**SCREENING FOR RETINOPATHY IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES MELLITUS**

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**ABSTRACT**

Diabetic retinopathy is a common cause of blindness in the United States. Fortunately, vision-preserving therapies are available when the disease process is detected early. While retinopathy screening is recommended by several expert panels, adherence to these guidelines is universally poor. In addition, the current guidelines for children may be too strict, resulting in a poor diagnostic yield and an unnecessarily high therapeutic and financial burden.

Mydriatic fundal photography was implemented into routine clinical visits at The Children’s Hospital of Pittsburgh (CHP) so that the prevalence of childhood retinopathy could be measured while studying the impact of streamlined screening services on adherence.

The prevalence of diabetic retinopathy in the study population was 2.4%. Subjects with retinopathy were older (17.1 vs. 15.3 years, p=0.05), with a longer duration of diabetes (10.2 vs. 7.1 years, p=0.007), and worse glycemic control (HbA1c 11.2% vs. 8.4%, p=0.008). Children who underwent screening through streamlined services at CHP were more likely to be African American (16% vs. 2%, p<0.0001), to have poor glycemic control (HbA1c 8.9% vs. 8.2%, p=0.0002), and to have evidence of retinopathy (4.7% vs. 0.4%, p=0.006).

These findings have significant public health implications. First, the current standard of care for diabetic retinopathy screening in childhood has very low yield, justifying a reconsideration of consensus guidelines. Second, repackaging screening services to reduce barriers may improve adherence, particularly for those members of the population at greatest risk for retinopathy. Third, healthcare delivery systems should consider implementing streamlined retinopathy screening services, as it may improve the early detection of disease on a population level.

**TABLE OF CONTENTS**

1. **INTRODUCTION…………………………………………………………………………................................................1**
2. **RESEARCH DESIGN AND METHODS…………………………………………………...........................................2**
3. **RESULTS…………………………………………………………………………………………...........................................3**
4. **CONCLUSIONS…………………………………………………………………………………...........................................6**

**BIBLIOGRAPHY…………………………………………………………………………………………...........................................9**

**LIST OF TABLES**

Table 1. Characteristics of all subjects who underwent screening………………………………………......................5

Table 2. Subject characteristics by retinopathy status……………………………………………………...........................5

Table 3. Subject characteristics by location of screening………………………………………………….........................6

1. **INTRODUCTION**

Diabetic retinopathy, which affects over 4 million Americans,1 is the most common cause of new-onset blindness in young people.2 Fortunately, when diabetic retinopathy is discovered early, vision preserving therapies are available.3 For this reason, the International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends that children with type 1 Diabetes Mellitus (T1DM) undergo annual screening beginning at age 10 years with as little as 2 years of diabetes duration.4 Similar recommendations have been made by the American Diabetes Association (ADA).5

Despite the value of retinopathy screening, adherence rates are poor. Recent estimates indicate that about 53% of diabetic adults and 66% of diabetic youth are adherent to consensus screening guidelines.6,7 A multitude of barriers are involved, including those related to healthcare access, transportation, school and workplace obligations, health literacy, and other socioeconomic resources. Meanwhile, the expectation to complete early and frequent retinopathy screening adds to the considerable financial and therapeutic burdens that exist for patients, families, and providers who deal with diabetes. In this context, the criteria for retinopathy screening and the modality by which it is offered ought to be the subject of continued scrutiny.

The current retinopathy screening recommendations for diabetic youth may be too strict. The data that inform these recommendations are, in part, derived from cohorts that predated The Diabetes Control and Complications Trial (DCCT), which demonstrated that intensive therapy reduces the risk of microvascular complications.8 In the wake of the DCCT, intensive therapy became the standard of care, likely precipitating a population-wide decline in the prevalence of diabetic retinopathy. Moreover, the standard of diabetes care has continued to evolve in the decades following the DCCT, with increased sophistication and utilization of several technologies, including insulin pumps and continuous glucose monitors. Perhaps most importantly, evidence of a declining prevalence of diabetic retinopathy in youth is starting to emerge in the literature.9-11 A recent chart review from a single diabetes clinic found that only 2 out of 130 youth subjects who met ADA screening guidelines had any evidence of retinopathy.9 A similar review of all diabetic youth who underwent a dilated eye exam by an ophthalmologist at a major center between 2009 and 2013 found that none of the 693 qualifying examinations were positive for diabetic retinopathy.10 Finally, a temporal decline in the prevalence of childhood retinopathy was illustrated by data from a large Australian pediatric diabetes center, which demonstrated a drop from 53% in the early 1990’s to 12% in the late 2000’s.11

If the prevalence of childhood diabetic retinopathy has truly fallen to the extent reported above, a relaxation of screening practices could reduce the burden of care without compromising the detection of disease. This balance would be improved even further if the delivery of screening services could be repackaged to facilitate adherence and maximize sensitivity.

In order to determine the prevalence of childhood diabetic retinopathy in a modern population, to identify the clinical characteristics associated with retinopathy, and to investigate the impact of streamlined screening delivery, digital fundal photography was incorporated into routine diabetes visits at a large pediatric diabetes center.

**2.0 RESEARCH DESIGN AND METHODS**

Beginning on February 1, 2015, mydriatic digital fundal photography was introduced as a clinical service at The Children’s Hospital of Pittsburgh (CHP) diabetes center, thereby allowing patients to undergo retinopathy screening during routine follow-up visits. Patients who accepted the offer of screening were directed to a nearby ophthalmology suite at the conclusion of their diabetes appointment, where a clinical photographer obtained mydriatric retinal images. These images were then uploaded into the medical record for formal interpretation by an ophthalmologist. Insurance companies were billed for this service, but no out-of-pocket payments were solicited from participating subjects.

The medical records of all subjects with T1DM aged at least 10 years with a diabetes duration of at least two years who presented to the diabetes center at CHP between February 1, 2015 and January 31, 2016 were then reviewed. This time frame was chosen to coincide with implementation of fundal photography into clinical diabetes visits. The study was approved by the Institutional Review Board of the University of Pittsburgh.

For those subjects who opted to undergo retinopathy screening at the CHP diabetes center, retinopathy status was assigned according to the formal interpretation made by the attending ophthalmologist in the medical record. For subjects who opted out of retinopathy screening at the CHP diabetes center, retinopathy status was assigned according to medical records obtained from outside ophthalmology practices.

Additional data extracted from the medical record included gender, race, age at the time of screening, age at the time of diabetes diagnosis, diabetes duration, BMI, blood pressure, insulin delivery method, total daily insulin dose, HbA1c, and lipid status. Measurements nearest to the date of retinopathy screening, ranging from 15 months before screening to 1 month after screening, were used for the assessment.

Descriptive statistics (mean, median, standard deviation, minimum, and maximum) were calculated for all continuous variables. Subject characteristics by retinopathy status and by screening location were compared. The chi square test and Fisher exact test were used for comparisons of categorical variables. The T-test and one way Anova were used for comparisons of continuous variables. A predetermined statistical significance was defined as p<= .05.

1. **RESULTS**

Retinopathy assessments were obtained for 418 individuals who met the above inclusion criteria during the study period. A total of 981 unique individuals who met these inclusion criteria presented to the CHP diabetes center over the study period, meaning that retinopathy assessments could not be obtained for 563 individuals (57.4%). In many of these cases, the individual had not undergone retinopathy screening during the yearlong study period. Of the 418 individuals for whom retinopathy assessments were obtained, 190 (45.5%) opted for screening at CHP, while 228 (54.5%) opted to undergo screening at outside ophthalmology practices.

The background characteristics of all subjects are presented in table 1. There was a roughly equal gender distribution; 56% of subjects were male and 44% of subjects were female. The majority of subjects were Caucasian (82%), while a lower percentage of subjects (16%) were African American. The average age at the time of retinopathy screening was 15.3 years, with a minimum of 10.0 years and a maximum of 23.9 years. The average duration of diabetes at the time of screening was 7.2 years, with a minimum of 2.0 years and a maximum of 18.2 years. The average HbA1c was 8.5%. More subjects received insulin by way of multiple daily injections (57%) than by way of continuous subcutaneous insulin injection (43%).

The subject characteristics by retinopathy status are presented in table 2. Evidence of diabetic retinopathy was found in 10 subjects, which represents 2.4% of those who underwent screening. In all 10 cases, the severity classification was mild, nonproliferative diabetic retinopathy. Subjects with evidence of retinopathy had a longer duration of diabetes than subjects without retinopathy (10.2 years vs. 7.1 years, p=0.007). In addition, subjects with evidence of retinopathy demonstrated worse glycemic control than subjects without retinopathy (HbA1c 11.2% vs. 8.4%, p=0.008). Finally, subjects with evidence of retinopathy appear to have been older at the time of screening (17.1 years vs. 15.3 years, p=0.05).

Among the 10 subjects with evidence of retinopathy, the shortest duration of diabetes was 6.5 years and the longest duration of diabetes was 15.9 years. Also among those found to have retinopathy, the youngest age at the time of screening was 13.4 years and the oldest age at the time of screening was 21.1 years. Finally, among those with retinopathy, the lowest HbA1c was 7.5%, while the highest HbA1c exceeded our instrument’s threshold for measurement of 14.0%.

Subject characteristics by screening location are reported in table 3. Of the 10 subjects who had evidence of retinopathy, 9 were screened at the CHP diabetes center, while just 1 was screened at an outside ophthalmology clinic. The prevalence of retinopathy across subjects was 2.4%. Among subjects screened at the CHP diabetes center, the prevalence of retinopathy was 4.7% (9/190), compared to just 0.4% (1/228) among those who underwent screening at outside ophthalmology clinics (p=0.006). Subjects who underwent screening at the CHP diabetes center were more likely to be African American (16% vs. 2%, p<0.0001), had worse glycemic control (HbA1c 8.9% vs. 8.2%, p=0.0002), appeared to have a higher LDL (98 mg/dL vs. 91 mg/dL, p=0.05), and were less likely to be using insulin pumps (33% vs. 51%, p=0.0001).

Table 1. Characteristics of all subjects who underwent screening

|  |  |
| --- | --- |
| Variables | N=418 |
| Gender (male/female) (%) | 56/44 |
| Race (Caucasian/African American/Other) (%) | 82/16/2 |
| Age at screening (years) | 15.3 +/- 2.9 |
| Age at DM diagnosis (years) | 8.1 +/- 3.8 |
| DM duration (years) | 7.2 +/- 3.7 |
| Insulin delivery method (MDI/CSII) (%) | 57/43 |
| Insulin dose (units/kg/day) | 0.95 +/- 0.3 |
| BMI (kg/m2) | 23.0 +/- 4.6 |
| BMI percentile | 69.8 +/- 24.3 |
| SBP percentile | 57.9 +/- 23.0 |
| DBP percentile | 69.7 +/- 16.8 |
| HbA1c (%) | 8.5 +/- 1.7 |
| Triglycerides (mg/dL) | 108 [59-133] |
| Total cholesterol (mg/dL) | 167 +/- 34 |
| HDL – cholesterol (mg/dL) | 58 +/- 15 |
| LDL – cholesterol (mg/dL) | 95 +/- 28 |

Table 2. Subject characteristics by retinopathy status

|  |  |  |  |
| --- | --- | --- | --- |
|  | Retinopathy Present  (n=10) | Retinopathy Absent  (n=408) | p |
| Location of screening  (CHP/outside) (%) | 90/10 | 44/55 | 0.006 |
| Gender (male/female) (%) | 60/40 | 56/44 | 1.00 |
| Race (C/AA/O) (%) | 80/20/0 | 90/8/2 | 0.32 |
| Age at screening (years) | 17.1 +/- 2.6 | 15.3 +/- 3.0 | 0.05 |
| Age at diagnosis (years) | 6.9 +/- 2.8 | 8.9 +/- 3.9 | 0.26 |
| DM duration (years) | 10.2 +/- 3.1 | 7.1 +/- 3.7 | 0.007 |
| Insulin delivery method (MDI/CSII) (%) | 66/33 | 57/43 | 0.74 |
| Insulin dose (units/kg/day) | 1.1 +/- 0.6 | 0.95 +/- 0.3 | 0.92 |
| BMI (kg/m2) | 23.6 +/- 4.6 | 23.0 +/- 4.6 | 0.78 |
| BMI percentile | 55.3 +/- 27.0 | 70.1 +/- 24.2 | 0.12 |
| SBP percentile | 56.7 +/- 33.1 | 58.0 +/- 22.9 | 0.97 |
| DBP percentile | 74.5 +/- 18.1 | 69.6 +/- 16.8 | 0.43 |
| HbA1c (%) | 11.2 +/- 2.9 | 8.4 +/- 1.6 | 0.008 |
| Triglycerides (mg/dL) | 128 [108-133] | 85 [58-133] | 0.022 |
| Total cholesterol (mg/dL) | 195 +/- 52 | 166 +/- 34 | 0.08 |
| HDL – cholesterol (mg/dL) | 62 +/- 16 | 58 +/- 15 | 0.30 |
| LDL – cholesterol (mg/dL) | 113 +/- 33 | 94 +/- 28 | 0.11 |

Table 3. Subject characteristics by location of screening

|  |  |  |  |
| --- | --- | --- | --- |
|  | Screening at CHP  (n=190) | Screening Outside  (n=228) | p |
| Retinopathy present (%) | 4.7 | 0.4 | 0.006 |
| Gender (male/female) (%) | 58/42 | 54/46 | 0.40 |
| Race (C/AA/O) (%) | 82/16/2 | 97/2/1 | <0.0001 |
| Age at screening (years) | 15.1 +/- 2.9 | 15.5 +/- 3.0 | 0.32 |
| Age at diagnosis (years) | 8.4 +/- 3.8 | 7.9 +/- 3.8 | 0.08 |
| DM duration (years) | 6.7 +/- 3.6 | 7.6 +/- 3.8 | 0.015 |
| Insulin delivery method (MDI/CSII) (%) | 67/33 | 49/51 | 0.0001 |
| Insulin dose (units/kg/day) | 0.97 +/- 0.3 | 0.93 +/- 0.2 | 0.14 |
| BMI (kg/m2) | 22.6 +/- 4.4 | 23.4 +/- 4.8 | 0.06 |
| BMI percentile | 68.0 +/- 24.5 | 71.4 +/- 24.0 | 0.16 |
| SBP percentile | 57.8 +/- 22.6 | 58.1 +/- 23.5 | 0.82 |
| DBP percentile | 70.3 +/- 16.3 | 69.2 +/- 17.2 | 0.63 |
| HbA1c (%) | 8.9 +/- 2.0 | 8.2 +/- 1.3 | 0.0002 |
| Triglycerides (mg/dL) | 88 [63-141] | 86 [58-127] | 0.46 |
| Total cholesterol (mg/dL) | 171 +/- 38 | 163 +/- 31 | 0.08 |
| HDL – cholesterol (mg/dL) | 59 +/- 15 | 57 +/- 14 | 0.14 |
| LDL – cholesterol (mg/dL) | 98 +/- 29 | 91 +/- 27 | 0.05 |

1. **CONCLUSIONS**

There was a striking difference between the subjects who opted to be screened during routine visits through our initiative and the subjects who opted to be screened at outside ophthalmology offices. Most notably, the prevalence of diabetic retinopathy was significantly higher among subjects screened through our in-house initiative (4.7%) than it was among subjects who opted to be screened through outside ophthalmology practices (0.4%). In addition, subjects screened through our in-house clinical initiative were more likely to be African American, to have poor glycemic control, to have dyslipidemia, and to be using insulin without a pump.

These observations may reflect the relative ease of undergoing screening during routine diabetes appointments, which bypasses several barriers to adherence, including those related to healthcare access, transportation, competing obligations, and personal finances. In addition, the superior sensitivity of mydriatic fundal photography may have contributed to the higher prevalence of retinopathy among subjects screened in our clinic.12

The overall prevalence of diabetic retinopathy in our patient population was 2.4%, which is quite low when compared to estimates that preceded the widespread adoption of intensive therapy inspired by the DCCT.13-14 On the other hand, the prevalence in our population is high when compared to two similar centers in the United States, where just 2 positive cases were found among 823 exams. 9-10 Interestingly, when analyzing only those members of our patient population who sought screening at outside ophthalmology practices, the exceedingly low retinopathy prevalence of 0.4% is on par with the recent reports from similar diabetes centers. The very low yield of screening at outside ophthalmology practices supports our argument that the consensus screening guidelines, as currently applied, are overly aggressive. In addition, the more robust yield of screening through our in-house initiative suggests that streamlining care while optimizing sensitivity improves adherence among those with the most risk of microvascular disease and leads to superior detection of disease.

Not surprisingly, the clinical features that were associated with retinopathy in our population were older age at the time of screening, longer duration of diabetes, and inferior glycemic control. These findings are consistent with prior studies and with the known pathophysiology of microvascular disease in diabetes.

Our study was affected by important limitations. While we were able to obtain screening reports for over 400 eligible subjects, there were several members of our patient population for whom no report could be obtained. These records could not be found despite painstaking efforts made by our research team, which included approaching patients in clinic, telephoning families at home, and reaching out to ophthalmology providers. Given the considerable effort made to obtain screening results for each qualifying member of our patient population, we suspect that the majority of missing reports were due to nonadherence to screening recommendations during the study period. Second, our study design did not include an assessment of retinopathy screening adherence rates prior to the implementation of in-house fundal photography. For this reason, our contention that in-house screening improves adherence for high-risk patients cannot be definitively demonstrated by our data. Third, the examination technique utilized by our in-house screening initiative did not match the technique employed by the majority of outside ophthalmology practices, complicating the comparison between the two groups. While this discrepancy indeed represents a source of bias, we argue that the integrity of our actual study aim is preserved, as this design allowed us to compare the “real-world” detection capabilities of private ophthalmology clinics, which represent the current standard of care, with our proposed modification to screening delivery.

Our findings carry several important clinical implications. First, our data lend strength to the growing evidence base of a low prevalence of retinopathy in pediatric populations. In our study, the youngest patient with evidence of retinopathy was 13 years old and the shortest diabetes duration to retinopathy was 6.5 years. Importantly, all ten subjects with retinopathy were described as having mild, non-proliferative disease, which does not meet criteria for an ophthalmologic intervention. For this reason, practitioners ought to consider delaying the initiation of retinopathy screening when glycemic control has been fair, particularly for those patients who will be traveling to ophthalmology clinics for their assessments. Second, our data suggest that pediatric diabetes practices ought to consider integrating fundal photography into routine follow-up services, as doing so may improve diagnostic yield while facilitating adherence, particularly for the segment of the population at greatest risk for retinopathy.

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