Screening for cystic fibrosis-related diabetes and prediabetes: Evaluating 1,5-anhydroglucitol, fructosamine, glycated albumin, and hemoglobin A1c

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Abstract

Objective: Dysglycemia is prevalent in cystic fibrosis (CF) but screening with annual oral glucose tolerance tests (OGTT) can be burdensome. We investigated alternate glycemic markers—hemoglobin A1c (HbA1c), 1,5-anhydroglucitol (1,5AG), fructosamine (FA), and glycated albumin (GA)—as screening tests for CF-related diabetes (CFRD) and pre-diabetes (CFPD) in youth with CF as defined by the gold-standard OGTT 2-hour glucose (2hG).

Methods: Youth 10 to 18 years with CF had a 1,5AG, FA, GA, HbA1c, and 2-hour OGTT collected. Correlations between all glycemic markers and 2hG were evaluated. Area under the receiver operative characteristic (ROC-AUC) curves were generated. Optimal cut points for predicting CFPD (2hG ≥ 140 mg/dL) and CFRD (2hG ≥ 200 mg/dL) were determined.

Results: Fifty-eight youth with CF were included (2hG < 140, n = 16; CFPD, n = 33; CFRD, n = 9; 41% male, mean ± SD age 14.2 ± 3.6 years, BMI *z*-score 0.0 ± 0.8, % predicted forced expiratory volume in 1 second [FEV1] 89.9 ± 15.1, % predicted forced vital capacity [FVC] 103.2 ± 14.6). ROC-AUC's for all alternate markers were low for CFPD (0.52–0.67) and CFRD (0.56–0.61). At a cut point of 5.5%, HbA1c had 78% sensitivity (95% CI: 0.45–0.94) and 41% specificity (95% CI: 0.28–0.55) for identifying CFRD, correlating to a ROC-AUC of 0.61 (95% CI: 0.42–0.8).

Conclusions: All alternate markers tested demonstrate poor diagnostic accuracy for identifying CFRD by 2hG.

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1 | BACKGROUND

Cystic fibrosis-related diabetes (CFRD) is common in the cystic fibrosis (CF) population and is increasing in prevalence as long-term survival rates increase.[1] While only 2% of children with CF are estimated to meet criteria for CFRD, this figure increases to 19% in adolescents and 40% to 50% in adults.[1] CFRD results from a combination of insulinopenia and to a lesser degree, insulin resistance.[2] CFRD is associated with poorer clinical outcomes including diminished lung function, suboptimal nutritional status as demonstrated by poor weight gain, and increased mortality risk.[3–6] Early treatment with insulin is associated with improved outcomes; thus, ensuring that CFRD is identified is critical.

The current gold-standard for CFRD screening and diagnosis is the oral glucose tolerance test (OGTT) and guidelines from the Cystic Fibrosis Foundation and the American Diabetes Association recommend annual screening in all patients with CF 10 years of age.[7] The Cystic Fibrosis Foundation Patient Registry's Annual Report reveals poor adherence to OGTT screening guidelines, as only 61.7% of individuals aged 10 to 17 years with CF who have not been previously diagnosed with CFRD had documented OGTT screening in 2017.[8] This number decreased to only 29.1% in individuals 18 years or older who meet the same criteria.[8] Poor adherence to OGTT screening is likely multifactorial and possible contributing factors include the time-consuming nature of the test, the necessary pretest fasting period, the need for serial blood draws, and the lack of familiarity with OGTT's in the pulmonary clinic setting. For this reason, determining the utility of simpler, non-fasting alternatives for CFRD screening is necessary.

Hemoglobin A1c (HbA1c) has been shown to be insensitive for detecting CFRD, as defined by current diagnostic thresholds, and although lower HbA1c cut points have been proposed to increase sensitivity for detecting CFRD, these cut points are controversial.[9,10] Historically, HbA1c has been thought to be an insensitive screening test in CFRD due to increased red blood cell turnover, thus resulting in an underestimation of glycemia.[11] However, a recent report by our group demonstrated a HbA1c and average glucose relationship in youth with CF that was, in fact, no different from other diabetes populations.[12]

Alternate measures of glycemia—fructosamine (FA), glycated albumin (GA), and 1,5-anhydroglucitol (1,5AG)—have been found, in other populations, to be potentially useful screening tests for diabetes.[13] A study of FA in a small population of adults with CF found that FA adjusted for total protein exhibited a positive correlation with 2hG on OGTT and a negative correlation with forced expiratory volume in 1 second (FEV1).[14] Unlike HbA1c, FA and GA are composed of non-immunoglobulin serum proteins that are not dependent on the half-life of red blood cells.[15,16] FA is formed when blood glucose covalently binds to serum proteins to form ketoamines[15] while GA is produced through the glycation of serum

albumin.[16] This process occurs approximately 10-fold faster with albumin than with hemoglobin and may be particularly useful for identifying situations of elevated postprandial hyperglycemia and increased glucose excursions.[16] Consequently, both alternative markers are not affected by increased red blood cell turnover and reflect more recent glycemic control over the preceding 14 to 21 days.[17] Another biomarker, 1,5AG, a naturally occurring dietary polyol, may also better reflect postprandial hyperglycemia as it competes with glucose for reabsorption in the kidneys.[18] Lower 1,5AG levels are seen in the setting of hyperglycemia and glucosuria over the preceding 1 to 2 weeks.[18]

The aim of this study was to investigate alternative markers of glycemia, specifically HbA1c, FA, GA, and 1,5AG, as screening tests for CFPD and CFRD.

2 | RESEARCH DESIGN AND METHODS

2.1 | Study population

Youth aged 10 to 18 years with a known diagnosis of CF were identified from pulmonary and endocrinology clinics and recruited to participate in a larger study on early glucose abnormalities in CF. Those individuals with available OGTT and alternate glycemic marker data who were not on insulin therapy were included in this analysis. Inclusion criteria for a diagnosis of CF included a positive newborn screen, positive sweat chloride test, and/or positive genetic test. Exclusion criteria included a known diagnosis of type 1 or type 2 diabetes mellitus, a history of insulin or other medications affecting glucose metabolism, including steroids, in the preceding 3 months, hospitalizations in the prior 6 weeks, or pregnancy. The study was approved by the Colorado Multiple Institutional Review Board (Aurora, Colorado) and age-appropriate consent and/or assent was obtained.

2.2 | Study visit

Participants presented to Children's Hospital Colorado Clinical and Translational Research Center for a single study visit. Height and weight were collected, and body mass index was calculated. A pediatric endocrinologist completed a physical exam including Tanner staging. Participant medical records were reviewed, and the following were recorded: CF genotype and pulmonary function testing from the most recent pulmonary clinic visit.

2.3 | Laboratory procedures

All participants were asked to fast for a minimum of 8 hours prior to the study visit. Blood was obtained for measurement of HbA1c, 1,5AG, FA, and GA. An OGTT was completed with samples collected for measurement of blood glucose and insulin levels at 0, 60, and 120 minutes after glucola was administered (1.75 g/kg; maximum dose of 75 g). Normoglycemia was defined as a 2hG < 140 mg/dL. CFPD was defined as a 2hG ≥ 140 mg/dL. CFRD was defined as a 2hG ≥ 200 mg/dL.

HbA1c was measured on a DCCT-aligned DCA Vantage Analyzer (Siemens, Deerfield, Illinois) with an inter-day coefficient variation (CV) of 2.8%. Measurements were obtained on a point-of-care device. The normal reference range for HbA1c is <5.7%.[19] FA was measured using a colorimetric assay with an inter-assay CV of 3% on the Roche Modular P

Chemistry Analyzer (Roche Diagnostics Corporation). The normal reference range for FA is 205 to 285 μmol/L.[20] Because FA originates from non-enzymatic glycation of proteins, it is both glucose and protein concentration dependent.[21] FA was corrected for albumin concentration with the following calculation: albumin-adjusted fructosamine (AAFA) = FA × 4/albumin. GA was measured as a percentage of glycated albumin relative to the total amount of albumin via an enzymatic method adapted to the Roche Analyzer per the Lucica GAL assay (Asahi Kasei Pharma, Tokyo, Japan) with an inter-assay CV of 2.1% and a mean of 22.7%. The normal reference range for GA is 11% to 16%.[22] FA and GA were measured in the lab of Dr. Michael Steffes at the University of Minnesota. 1,5AG was measured via a colorimetric assay (GlycoMark, Tomen America, New York) with an inter-assay CV of 4.1% at 4.67 μg/mL. The normal reference range for 1,5AG is 10 to 31 μg/mL.[23]

Spirometry data were gathered from routine pulmonary clinic visits. Forced expiratory volume in 1 second % predicted (FEV1) and forced vital capacity % predicted (FVC) were collected from the most recent CF clinic visit where the participant was noted to be at baseline health status. Values were calculated as percentages of normal per the Global Lung Initiative (GLI), a standard measure of reporting lung function that is adjusted for age, sex, height, and race/ethnicity.[24]

2.4 | Statistical analysis

Mean (±SD) for normally distributed measures and median (IQR) for skewed measures were reported. An overall analysis of variance F test or Cochran-Mantel-Haenszel test was used to assess differences between the three groups of participants. Pearson's correlation coefficient was used to determine the correlation between estimates of glycemia (HbA1c [%], 1,5-AG [μg/mL], FA [μmol/L], GA [%]) and the 2hG on OGTT. Logistic regression models assessed the ability of the alternate markers to predict 2hG categories (CFPD 140 mg/dL and CFRD 200 mg/dL) by comparing area under the receiver operating characteristic curve (ROC-AUC). The cut points for alternate markers that maximized the Youden index for 2hG categories (CFPD and CFRD) were determined. Participants were categorized as either above or below the identified cut points for each alternate glycemic marker. Welch's t tests compared the lung function between groups to assess for any differences in FEV1 and FVC. Statistical significance level was set at alpha < .05 level. The data analysis was performed using SAS software 9.4 (Cary, North Carolina).

3 | RESULTS

Fifty-eight youth with CF were included in this analysis. Demographic characteristics are presented in Table 1. Participants had a mean age of 14.2 ± 3.6 years and a mean BMI = z-score − 0.02 ± 0.82. Forty-one percent were male, 91% were white, 7% were Hispanic, and 2% were black. Sixteen participants had normal glucose tolerance (28%), 33 had CFPD (57%), and 9 had CFRD (15%). Table 1 presents mean values for each alternate marker when classified by 2hG (normoglycemia [NG] vs CFPD vs CFRD). HbA1c, FA, and GA correlated with 2hG (0.38, 0.27, 0.28; p < .05); however, only HbA1c was significantly different among each of the three 2hG groups.

ROC curves were generated to determine optimal cut points that maximize sensitivity and specificity for detecting a 2hG ≥ 200 mg/dL and ≥ 140 mg/dL (Figure 1A,B). ROC-AUCs for all alternate markers were low for both CFPD (AUC's 0.52–0.67) and CFRD (AUC's 0.56–0.61). HbA1c had the highest ROC-AUC of 0.61 (95% CI: 0.42–0.8) for identifying CFRD and 0.67 (95% CI: 0.53–0.8) for CFPD. Optimal cut points for identifying CFRD by 2hG for each alternate marker are as follows: HbA1c = 5.5%, FA = 225 μmol/L, AAFA = 59 μmol/g, GA = 14%, and 1,5AG = 20.4 mcg/mL (Table 2).

FEV1 and FVC measurements for individuals who fell above and below the identified cut points for each alternate glycemic marker were compared. Individuals who fell above the HbA1c cut point of 5.5% demonstrated a significant difference in FVC when compared to individuals who fell below the cut point (105% vs. 96%, $p = .02$). FEV1 was higher in those with HbA1c levels below this cut point vs. those with HbA1c levels above this point; however, the difference was not statistically significant (96% vs. 88%, $p = .06$). Pulmonary function data reflected a relatively healthy cohort of youth with CF with an average FEV1 = $89.9 \pm 15.1\%$ and a FVC = $103.2 \pm 14.6\%$.

4 | DISCUSSION

This is the first study to examine four simple glycemic estimates as potential screening tools for CFPD and CFRD. In contrast to studies in non-CF populations, these tests demonstrated a poor ability to identify CFPD and CFRD as defined by the gold-standard 2hG on OGTT. HbA1c had the highest sensitivity and specificity for detecting CFPD and CFRD, but at a lower cut point than previously reported and with a modest ROC-AUC of 0.61 and 0.67, respectively. Therefore, in this population of youth with CF and high rates of early dysglycemia, none of these simpler glycemic estimates appear suitable for replacing OGTT for diabetes screening.

Our understanding of the meaning of HbA1c, and what it reflects in CF, has evolved over time. Traditionally, HbA1c has been shunned as a screening test for CFRD due to concerns for inaccuracies in the CF population speculated to be secondary to shortened red blood cell lifespan, chronic iron deficiency anemia, and/or alterations in hemoglobin glycation rates.[11,25] A recent publication by our group, however, found that the relationship between HbA1c and mean plasma glucose in a cohort of youth with CFRD was similar to that reported in landmark studies in individuals with type 1 and type 2 diabetes.[12] A previously published small study involving 20 adults with CF came to similar conclusions.[26] Reports on the utility of HbA1c as a screening test for CFRD, defined by the OGTT, have been conflicting. Burgess et al found that screening for CFRD using a HbA1c cut point of 5.8% had a 93.8% sensitivity and reduced the need for an OGTT by 50%; however, it is notable that their study methods differed from ours as the mean age of their participants was older at 31.7 ± 10.4 years and HbA1c methodology was different.[9] In contrast, Boudreau et al found that the same HbA1c cut point of 5.8% only had a 68.2% sensitivity for identifying CFRD and decreasing the HbA1c cut point to 5.5% was noted to increase the sensitivity to 95%.[10] Our study demonstrated a similar optimal HbA1c cut point of 5.5%; however, it was associated with a lower sensitivity of 80% and a poor specificity. One explanation for these discrepancies may be the different analytical performances of the assays used.[27,28]

Additionally, for each alternate glycemic marker we completed a dichotomous assessment of pulmonary function of individuals who fell above the cut point maximizing sensitivity and specificity for identifying either CFRD or CFPD vs. those who fell below the cut point. Notably, the only cut point that identified individuals with better vs. worse pulmonary function was the HbA1c cut point of 5.5% for identifying CFRD. However, there was no difference in pulmonary function between glycemic groups categorized by the gold-standard 2hG on OGTT. Therefore, the significance of the HbA1c and its relationship to pulmonary function requires further study. Of note, other studies have shown that earlier time points on the OGTT (i.e., 30 minutes and 1 hour) may more accurately identify early clinical changes in pulmonary function than the 2hG.[29,30]

Fructosamine is a ketoamine formed secondary to non-enzymatic protein glycation and it has traditionally been used in situations where HbA1c is unreliable.[18] Studies have shown that FA correlates with total protein and albumin concentrations; consequently, correction for total protein or albumin improves both diagnostic performance and correlation with HbA1c in identifying diabetes.[14,31] A small study recently examined the utility of FA in CFRD and found that FA appeared to be a reliable tool for CFRD screening and correlated inversely with FEV1 in individuals with CFRD.[14] The findings in our population, however, differ and this may be secondary to differences in demographics as our population was younger and included a higher proportion of individuals with CFPD and CFRD. Our population was also healthier overall with less variability in pulmonary function.

Like FA, GA is produced through glycation of albumin and reflects mean plasma glucose over the preceding 2 to 3 weeks.[16,17] This study is the first to evaluate the use of GA in the CF population. Studies in non-CF populations have suggested utility of GA as a screening test,[32] but no studies have previously assessed this marker in the CF population. GA has been described to more accurately identify situations of increased BG variability and postprandial hyperglycemia,[16] and both glucose patterns are seen in early CFRD. However, GA was not identified as a useful tool for CFPD or CFRD screening in our cohort.

Last, 1,5AG, a naturally occurring dietary polyol that competes with glucose for reabsorption in the kidneys, reflects BG control over the preceding few days to 2 weeks.[18] In a study of glycemic excursions in individuals with type 1 and type 2 diabetes, Dungan et al found that 1,5AG better identified postprandial glucose excursions on CGM than either HbA1c or FA.[33] A study in Japanese adults found that 1,5AG maximized sensitivity and specificity in predicting type 2 diabetes as defined by OGTT when compared to both HbA1c and FA.[34] Only one prior study has assessed 1,5AG as a screening test for CFRD, but this study was limited to 10 adults with CF and found no correlation with 2hG or HbA1c.[35] Similarly, we did not demonstrate clinical utility for 1,5AG in diagnosing CFRD.

While we specifically evaluated the utility of 1,5AG, FA, GA, and HbA1c as screening markers for detecting dysglycemia in the CF population, further study is required to determine whether these tools may have value for monitoring glycemia over time in individuals with CFRD. Additionally, it is important to note that all four alternative markers estimate average glycemia over various time periods. In early CFRD, where postprandial glycemic excursions are the most common abnormality, simple estimates of average

glycemia may not reveal abnormalities that OGTT or other screening tools such as continuous glucose monitoring can detect. Continued examination of these markers and their relationship to prospective clinical outcomes is needed.

5 | STRENGTHS AND LIMITATIONS

Our study presents novel data evaluating the use of four alternative glycemic markers not previously studied concurrently in the CF population. These markers, however, demonstrated poor utility in identifying CFRD and CFPD, as defined by the 2-hour OGTT glucose, in our group of CF youth. Studies including larger sample sizes and a wider age range of individuals with CF are needed. However, it is important to remember that the OGTT criteria for diagnosing CFRD were adapted from cut points established to detect microvascular disease in individuals at risk for type 2 diabetes[36,37] and are not CF-population specific. Additional studies to identify the optimal OGTT cut points for predicting CF-relevant clinical outcomes are needed.

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Abbreviations:

1,5AG	1,5-anhydroglucitol
2hG	2-hour glucose
AAFA	albumin-adjusted fructosamine
BMI	body mass index
CF	cystic fibrosis
CFPD	cystic fibrosis related prediabetes
CFRD	cystic fibrosis related diabetes
FA	fructosamine
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity

GA	glycated albumin
HbA1c	hemoglobin A1c
OGTT	oral glucose tolerance test
ROC-AUC	area under the receiver operating characteristic curve

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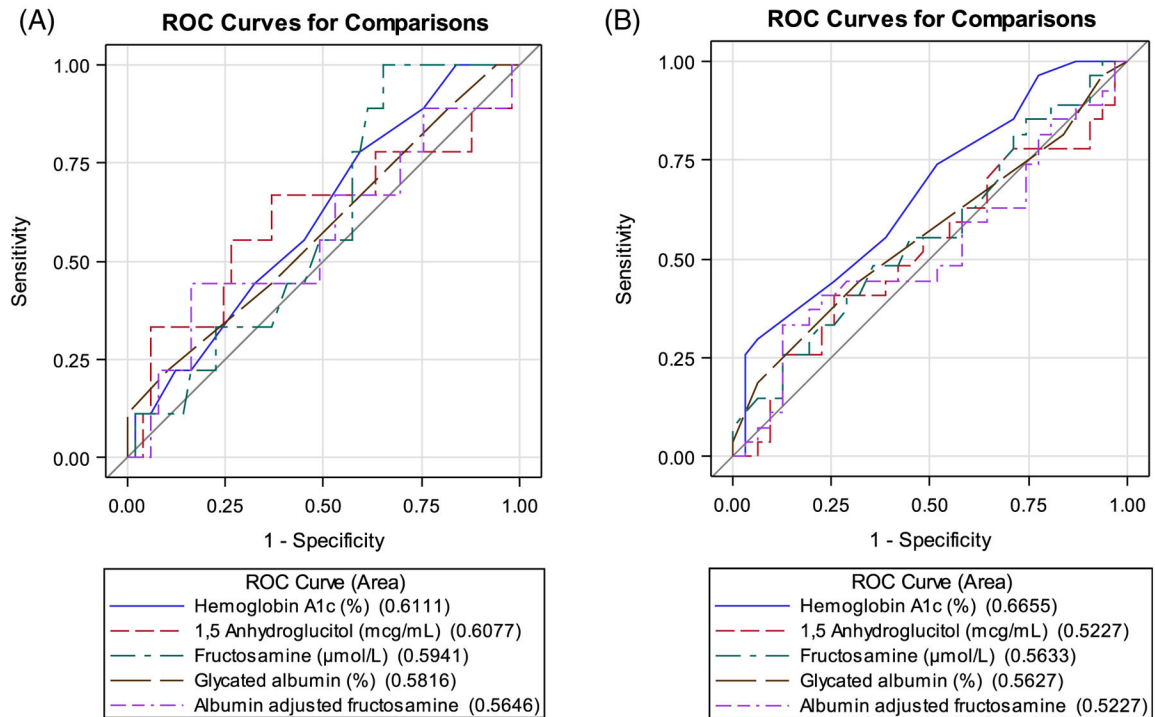
FIGURE 1.

(A) Oral glucose tolerance test 2-hour glucose 200 mg/dL. Area under the receiver operating characteristic (ROC-AUC) curve measurements for alternative glycemic markers at predicting cystic fibrosis-related diabetes. ROC-AUC values (95% CI): hemoglobin A1c 0.61 (0.42, 0.80), 1,5-anhydroglucitol 0.61 (0.37, 0.85), fructosamine 0.59 (0.42, 0.77), glycated albumin 0.58 (0.37, 0.79), and albumin-adjusted fructosamine 0.56 (0.33, 0.80). All associated p-values were non-significant. (B) Oral glucose tolerance test 2-hour glucose 140 mg/dL. Area under the receiver operating characteristic (ROC-AUC) curve measurements for alterative glycemic markers at predicting cystic fibrosis-related pre-diabetes. ROC-AUC values (95% CI): hemoglobin A1c 0.67 (0.53, 0.8), 1,5-anhydroglucitol 0.52 (0.37, 0.68), fructosamine 0.56 (0.41, 0.71), glycated albumin 0.56 (0.42, 0.71), and albumin-adjusted fructosamine 0.52 (0.37, 0.69). All associated p-values were non-significant

TABLE 1

Demographics and baseline mean values for alternate markers categorized by 2-hour glucose (2hG)

	Mean for all (N = 58)	NG: 2hG < 140 mg/dL (N = 16)	CFPD: 2hG 140 mg/dL (N = 33)	CFRD: 2hG 200 mg/dL (N = 9)	p-value
Age (years)	14.2 ± 3.6	13.9 ± 3.8	14.3 ± 3.7	13.9 ± 3.2	.91
Male, N (%)	24 (41.4)	6 (37.5)	16 (48.5)	2 (22.2)	.34
Race, N (%)					.47
White	53 (91.4)	14 (87.5)	30 (90.9)	9 (100.0)	
Hispanic	4 (6.9)	1 (6.2)	3 (9.1)	0 (0.0)	
Black	1 (1.7)	1 (6.2)	0 (0.0)	0 (0.0)	
BMI z-score	−0.02 ± 0.82	−0.20 ± 0.77	0.15 ± 0.84	−0.29 ± 0.82	.22
FEV1 (%)	89.89 ± 15.14	93.39 ± 11.03	88.42 ± 16.71	89.01 ± 16.29	.60
FVC (%)	103.19 ± 14.60	104.50 ± 10.66	101.52 ± 16.39	107.00 ± 14.14	.56
Pancreatic sufficiency status, n (% sufficient)	4 (6.9)	3 (18.8)	1 (3.0)	0 (0.0)	.09
G-tube feedings present, n (% yes)	8 (13.8)	2 (12.5)	4 (12.1)	2 (22.2)	.73
Genotype class, n (%)					.02
Class I-III	44 (77.2)	8 (53.3)	28 (84.8)	8 (88.9)	
Class IV-V	6 (10.5)	5 (33.3)	1 (3.0)	0 (0.0)	
OGTT glucose (mg/dL)					
0 min	95.81 ± 9.95	86.56 ± 6.61	98.39 ± 7.35	102.78 ± 12.43	<.01
60 min	197.28 ± 59.75	142.31 ± 30.67	206.64 ± 46.09	260.67 ± 65.19	<.01
120 min	141.71 ± 44.62	107.25 ± 17.15	137.61 ± 32.52	218.00 ± 20.32	<.01
OGTT insulin (mcIU/ml)					
0 min	4.52 ± 3.03	3.50 ± 1.63	4.73 ± 3.39	5.56 ± 3.32	.23
60 min	45.35 ± 36.15	32.89 ± 30.94	51.19 ± 40.57	38.86 ± 17.45	.38
120 min	46.02 ± 35.96	24.11 ± 15.51	48.67 ± 37.45	64.00 ± 39.02	.07
Hemoglobin A1c (%)	5.5 ± 0.3 (min-max 4.6–6.5)	5.34 ± 0.26	5.62 ± 0.29	5.64 ± 0.27	<.01
1,5-Anhydroglucitol (mcg/ml)	19.14 ± 6.63 (min-max 4.9–39.8)	19.24 ± 7.53	18.64 ± 5.91	20.78 ± 7.97	.70
Fructosamine (μmol/L)	233.1 ± 18.79 (min-max 182–267)	228 ± 21.06	234 ± 18.76	238.89 ± 13.49	.35
Glycated albumin (%)	12.29 ± 1.04 (min-max 10–15)	12.19 ± 0.75	12.24 ± 1.12	12.67 ± 1.22	.51
Total albumin-adjusted fructosamine	55.49 ± 4.68 (min-max 45.5–67.37)	55.03 ± 3.74	55.36 ± 5.07	56.08 ± 5.35	.87

Note: Pulmonary function data were available for 49 of the 58 total participants. Data are presented as mean ± SD or number, N (%).

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Abbreviations: BMI, body mass index; CFPD, cystic fibrosis-related pre-diabetes; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; NG, normoglycemia.

TABLE 2

Comparisons of the optimal cutoffs, sensitivities, and specificities of five alternative markers for predicting cystic fibrosis-related diabetes as defined by the gold-standard oral glucose tolerance test 2-hour glucose   200 mg/dL

Measure	Optimal cutoff	Sensitivity (95% CI)	Specificity (95% CI)
Hemoglobin A1c (%)	5.5	0.78 (0.45, 0.94)	0.41 (0.28, 0.55)
1,5-Anhydroglucitol (mcg/mL)	20.4	0.67 (0.35, 0.88)	0.63 (0.49, 0.75)
Fructosamine (μmol/L)	225	1.0 (0.7, 1.0)	0.35 (0.23, 0.49)
Glycated albumin (%)	14	0.22 (0.06, 0.55)	0.9 (0.78, 0.96)
Albumin-adjusted fructosamine	59	0.44 (0.19, 0.73)	0.84 (0.71, 0.91)