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Incidence and Risk Factors for Developing Diabetic Retinopathy among Youths with Type 1 or Type 2 Diabetes throughout the United States

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Purpose: Despite the increasing prevalence of type 2 diabetes mellitus (T2DM) among children and adolescents, little is known about their risk of developing diabetic retinopathy (DR). We sought to identify risk factors for DR in youths with diabetes mellitus, to compare DR rates for youths with type 1 diabetes mellitus (T1DM) and those with T2DM, and to assess whether adherence to DR screening guidelines promoted by the American Academy of Ophthalmology, American Academy of Pediatrics, and American Diabetes Association adequately capture youths with DR.

Design: Retrospective observational longitudinal cohort study.

Participants: Youths aged ≤21 years with newly diagnosed T1DM or T2DM who were enrolled in a large US managed-care network.

Methods: In this study of youths aged ≤21 years with newly diagnosed T1DM or T2DM who were under ophthalmic surveillance, we identified the incidence and timing of DR onset. Kaplan–Meier survival curves assessed the timing of initial diagnosis of DR for participants. Multivariable Cox proportional hazard regression modeling identified factors associated with the hazard of developing DR. Model predictors were age and calendar year at initial diabetes mellitus diagnosis, sex, race/ethnicity, net worth, and glycated hemoglobin A_{1c} fraction (HbA_{1c}).

Main Outcome Measures: Hazard ratios (HRs) with 95% confidence intervals (CIs) for developing DR.

Results: Among the 2240 youths with T1DM and 1768 youths with T2DM, 20.1% and 7.2% developed DR over a median follow-up time of 3.2 and 3.1 years, respectively. Survival curves demonstrated that youths with T1DM developed DR faster than youths with T2DM ($P < 0.0001$). For every 1-point increase in HbA_{1c}, the hazard for DR increased by 20% (HR = 1.20; 95% CI 1.06–1.35) and 30% (HR = 1.30; 95% CI 1.08–1.56) among youths with T1DM and T2DM, respectively. Current guidelines suggest that ophthalmic screening begin 3 to 5 years after initial diabetes mellitus diagnosis, at which point in our study, >18% of youths with T1DM had already received ≥1 DR diagnosis.

Conclusions: Youths with T1DM or T2DM exhibit a considerable risk for DR and should undergo regular screenings by eye-care professionals to ensure timely DR diagnosis and limit progression to vision-threatening disease. *Ophthalmology 2016;■:1–7 © 2016 by the American Academy of Ophthalmology*

The incidence of type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) is rising among children and adolescents worldwide.[1–3] Whereas in past decades the great majority of youths with diabetes mellitus (DM) had T1DM, T2DM now accounts for nearly one half of all new DM diagnoses among adolescents, concurrent with the rise of childhood obesity.[4,5]

Diabetic retinopathy (DR) is a serious complication that is often asymptomatic in early stages but may progress to sight-threatening disease.[6–9] Risk factors for DR in youths with T1DM include disease duration and the timing of puberty.[10,11] Accordingly, various clinical practice guidelines for the ophthalmic screening of youths with T1DM have been developed, although medical professional societies differ in their recommended timing of monitoring. The American Academy of Ophthalmology (AAO) recommends an initial screening 5 years after T1DM onset.[12] The American Diabetes Association (ADA) recommends an initial screening 3 to 5 years after T1DM onset for patients ≥10 years of age[13]; the American Academy of Pediatrics (AAP) recommends the same for patients 9 years of age or older.[10] A recent study suggested that a delay in initial ophthalmic screening until 15 years of age is acceptable.[14] Optimizing DM control, as measured by glycated hemoglobin A_{1c} fraction (HbA_{1c}), is recommended in all these guidelines.[10]

The ADA and AAO recommendations for youths with T2DM—which is to screen at initial DM diagnosis—are based on limited data,[15,16] as T2DM has only recently become more common among youths. Thus, it is essential to

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characterize the development of DR and the need for interventions among youths with T2DM to guide the creation of evidence-based practice guidelines aimed at detecting and treating DR before vision is threatened.

We evaluated the DR incidence among youths with T1DM and T2DM enrolled in a large managed-care network in the United States. We sought to (a) identify risk factors for DR development in youths with T1DM and T2DM; (b) investigate whether DM control, as measured by HbA_{1c}, is associated with DR development; and (c) estimate the proportion of youths with each DM type requiring laser or surgical intervention for DR. Finally, we applied the existing T1DM ophthalmic screening guidelines of the AAO, AAP, and ADA to the youths with T1DM in this data set to assess whether delays in initial DR diagnosis would result.

Methods

Data Source

The Clinformatics Data Mart database (OptumInsight, Eden Prairie, MN), a data set that has been used previously to study ocular diseases,[17–19] contains detailed records of beneficiaries in a large, nationwide managed-care network in the United States. We accessed data on all beneficiaries 21 years of age or younger at their initial enrollment during January 1, 2001, through December 31, 2014. Medical claims from inpatient and outpatient health care encounters and associated International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes[20] for all ocular and nonocular conditions were available, as was information on age, sex, race/ethnicity, and household net worth. Results of HbA_{1c} tests were available for a subset of enrollees who had this test done at an outpatient laboratory. Enrollees in the Clinformatics Data Mart have a sociodemographic profile very similar to that of those with other types of private health insurance throughout the United States (Sulzicki M, OptumInsight, personal communication, July 2015). Data were stripped of all protected health information prior to release from OptumInsight. The University of Michigan Institutional Review Board approved this study, which involved de-identified data.

Study Participants

Eligible participants were aged ≤21 years at plan enrollment, continuously enrolled in the medical plan for ≥3 years, and had ≥2 DM diagnoses (ICD-9-CM codes 250.xx or 362.01–362.07) on separate dates. Individuals who never filled a prescription for insulin or an oral hypoglycemic agent were excluded. To help exclude nonincident DM cases, the first DM diagnosis must have occurred at least 12 months after plan enrollment. Only youths with ≥1 ophthalmologist- or optometrist-performed examinations after the initial DM diagnosis were included. Individuals lacking information on race/ethnicity or household net worth were also excluded.

Diabetes Type: Classification

Enrollees were classified with T1DM or T2DM based on a previously validated algorithm.[21] Children younger than 10 years of age at their first DM diagnosis were considered to have T1DM. Among youths 10 years or older, those who were prescribed only insulin in the 730 days after the initial diagnosis were also considered to have T1DM. The remaining individuals were classified as having T2DM. In this group, patients must have filled an oral hypoglycemic (e.g., metformin, sulfonylureas) prescription, with or without a concurrent insulin prescription, within 730 days of their initial diagnosis. This algorithm had a sensitivity and specificity of 98.6% and 78.2%, respectively, for detecting T1DM, and 83.2% and 97.5% for T2DM, among youths in a Canadian study.[21]

Outcome

The primary outcome was DR development, diagnosed by an optometrist or ophthalmologist and coded appropriately (ICD-9-CM 250.50–250.53 or 362.01–362.07). The billing codes capture patients with nonproliferative DR (362.03–362.06), proliferative DR (362.02), or diabetic macular edema (362.07). Patients with only 250.50 to 250.53 or 362.01 were considered to have nonspecific DR. Current Procedural Terminology (CPT; American Medical Association, Chicago, IL) billing codes were used to determine whether patients underwent DR interventions, including panretinal photocoagulation (CPT 67228), focal laser treatment (CPT 67210), or intravitreal injection (CPT 67028).

Analysis

Data analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC); Kaplan–Meier curves were created using GraphPad Prism 6.0 (GraphPad Software, San Diego, CA). Characteristics of the study population were summarized using medians and interquartile ranges (IQRs) for continuous variables and frequencies and percentages for categorical variables.

Retinopathy Incidence, Risk Factors

Incidence of DR was calculated as the number of youths with newly diagnosed DR per thousand person-years of follow-up. Kaplan–Meier survival curves assessed the timing from first DM diagnosis to initial DR diagnosis in youths with T1DM or T2DM; groups were compared using the log-rank test. Multivariable Cox proportional hazard regression modeling evaluated the extent to which sociodemographic factors affected the hazard for DR for youths with each DM type. Model predictors were age, sex, race/ethnicity, household net worth, and calendar year at initial DM diagnosis (e.g., 2008, 2009).

Hemoglobin A_{1c}

For patients who had ≥1 HbA_{1c} test performed at an outpatient laboratory, the first value ≥6 months after initial DM diagnosis was analyzed. This allowed for initiation of treatment and initial stabilization of DM. The test must have also been performed before the initial DR diagnosis. The distribution of HbA_{1c} values was evaluated by medians and IQRs. The Wilcoxon rank sum test compared the distributions between groups (T1DM vs. T2DM, with DR vs. without DR). Additional Cox proportional hazard models were constructed to evaluate HbA_{1c} as a predictor for DR development among youths with T1DM or T2DM. Model covariates included age at first DM diagnosis, sex, race/ethnicity, household worth, and calendar year of initial DM diagnosis. Cox models were left-truncated because to be eligible for the outcome, a patient's HbA_{1c} laboratory values must have preceded her initial DR diagnosis.

Diagnostic Timing under Current Screening Guidelines

Using Kaplan–Meier survival analysis estimates, we calculated the percentage of youths with DM who developed DR and would have