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Original Research

Cystic Fibrosis-Related Diabetes Screening in Adults: A Gap Analysis and Evaluation of Accuracy of Glycated Hemoglobin Levels

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Key Messages

- On average, 48.5% of eligible individuals were screened each year for cystic fibrosis-related diabetes by oral glucose tolerance tests.
- A glycated hemoglobin threshold of 5.5% had a sensitivity of 91.8% and a specificity of 34.1% for the diagnosis of cystic fibrosis-related diabetes.
- Glycated hemoglobin levels cannot be used to identify impaired glucose tolerance.

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ABSTRACT

Objectives: We sought to identify the gap in cystic fibrosis-related diabetes (CFRD) screening by means of an oral glucose tolerance test (OGTT) in our tertiary care clinic. Our second aim was to identify the glycated hemoglobin level (A1C) threshold that optimizes sensitivity and specificity for predicting CFRD and impaired glucose tolerance.
Methods: This retrospective study used data housed in the Toronto cystic fibrosis (CF) database. The study population included all adult (≥18 years of age) patients seen in the CF clinic between January 1, 2008, and December 31, 2015. Descriptive statistics were used for the OGTT gap analysis; the CFRD screening rate was calculated on an annual basis as the proportion of eligible patients who received OGTTs. Sensitivity and specificity were calculated using OGTTs as the reference standard and A1C levels as the index test on a sample size of 320 patients.
Results: On average, 48.5% of eligible individuals were screened each year for CFRD by OGTTs. A1C thresholds of 5.5% had a sensitivity of 91.8% (75%) and a specificity of 34.1% (33.4%) for the diagnosis of CFRD (and impaired glucose tolerance), respectively. Of the 229 patients with A1C levels <5.5%, 5 test results (2.2%) had OGTTs indicative of CFRD.
Conclusions: The rate of CFRD screening is suboptimal. An alternative screening algorithm using an A1C threshold of 5.5% has the potential to reduce the requirement for OGTTs by 36.7%. A1C levels cannot be used to identify impaired glucose tolerance.

Mots clés :
diabète associé à la fibrose kystique
concentrations d'hémoglobine glyquée
dépistage

RÉSUMÉ

Objectifs : Nous avons cherché à déterminer les lacunes du dépistage du diabète associé à la fibrose kystique (DAFK) réalisé au moyen des épreuves d'hyperglycémie provoquée par voie orale (ÉHPVO) à notre clinique de soins tertiaires. Notre deuxième objectif était de déterminer le seuil de la concentration en hémoglobine glyquée (A1c) qui optimise la sensibilité et la spécificité de prédiction du DAFK et de la détérioration de la tolérance au glucose.

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Méthodes : La présente étude rétrospective s'est basée sur les données stockées dans la base de données de fibrose kystique (FK) de Toronto. La population étudiée regroupait tous les patients adultes (≥18 ans) vus à la clinique de FK entre le 1er janvier 2008 et le 31 décembre 2015. Nous avons eu recours aux statistiques descriptives pour analyser les lacunes liées à l'ÉHPVO; nous avons calculé le taux de dépistage du DAFK sur une base annuelle au prorata des patients admissibles qui subissaient des ÉHPVO. Les ÉHPVO ont servi d'étalon de référence pour calculer la sensibilité et la spécificité, et les concentrations de l'A1c ont servi de « test index » sur un échantillon de 320 patients.
Résultats : En moyenne, 48,5 % des individus admissibles subissaient chaque année un dépistage du DAFK au moyen des ÉHPVO. Les seuils de l'A1c de 5,5 % montraient respectivement une sensibilité de 91,8 % (75 %) et une spécificité de 34,1 % (33,4 %) pour le diagnostic du DAFK (et la détérioration de la tolérance au glucose). Parmi les 229 patients ayant des concentrations de l'A1c<5,5 %, 5 résultats d'ÉHPVO (2,2 %) révélaient un DAFK.
Conclusions : Le taux de dépistage du DAFK est sous-optimal. Un autre algorithme de dépistage utilisant un seuil d'A1c de 5,5 % a le potentiel de diminuer le recours aux ÉHPVO de 36,7 %. Les concentrations de l'A1c ne peuvent pas être utilisées pour déterminer la détérioration de la tolérance au glucose.

Introduction

Cystic fibrosis (CF) is an autosomal recessive genetic condition that occurs in 1 of 3600 births (1). A mutation in the cystic fibrosis transmembrane conductance regulator gene is responsible for the loss of chloride transport in epithelial cells, leading to the accumulation of thick and viscous fluid in various organs, such as the lung and pancreas (2). The median survival of patients with CF has significantly increased and is currently estimated at 50.9 years in Canada and 40.6 years in the United States (3). With longer lifespans, an increase in disease-related complications has become evident.

Cystic fibrosis-related diabetes (CFRD) is the most common extrapulmonary comorbidity of CF and is estimated to affect approximately one-quarter of all individuals with CF in North America; its prevalence increases with age (4,5). CFRD has pathophysiologic features of both type 1 and type 2 diabetes mellitus, with insulin deficiency and resistance (6). CFRD is more common in individuals with severe cystic fibrosis transmembrane conductance regulator mutations and is associated with a higher degree of exocrine pancreatic dysfunction (2,7). Individuals with CF and the F508del mutation are at a higher risk for CFRD than other genotypes; this is the most common mutation in both Canada (89.7%) and the United States (86.4%) (4–5).

Early detection of CFRD is important because its development has been associated with a decline in lung function, deterioration of nutritional status and reduction in life expectancy (8,9). Insulin has positive anabolic effects and has been shown to improve clinical outcomes (8,10). The American Diabetes Association CFRD guidelines recommend screening for CFRD by means of an annual oral glucose tolerance test (OGTT) beginning at the age of 10 (11).

OGTTs have multiple drawbacks, including the necessity for multiple blood draws, the requirement of an overnight fast and the 2-h time requirement for test completion. This inconvenience is not insignificant when considered in the context of the frequent and extensive testing required for assessment of pulmonary and gastrointestinal disease in CF. The American Cystic Fibrosis Foundation Patient Registry (5) has estimated that only 29.1% of adult patients with CF comply with their annual OGTTs, further supporting the notion that a more acceptable test is needed. In addition, the diagnostic thresholds established for diabetes using the OGTT were developed to detect the risk for retinopathy, not for clinically relevant CF outcomes, such as lung function or nutrition status (12).

Glycated hemoglobin (A1C) levels are commonly used as the first-line screening test for type 2 diabetes in North America because of its convenience and good operating characteristics (13). The main argument against the use of A1C levels in screening for CFRD is the potential lack of correlation between A1C levels and OGTT results (14). This argument has been debated and is based on the premise that A1C levels can be falsely low in people with CF due to a reduction in red blood cell life span resulting from inflammation, hypoxia and splenic sequestration in individuals with portal hypertension (6,14). The 2010 American Diabetes Association guidelines (11) state that A1C levels should not be used for CFRD screening, a recommendation based on results from 6 studies in 477 patients, in which a subset of individuals had OGTT diagnoses of CFRD even though their A1C levels were "normal" (9,12–16). Achieving high sensitivity is important for any screening test; therefore, this finding was alarming. It should, however, be noted that these studies possessed a number of limitations, including a low prevalence of CFRD in the study's participants, a small sample size and variability in the definition of "normal" A1C levels (17,18). The exclusion of unwell individuals, who had increased insulin resistance and intermittently abnormal OGTT results, was not routinely reported, nor was the presence of liver disease. Recently, a number of studies have evaluated A1C levels as a possible screening test for CFRD, and they have yielded promising results (19–21).

Methods

This retrospective analysis used existing data housed in the Toronto CF database. The study consisted of 2 main components. First, we conducted a gap analysis to understand the rate of CFRD screening in our clinic. Second, we conducted a sensitivity and specificity analysis comparing incremental A1C thresholds against the reference standard—an OGTT—in the diagnosis of impaired glucose tolerance (IGT) and CFRD.

Participants

The study population included all adult (≥18 years) patients who were seen in the CF clinic between January 1, 2008, and December 31, 2015. At the time of manuscript preparation, 490 adult patients were being followed actively in our academic tertiary care clinic, making it one of the largest CF centers in North America.

For the CFRD screening gap analysis, all patients without previous diagnoses of CFRD were included. OGTTs performed after lung transplantation were excluded because their follow-up care occurs at a different institution. For the sensitivity and specificity analysis, all patients without CFRD who had both an OGTT and an A1C test performed within 90 days of each other were included. Patients were excluded if they met 1 of the following criteria: 1) CF exacerbation at the time of the OGTT, defined as an OGTT within 14 days preceding a hospital admission; 2) recent use of systemic corticosteroids, defined as any oral steroid use at the clinic visit prior to the OGTT measurement; 3) pregnancy at the time of the OGTT or A1C testing; 4) use of enteral feeds within 90 days of the OGTT; or 5) previous lung or liver transplantation.

Outcomes

The 2 main outcomes of interest were: 1) to determine the percentage of patients with CF who received annual screening for CFRD by means of OGTTs; 2) to determine the A1C threshold that optimizes sensitivity and specificity for predicting CFRD and IGT, as determined by the OGTT results.

Statistical analysis

Descriptive statistics for patient demographics were calculated as frequency (proportion) for categorical variables and median (range) for continuous variables. The rate of CFRD screening was calculated in 2 ways: 1) at yearly time intervals from 2008 to 2015 (the number who completed OGTTs in the preceding 15 months/number of people seen in the CF clinic); 2) a summary of the number of OGTTs completed per patient over the time period during which they were eligible for screening.

Sensitivity and specificity were calculated using the OGTT as the reference standard and the A1C level as the index test; 95% confidence intervals were calculated using the Clopper-Pearson method. IGT was defined as a fasting plasma glucose level <7.0 mmol/L and a 2-h plasma glucose level of 7.8 to 11 mmol/L. CFRD was defined as a fasting plasma glucose level of ≥7.0 mmol/L, a 2-h plasma glucose level of ≥11.1 mmol/L or an A1C level of ≥6.5%. Various A1C thresholds (5.5% to 5.9%) were used to define the absence or presence of IGT and CFRD. A receiver operator characteristic curve was drawn for both IGT and CFRD. The best A1C threshold was chosen by selecting the cutpoint closest to the (0,1) point on the receiver operator characteristic curve. Using the Everard formula and assuming 95% sensitivity and a type I error rate of 5%, a sample size of 218 was calculated (22). The open-source statistical software R, v. 3.3.1, was used to conduct all analyses.

A1C measurement

In healthy individuals, the biological variability of A1C levels is 2%. This study used a Roche (Basel, Switzerland) immunoassay for all A1C assessments, which has an analytical variability of <5%.

Results

OGTT gap analysis

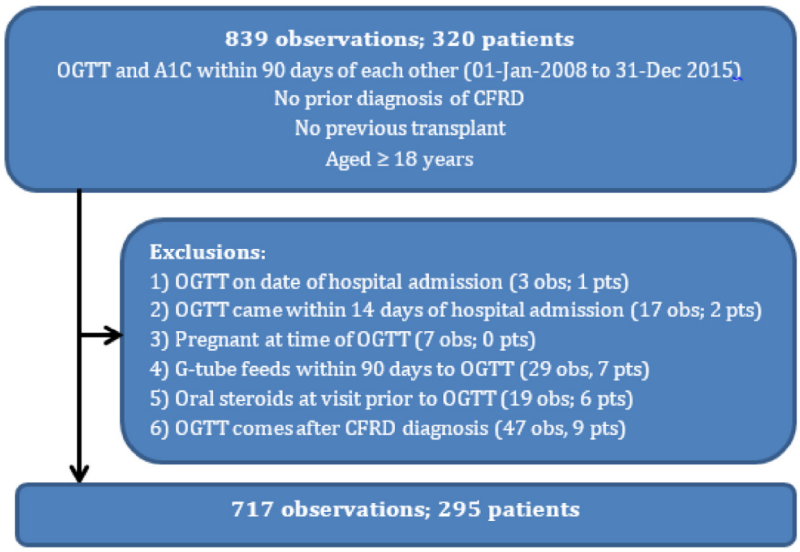
Of the 685 adults who visited the clinic between 2008 and 2015, 512 met the criteria for inclusion in the analysis; 22.9% (157) had previous diagnoses of CFRD. On average, 48.5% of patients with CF underwent annual screening for CFRD. More than one-quarter (146/512, or 28.5%) of the patients failed to have at least 1 OGTT during the study period. When examining the patient-level data, the median percentage of OGTTs completed per person, of those who were eligible, was 40.0% (0 to 100%).

Sensitivity and specificity analysis

Overall, 839 OGTTs were performed in 320 patients within 90 days of A1C level measurements. After the exclusion criteria were applied, the analysis was performed on a population of 295 patients and 717 occurrences (Figure 1).

Patient- and OGTT-level clinical and demographic data are summarized in Table 1. Approximately 60% (n=178) of the patients were male; the median age at the time of the OGTT was 30.3 years (18.1 to 69.7); 79.0% were homo- or heterozygous for the F508del mutation; and the median forced expiratory volume in 1 second predicted was 67.21% (range, 16.6% to 123.0%). The median A1C level was 5.6%, with a range of 4.6% to 7.6%. Of all OGTTs, 128 (17.9%) were indicative of IGT, and 61 (8.5%) showed CFRD.

The sensitivity and specificity analysis of incremental A1C thresholds in the diagnosis of CFRD and IGT is shown in Table 2. An A1C threshold of 5.5% has a sensitivity of 91.8% and a specificity of 34.1% for the diagnosis of CFRD. Higher A1C thresholds resulted in a reduction in sensitivity, which was well below the prespecified goal of 95% (20). Of the 229 patients with A1C levels <5.5%, 5 test results (2.2%) had OGTTs indicative of CFRD. An A1C threshold of 5.5% had a sensitivity of 75% and a specificity of 33.4% for IGT. Of the patients who had OGTTs indicative of IGT (89 patients), 36% (32 patients) had corresponding A1C levels of <5.5%. The receiver operating characteristic curves for A1C levels in the diagnosis of IGT and CFRD were drawn. For CFRD, the inflection point was 5.8%, which yielded a



A1C, glycated hemoglobin levels; *CFRD,* cystic fibrosis-related diabetes; *obs,* observation; *OGTT,* oral glucose tolerance test; *pts,* patients.

Figure 1. Consort diagram sensitivity and specificity analysis.

Table 1
Clinical and demographic data: Patient level (N=295) and OGTT level (N=717)

Patient-level data		
Variable	Frequency	Proportion
Gender		
Female	117	39.7%
Genotype		
Heterozygous dF508	134	45.4%
Homozygous dF508	99	33.6%
Other	48	16.3%
Missing	14	4.8%
Number of OGTT results per patient		
Median (range)	2	1–6
1 test	103	34.9%
2 tests	71	24.1%
3 tests	53	18.0%
≥4 tests	68	23.1%

OGTT-level data		
Variable	Median/ frequency	Range/ proportion
Age at OGTT (years)		
Median (range)	30.3	18.1–69.7
FEV_1 (L)		
Closest to OGTT, median (range)	2.44	0.58–5.97
FEV_1 % predicted		
Closest to OGTT, median (range)	67.21	16.56–123
Nutritional measures		
Weight (kg), median (range)	67.2	38–121
BMI (kg/m^2), median (range)	22.9	14.3–39.7
# Hospitalizations year prior to OGTT	0	0–4
Frequency of IV antibiotics year prior	0	0–24
Outcomes		
A1C, median (range) %	5.6	4.6–7.6
OGTT 2-h post, median (range) mmol/L	5.9	1.6–19.7
FPG, median (range) mmol/L	5.2	3.3–10.6
OGTT indicative of IGT*	128	17.9%
OGTT indicative of CFRD†	61	8.5%

A1C, glycated hemoglobin levels; *BMI,* body mass index; *CFRD,* cystic fibrosis-related diabetes; *FEV_1,* forced expiratory volume in 1 second; *FPG,* fasting plasma glucose levels; *IGT,* impaired glucose tolerance; *IV,* intravenous; *OGTT,* oral glucose tolerance test; *PG,* plasma glucose levels.

* IGT is defined as FPG <7.0 mmol/L and 2-h PG 7.8 to 11 mmol/L.

† CFRD is defined as FPG ≥7.0 mmol/L or 2-h PG ≥11.1 mmol/L or A1C ≥6.5%.

sensitivity of 67.2% and a specificity of 70.3%; the area under the curve was 0.76. For IGT, the inflection point was 5.7%, which yielded a sensitivity of 52.3% and specificity of 60.3%; the area under the curve was 0.59.

Using the A1C cutpoints of <5.5% and >6.4%, 229 OGTTs could have been saved during the study period. In addition, 55 A1C tests during the study period were diagnostic of diabetes at ≥6.5% (not all had associated OGTTs); therefore, 284 OGTTs overall could be saved (36.7% of all OGTTs).

Discussion

Our research demonstrates a true gap in screening for CFRD, with only 48.5% of patients having undergone annual OGTTs. To our knowledge, this is the first Canadian study to report the average CFRD screening rate over an 8-year period. The CFRD screening rate was previously evaluated in the Montreal CF Cohort over a 1-year period beginning in May 2015, and it found similar results, with only 47.2% of patients attending their scheduled OGTT appointments (6). Unlike in the United States, the Canadian CF registry does not collect CFRD screening; thus, it is unknown whether our rates are comparable to those of the nation as a whole. The screening rate in our study, however, is higher than that reported by the American CF patient registry (29.1%) (5). A possible explanation is the exclusion of transplant patients from our study; in our analysis, 81 patients were excluded for this reason, while the American CF registry included 210 patients who had had lung transplants (5). Given the complexity of treatment following lung transplantation, it is possible that diabetes screening is not prioritized, leading to lower completion rates in this group.

Because of concerns about patients' acceptance of OGTTs, the hunt is underway to find a nonfasting, single-blood-draw alternative. In our patient population, we identified that an A1C threshold of 5.5% had a high sensitivity (91.8%) for the diagnosis of CFRD, safely ruling out the disease. The associated specificity, however, was low; therefore, a result above this threshold is not adequate for confirming the diagnosis. Given that the higher 6.5% A1C threshold is used in the diagnosis of diabetes, we propose that an alternative screening schedule could be adopted. In this screening schedule, A1C levels would be universally performed in the well, out-patient population with CF, with the requirement for an OGTT only if the A1C level falls between 5.5% and 6.4% (Figure 2).

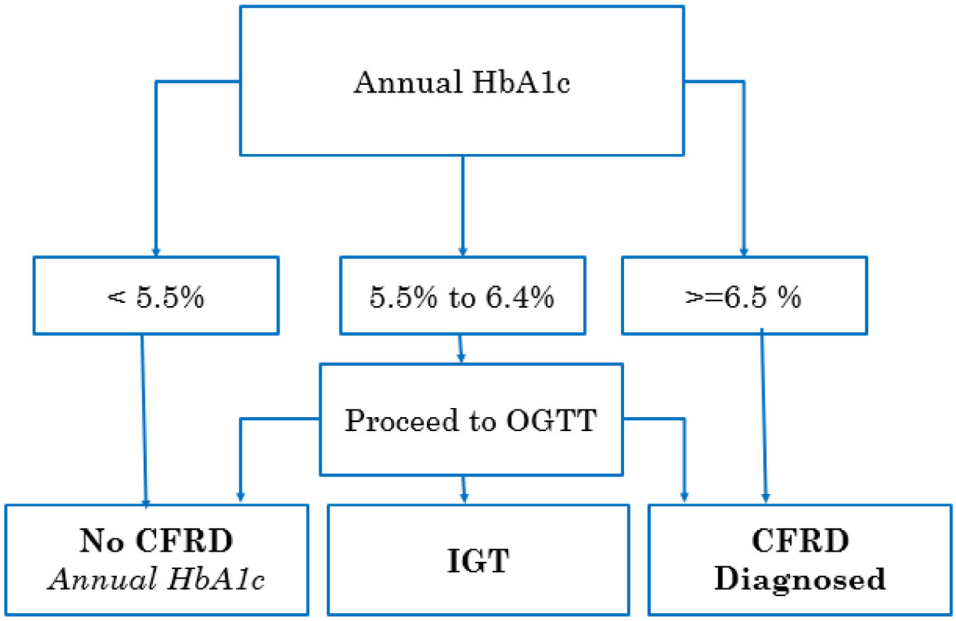
Our results are consistent with other recent publications on the subject. Boudreau et al (19) retrospectively evaluated 207 patients and found that an A1C threshold of 5.5% had a sensitivity of 95.5% and a specificity of 31.4% for the diagnosis of CFRD. They concluded that A1C levels could not yet be used for CFRD screening because the low cutoff of 5.5% would not spare many individuals from requiring an OGTT. Our results, on the contrary, indicate that using this threshold could save a significant proportion of OGTTs. Using an alternative screening approach, 284 OGTTs could have been avoided over the 8-year study period, representing 36.7% of all OGTTs performed. Therefore, we conclude that there is a role for A1C in the screening algorithm for CFRD. In a similar analysis, Burgess et al (20) prospectively evaluated 335 adult patients with CF for IGT/CFRD. They found that an A1C threshold of 5.8% had a sensitivity of 93.8% and a specificity of 53%. Our study did not show such robust operating characteristics when using a threshold of 5.8%. This might be explained by the higher frequency of the homozygous F508del genotype (48.4% vs. 33.6%) and the lower prevalence of CFRD in the Burgess cohort compared to our population (4.8% vs. 8.5%). Similar to our findings, Burgess et al (20) suggested that performing initial screening of A1C levels could significantly reduce the need for OGTTs by 51% if the 5.8% threshold is utilized. A Swiss group also evaluated the 5.8% screening threshold and found a low sensitivity of 47% in their cohort of 80 patients (21). It should be highlighted that all the patients included in this analysis had profound impairments in lung function and were being considered for lung transplantation. Certainly, in our analysis, we excluded patients who were unwell at the time of OGTT testing; as a result, we agree with the notion that A1C screening should be applied only to the stable outpatient population.

Our study demonstrates that A1C is not an accurate test for the diagnosis of IGT. Previous studies have shown that minimal degrees of impairment in glucose homeostasis are associated with a decline in lung function, nutritional status and survival; however, existing data do not support the beneficial effects of insulin in reversing or preventing these outcomes in IGT (23,24). Until the results of a randomized controlled trial evaluating the early initiation of insulin in this population become available, the use of insulin in IGT remains controversial (12). Also, of importance, the progression from IGT to CFRD is not linear. A study examining the natural history of IGT has shown that approximately 58% of patients revert to normal glucose tolerance over 5 years, and only 14% progress to CFRD (25). Therefore, the ability to identify individuals with IGT based on A1C parameters may not influence management decisions. Given that 36% of patients with IGT based on OGTTs had corresponding A1C levels <5.5%, we believe that the alternative screening algorithm proposed in Figure 2 could still be utilized in this subset of patients.

Table 2
Sensitivity and specificity of A1C for predicting CFRD and IGT

A1C %	# True-positive	# True-negative	# False-positive	# False-negative	Sensitivity	Specificity
CFRD						
5.5	56	224	432	5	91.8 (95% CI: 81.9–97.3)	34.1 (95% CI: 30.5–37.9)
5.6	50	304	352	11	82 (95% CI: 70–90.6)	46.3 (95% CI: 42.5–50.2)
5.7	43	398	258	18	70.5 (95% CI: 57.4–81.5)	60.7 (95% CI: 56.8–64.4)
5.8	41	461	195	20	67.2 (95% CI: 54–78.7)	70.3 (95% CI: 66.6–73.8)
5.9	37	518	138	24	60.7 (95% CI: 47.3–72.9)	79 (95% CI: 75.6–82)
IGT						
5.5	96	197	392	32	75 (95% CI: 66.6–82.2)	33.4 (95% CI: 29.6–37.4)
5.6	85	272	317	43	66.4 (95% CI: 57.5–74.5)	46.2 (95% CI: 42.1–50.3)
5.7	67	355	234	61	52.3 (95% CI: 43.3–61.2)	60.3 (95% CI: 56.2–64.2)
5.8	56	409	180	72	43.8 (95% CI: 35–52.8)	69.4 (95% CI: 65.5–73.1)
5.9	48	462	127	80	37.5 (95% CI: 29.1–46.5)	78.4 (95% CI: 74.9–81.7)

A1C, glycated hemoglobin levels; *CI,* confidence interval; *CFRD,* cystic fibrosis-related diabetes; *IGT,* impaired glucose tolerance.



HbA1c, glycated hemoglobin levels; *CFRD,* cystic fibrosis-related diabetes; *IGT,* impaired glucose tolerance; *OGTT,* oral glucose tolerance test.

Figure 2. Alternative screening strategy for CFRD.

There are a number of strengths to note in this study. First, we utilized data from a large cohort of patients with CF. Our sample-size calculation was powered to detect a high sensitivity of 95%. Second, this study served as a validation study and prospectively examined 2 A1C thresholds (5.5% and 5.8%) that had been identified previously in the literature. Third, we were able to identify an A1C threshold that reliably ruled out CFRD. Based on our results, we were able to devise a screening algorithm that has the potential to reduce OGTTs by 36.7%. Finally, our gap analysis identified a consistently low rate of CFRD screening over the past 8 years and has become a critical platform for improvement in our clinic.

The main limitation of our study was the identification of 5 OGTT results that were indicative of CFRD with an associated A1C level of less than 5.5%. Two OGTTs are required to make a formal diagnosis of CFRD; therefore, it is unknown which of these OGTT results truly resulted in a diagnosis of CFRD. The requirement for insulin therapy is not synonymous with a diagnosis of CFRD; therefore, the false-negative A1C results in our study may not have actually resulted in a change in management. Such was the case in the study by Burgess et al, in which the 1 patient with a false-negative A1C result did not require insulin therapy after completing home glucose monitoring (20). The second study limitation pertains to data omission due to its manual entry into the database. Currently, there are no quality-control measures in place and it is, therefore, possible that the rate of CFRD screening was falsely low. Third, repeated OGTT measurements for individual patients were treated

independently. To ensure that this did not falsely inflate the results, we performed a sensitivity analysis using the first OGTT per patient and the last OGTT per patient, so that we had unique independent observations; we found that the results remained unchanged. Finally, we did not evaluate A1C levels in the context of clinically significant CF outcomes, such as lung function and nutrition status. This has, however, been evaluated previously in multiple studies, showing that an increase in A1C level is inversely associated with lung function (20) and an increased risk for mortality (26). Novel screening methods have been proposed recently for the diagnosis of CFRD, including fractional serum fructosamine, intermediate peak glucose concentrations (30, 60 and 90 minutes) and continuous glucose monitoring, which have also been associated with a decline in lung function and weight (6,27).

Conclusions

In summary, OGTTs place an additional burden on individuals with CF. We identified that the rate of CFRD screening was low in our practice. The quest for a nonfasting, less time-consuming alternative is ongoing. A1C screening may offer a potential solution for some individuals, though a proportion of individuals would still require OGTTs. Our clinic plans to adopt a screening strategy in which A1C levels will be used as the first-line screening test, with OGTTs being performed only if the A1C level is between 5.5% and 6.4%. A1C levels cannot be used to identify IGT; therefore, if data become available that show a beneficial effect of insulin therapy on clinically relevant CF outcomes this test would need to be abandoned for screening purposes.

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Author Disclosures

Conflicts of interest: None.

Author Contributions

JG contributed to the conception and design, analysis and interpretation of data and drafted the manuscript; ET contributed to the conception, analysis, design and drafting of the manuscript; EE contributed to the analysis of the data and the drafting of the manuscript; JS contributed to the data analysis and the drafting of the manuscript; JG and JS had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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