Short-Term Change in Measures of Glycemia in Obese Youth Meeting Criteria for Prediabetes: A Retrospective Chart Review

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Abstract

Background: The prevalence of youth diagnosed with prediabetes is increasing, yet there is a lack of guidelines on how to manage this condition clinically. **Objectives:** The aim was to determine the short-term outcomes of patients referred with prediabetes and to determine predictors of worsening dysglycemia in youth. **Study Design:** This is a retrospective chart review of patients referred to our Youth Diabetes Prevention Clinic (YDPC) with laboratory tests indicating an increased risk for type 2 diabetes (T2D). We defined glycemic categories by HbA1c with normoglycemia as HbA1c <5.7%, prediabetes I (P1) as HbA1c 5.7 to <6.0%, and prediabetes II (P2) as HbA1c 6.0 to <6.5%. We compared HbA1c at the time of referral (screening HbA1c) and at the YDPC visit (YDPC HbA1c) to assess for improvement or worsening. Multinomial logistic regression was used to assess predictors of prediabetes. **Results:** Among 562 patients seen, 336 had both screening and YDPC HbA1c values. Race ($p < 0.001$) and screening glycemic category ($p < 0.001$) were significantly associated with dysglycemia at the YDPC visit, while sex ($p =$

0.50), BMI z-score change ($p = 0.27$), and days from referral ($p = 0.83$) were not. As compared to those who reverted to normoglycemia, patients with prediabetes at YDPC were 7 times more likely to have a higher screening HbA1c (both P1 and P2). The majority of patients referred with prediabetes had lower HbA1c at the YDPC (75.4–82.6%). **Conclusion:** Patients with screening HbA1c <6% might benefit from a 4-month follow-up at primary care while recommending lifestyle changes. Patients of minority race and screening HbA1c $\geq 6\%$ are more likely to have a persistent elevation of HbA1c.

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Introduction

Type 2 diabetes (T2D) is increasing in youth, yet most obese youth do not develop T2D during childhood [1]. The most recent estimate of the incidence of T2D in US youth is ~5,300 cases per year [1]. Prediabetes, a prelude to T2D, is defined as the presence of impaired glucose tolerance and/or impaired fasting glucose and/or elevated hemoglobin A1c (HbA1c 5.7 to <6.5%) [2]. The prevalence of prediabetes varies according to the method by which it is measured and is estimated to occur in ~10 to

30% of youth with obesity [3–6]. HbA1c is commonly utilized for screening purposes due to its relative convenience. However, the majority of obese youth with HbA1c in the prediabetes range does not have rapidly progressive dysglycemia, otherwise, the incidence of T2D in youth would be much higher. Prediabetes is often a transient state with up to 60% of youth meeting criteria reverting to normal glycemic tolerance (NGT) within 2 years [7]. Currently, evidence based guidelines for evaluation and treatment of obese youth with HbA1c in the prediabetes range are lacking, with clinical practice primarily based on expert opinion rather than pediatric data [8].

To address the lack of evidence to inform the clinical follow-up of obese youth with an elevated HbA1c in the prediabetes range, we performed a retrospective chart review of short-term outcomes for patients who were screened for T2D by their primary care provider and subsequently referred for evaluation and treatment in our subspecialty clinic: the Youth Diabetes Prevention Clinic (YDPC). The objective of this study was to determine the proportion of patients who, between the time of their primary care and subspecialty clinic visits, had worsening, stabilization, or improvement in HbA1c. We also wanted to assess for predictors of persistent dysglycemia. We hypothesized that the majority of referred patients would not have progressive worsening of HbA1c, and that those with higher HbA1c at referral (screening HbA1c) would be more likely to have continued or progressive elevation in HbA1c (YDPC HbA1c).

Methods

This is a retrospective chart review of patients referred to the Riley Hospital for Children at Indiana University Health YDPC, a pediatric endocrinology clinic that evaluates and treats patients for prediabetes or early T2D. Referral to YDPC is from private and affiliated primary care practices in Indianapolis and throughout the state of Indiana. YDPC is reserved for youth with a BMI $\geq$ 85th percentile with HbA1c 5.7–7.5% or with other criteria suggesting a high risk for T2D, such as a family history of T2D in a first or second degree relative or maternal history of gestational diabetes. The American Diabetes Association (ADA) defines three stages of glycemic control based on HbA1c: (1) normal glycemia: HbA1c $<$ 5.7%; (2) prediabetes: $5.7 \leq$ HbA1c $<$ 6.5%; and (3) T2D: HbA1c $\geq$ 6.5% [2]. We subcategorized HbA1c in the prediabetes range into: prediabetes I (P1) defined as $5.7 \leq$ HbA1c $<$ 6.0%; and prediabetes II (P2) defined as $6.0 \leq$ HbA1c $<$ 6.5%, because there is a lack of consensus for the lower HbA1c cutoff point with some experts recommending 6.0% instead of 5.7% [9]. A subgroup of patients had screening fasting plasma glucose (FPG) levels from the time of referral. In a separate analysis, we classified this subgroup based on both screening HbA1c and FPG as follows: (1) normal

glycemia: HbA1c $<$ 5.7% and FPG $<$ 100 mg/dL; (2) P1: $5.7 \leq$ HbA1c $<$ 6.0% and FPG $<$ 100 mg/dL; (3) P2: $6.0 \leq$ HbA1c $<$ 6.5% or $100 \leq$ FPG $\leq$ 125 mg/dL; (4) T2D: HbA1c $\geq$ 6.5% or FPG $\geq$ 126 mg/dL.

At the YDPC clinic, patients' demographics were self-reported and anthropometric and glycemic measures were obtained. Height was measured according to clinic protocol to the nearest 0.1 cm using a wall-mounted stadiometer (Ayrton Model S100, Prior Lake, MN, USA) and weight was measured to the nearest 0.1 kg using a calibrated electronic scale (Scale-Tronix Model 5002). Point-of-care laboratory values were measured using the iSTAT system for FPG (Abbott Point of Care, Princeton, NJ, USA) and DCA Vantage analyzer for HbA1c which is certified by the National Glycohemoglobin Standardization Program (NGSP; Siemens Medical Solutions USA, Inc., Malvern, PA, USA). Data from the electronic medical record were entered in REDCap (Vanderbilt University, Nashville, TN, USA), a web-based database, for the purposes of data analysis for this study [10]. The referral screening laboratory values were documented from copies provided by referring physicians. These tests were performed at various local Clinical and Laboratory Improvement Amendments of 1988 (CLIA) certified medical testing laboratories located across the state of Indiana, which limited the documentation of the assays utilized. For the purposes of this analysis, we included all patients who were referred for concern of high risk for T2D, whether in the NGT or in the prediabetes range. We excluded any patient with HbA1c $\geq$ 6.5% and any patient on glucose-lowering medication such as metformin. Data were analyzed with Statistical Package for the Social Sciences 26 (SPSS version 26) software using ANOVA and Pearson's χ^2 to compare patient characteristics at baseline. We included the outliers in the analysis because removing them did not change the results. We also ran a bivariate analysis followed by a multinomial logistic regression to assess predictors of glycemic category at the YDPC visit, since the dependent variables were both continuous and categorical.

To compare glycemic measures between referral (screening) and the specialty clinic visit (YDPC), we grouped patients into the predefined glycemic categories based on screening and YDPC laboratory test results. Patients who met criteria for a better glycemic category at the YDPC visit compared to at the time of referral were considered to have improved; those who met criteria for a worse glycemic category at the YDPC visit were considered to have worsened; those who remained in the same category were considered stable. We included patients referred between September 2014 and April 2018.

Results

The characteristics of the patient population are shown in Table 1. Among the 562 patients seen at the YDPC during the study time interval, 336 had screening and YDPC HbA1c values, and 98 had both screening and YDPC HbA1c and FPG values. Among those, 10 patients presented already on metformin treatment, 9 of which had prediabetes. All other patients were drug-naïve. Twenty patients had T2D at referral. We excluded all patients who were referred to YDPC on metformin and all those who

Table 1. Patient characteristics by HbA1c category at the time of referral

	NGT (<i>n</i> = 71)	P1 (<i>n</i> = 132)	P2 (<i>n</i> = 104)	<i>p</i> value
Age, years	13.5±2.6	12.8±2.6	13.2±2.8	0.17
Female sex	35 (49.3)	83 (62.9)	51 (49.0)	0.05*
Race/ethnicity				<0.01*
White	39 (54.9)	54 (40.9)	24 (23.1)	
Black/African American	16 (22.5)	46 (34.8)	53 (51.0)	
Hispanic or Latino	8 (11.2)	3 (2.3)	9 (8.7)	
Other	4 (5.7)	10 (7.6)	7 (6.7)	
Declined or missing	4 (5.7)	19 (14.4)	11 (10.5)	
BMI z-score	2.3±0.5	2.1±0.7	2.3±0.6	0.17
HbA1c, %	5.3±0.2	5.8±0.1	6.1±0.1	<0.01*
Days to YDPC specialty clinic visit	130±82	159±123	136±109	0.34

Data are presented as *n* (%) or mean ± SD. * Statistical significance with *p* < 0.05. YDPC, Youth Diabetes Prevention Clinic; HbA1c, glycosylated hemoglobin A1c; BMI, body mass index; NGT, normal glucose tolerance; P1, prediabetes category 1: 5.7 ≤ HbA1c <6.0%; P2, prediabetes category 2: 6.0 ≤ HbA1c <6.5%.

had HbA1c in the diabetes range. The total number of included patients was 307 with a mean age of 13.1 ± 2.6 years and with 55% being female (Table 1). The P1 group had a higher percentage of female participants (*p* = 0.05). Race/ethnicity varied by HbA1c group, and a higher percentage of patients in the P2 group were Black/African American (*p* = 0.01). The mean time between referral and the YDPC visit was 145 ± 112 days. At the time of referral, screening HbA1c was in the normal range in 23%, between 5.7 and 6.0% (P1) in 43%, at or above 6.0–6.5% (P2) in 34%.

We used a bivariate analysis followed by a multinomial logistic regression model to assess for factors that might be predictive of glycemic category on follow-up (race, sex, BMI z-score change, days between referral and YDPC visits, and glycemic category on presentation). Bivariate results showed that race was associated with P1 (*p* < 0.001, OR 3.2) and P2 (*p* = 0.02, OR 4.5); referral glycemic category was also significantly associated with P1 (*p* < 0.001, OR 8.2) and P2 (*p* = 0.02, OR 9.9). Sex (*p* = 0.50), BMI z-score change (*p* = 0.27), and days from referral (*p* = 0.83) were not associated with YDPC glycemic category. Including only race (*p* = 0.01) and referral glycemic category (*p* < 0.01) in a multinomial logistic regression (Table 2) showed that, as compared to patients who presented to YDPC with NGT, patients who presented to YDPC with prediabetes (in each group; P1 and P2) were almost 7 times more likely to have had a higher glycemic category for screening. Race and glycemic category were not predictive of laboratory values indicative of T2D at the YDPC clinic visit (*p* > 0.05).

Table 3 shows the glycemic categories of patients at referral (screening) and at the YDPC visit based on their

Table 2. Predictors of dysglycemia (*n* = 272)

Status on follow-up	B	OR	<i>p</i> value
P1			
Status at referral	1.96	7.15	<0.01*
Race	0.94	2.57	<0.01*
P2			
Status at referral	1.99	7.34	0.04*
Race	1.26	3.55	0.05
T2D			
Status at referral	10.30	30,015.37	0.24
Race	0.10	1.10	0.90

P1, prediabetes category 1: 5.7 ≤ HbA1c <6.0%; P2, prediabetes category 2: 6.0 ≤ HbA1c <6.5%. * Statistical significance with *p* < 0.05. The reference glycemic category was NGT and the reference race was Non-Hispanic White, as this race is known to have a lower risk for T2D.

glycemic category defined by HbA1c only, and defined by FPG and HbA1c in those who had both measures. In the groups defined by both HbA1c and FPG, none of the patients developed T2D within the period of this project (150 ± 121 days).

The percentages of patients meeting criteria for improved, worsened, and stable glycemic categories defined by HbA1c only are shown in Figure 1 (left panel). Among the patients who were referred with prediabetes (*n* = 234), 56% had HbA1c 5.7 to <6.0% (P1) and 44% had HbA1c 6.0 to <6.5 (P2). At YDPC, the majority of the patients with P1 improved (75.4%); similar to those with P2 where 83.7% improved.

Table 3. Patient glycemic category at referral versus YDPC

YDPC glycemic category defined by HbA1c	Referral glycemic category defined by HbA1c only		
	NGT (<i>n</i> = 70)	P1 (<i>n</i> = 130)	P2 (<i>n</i> = 104)
NGT (<i>n</i> = 206)	65 (92.9)	98 (75.4)	43 (41.4)
P1 (<i>n</i> = 71)	4 (5.7)	23 (17.7)	44 (42.3)
P2 (<i>n</i> = 21)	1 (1.4)	7 (5.4)	13 (12.5)
T2D (<i>n</i> = 6)	0 (0.0)	2 (1.5)	4 (3.8)

YDPC glycemic category defined by both HbA1c and FPG	Referral glycemic category defined by HbA1c and FPG		
	NGT (<i>n</i> = 17)	P1 (<i>n</i> = 18)	P2 (<i>n</i> = 33)
NGT (<i>n</i> = 36)	17 (100.0)	8 (44.4)	11 (33.3)
P1 (<i>n</i> = 117)	0 (0.0)	1 (5.6)	6 (18.2)
P2 (<i>n</i> = 25)	0 (0.0)	9 (50.0)	16 (48.5)
T2D (<i>n</i> = 0)	0 (0.0)	0 (0.0)	0 (0.0)

Data are presented as *n* (%). YDPC, Youth Diabetes Prevention Clinic; Glycemic category defined by HbA1c: P1, prediabetes category 1: $5.7 \leq \text{HbA1c} < 6.0\%$; P2, prediabetes category 2: $6.0 \leq \text{HbA1c} < 6.5\%$. Glycemic category defined by HbA1c and FPG: P1, prediabetes category 1: $5.7 \leq \text{HbA1c} < 6.0\%$, and $\text{FPG} < 100 \text{ mg/dL}$; P2, prediabetes category 2: $6.0 \leq \text{HbA1c} < 6.5\%$ or $100 \leq \text{FPG} \leq 125 \text{ mg/dL}$.

Fig. 1. The glycemic outcomes of patients who presented with prediabetes.

In the group of patients with both screening and YDPC FPG and HbA1c, the percentages of those meeting criteria for improved, worsened, and stable glycemic categories are shown in Figure 1 (right panel). In the group of patients with prediabetes (*n* = 51), 35% were in the P1 category and 65% were in the P2 category. At YDPC, 44.4% of those in the P1 category improved, while 55.6% worsened or were stable. In the P2 category, 51.5% improved while 48.5% were stable.

Discussion

Screening according to ADA criteria is expected to increase the detection of dysglycemia in youth at high risk for T2D. Our study used actual patient data to illustrate the short-term clinical outcomes of measures of glycemia in obese youth meeting increased-risk criteria for T2D. In this study, we found that the majority of pediatric patients screened with HbA1c had improved HbA1c

during the interval between referral and subspecialty clinic visits (75.4–83.7%). In the average time between referral and the YDPC visit (5 months), patients with HbA1c 5.7 to <6.0% were unlikely to worsen, and a very low percentage (<2%) developed T2D. Patients with HbA1c 6.0 to <6.5% were also unlikely to worsen or develop T2D in the short 5-month average follow-up period. We noted that after adding FPG to the definition of glycemic categories, no one in the sample progressed to meeting criteria for T2D in either the NGT or prediabetes groups. Interestingly, patients categorized by both HbA1c and FPG were less likely to improve in the short-term, as 44.4% in the P1 category improved and 51.5% in the P2 category improved. However, this is not necessarily because of worse screening laboratory values at referral as P1 categorized by both tests (HbA1c 5.7 to 6.0% and FPG <100 mg/dL) does not implicate a higher risk group than P1 categorized by HbA1c alone. It could be that the suspicion for diabetes by the referring physicians was greater for those patients who had both tests done, and therefore these patients were at truly greater risk for progressive diabetes for reasons that cannot be identified by our study.

The hypothesis that patients with higher HbA1c at referral would be more likely to have progressive dysglycemia was confirmed. Our analysis has shown that patients who had prediabetes at the YDPC visit were more likely to have been referred with a higher screening HbA1c. The high improvement rates and the lower risk of progression of patients with HbA1c 5.7 to <6.0% signifies that it may be appropriate for primary care providers to schedule a repeat HbA1c and follow-up within 4 months with patients presenting with mild elevations in HbA1c without other signs or symptoms of diabetes (polyuria, polydipsia, or unintentional weight loss). Patients with higher HbA1c (HbA1c $\geq$ 6%) and those patients of minority race or ethnicity are at greater risk for progression of dysglycemia and should be referred accordingly.

Hyperglycemia in adolescence is particularly challenging because it might be a reversible process that is associated with puberty, particularly prediabetes in adolescents who are at risk for T2D [11, 12] or it might be type 1 diabetes which remains to be the most common form of diabetes in youth. Youth with HbA1c in the diabetes range should always be evaluated and treated expediently, since T2D often progresses rapidly [13], and type 1 diabetes is still the most common type of diabetes in youth and hence should be ruled out in any pediatric patient with evidence of hyperglycemia. Patients with signs or symptoms of diabetes including polyuria, polydipsia, or unintentional

weight loss and elevated HbA1c should be evaluated for type 1 diabetes expediently.

Our study documented improved glycemia at the time of the subspecialty clinic visit compared to the referral visit within 5 months in patients at risk for T2D and patients with prediabetes; this could be due to lifestyle changes implemented by the patients. Although we did not formally collect this data, many patients endorsed during their clinic visits that their health care providers had counseled them to eliminate sugar-sweetened beverages and juice. This is a reasonable brief intervention, that is recommended by the ADA [14], and that can be done in busy primary care practices with impactful results. It is possible that the difference in mean HbA1c values at the time of referral and at the subspecialty clinic is due to laboratory variability; however, this would be expected to lead to variable differences with some being higher and some being lower. Nevertheless, we cannot rule out laboratory variability, as previous reports have documented up to 0.5% of intermethod variability for HbA1c in youth [15]. Clearly, the lower HbA1c at the time of the subspecialty clinic visit is not consistent with progression of dysglycemia during the first 5 months after screening and referral.

The strengths of this project lie in that this is a real-world evaluation of a challenging condition, prediabetes, in a young patient population. Our results suggest that a majority of youth with HbA1c <6.0% did not have rapid progression of dysglycemia in the short term. This also is the first paper to our knowledge that tries to set the stage to address the guideline gap when it comes to prediabetes in adolescents. The limitations, however, include that the documented changes in HbA1c could be partly due to systematic biases in HbA1c measurements as referral and YDPC HbA1c were measured differently, and we could not have taken into account the sensitivities of the different modalities used. We tried to address this limitation by defining our outcomes as glycemic categories rather than as absolute reductions in HbA1c values. We also do not have data with regard to the extent of lifestyle counseling performed prior to the specialty clinic visit. Moreover, we did not have Tanner staging data from referrals to assess for any pubertal changes at YDPC which would have allowed including pubertal stage as a confounding factor in our analysis. However, we do not think that the pubertal changes were drastic due to the relatively short duration between both visits. It is also noteworthy that our results showed that race and glycemic category at referral were both predictive of prediabetes but were not predictive of the development of T2D. This might be due to a type II

error given the fact that the patient population that developed T2D was a minority accounting for only 2% ($n = 6$). The low number of patients progressing to T2D will inadvertently lead to a low sample size, which raises the question of the presence of a type II error in the analysis.

Conclusion

The majority of youth with obesity presenting with HbA1c in the prediabetes range had lower HbA1c within 5 months. Dietary consultation and follow-up of youth with obesity and HbA1c <6% within 4 months at primary care clinics is a reasonable option, especially with the paucity of pediatric endocrinologists and prolonged waiting times. Youth with higher HbA1c (HbA1c ≥ 6 to <6.5%) and belonging to a minority race are more likely to have progressive dysglycemia in the short term and hence could benefit from seeing a specialist. Youth meeting diagnostic criteria for diabetes should always be promptly referred for further evaluation and treatment.

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References

- 1 Mayer-Davis EJ, Lawrence JM, Dabelea D, Divers J, Isom S, Dolan L, et al.; SEARCH for Diabetes in Youth Study. Incidence Trends of Type 1 and Type 2 Diabetes among Youths, 2002–2012. *N Engl J Med*. 2017 Apr;376(15):1419–29.
- 2 American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2019. *Diabetes Care*. 2019 Jan;42 Suppl 1:S13–28.
- 3 Williams DE, Cadwell BL, Cheng YJ, Cowie CC, Gregg EW, Geiss LS, et al. Prevalence of impaired fasting glucose and its relationship with cardiovascular disease risk factors in US adolescents, 1999–2000. *Pediatrics*. 2005 Nov;116(5):1122–6.
- 4 Duncan GE. Prevalence of diabetes and impaired fasting glucose levels among US adolescents: National Health and Nutrition Examination Survey, 1999–2002. *Arch Pediatr Adolesc Med*. 2006 May;160(5):523–8.
- 5 Baranowski T, Cooper DM, Harrell J, Hirst K, Kaufman FR, Goran M, et al.; STOPP-T2D Prevention Study Group. Presence of diabetes risk factors in a large U.S. eighth-grade cohort. *Diabetes Care*. 2006 Feb;29(2):212–7.
- 6 Sinha R, Fisch G, Teague B, Tamborlane WV, Banyas B, Allen K, et al. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. *N Engl J Med*. 2002 Mar;346(11):802–10.
- 7 Weiss R, Taksali SE, Tamborlane WV, Burgert TS, Savoye M, Caprio S. Predictors of changes in glucose tolerance status in obese youth. *Diabetes Care*. 2005 Apr;28(4):902–9.
- 8 Haemer MA, Grow HM, Fernandez C, Lukasiewicz GJ, Rhodes ET, Shaffer LA, et al. Addressing prediabetes in childhood obesity treatment programs: support from research and current practice. *Child Obes*. 2014 Aug;10(4):292–303.
- 9 International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care*. 2009 Jul;32(7):1327–34.
- 10 Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009 Apr;42(2):377–81.
- 11 Goran MI, Gower BA. Longitudinal study on pubertal insulin resistance. *Diabetes*. 2001 Nov;50(11):2444–50.
- 12 Lee JM, Okumura MJ, Davis MM, Herman WH, Gurney JG. Prevalence and determinants of insulin resistance among U.S. adolescents: a population-based study. *Diabetes Care*. 2006 Nov;29(11):2427–32.
- 13 D'Adamo E, Caprio S. Type 2 Diabetes in Youth: Epidemiology and Pathophysiology. *Diabetes Care*. 2011 May;34 Suppl 2:S161–5.
- 14 Children and Adolescents: Standards of Medical Care in Diabetes-2019. *Diabetes Care*. 2019 Jan;42(Suppl 1):S148–S164.
- 15 Chan CL, McFann K, Newnes L, Nadeau KJ, Zeitler PS, Kelsey M. Hemoglobin A1c assay variations and implications for diabetes screening in obese youth. *Pediatr Diabetes*. 2014 Dec;15(8):557–63.

Statement of Ethics

The Human Research office at the Institutional Review Board (IRB) at Indiana University approved the study protocol.

Disclosure Statement

H.K.E.M., B.M.M., L.Y.-S., and S.E.A. do not have any conflicts of interest to disclose. Dr. Hannon reports personal fees from Eli Lilly, Inc., outside the submitted work.

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Author Contributions

S.E.A.: data entry. H.K.E.M., L.Y.-S., B.M.M., and T.S.H.: data analysis. H.K.E.M., L.Y.-S., and T.S.H.: wrote the manuscript. B.M.M., S.E.A., and T.S.H.: reviewed the manuscript. All authors agree to the content and data.