



# Hemoglobin A<sub>1c</sub> Accurately Predicts Continuous Glucose Monitoring–Derived Average Glucose in Youth and Young Adults With Cystic Fibrosis

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Christine L. Chan,<sup>1</sup> Emma Hope,<sup>1</sup>  
Jessica Thurston,<sup>1,2</sup> Timothy Vigers,<sup>1</sup>  
Laura Pyle,<sup>1,2</sup> Philip S. Zeitler,<sup>1</sup> and  
Kristen J. Nadeau<sup>1</sup>

## OBJECTIVE

In cystic fibrosis (CF), hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) is thought to underestimate glycemia. However, few studies have directly assessed the relationship between HbA<sub>1c</sub> and average glucose in CF. We determined the relationships among glycemic markers—HbA<sub>1c</sub>, fructosamine (FA), glycated albumin (%GA), and 1,5-anhydroglucitol (1,5-AG)—and continuous glucose monitoring (CGM) in CF, hypothesizing that alternate markers would better predict average sensor glucose (ASG) than HbA<sub>1c</sub>.

## RESEARCH DESIGN AND METHODS

CF participants and a group of healthy control subjects (HCs), ages 6–25 years, wore CGM for up to 7 days. Pearson correlations assessed the relationships between CGM variables and HbA<sub>1c</sub>, FA, %GA, and 1,5-AG. The regression line between HbA<sub>1c</sub> and ASG was compared in CF versus HC. Linear regressions determined whether alternate markers predicted ASG after adjustment for HbA<sub>1c</sub>.

## RESULTS

CF ( $n = 93$ ) and HC ( $n = 29$ ) groups wore CGM for  $5.2 \pm 1$  days. CF participants were  $14 \pm 3$  years of age and 47% were male, with a BMI z score  $-0.1 \pm 0.8$  and no different from HCs in age, sex, or BMI. Mean HbA<sub>1c</sub> in CF was  $5.7 \pm 0.8\%$  ( $39 \pm 9$  mmol/mol) vs. HC  $5.1 \pm 0.2\%$  ( $32 \pm 2$  mmol/mol) ( $P < 0.0001$ ). All glycemic markers correlated with ASG ( $P \leq 0.01$ ): HbA<sub>1c</sub> ( $r = 0.86$ ), FA ( $r = 0.69$ ), %GA ( $r = 0.83$ ), and 1,5-AG ( $r = -0.26$ ). The regression line between ASG and HbA<sub>1c</sub> did not differ in CF versus HC ( $P = 0.44$ ). After adjustment for HbA<sub>1c</sub>, %GA continued to predict ASG ( $P = 0.0009$ ) in CF.

## CONCLUSIONS

HbA<sub>1c</sub> does not underestimate ASG in CF as previously assumed. No alternate glycemic marker correlated more strongly with ASG than HbA<sub>1c</sub>. %GA shows strong correlation with ASG and added to the prediction of ASG beyond HbA<sub>1c</sub>. However, we are not advocating use of HbA<sub>1c</sub> for diabetes screening in CF based on these results. Further study will determine whether glycemic measures other than ASG differ among different types of diabetes for a given HbA<sub>1c</sub>.

<sup>1</sup>Division of Pediatric Endocrinology, Department of Pediatrics, Children's Hospital Colorado, University of Colorado Anschutz Medical Campus, Aurora, CO

<sup>2</sup>Department of Biostatistics, Colorado School of Public Health, Aurora, CO

Corresponding author: Christine L. Chan, [christinel.chan@childrenscolorado.org](mailto:christinel.chan@childrenscolorado.org).

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A strong linear relationship between average glucose and hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) in adults with type 1 and type 2 diabetes (1,2) has been well described. The Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up study have also demonstrated clear correlations between HbA<sub>1c</sub> and the development of microvascular and macrovascular complications in these populations (3,4). However, studies of the association between HbA<sub>1c</sub> and average glucose in individuals with cystic fibrosis (CF) have been limited, and there is controversy surrounding the utility of HbA<sub>1c</sub> in individuals with CF (5–7). HbA<sub>1c</sub> has been described as insensitive for diabetes screening compared with the oral glucose tolerance test (OGTT) in CF (5,8). There has also been speculation that HbA<sub>1c</sub> underestimates average glucose in CF owing to an increased rate of red blood cell turnover (9,10) and high vitamin E intake, resulting in decreased glycosylation (11). However, the evidence for these explanations is limited and the exact reasons behind why HbA<sub>1c</sub> might perform differently in individuals with CF are not well understood.

There is growing interest in the use of alternate markers of glycemia—fructosamine (FA), glycated albumin (GA), and 1,5-anhydroglucitol (1,5-AG)—for diabetes screening and glucose management (12–14), particularly in settings where HbA<sub>1c</sub> may be unreliable (15,16). With the exception of a small study including FA in adults with CF (7), the association between these alternate markers and average glucose in individuals with CF has not been studied.

Our group previously found that alternate glycemic markers correlate with multiple continuous glucose monitoring (CGM) variables (17) and that these markers are sensitive for detecting type 2 diabetes in obese youth with prediabetes (14). Therefore, we enrolled participants with CF and a group of healthy control subjects (HCs) into a study—the Glycemic Monitoring in Cystic Fibrosis Study (GeM-CF)—aimed at characterizing free-living glucose patterns across the glycemic spectrum and have collected alternate markers of glycemia in this cohort. Our objectives here were to examine the relationships among CGM measures (including measures of average glucose, hyperglycemia, and glucose variability) and HbA<sub>1c</sub>, FA, GA, and 1,5-AG in CF compared with HC groups.

We also specifically examined the relationship between average sensor glucose (ASG) and HbA<sub>1c</sub> and compared our findings with those previously described in the DCCT and A1c-Derived Average Glucose (ADAG) cohorts (1,2). Given the speculation surrounding the relationship between HbA<sub>1c</sub> and average glucose in individuals with CF, we hypothesized that alternate measures of glycemia would better predict average glucose than HbA<sub>1c</sub> in this population. Furthermore, because studies in adults with type 1 and type 2 diabetes have suggested that these alternate markers, particularly 1,5-AG and GA, may better predict glucose variability than HbA<sub>1c</sub> (18,19), we also assessed whether alternate markers would outperform HbA<sub>1c</sub> in predicting glycemic variability—specifically, SD, coefficient of variation (CV), and mean amplitude of glycemic excursions (MAGE)—measured by CGM in our CF participants. Despite existing concerns regarding the HbA<sub>1c</sub>–average glucose relationship in CF, HbA<sub>1c</sub> is still commonly used for monitoring glycemic control in individuals with CF-related diabetes (CFRD). Given the importance of glycemic control in reducing pulmonary function decline and mortality in CF (20,21), the findings from this study will better define the optimal tool for monitoring of glycemic control in this population.

## RESEARCH DESIGN AND METHODS

### Study Population

CF and HC participants ages 6–25 years were recruited. CF participants were recruited from our pulmonary and diabetes clinics. HC participants were identified from general endocrine clinics and with recruitment flyers and emails sent to faculty, staff, and students at the University of Colorado Anschutz Medical Campus. Inclusion criteria for CF participants included a diagnosis of CF by newborn screen, sweat chloride testing, or genetic testing. CF patients with glucose abnormalities along the entire glycemic spectrum (i.e., those with normal glycemia, abnormal glycemia, and CFRD) were included. Exclusion criteria for CF included a BMI >85th percentile, known type 1 or type 2 diabetes, use of medications affecting glucose other than insulin (e.g., systemic steroids) in the prior 3 months, changes in insulin dosing in the past 3 months, hospitalization in the prior 6 weeks, or pregnancy. Exclusion criteria for the HC group included known diagnosis

of diabetes or prediabetes, BMI ≥85th percentile, chronic disease, acute illness, or pregnancy. This study was approved by the Colorado Multiple Institutional Review Board (Aurora, CO), and appropriate consent and assent were obtained.

### Study Visit

Study visits took place in the Clinical and Translational Research Center at Children’s Hospital Colorado. Height, weight, BMI, and hip and waist circumference were obtained and physical exam and Tanner staging were completed by a pediatric endocrinologist. CF genotype, presence of pancreatic insufficiency, gastrostomy tube feedings, and use of a CFTR modulator, as well as baseline lung function data from the most recent pulmonary clinic visit, were collected via chart review.

All participants wore a blinded iPro2 CGM (Medtronic, Inc., Northridge, CA) for a minimum of 3 and up to 7 days. They were provided a glucometer (OneTouch; LifeScan) and trained to collect capillary blood glucoses four times daily—prior to meals and at bedtime—and to keep a food log during the week of CGM wear. HC participants underwent an OGTT and collection of baseline laboratories, including HbA<sub>1c</sub> and alternate glycemic markers—FA, GA, and 1,5-AG—on the day of CGM placement. CF participants returned 1 week after CGM placement to undergo the OGTT and collection of HbA<sub>1c</sub> and alternate glycemic markers. The rationale for two study visits for CF patients was to collect CGM data preceding the venipuncture for collection of alternate markers. For example, 1,5-AG reflects glucose patterns in the preceding 2–4 days. However, as HC subjects are not expected to have significant CGM variability, and to minimize the burden associated with coming in for multiple study visits, we combined the CGM placement, blood draw, and OGTT into a single visit, with the CGM device returned by mail.

### Laboratory Procedures

Participants arrived to the outpatient research center between 8:00 A.M. and 10:00 A.M. after a minimum of 8 h of fasting. CF participants with known diabetes on insulin were asked to withhold long-acting insulin for 24 h prior to the visit and short-acting insulin within 4 h of the study visit. Fasting blood glucose was obtained. Glucola was administered at a dose of 1.75 g/kg (maximum dose of 75 g) followed

by a 1-h glucose measurement in CF participants and a 2-h glucose measurement in HC and CF participants. HbA<sub>1c</sub> and OGTT results were used to exclude prediabetes and diabetes in HC participants, and OGTT results were used to classify participants with CF into categories based on glycemic status: normal glycemia (fasting plasma glucose <100 mg/dL, 1-h glucose value <200 mg/dL, and 2-h glucose value <140 mg/dL), abnormal glycemia (fasting plasma glucose 100–125 mg/dL, 1-h glucose >200 mg/dL, and/or 2-h glucose 140–199 mg/dL), and CFRD (fasting plasma glucose ≥126 mg/dL and/or 2-h glucose ≥200 mg/dL).

HbA<sub>1c</sub> was measured on a DCA Vantage Analyzer (Siemens, Deerfield, IL), a DCCT-aligned instrument, with an interday CV of 2.8%. FA was measured on the Roche Modular P Chemistry Analyzer (Roche Diagnostics Corporation) using a colorimetric assay, with interassay CV of 3%. GA was measured with the Lucica GA-L assay (Asahi Kasei Pharma, Tokyo, Japan), an enzymatic method adapted to the Roche Analyzer and calculated as the percentage of GA relative to total albumin (%GA), with an interassay CV of 2.1% (mean 22.7%). Both FA and GA tests were run in Dr. Michael Steffes' laboratory at the University of Minnesota. Because FA is also dependent on total protein but not routinely corrected for this, we used albumin as an estimate for total protein and also assessed FA-adjusted albumin by including albumin as a covariate in the model. 1,5-AG was measured with GlycoMark (Tomen America, New York, NY), a commercially available colorimetric assay, with an interassay CV of 4.1% at 4.67 μg/mL.

### CGM Measures

CGM summary variables were calculated with R, version 3.1.1, software (R Foundation for Statistical Computing, Vienna, Austria [<https://www.r-project.org>]) after manual review of raw glucose values downloaded from CGM software. Analysis of CGM data has previously been described (22). Briefly, CGM measures were calculated in each participant in contiguous 24-h intervals to include an equal percentage of daytime versus nighttime sensor glucoses (288 sensor glucose values per day). Sensor data dependent on total duration of CGM wear, including time spent above/under a glucose cut point, area under the curve (AUC), and number of excursions, were averaged

over the total days of CGM wear. MAGE was calculated using EasyGV, version 9.0.R2 (University of Oxford).

### Statistical Analysis

Descriptive statistics were calculated by cohort (HC vs. CF). Group comparisons were performed using Satterthwaite two-sample *t* tests and Kolmogorov-Smirnov tests for continuous variables and  $\chi^2$  and Fisher exact tests for categorical variables. Pearson correlation coefficients were calculated for HbA<sub>1c</sub>, 1,5-AG, FA, and %GA versus CGM measures for all CF participants. Multiple linear regression models were used to determine whether the alternative markers predicted a given CGM measure (e.g., mean glucose and measures of glycemic variability such as SD and MAGE) after adjustment for HbA<sub>1c</sub>. To test whether the relationship between ASG and HbA<sub>1c</sub> was similar in the CF cohort compared with HC, we used a linear regression model with an interaction term for HbA<sub>1c</sub> and HC. To evaluate whether the relationship between ASG and HbA<sub>1c</sub> was similar in the CF cohort compared with the DCCT and ADAG cohorts, we used the test described by Clogg et al. (23).

### RESULTS

A total of 135 youth and young adults (*n* = 101 CF and *n* = 34 HC) were enrolled. Of those with CF, four had incomplete CGM data, one had a diagnosis of CFTR-related metabolic syndrome, one did not return the glucometer for CGM calibration, and two were diagnosed with pulmonary exacerbations and started on steroids shortly after CGM placement. Among the HCs, four had incomplete CGM data and one had a prediabetes result on the OGTT and was excluded from analysis. Data from the remaining 93 CF and 29 HC participants were included in the final analysis. Descriptive statistics are presented in Table 1. There were no significant differences in age, BMI *z* score, Tanner stage, race, or sex between HC and CF participants. Of the participants with CF, 24 had normal glycemia, 41 had abnormal glycemia, and 28 had CFRD. CF participants had higher fasting and 1- and 2-h OGTT glucose values, higher HbA<sub>1c</sub>, %GA, and lower 1,5-AG than HC. FA values were higher in the overall group of CF participants compared with HC, but this did not reach statistical significance (*P* = 0.06).

CGM results are presented in Table 1. CF and HC wore CGM for a mean ± SD

of 5.2 ± 1 days and obtained 4.0 ± 1 glucometer readings/day for calibration. CGM measures of average glucose, hyperglycemia (maximum glucose, % time spent >140 and >200 mg/dL, and excursions >140 and >200 mg/dL), and glycemic variability (SD, CV, and MAGE) were greater in the CF cohort compared with HC. Minimum sensor glucose and % time spent with glucose level <70 mg/dL were no different between the two groups. CGM results for the CF participants grouped by glycemic category are included in Supplementary Table 1.

Figure 1 compares the regressions of HbA<sub>1c</sub> against average glucose in our CF cohort and in two historical studies of glucose profiles in adults with type 1 diabetes from the DCCT, as well as the ADAG study, which included adults with type 1 and type 2 diabetes as well as control subjects without diabetes. Data from HCs are also plotted. There was no difference in the relationship between HbA<sub>1c</sub> and average glucose between our CF and HC participants (*P* = 0.44). We next compared the relationship between HbA<sub>1c</sub> and average glucose in our CF group with that published in the ADAG study (1), and there were no significant differences in the slope (*P* = 0.15) or intercept (*P* = 0.16) between the two cohorts. We then compared the relationship between HbA<sub>1c</sub> and average glucose in our CF group with that published in the DCCT (2), and although there was a difference in the slope of the regression lines (*P* = 0.04), there was no significant difference in the intercept of the regression lines (*P* = 0.22), between the two cohorts.

Table 2 presents Pearson correlation coefficients between CGM variables and HbA<sub>1c</sub> and alternate glycemic markers in CF participants. All four glycemic measures correlated well with multiple CGM variables, including measures of average glucose, hyperglycemia, and glycemic variability. The magnitude of the correlation coefficients between these glycemic estimates and CGM variables was no greater with any of the alternative markers than with HbA<sub>1c</sub>. All four glycemic measures also correlated with fasting plasma glucose and the 2-h glucose on OGTT, and none of the alternate markers correlated with OGTT measures more strongly than HbA<sub>1c</sub>.

Table 3 presents results of regression of the alternate glycemic markers on ASG,

**Table 1—Demographics and CGM measures**

	CF	HC	<i>P</i>
<i>n</i>	93	29	
Age (years)	14 ± 3	14 ± 4	0.99
Male	44 (47)	12 (41)	0.58
BMI z score	−0.09 ± 0.8	−0.29 ± 0.7	0.21
Weight (kg)	49.4 ± 13.3	46.2 ± 14.7	0.31
Height (cm)	157.8 ± 13.3	155.0 ± 16.1	0.39
Race			0.20
White	83 (89)	25 (86)	
Hispanic	9 (10)	2 (7)	
Other	1 (1)	2 (7)	
Genotype			
Classes I–III	84 (90)		
Classes IV and V	4 (4)		
Unidentified	5 (6)		
Pancreatic insufficient	90 (97)		
Gastronomy tube feedings	18 (19)		
CFTR modulator use	28 (30)		
Insulin use	23 (25)		
FVC (%)	98 ± 14		
FEV <sub>1</sub> (%)	90 ± 13		
Fasting plasma glucose (mg/dL)	97 ± 22	88 ± 8	<0.0007
1-h plasma glucose (mg/dL)	201 ± 61	112 ± 26 ( <i>n</i> = 12)	<0.0001
2-h plasma glucose (mg/dL)	150 ± 50	107 ± 22	<0.0001
CF and normal glycemia	24 (26)		
CF and abnormal glycemia	41 (44)		
CF-related diabetes	28 (30)		
HbA <sub>1c</sub> [% (mmol/mol)]	5.7 ± 0.8 (39 ± 9)	5.1 ± 0.2 (32 ± 2)	<0.0001
FA (mmol/L)	243 ± 34	234 ± 16	0.06
Total albumin (g/dL)	4.2 ± 0.4	4.4 ± 0.3	0.03
GA (%)	13.0 ± 2.7	12.1 ± 0.9	0.01
1,5-AG (μg/mL)	18.9 ± 7.4	23.7 ± 8.2	0.008
CGM measures			
Average glucose (mg/dL)	116 ± 29	101 ± 10	<0.0001
Average day glucose (mg/dL)	118 ± 31	101 ± 10	<0.0001
Average night glucose (mg/dL)	112 ± 27	99 ± 9	0.0001
Maximum day glucose (mg/dL)	217 ± 59	148 ± 23	<0.0001
Maximum night glucose (mg/dL)	170 ± 52	135 ± 23	<0.0001
Minimum glucose (mg/dL)	63 ± 13	66 ± 10	0.21
Average AUC/day (mg/min/dL)	1.7 × 10 <sup>5</sup> ± 4.2 × 10 <sup>4</sup>	1.4 × 10 <sup>5</sup> ± 1.4 × 10 <sup>4</sup>	<0.0001
Excursions >140/day	2.8 ± 1.5	0.8 ± 1	<0.0001
Excursions >200/day	0.5 ± 0.7	0 ± 0	<0.0001
% time >140 mg/dL	14 ± 17	1.9 ± 4.6	<0.0001
% time >200 mg/dL	3 ± 13	0 ± 0	0.03
% time <70 mg/dL	2 ± 4	1.6 ± 2.4	0.18
% time <60 mg/dL	1 ± 3	0.2 ± 0.5	0.01
SD (mg/dL)	25 ± 13	13 ± 3	<0.0001
CV	0.2 ± 0.06	0.1 ± 0.03	<0.0001
MAGE (mg/dL)	58 ± 28	27 ± 8	<0.0001

Data are mean ± SD or *n* (%) unless otherwise indicated. FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity.

SD, CV, and MAGE, with adjustment for HbA<sub>1c</sub> in the CF cohort. Only %GA predicted variability in average glucose and SD beyond that explained by HbA<sub>1c</sub> alone. Assays for %GA take into account total albumin levels, an important consideration in individuals with CF, where malnutrition

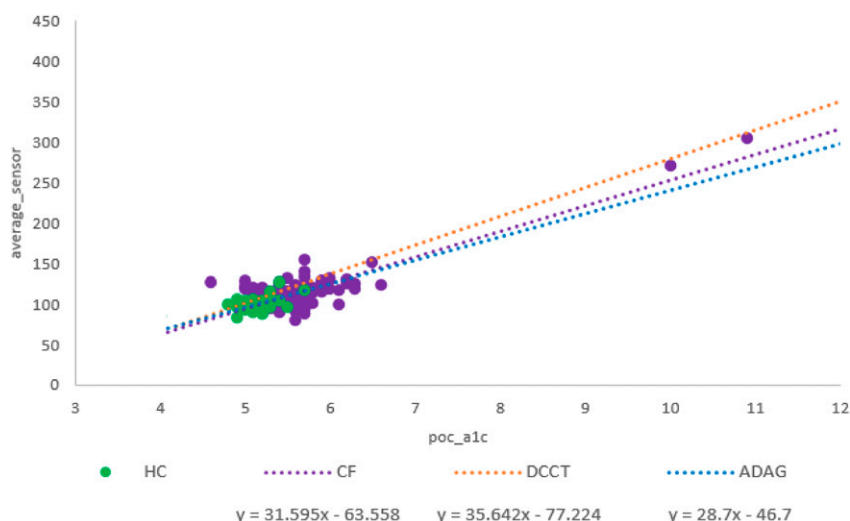
is a concern and albumin levels are often decreased. Our cohort of CF participants had significantly lower albumin levels than HC (*P* = 0.03, Table 1). However, FA measurements, which are also dependent on total protein, are not routinely adjusted for total albumin. Given

the lower levels of albumin in our CF cohort, we performed further analysis of FA with adjustment for albumin. However, despite this correction, FA still failed to predict ASG, SD, CV, and MAGE beyond that explained by HbA<sub>1c</sub>.

## CONCLUSIONS

Our report is the largest to date to describe the relationship between average glucose and HbA<sub>1c</sub> in CF, and it is the first study to examine the relationships among three nontraditional markers of glycemia and multiple CGM measures in CF. Importantly, in contrast to previous reports in the literature, we found that HbA<sub>1c</sub> correlated well with multiple glycemic measures on CGM in CF and that HbA<sub>1c</sub> did not behave differently in CF than in HCs or in adults with type 1 or type 2 diabetes. Therefore, these results support a strong correlation between HbA<sub>1c</sub> and average glucose similar to that seen in individuals without diabetes, as well as those with type 1 and type 2 diabetes (1), and verify findings from a smaller previous report (6) in adults with CF. All nontraditional glycemic markers correlated with average glucose, but of the three, %GA showed the strongest relationship with average glucose, with a correlation similar to that seen between HbA<sub>1c</sub> and average glucose in this population.

We also found correlations between these glycemic markers and multiple components of the CGM profile. Notably, however, none of the alternate markers correlated more strongly with any CGM measure than HbA<sub>1c</sub>. Only one other article has examined the relationship between an alternate glycemic marker, FA, and average glucose in individuals with CFRD (7), but the sample size was small (*n* = 13) and HbA<sub>1c</sub> distribution narrow (mean ± SD 6.4 ± 0.6% and range 5.5–7.3%). These authors concluded that there was no relationship between FA and average glucose in CF. However, they also did not find a significant relationship between FA and average glucose in their equally small group of participants with type 1 diabetes (*n* = 15), a correlation that has been well documented in larger studies, suggesting that their findings were constrained by low power. No studies have previously examined GA or 1,5-AG as a tool for monitoring glycemic control in any CF population. Although both correlated with multiple CGM variables, a novel



**Figure 1**—Scatterplots of HbA<sub>1c</sub> vs. ASG. ADAG = adults with type 1 diabetes and type 2 diabetes and control subjects in the study by Rohlfing et al. (2). DCCT = adults with type 1 diabetes in the study by Nathan et al. (1). CF and HC = our cohort.

finding in our study is that GA performed comparably with HbA<sub>1c</sub> and, additionally, added to the prediction of mean glucose and SD even after adjustment for HbA<sub>1c</sub>. 1,5-AG has been touted as a useful marker of glycemic excursions (24); however, in this cohort of CF youth and young adults, it did not outperform HbA<sub>1c</sub> in predicting SD, CV, or MAGE. Notably, CF participants on insulin were instructed to hold long-

acting insulin for 24 h and short-acting insulin for 4 h before the study visit, which conceivably could have impacted 1,5-AG results. However, we would have expected this to bias results in favor of this short-term alternate marker, which was not seen. Therefore, in scenarios where HbA<sub>1c</sub> may be unreliable, such as anemia or hemoglobinopathies in individuals with CF, GA, reported as %GA

with correction for total albumin, appears to be a suitable alternative. However, its utility may be limited until the test becomes more widely available.

The relationship between HbA<sub>1c</sub> and average glucose has been called into question based on reports describing poor sensitivity of HbA<sub>1c</sub> for diagnosing CFRD detected by OGTT (5,25,26). Langg et al. (26) reported a normal HbA<sub>1c</sub> in 70% of 46 patients diagnosed with CFRD by OGTT. Holl et al. (25) found that only 1 of 13 patients with CF diagnosed with diabetes by American Diabetes Association and World Health Organization criteria had an HbA<sub>1c</sub> >6.5%, while 3 had an HbA<sub>1c</sub> between 5.7 and 6.5% and 9 had a normal HbA<sub>1c</sub> (<5.7%); the 2-h glucose for patients with HbA<sub>1c</sub> <5.7% was no different than for those with HbA<sub>1c</sub> ≥5.7%. Burgess et al. (8) found that a lower HbA<sub>1c</sub> threshold of 5.8% appeared to improve sensitivity of this test to 93% for detecting diabetes by OGTT; in contrast, Boudreau et al. (5) retested this threshold, and in their cohort, HbA<sub>1c</sub> only had a sensitivity of 68% for identifying CFRD by OGTT. However, the conclusion that HbA<sub>1c</sub> therefore underestimates glycemia in CF based on comparisons with the OGTT is inaccurate, as HbA<sub>1c</sub> and OGTT are in fact measuring two different components of glycemia and are not interchangeable. HbA<sub>1c</sub> reflects a weighted mean of glucose levels over the past 3 months, while the OGTT 2-h glucose is a single measurement of an individual's response to an oral glucose load. Therefore, a low concordance for diagnosing diabetes between the two tests in CF should not lead to the conclusion that HbA<sub>1c</sub> underestimates average glucose. Moreover, poor sensitivity of HbA<sub>1c</sub> in diagnosing diabetes by OGTT is not confined to CF and has been documented in other populations (27,28).

Only two small studies, to our knowledge, have attempted to directly examine the relationship between HbA<sub>1c</sub> and average glucose in CF, with contradictory results. Godbout et al. (7) did not find a relationship between HbA<sub>1c</sub> and mean plasma glucose (measured by capillary blood glucose testing pre- and postmeal, bedtime, and overnight), collected 3 days/month over 3 months in 13 adults with CF. However, the study may have been underpowered and without a wide enough distribution of HbA<sub>1c</sub> values (5.5–7.3% [37–56 mmol/mol]). In contrast, in a pilot study by Brennan et al. (6) on the

**Table 2**—Pearson correlation coefficients between HbA<sub>1c</sub> and alternative markers versus CGM variables in CF participants

CGM variable	HbA <sub>1c</sub>	1,5-AG	FA	%GA
Average glucose	0.86§	−0.26*	0.69§	0.83§
Average day glucose	0.87§	−0.28†	0.66§	0.83§
Average night glucose	0.77§	−0.17	0.70§	0.78§
Maximum day glucose	0.51§	−0.23*	0.34†	0.49§
Maximum night glucose	0.59§	−0.18	0.48§	0.62§
Minimum sensor glucose	−0.26*	0.26*	−0.26*	−0.32†
Average AUC/day	0.86§	−0.26*	0.69§	0.83§
Excursions >140/day	−0.08	0.15	−0.17	−0.09
Excursions >200/day	0.31†	−0.18	0.16	0.27*
% time >140 mg/dL	0.77§	−0.23*	0.61§	0.73§
% time >200 mg/dL	0.91§	−0.36‡	0.78§	0.90§
% time <70 mg/dL	−0.02	−0.09	−0.03	−0.02
% time <60 mg/dL	−0.01	−0.03	−0.05	−0.02
SD	0.77§	−0.34‡	0.55§	0.74§
CV	0.40§	−0.30†	0.21*	0.34‡
MAGE	0.61§	−0.32†	0.41§	0.60§
OGTT measures				
Fasting plasma glucose	0.62§	−0.27†	0.61§	0.62§
1-h glucose	0.29†	−0.23*	0.18	0.26*
2-h glucose	0.57§	−0.30†	0.34‡	0.46§

\*P < 0.05; †P < 0.01; ‡P < 0.001; §P < 0.0001.

**Table 3—Regression of alternate markers on CGM measures of glycemia in CF**

Model	Covariate	Outcome	Regression coefficient $\pm$ SE*	P
1	FA	Mean glucose	0.09 $\pm$ 0.07	0.21
2	FA	SD	−0.02 $\pm$ 0.04	0.63
3	FA	MAGE	−0.07 $\pm$ 0.11	0.48
4	FA	CV	−3 $\times$ 10 <sup>−4</sup> $\pm$ 3 $\times$ 10 <sup>−4</sup>	0.29
5	GA	Mean glucose	3.79 $\pm$ 1.07	0.0009
6	GA	SD	1.51 $\pm$ 0.61	0.015
7	GA	MAGE	3.08 $\pm$ 1.71	0.08
8	GA	CV	0.003 $\pm$ 0.005	0.40
9	1,5-AG	Mean glucose	0.18 $\pm$ 0.23	0.43
10	1,5-AG	SD	−0.15 $\pm$ 0.12	0.24
11	1,5-AG	MAGE	−0.48 $\pm$ 0.34	0.17
12	1,5-AG	CV	−0.001 $\pm$ 0.001	0.11
13	FA-albumin adjusted	Mean glucose	0.11 $\pm$ 0.08	0.16
14	FA-albumin adjusted	SD	0.02 $\pm$ 0.04	0.64
15	FA-albumin adjusted	MAGE	0.04 $\pm$ 0.12	0.76
16	FA-albumin adjusted	CV	2 $\times$ 10 <sup>−5</sup> $\pm$ 3 $\times$ 10 <sup>−4</sup>	0.94

\*Adjusted for HbA<sub>1c</sub>.

relationship between HbA<sub>1c</sub> and mean glucose measured by CGM over a 48-h period in 20 adults with CF, 10 with CFRD, and a wider range of HbA<sub>1c</sub> values (4 to >9% [20 to >75 mmol/mol]), the authors found a relationship between HbA<sub>1c</sub> and mean glucose similar to that described in the DCCT. Our study confirms the findings of the latter article, shows an HbA<sub>1c</sub> and average glucose relationship similar to that in other populations with diabetes, and includes a much larger sample size of individuals with CF and wider range of HbA<sub>1c</sub> values (4.6–10.9%, 27–96 mmol/mol).

Increased red blood cell turnover in CF has been proposed as an explanation for lower HbA<sub>1c</sub> values in individuals with CF; however, evidence to support this claim is limited. Only two small studies on red blood cell half-life in adults with CF have been reported, one of which was a conference abstract (9,10). The study by Wagener et al. (10) found “minimally decreased” red blood cell turnover in 6 of 10 patients with CF. The conference abstract found no differences in red blood cell half-life in nine adults with CF compared with normal values, although two patients studied during acute exacerbation did have more rapid red blood cell turnover. In contrast, iron deficiency anemia has been reported as common in CF (29), and iron deficiency is typically associated with higher HbA<sub>1c</sub> owing to decreases in red blood cell turnover (11), further confounding this relationship.

Furthermore, it is important to remember that significant interindividual variability in glycation rates exists and this phenomenon has been well described in individuals with type 1 diabetes (1,15). A recent study modeling hemoglobin glycation and red blood cell kinetics suggests that all glucose-independent variation in HbA<sub>1c</sub> may in fact be explained by interindividual differences in red blood cell turnover (30). Although iron indices and red blood cell kinetics were not assessed in our cohort, our findings suggest that the relationship between HbA<sub>1c</sub> and average glucose in individuals with CF is not significantly different from that seen within the general population.

Whether average glucose is the best measure of glycemic control is also a subject of debate. Other glycemic measures such as glucose variability—as measured by the amplitude and duration of glycemic excursions—are not reflected by HbA<sub>1c</sub> and have been proposed as potentially important determinants of micro- and macrovascular disease (31–33) in type 1 and type 2 diabetes. We previously reported associations between glycemic variability captured by CGM and retrospective lung function decline in CF (22). Nontraditional markers of glycemia have been proposed as potentially better indicators of acute glucose fluctuations (34) and glucose excursion (18) than HbA<sub>1c</sub> in other populations with diabetes. Therefore, we also assessed the correlations between HbA<sub>1c</sub> and our alternate markers,

with SD, CV, and MAGE, and found good correlations, although only GA continued to explain some of this variability after adjustment for HbA<sub>1c</sub>.

### Limitations

Our estimates for average glucose were generated from 1 week of CGM wear, while HbA<sub>1c</sub> represents a weighted measure of average glucose over the preceding 3 to 4 months. Glucose levels in the preceding 30 days have been found to contribute to ~50% of the final HbA<sub>1c</sub> result, while glucose levels from 90 to 120 days prior only contribute ~10% (2). Although the DCCT (via seven-point capillary blood glucose profiles submitted at quarterly visits) and ADAG studies collected measures of average glycemia intermittently over the preceding months, published reports have validated the Nathan equation and HbA<sub>1c</sub>-to-average blood glucose relationship from only 24 h of CGM data (35). In addition to red blood cell turnover, renal failure also impacts HbA<sub>1c</sub> owing to a complex interplay of contributing factors including uremia and alterations in red blood cell life span (11). We did not obtain measures of renal function, another limitation of this study, although renal failure is not a typical complication seen in adolescents with CF and would not be expected in an asymptomatic, healthy child. Most individuals in this study had HbA<sub>1c</sub> values <7%, which makes extrapolation of the HbA<sub>1c</sub> and average glucose relationship more difficult. We attempted to enroll as many participants as possible with higher HbA<sub>1c</sub> values, but given the early stage of disease in most youth with CF, we were limited by the range of CFRD severity in our clinic population. Although we would not expect physiology underlying the HbA<sub>1c</sub>-mean glucose relationship to change at different HbA<sub>1c</sub> values, whether adults with CF with lower pulmonary function or individuals with frequent pulmonary exacerbations and extended periods of chronic inflammation might have greater red blood cell turnover and a different HbA<sub>1c</sub>-ASG relationship requires further study. Furthermore, whether individuals with CF, compared with those with prediabetes or type 2 diabetes, for example, have greater hyperglycemia or glucose variability by measures other than average glucose for a given HbA<sub>1c</sub> requires further study.

Notably, whether HbA<sub>1c</sub> is an appropriate screening test for CFRD was not

specifically addressed in this analysis, and we are not advocating use of HbA<sub>1c</sub> for routine CFRD screening based on this study's findings. When OGTT cut points by American Diabetes Association criteria are applied to define CFRD, prior studies have found that HbA<sub>1c</sub> underperforms. Although the OGTT identifies individuals with CF with diabetes and clinical decline that improves after initiation of insulin therapy (36,37), current cut points were derived from populations with type 2 diabetes with the goal of identifying those at risk for retinopathy, and the best tests for screening and diagnosing CFRD are yet to be determined. Whether CFRD might be redefined by CF-specific cut points including abnormalities of intermediate OGTT time points (38) or CGM (39), in order to better identify those at risk for pulmonopathy or nutritional decline from abnormalities in glucose metabolism, requires further study.

### Conclusion

Both HbA<sub>1c</sub> and nontraditional markers of glycemia correlate well with multiple glycemic patterns on CGM in CF. None of the alternate markers outperformed HbA<sub>1c</sub> at predicting average glucose, but we have extended the literature showing that GA is also correlated with glycemic control in CF. Prospective studies examining the relationship between glycemic outcomes other than average glucose or HbA<sub>1c</sub> and CF-relevant clinical outcomes are needed.

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