Lessons From Continuous Glucose Monitoring in Youth With Pre–Type 1 Diabetes, Obesity, and Cystic Fibrosis

Christine L. Chan,[1] Andrea K. Steck,[2] Cameron Severn,[3] Laura Pyle,[3] Marian Rewers,[2] and Philip S. Zeitler[1]

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Glucose abnormalities exist in the prediabetic state well before a diagnosis of diabetes is made, and continuous glucose monitoring (CGM) is a sensitive method to detect these early abnormalities. Although insufficient data exist to support CGM for diagnosing diabetes, glucose patterns on CGM can provide insight into disease pathophysiology. Our group has used CGM to study early dysglycemia in several populations of youth at risk for diabetes—specifically, type 1 diabetes (T1D), type 2 diabetes (T2D), and cystic fibrosis–related diabetes (CFRD). We hypothesized that, in youth at risk for different types of diabetes matched by HbA_{1c}, average sensor glucose would be no different, but specific CGM measures might differ among groups.

For this analysis, we combined data from three groups of youth: *1*) antibody-positive (Ab^+) children from DAISY (Diabetes Autoimmunity Study in the Young) (1), *2*) youth with cystic fibrosis (CF) from the Glycemic Monitoring in Cystic Fibrosis Study (NCT02211235, ClinicalTrials.gov), and *3*) overweight/obese youth with BMI ≥85th percentile at risk for T2D (2). Inclusion criteria were ages 10–18 years and HbA_{1c} <6.5% (48 mmol/mol) with concurrent CGM data. Oral glucose tolerance testing (OGTT) was not performed in all youth and, therefore, not included in this analysis. The pre-T1D youth had ≥2 positive autoantibodies; CF youth had a confirmed diagnosis of CF based on newborn screen, sweat chloride testing, and/or genetic testing; and overweight/obese youth had a BMI ≥85th percentile. Exclusion criteria included known diabetes or use of medications affecting glucose metabolism including insulin. As there were fewer DAISY individuals, this group was matched up to 1:2 to CF and overweight/obese participants by HbA_{1c} category, determined by dividing the participants' HbA_{1c} range into tertiles: *1*) 4.9–5.3% (30–34 mmol/mol), *2*) 5.4–5.8% (36–40 mmol/mol), and *3*) 5.9–6.3% (41–45 mmol/mol).

A total of 108 participants were included (Table 1). As hypothesized, average sensor glucose levels on CGM were no different among groups. However, multiple measures of glycemic variability, including maximum glucose, standard deviation, and mean amplitude of glycemic excursions were significantly higher in youth with CF and pre-T1D.

This is the first report to compare glycemic profiles captured by CGM in three distinct populations of youth at risk for diabetes. These results highlight interesting similarities and differences in pathophysiology among the three disease states. Progressive β-cell failure and insulin deficiency are the primary drivers of disease in T1D and CFRD, and our findings suggest that early insulin insufficiency, as captured by CGM, manifests as glucose excursions and increased glycemic variability in the prediabetic state despite normal mean glucose levels. In T2D, progressive insulin resistance is followed by development of β-cell failure. In early stages of disease, insulin resistance, including hepatic insulin resistance, is the predominant metabolic defect and may be associated with increases in fasting and average glucose relative to normal-weight individuals (2), but with less glycemic variability than seen in youth at high risk for T1D and CFRD. We have previously shown that HbA_{1c} does not underestimate average glucose in youth with CF as previously assumed (3). Here, we make the point that HbA_{1c} may be normal, despite hyperglycemia and increased glycemic variability, not only in individuals with CF but also in Ab^+ individuals pre-T1D. Therefore, the tendency for HbA_{1c} to "underestimate" hyperglycemia is not unique to CF but, in fact, merely another example of the "fallacy of average" described by Bergenstal and colleagues (4).

These findings have implications for how we screen for diabetes in different

[1]*Pediatric Endocrinology, Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO*
[2]*Barbara Davis Center for Childhood Diabetes, University of Colorado School of Medicine, Aurora, CO*
[3]*Department of Biostatistics, Colorado School of Public Health, Aurora, CO*

Corresponding author: Christine L. Chan, christinel.chan@childrenscolorado.org

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Table 1—Demographics and clinical characteristics by CF, Pre-T1D, and obese/Pre-T2D group

	CF (N = 42)	Pre-T1D (N = 24)	Obese/Pre-T2D (N = 42)	P value
Demographic variable				
Age (years)	13.3 (0.5)	15.6 (0.9)	14.6 (0.4)	**0.02**[a]
Male, *n* (%)	21 (50)	11 (46)	13 (31)	0.25
Race, *n* (%)				**<0.001**[b]
Non-Hispanic White	39 (93)	19 (79)	15 (36)	
African American	0 (0)	0 (0)	4 (10)	
Hispanic	2 (5)	5 (21)	22 (52)	
Other	1 (2)	0 (0)	1 (2)	
BMI *z*-score	−0.08 (0.1)	0.06 (0.2)	3.1 (0.2)	**<0.001**[b]
Weight (kg)	45.5 (2.1)	54.9 (3.2)	92.4 (3.8)	**<0.001**[b]
Height (cm)	153 (2.2)	162 (3.3)	163 (1.5)	**0.001**[c]
HbA_{1c} (%)†	5.6 (0.04)	5.5 (0.08)	5.6 (0.05)	0.89
CGM variable*				
Duration of CGM wear (days)	5.2 (0.1)	3.8 (0.1)	2.0 (0.1)	**<0.0001**[a,b]
Average glucose (mg/dL)	111 (2)	113 (3)	114 (2)	0.60
Day average glucose (mg/dL)	112 (2)	112 (3)	115 (2)	0.58
Night average glucose (mg/dL)	108 (3)	114 (4)	111 (3)	0.54
Maximum glucose (mg/dL)	208 (7)	202 (9)	162 (7)	**0.0001**[b]
Day maximum glucose (mg/dL)	206 (7)	200 (9)	160 (7)	**0.0001**[b]
Night maximum glucose (mg/dL)	164 (6)	174 (7)	145 (6)	**0.01**[b]
Minimum glucose (mg/dL)	64 (2)	60 (3)	77 (2)	**<0.0001**[b]
Day minimum glucose (mg/dL)	66 (2)	61 (3)	81 (2)	**<0.0001**[b]
Night minimum glucose (mg/dL)	73 (2)	74 (3)	86 (3)	**0.004**[b]
Standard deviation (mg/dL)	22 (1)	24 (3)	16 (1)	**0.002**[b]
Coefficient of variation	0.2 (0.01)	0.2 (0.01)	0.14 (0.01)	**<0.0001**[b]
Mean amplitude of glycemic excursions	41 (3)	45 (4)	27 (3)	**0.006**[b]
Mean of daily differences	22 (2)	26 (2)	17 (2)	**0.02**[b]
% Time >140 mg/dL	10 (3)	15 (3)	13 (3)	0.58
% Time >180 mg/dL	1.9 (0.8)	4.1 (1.0)	1.3 (0.7)	0.15
% Time >200 mg/dL	0.9 (0.5)	2.5 (0.7)	0.4 (0.5)	0.12
% Time >250 mg/dL	0.15 (0.3)	1.2 (0.4)	0.01 (0.3)	0.09
% Time <60 mg/dL	1.2 (0.4)	0.8 (0.5)	0.2 (0.4)	0.26
% Time <70 mg/dL	2.6 (0.7)	3.3 (1.0)	0.9 (0.8)	0.12

Data are mean (SE) unless otherwise indicated. Groups were compared using linear mixed models for continuous variables, conditional logistic regression for sex, and the χ^2 test for race. Pairwise comparisons were adjusted using the Tukey method. Boldface type indicates statistical significance. *CGM P values adjusted for multiple comparisons to control the false discovery rate at 5%. †Minimum and maximum HbA_{1c} were 5.2–6.2% (CF), 5.0–6.3% (pre-T1D), and 5.0–6.3% (obese/pre-T2D). [a]Pre-T1D different from CF. [b]Obese/pre-T2D different from CF and pre-T1D. [c]Pre-T1D and obese/pre-T2D different from CF.

populations. Given the high prevalence of diabetes in individuals with CF and low sensitivity of HbA_{1c} relative to OGTT for diagnosing CFRD, screening with HbA_{1c} is not recommended in this population. Given the relatively lower prevalence of T1D in the general community, routine screening for T1D is not current clinical practice. With autoantibody screening programs (e.g., https://www.askhealth.org/), however, individuals at high risk for progression to T1D are being identified well before symptoms manifest and, as seen in patients with CF, HbA_{1c} in the Ab^+ pre-T1D population may be normal despite the presence of hyperglycemia. In contrast, the prevalence of youth-onset T2D is still low. Arguably, given the ease of collecting HbA_{1c} over OGTT, the often-rapid progression to diabetes, and low likelihood of undiagnosed cases of youth-onset T2D, HbA_{1c} remains an adequate screening tool in the obese pediatric population.

In conclusion, CGM informs our understanding of the early stages of diabetes progression in youth with different forms of diabetes. As CGM becomes increasingly accurate, in certain groups with high prevalence of diabetes, it may eventually be the new standard for diagnosing diabetes (5). Longitudinal studies within our research group to determine which CGM variables predict increased risk for disease-specific complications are ongoing.

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References

1. Steck AK, Dong F, Taki I, Hoffman M, Klingensmith GJ, Rewers MJ. Early hyperglycemia detected by continuous glucose monitoring in children at risk for type 1 diabetes. Diabetes Care 2014;37:2031–2033

2. Chan CL, Pyle L, Newnes L, Nadeau KJ, Zeitler PS, Kelsey MM. Continuous glucose monitoring and its relationship to hemoglobin A1c and oral glucose tolerance testing in obese and prediabetic youth. J Clin Endocrinol Metab 2015;100:902–910

3. Chan CL, Hope E, Thurston J, et al. Hemoglobin A_{1c} accurately predicts continuous glucose monitoring-derived average glucose in youth and young adults with cystic fibrosis. Diabetes Care 2018;41:1406–1413

4. Beck RW, Connor CG, Mullen DM, Wesley DM, Bergenstal RM. The fallacy of average: how using HbA_{1c} alone to assess glycemic control can be misleading. Diabetes Care 2017;40:994–999

5. Steck AK, Dong F, Taki I, et al. continuous glucose monitoring predicts progression to diabetes in autoantibody positive children. J Clin Endocrinol Metab 2019;104:3337–3344