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

Hala K. El Mikati, MD [1,2] , Brett M. McKinney BS [1,2], Lisa Yazel-Smith MS, MCHES, [1,2], Sarah E. Alders [3], Tamara S. Hannon, MD, MS[1,2]

[1] Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN, USA.

[2] Department of Pediatric and Adolescent Comparative Effectiveness Research, Indiana University School of Medicine, Indianapolis, IN, US

[3] Indiana University School of Nursing, Indianapolis, Indiana

Running head: Short-Term Glycemic Outcomes in Obese Youth with Prediabetes

***Corresponding author**

Hala K. El-Mikati:

Indiana University School of Medicine, Indianapolis, IN

Address: Indiana University School of Medicine, 410 West 10th Street, Suite 2000A, Indianapolis, IN 46202, USA

Tel: (317) 274-3888

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Helmikat@iu.edu

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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 objective of this study was to determine the short-term outcomes of patients referred to our youth diabetes prevention clinic(YDPC) with prediabetes and to determine predictors of worsening dysglycemia in this population.

Study Design: This is a retrospective chart review of patients referred to YDPC with high-risk for type 2 diabetes(T2D) . We compared HbA1c at referral and YDPC to assess for improvement, worsening and stabilization. We also used multinomial logistic regression to assess for predictors of prediabetes.

Results: Among the 562 patients seen at the YDPC, 336 had HbA1c from both referral and YDPC visits . Race($p<0.001$) and referral glycemic category($p<0.001$) were significantly associated with dysglycemia at YDPC, 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 been referred with a higher HbA1c. The majority of patients referred with prediabetes improved at YDPC(75.4 – 82.6%).

Conclusion: Patients with screening HbA1c<6% might benefit from 4-months follow-up at primary care while recommending lifestyle changes. Patients of minority race and a higher HbA1c should be promptly referred to endocrinology.

Introduction

Type 2 diabetes (T2D) is increasing in youth, yet most obese youth do not develop T2D during childhood(1). The most recent estimates of the incidence of T2D in U.S. youth is ~5,300 cases per year(1). Prediabetes, a prelude to T2D, is defined as the presence of impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG) 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 ~10-30% 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 two 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 a subspecialty clinic: 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 dysglycemia which can be helpful for future guidelines. We hypothesized that the majority of referred patients would not have had progressive worsening of HbA1c by the time they were seen in the

subspecialty clinic, and that those with higher HbA1c at referral would be more likely to have continued or progressive elevation in 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 $\geq 85^{th}$ percentile with HbA1c 5.7 – 7.5% or with other criteria suggesting 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 ≤ HbA1c < 6.5%; and 3) T2D: HbA1c ≥6.5%(2). We categorized HbA1c in the prediabetes range into: prediabetes category I (P1) defined as 5.7 ≤ HbA1c < 6.0%; and prediabetes category II (P2) defined as 6.0 ≤ HbA1c < 6.5 % because there is a lack of consensus on the lower cut-off point for HbA1c in the prediabetes range with some experts recommending 6.0% instead of 5.7%(9). A subgroup of the patients had fasting plasma glucose (FPG) levels from the time of referral. For a separate analysis, we classified this subgroup based on both HbA1c and FPG as follows, 1) normal glycemia: HbA1c < 5.7% and FPG <100 mg/dL; 2) P1: 5.7 ≤ HbA1c < 6.0%, and FPG <100 mg/dL; 3) P2: 6.0 ≤ HbA1c < 6.5% or 100 ≤ FPG ≤ 125mg/dL; 4) T2D: HbA1c ≥ 6.5% or FPG ≥ 126mg/dL.

At the YDPC clinic, patients' demographics are self-reported and anthropometric and glycemic measures are obtained. Height is measured according to clinic protocol to the nearest 0.1 cm using a wall-mounted stadiometer (Ayrton Model S100, Prior Lake, MN) and weight is

measured to the nearest 0.1 kg using a calibrated electronic scale (Scale-Tronix Model 5002). Point-of-care FPG and HbA1c are measured using the iSTAT system for FPG (Abott Point of care, Princeton, NJ) and DCA Vantage analyzer for HbA1c which is certified by the National Glycohemoglobin Standardization Program (NGSP) (Siemens Medical Solutions USA, Inc., Malvern, PA). Data from the electronic medical record were entered in REDCap, a web based database, for the purposes of data analysis for this study(10). The referral labs were documented from copies provided by referring physicians. The lab tests were performed at various local Clinical and Laboratory Improvement Amendments of 1988 (CLIA) certified medical testing laboratories located all over the state of Indiana, which limited the documentation of the assays utilized. For the purposes of this analysis, we only included the patients who were referred at a high risk for type 2 diabetes, whether in the NGT or in the prediabetes range. We excluded any patient who had HbA1c ≥6.5% and any patient who was on Metformin to be able to describe the natural history of prediabetes. Data was analyzed using Statistical Package for the Social Sciences 26 (SPSS v26) software using multinomial logistic regression to assess for the predictors of glycemic category at follow-up since the dependent variables were both continuous and categorical.

To compare glycemic measures between referral and the specialty clinic visit, we categorized patients into the predefined glycemic categories at referral and at the YDPC visit. Patients who met criteria for a better glycemic category at the subspecialty visit compared to referral were considered to have improved; those who met criteria for a worse glycemic category at the subspecialty 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.

The Indiana University Institutional Review Board (IRB) approved the study protocol.

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 HbA1c from both referral and subspecialty clinic visits, and 98 had both HbA1c and FPG documented at referral and subspecialty clinic visits. Among those, ten patients presented already on metformin; nine of which had prediabetes. All other patients were drug-naïve. Twenty patients had T2D on presentation. We excluded all of the patients who presented on metformin and all of those who 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 mean time between referral and follow-up was for this cohort 145 ± 112 days. At the time of referral, HbA1c was in the normal range in 23%, between 5.7 and 6.0% (P1) in 43%, at or above 6.0 to 6.5% (P2) in 34%.

To assess for predictors of dysglycemia, a bivariate analysis followed by a multinomial logistic regression model was used to assess factors that might be predictive of glycemic control on follow-up (race, sex, BMI z-score change, days between referral and YDPC visits, and glycemic category on presentation). Race ($p<0.001$) and referral glycemic category ($p<0.001$) were significantly associated with dysglycemia at YDPC, while 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 (both P1 and P2) were 7 times more likely to have had a higher glycemic category on referral. 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 and at YDPC based on their glycemic category defined by HbA1c only, and defined by FPG and HbA1c in those who had both measures at referral. 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 who had improved, worsened, and stable glycemic category 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-<6.0% (P1) and 44% had HbA1c 6.0-<6.5 (P2). At YDPC, the majority of the patients with P1 improved (75.4%); similar to those with P2 where 83.7% improved.

In the group of patients with both FPG and HbA1c, the percentage 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% had an HbA1c in the P1 category and 65% had an HbA1c in the P2 category. Among the patients with P1, 44.4% improved as compared to those with P2 whereby 51.5% improved.

Discussion

Screening according to ADA criteria is expected to increase the detection of dysglycemia in youth at high risk for T2D. Our study used a real life experience to illustrate the short-term clinical outcomes of measures of glycemia in obese youth who were screened and then had repeat screening approximately 5 months later. In this study, we found that the majority of pediatric patients who were referred for evaluation and treatment of obesity and prediabetes had improved measures of glycemia 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-<6.0% were unlikely to worsen with a very low proportion (<2%) developing T2D. Patients with HbA1c 6.0-<6.5% were also unlikely to develop T2D in the short-term, but a higher percentage did have progressive elevation in HbA1c (3.8%). We noted that after adding FPG to the definition of glycemic categories, no one progressed to meeting criteria for T2D in either the NGT or prediabetes groups. These high improvement rates in glycemia signify that it may be appropriate for primary care providers to schedule a repeat HbA1c within 4 months of the first documented elevation in HbA1c before referring to a specialist, particularly if the HbA1c was 5.7-<6.0% .

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 YDPC were more likely to have been referred with a higher HbA1c (≥6.0%). Thus, follow-up within 4 months for patients who present with mild elevations in HbA1c (HbA1c 5.7-<6.0%) is a reasonable strategy for obese youth with mildly elevated HbA1c and without other signs or symptoms of diabetes (polyuria, polydipsia, or unintentional weight loss).

Patients with higher HbA1c (HbA1c ≥ 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 inter-method 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 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 the 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.

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% - <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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Statement of Ethics

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

Disclosure Statement

HE, BM, LS, SA do not have any conflicts of interests to disclose.

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Authors Contributions

SA data entry, HE, LS, BM, TH data analysis, HE, LS, TH wrote manuscript, BM, SA and TH reviewed the manuscript. All of the authors agree to the content and data.

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Figure 1: The glycemic outcomes of patients who presented with prediabetes.

Table 1: Patient Characteristics by HbA1c Category at the Time of Referral

	NGT (N=71)	P1 (N=132)	P2 (N=104)
Age (years)	13.5 ± 2.6	12.8 ± 2.6	13.2 ± 2.8
Gender (F)	35 (49.3)	83 (62.9)	51 (49.0)
Race/Ethnicity			
White	39 (54.9)	54 (40.9)	24 (23.1)
Black/African American	16 (22.5)	46 (34.8)	53 (51)
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
HbA1c (%)	5.3 ± 0.2	5.8 ± 0.1	6.1 ± 0.1
Days to YDPC specialty clinic visit	130 ± 82	159 ± 123	136 ± 109

Data are presented as N (%) or means ± standard deviation. YDPC: Youth Diabetes Prevention Clinic. HbA1c: glycosylated hemoglobin A1c. BMI: Body mass index, NGT: normal glucose tolerance, P1: prediabetes category 1 with: $5.7 \leq HbA1c < 6.0\%$, P2: prediabetes category 2 P2: $6.0 \leq HbA1c < 6.5\%$.

Table 2: The predictors of dysglycemia, N= 272.

Status on follow-up		B	Odds Ratio	P-value
P1	Status at referral	1.96	7.15	<0.01*
	Race	-0.94	0.38	<0.01*
P2	Status at referral	1.99	7.34	0.04 *
	Race	-1.26	0.28	0.05
T2D	Status at referral	10.30	30015.37	0.24
	Race	-0.10	0.90	0.90

P1: prediabetes category 1 with P1: $5.7 \leq HbA1c < 6.0\%$, P2: prediabetes category 2 P2: $6.0 \leq HbA1c < 6.5\%$ (*) denotes statistical significance with $p<0.05$.

Table 3: Patient Glycemic Category at Referral versus Youth Diabetes Prevention Clinic Visit

		Referral Glycemic Category Defined by HbA1c Only		
		NGT (N=70)	P1 (N= 130)	P2 (N=104)
YDPC glycemic category defined by HbA1c	NGT (N=206)	65 (92.9)	98 (75.4)	43(41.4)
	P1 (N=71)	4 (5.7)	23 (17.7)	44(42.3)
	P2 (N=21)	1 (1.4)	7 (5.4)	13(12.5)
	T2D (N=6)	0 (0.0)	2 (1.5)	4 (3.8)
		Referral Glycemic Category defined by HbA1c and FPG		
		NGT (N=17)	P1 (N=18)	P2 (N= 33)
YDPC glycemic category defined by both HbA1c and FPG	NGT (N=36)	17 (100.0)	8 (44.4)	11 (33.3)
	P1 (N=117)	0(0.0)	1 (5.6)	6 (18.2)
	P2 (N=25)	0(0.0)	9 (50.0)	16 (48.5)
	T2D (N=0)	0 (0.0)	0 (0.0)	0(0.0)

Data is presented as N(%).YDPC: Youth Diabetes Prevention Clinic. Glycemic category defined by HbA1c: P1: prediabetes category 1 with P1: $5.7 \leq$ HbA1c $< 6.0\%$, P2: prediabetes category 2 with $6.0 \leq$ HbA1c $< 6.5\%$. Glycemic category defined by HbA1c and FPG: P1: prediabetes category 1 with: $5.7 \leq$ HbA1c $< 6.0\%$, and FPG <100 mg/dL, P2: prediabetes category 2 with $6.0 \leq$ HbA1c $< 6.5\%$ or $100 \leq$ FPG ≤ 125mg/dL.

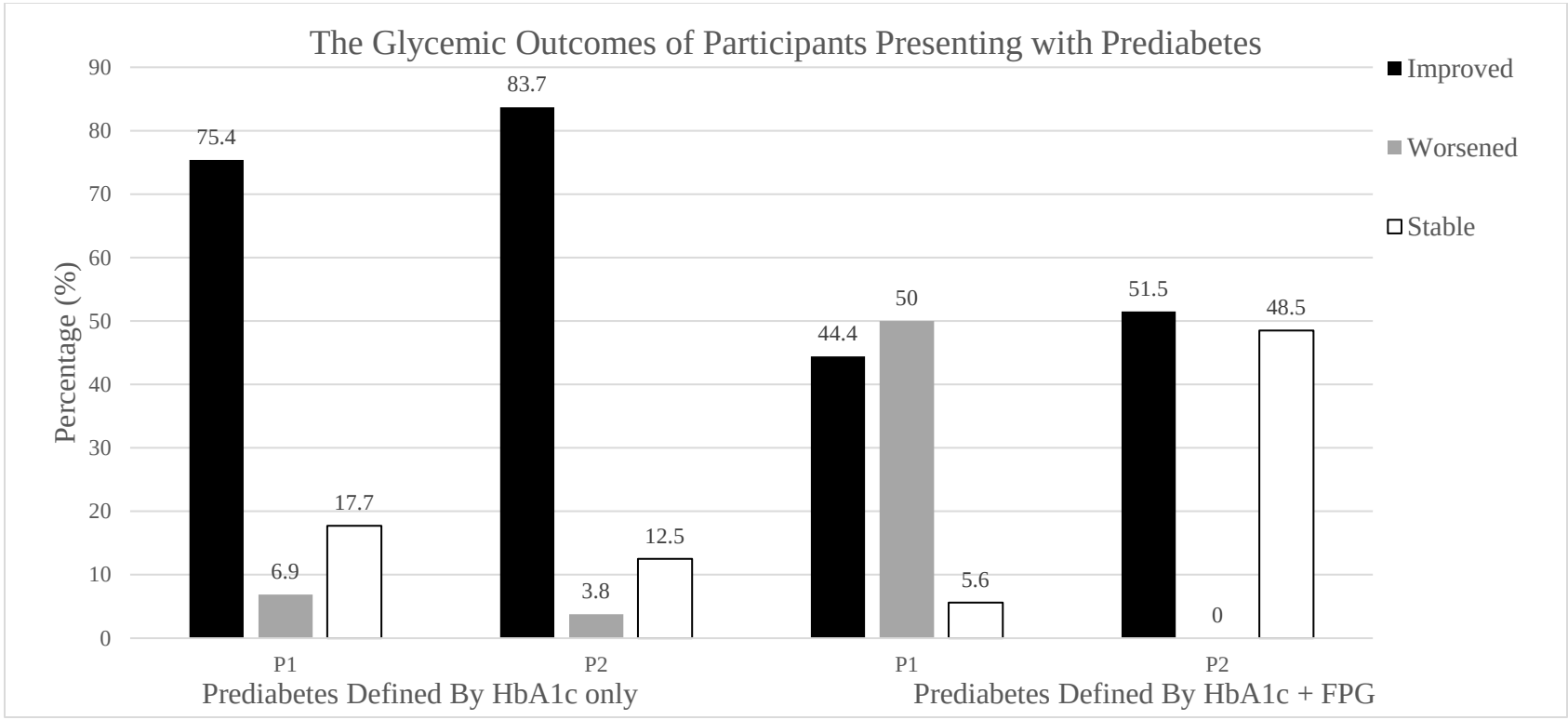
The Glycemic Outcomes of Participants Presenting with Prediabetes
Percentage (%)
90
80
70
60
50
40
30
20
10
0
75.4
6.9
17.7
83.7
3.8
12.5
44.4
50
5.6
51.5
0
48.5
P1
P2
P1
P2
Prediabetes Defined By HbA1c only
Prediabetes Defined By HbA1c + FPG
Improved
Worsened
Stable

Figure 1.