table 3, systolic blood pressure was significantly associated ($P = .026$) with the risk for DR. In patients with T1D, elevated diastolic blood

pressure was significantly associated with the risk for DR ($P = .045$). In patients with T2D, there was a trend toward BMI ($P = .07$) and systolic blood pressure ($P = .057$) being associated with DR. In the univariate analysis insurance type was not significantly associated with DR. Multivariate analysis did not detect significant associations.

Among all patients, the mean HbA1c was higher in the patients with DR (9.8% vs 9.1%, $P = .405$), although this was not significant. When we employed a cutoff of 8% for HbA1c and examined it as a binomial variable (271 vs 72 participants), we found that participants with an HbA1c >8% had a higher risk of DR ($P = .049$), while none of the patients in this cohort with an HbA1c <8% had DR.

4 | DISCUSSION

In this diverse cohort of youth with diabetes undergoing DR screening at a tertiary eye care center, the overall prevalence of DR was low at 3.8%, with rates of 3.4% in T1D, and 6% in T2D. This cohort included relatively high diversity with 31.1% non-Hispanic Black participants. Further, the severity of identified DR was mild (69%, n = 9) or moderate (23%, n = 3), with only one patient with proliferative DR requiring treatment. Patients with an HbA1c >8% had a higher risk for development of DR.

Previous studies estimating incidence of DR in youth with diabetes have ranged from 3.8% to 20%, depending on the population studied and study design.[12–17] As this cohort was seen at a tertiary ophthalmologic center, we expected that prevalence might be higher than reported due to referrals and second opinions. Indeed, 67% of participants came from zip codes outside of Baltimore city, where the ophthalmology clinic is located, demonstrating the wide catchment area.[28] Alternatively, patients obtaining DR screening may include those with better adherence. Patients included in this study had higher mean A1c values than reported among SEARCH trial participants suggesting DR screening at our tertiary center did not attract a lower risk population.[2] We found a low prevalence, and an overall mild severity of DR cases identified in the pediatric and adolescent population.

Since the implementation of intensive insulin management following the results of the DCCT trial, the prevalence of DR has declined, and more recent prevalence rates in youth with diabetes are lower than reported prior to 2000. While studies before the year 2000 demonstrated DR prevalence of 14% to 20% in T1D,[12,15] most studies since then have shown prevalence rates near 4% in T1D.[13,14,16] The SEARCH study found DR prevalence rates among patients less than 20 years of age to be 5.4% in T1D.[2] A prospective study (n = 236, 86% T1D; average duration 5.5 years) utilizing non-mydriatic fundus imaging for DR screening in a pediatric center in Alabama detected DR in 3.9% of participants.[16] Additionally, DCCT/EDIC study adolescent cohort follow-up (n = 195) showed a 75% reduction in prevalence and progression of DR among the intensive control group at a 4-year follow-up. The T1D exchange registry (n = 12 535) was not able to find treatable DR in their large study population.[6,29] We similarly found low prevalence rates of DR in youth with T1D, further contributing to the overall data that the prevalence of DR is low, and treatable DR is uncommon in the population of youth with T1D.

While there has been a decline in the prevalence of DR in T1D, there is concern for rising prevalence of T2D and associated complications. The SEARCH study found DR prevalence rates of 9.1% after 7.9 years in T2D,[2] and the TODAY study found a DR prevalence rate of 13.7% at 4.5 years after diagnosis in adolescents with T2D.[17] These patients remain followed-up in the TODAY2 study, and at a mean duration of diabetes of 12 years have been found to have a 49% incidence of DR with progression of disease severity.[30]

The current ADA screening guidelines for DR in T1D includes an initial dilated eye examination 3 to 5 years after diagnosis once the child is 11 years old or puberty has started, followed by less frequent examinations up to every 4 years if HbA1c is <8%.[10] However, with low incidence rates and mild severity of DR in youth with T1D, there is a need to reevaluate screening guidelines and incorporate risk factors into screening recommendations. Based on a review of DCCT data, Gubitosi-Klug et al suggested that among a subgroup of patients a single DR screening in childhood may be safe and less costly.[31] Similar to previous studies, we identified elevated HbA1c as a risk factor for DR, and we found no DR in patients with an HbA1c <8%. The DCCT trial provides the strongest evidence that HbA1c is a key predictor of retinopathy.[24,32] Further, the DCCT/EDIC trial utilized a Markov model incorporating HbA1c and current DR stage to suggest that tailored screening up to 4-year intervals would be safe and cost-effective.[33] Other authors have suggested DR screening at 2-year intervals in low risk groups, characterized by good glycemic control and history of normal DR screening.[34] Our findings that children with HbA1c < 8% had lower risk for DR further supports wider screening intervals. Additionally, in our cohort, the time to develop more than mild DR was a mean of 14 years. These data, in conjunction with other studies demonstrating rare treatment indications for DR prior to age 20, further support DR screening guideline reevaluation in T1D.[6,29] The individualized screening for diabetic retinopathy (ISDR) study is currently conducting a randomized controlled trial to determine the safety and acceptability of annual vs risk-based screening at intervals up to 2 years in children older than 12 years with diabetes and will likely provide further data to support screening guideline changes.[35] Given the ability to identify risk factors for DR in individualized patients, there is an opportunity to lessen DR screening guidelines in T1D in a safe and cost-effective manner.[25,33]

In T2D, the current ADA screening guidelines recommend dilated eye examination at diagnosis and annual until adequate glycemic control is achieved.[10] Patients in our population with T2D had a relatively short duration of diabetes when diagnosed with DR, which is consistent with other studies.[27] The TODAY and TODAY2 studies present the clearest evidence that T2D is a significant risk factor for vision threatening and treatable DR in the first 12 years of disease.[27] Studies have identified obesity, hypertension, poor glycemic control, and duration of diabetes as risk factors for DR in T2D.[2,17] With the high incidence of DR in T2D, the guidelines to screen for DR at diagnosis are well supported. However, screening rates remain low in this population,[11] and thus implementation of point-of-care screening in the endocrine office setting could improve screening rates while being cost-effective.

Our T1D cohort is unique in that it included a large minority population with 26.7% black participants—a higher rate than other reported cohorts with less than 10%.[1,36] We noted

significantly higher HbA1c values in black and Hispanic patients when compared with white patients, which has also been noted in previous studies.[36,37] Racial disparities in glycemic control and diabetes management have been previously reported.[36,37] In our cohort, there was a trend toward more DR in non-Hispanic black participants compared with other races, and non-Hispanic blacks with DR also had significantly higher HbA1c relative to non-Hispanic whites individuals with DR.

While this study confirms low incidence of DR, in a diverse study population, there are several limitations to this study. First, this was a retrospective investigation and thus limited by data availability and EMR implementation since 2013. In some cases, HbA1c, blood pressure, and BMI data were collected separately from the ophthalmology visit resulting in a time gap between DR screening and patient characteristics. Further, only a single, but large, ophthalmologic referral center was included. Since the total cases of DR was low, especially among patients with T2D, further analysis of risk factors was not possible in this cohort.

5 | CONCLUSION

Screening and management of DR in youth with T1D and T2D are on the divergent courses. DR in T1D has decreased in prevalence since the implementation of intensive insulin therapy, thus the screening guidelines have recently been liberalized especially among low risk patients with HbA1c under 8%, which is supported by this cohort. With the increasing prevalence of T2D in youth,[2] and a high prevalence of early diabetes complications, DR in T2D is a growing problem that needs to be screened for promptly and regularly.

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TABLE 1

Characteristics of study participants by diabetes type (excluding other diabetes type)

	Total (n = 343)	type 1 DM (n = 293)	type 2 DM (n = 50)	*P* value
Age at eye exam (SD, yr)	16.1 (±3.99)	15.8 (±4.09)	18.1 (±2.62)	<.001
Age at diabetes diagnosis	12.5 (±4.71)	11.5 (±4.45)	17.0 (±2.98)	<.001
Duration of diabetes diagnosis	3.7 (±3.28)	4.1 (±3.32)	1.1 (±1.26)	<.001
Male sex, n (%)	152 (44.3%)	135 (46.1%)	17 (34.0%)	.112
Race/ethnicity				<.001
Non-Hispanic white	185 (54.7%)	173 (60.1%)	12 (24.0%)	
Non-Hispanic black	105 (31.1%)	77 (26.7%)	28 (56.0%)	
Hispanic	20 (5.9%)	14 (4.9%)	6 (12.0%)	
Other	28 (8.2%)	24 (8.3%)	4 (8.0%)	
Missing = 5				
HgbA1c (n = 212)				
Mean (SD, %)	8.9 (±2.32)	9.2 (±2.20)	8.1 (±2.77)	.050
Median (IQR)	8.6 (2.57)	8.7 (2.44)	7.5 (3.79)	
HbA1c > 8%	145 (66.2%)	130 (71.8%)	17 (53.1%)	<.001
HbA1c ≤ 8%	74 (33.8%)	51 (28.2%)	15 (46.9%)	
BMI (n = 247)				
Mean (SD, kg/m^2)	27.0 (±14.97)	25.4 (±15.31)	35.6 (±9.30)	<.001
BP (nominal value), mean (SD) (n = 256)				
Systolic BP (mmHg)	116.7 (±13.32)	115.4 (±12.40)	124.0 (±15.63)	.002
Diastolic BP	69.3 (±9.50)	68.5 (±8.96)	73.5 (±11.12)	.009
Mean arterial pressure	85.1 (±9.56)	84.1 (±9.02)	90.3 (±10.64)	<.001
Insurance				
Commercial	194 (59.9%)	166 (61.9%)	21 (45.7%)	.182
Medicaid	117 (35.1%)	90 (33.6%)	24 (52.2%)	
Other	13 (4.01%)	12 (4.5%)	1 (2.2%)	
Diabetic retinopathy				.415
Prevalence	13 (3.8%)	10 (3.4%)	3 (6.0%)	

Abbreviation: DM, diabetes mellitus.

TABLE 2

Prevalence of diabetic retinopathy

DR severity	T1D (n = 293)	T2D (n = 50)
None	283	47
Mild DR	6	3
Moderate DR	3	0
Severe non-proliferative DR	0	0
Proliferative DR	1	0

Abbreviations: DR, diabetic retinopathy; T1D, type 1 diabetes; T2D, type 2 diabetes.

TABLE 3

Univariate risk factors for diabetic retinopathy

Univariate analysis									
	Type 1 diabetes			**Type 2 diabetes**			**All diabetes**		
Variable	**Odds ratio**	**SE**	***P*** **> |z|**	**Odds ratio**	**SE**	***P*** **> |z|**	**Odds ratio**	**SE**	***P*** **> |z|**
Age	1.160	0.118	.144	0.783	0.165	.247	1.100	0.092	.252
Male gender	0.490	0.343	.309	1.000			0.367	0.245	.133
Race									
White (non-Hispanic)	Reference category			Reference category			Reference category		
Black (non-Hispanic)	1.525	1.007	.523	0.846	1.080	.896	1.513	0.862	.468
Hispanic	1.000			1.000			1.000		
Other	1.000			1.000			1.000		
Duration of diabetes	1.068	0.113	.531	1.610	0.707	.278	1.070	0.102	.479
Mean A1c	1.140	0.157	.340	1.299	0.447	.447	1.176	0.144	.183
BMI	1.001	0.020	.945	1.241	0.150	.073	1.009	0.013	.497
BP systolic	1.037	0.029	.193	1.092	0.051	.057	1.049	0.023	**.026**
BP diastolic	1.072	0.037	**.045**	0.922	0.073	0.307	1.038	0.031	.215
MAP	1.073	0.040	.055	1.024	0.070	.728	1.058	0.032	.064
Insurance type									
Private	Reference category			Reference category			Reference category		
Medicare/Medicaid	1.11	0.82	.888	1.000			0.70	0.49	.615
None	2.93	3.33	.346	1.000			4.86	4.18	.066

Note: Bold values represent statistically significant p-values below 0.05.

Abbreviation: BMI, body mass index.