Can J Diabetes 43 (2019) 161–162

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

Letter to the Editor

Validation of a Stepwise Approach Using Glycated Hemoglobin Levels to Reduce the Number of Required Oral Glucose Tolerance Tests to Screen for Cystic Fibrosis–Related Diabetes in Adults

To the Editor:

We read with great interest the recent article by Gilmour et al that proposed a stepwise approach to simplifying cystic fibrosis (CF)-related diabetes (CFRD) screening (1). Because of the very high frequency of CFRD (prevalence increases from 10% in childhood to nearly 50% in adulthood), its association with adverse clinical outcomes (weight and/or lung function loss as well as early mortality) and the low sensitivity of simple screening methods (e.g. glycated hemoglobin [A1C] levels), annual oral glucose tolerance tests (OGTTs) are recommended (2,3). However, OGTTs add to the already high CF care burden and are criticized by both patients and health-care teams as unpleasant and inconvenient tests. Indeed, screening rates remain below 50% in most centres (4,5). To reduce the number of required tests, Gilmour et al proposed undertaking OGTT screening only in patients with A1C levels above 5.4%. According to Gilmour et al, in 295 patients with CF, using A1C levels as the first step would reduce the number of required OGTTs by 36.7%, and this strategy would still find 91.8% of patients with de novo CFRD. An essential step to validate this elegant strategy is external validation.

We undertook a similar analysis in the glycone database, regrouping the OGTTs of 345 patients with CF and their concomitant A1C values from Lyon, France and Montreal, Canada. The glycone database includes patients from the Mucodata Cohort (Lyon, France) and from the Montreal CF Cohort (Montreal, Canada). In both centres, all adult patients without diabetes (18 years of age or older) participate in annual OGTTs upon arrival at the adult clinic. On the day of the OGTT, clinical data, including pulmonary function, body mass index and A1C values, are measured (clinical parameters are shown in Table 1). When diabetes is diagnosed, patients are excluded from further annual CFRD screening programs and are referred to endocrinologists for monitoring and treatment of the glycemic excursions. In both databases, patients have similar genotype severity, sex ratio and age. All patients must be clinically stable for at least 1 month prior to and at the time of the OGTTs. Otherwise, the test is postponed. We used the OGTT as the standard screening method to evaluate A1C sensitivity and specificity at various thresholds and calculated 95% confidence intervals using the Clopper-Pearson method (Table 2). In this dataset, using the proposed 5.5% A1C threshold provides a sensitivity of 90.9% and a specificity of 29.7% to identify patients with de novo CFRD, reducing the number of required OGTTs by 23.5%. Importantly, using this A1C threshold, 9.1% of patients with de novo CFRD would be missed (Table 2). A lower threshold (≥5.4%) would allow finding 94.5% of patients with de novo CFRD but would reduce required OGTTs by only 18.6% (Table 1).

Although our results do not allow such a large OGTT testing reduction as that suggested by Gilmour et al (23.5% vs. 36.7%), our analysis reinforces the evidence that a stepwise approach probably significantly reduces the number of required OGTTs. Similar to the observations of Gilmour et al observed in Toronto, 47.2% of patients in Montreal attended their annual OGTTs in 2016 (48.5% in Toronto). Of the absent patients, 35.1% called to cancel or reschedule their tests, and 64.9% did not appear for their appointments (data not available for French patients) (4). These particularly low participation rates reinforce our research objective of finding ways of reducing this burden on patients. In addition, because patients with CF perform several routine blood tests every year, it would be possible to undertake A1C testing twice a year and send the patients for OGTTs as soon as their A1C values rise above 5.4%. Such a strategy would probably allow for diagnosing the few missed patients with de novo CFRD in a reasonable time frame and with minimal risk that such patients would be exposed to unacceptable risks.

The proposed stepwise approach of scheduling OGTTs if the A1C values are ≥5.5%, with a reduction in the number of required OGTTs, is now validated in 2 different datasets, providing substantial evidence that it is valid. Awaiting evidence-based data about

Table 1
Characteristics of the patients in the glycone database on the day of the OGTT

	Glycone cohort (N=345)
Age (years)	24.6±6.5
Sex (% of women)	42.6
Genotype (%)	
Homozygous dF508	56.3
Heterozygous dF508	35.9
Other	7.3
Pulmonary function (FEV1%)	66.2±21.6
Body mass index (kg/m^2)	20.9±2.6
Incidence of CFRD (%)	15.9
A1C (%)	5.8±0.5

A1C, glycated hemoglobin; *CFRD*, cystic fibrosis-related diabetes; *FEV1*, forced expiratory volume in 1 s (predicted value in %); *OGTT*, oral glucose tolerance test.
Note: Variables are expressed as mean ± standard error, except for categorical variables, which are expressed as percentages (%).

DOI of original article: https://doi.org/10.1016/j.jcjd.2018.04.008

https://doi.org/10.1016/j.jcjd.2018.11.005

Table 2
Sensitivity and specificity of A1C levels to screen for CFRD

A1C	No. true-positive	No. true-negative	No. false-positive	No. false-negative	Sensitivity (%)	Specificity (%)
5.5	50	76	214	5	90.9 (95% CI: 79.3–96.6)	26.2 (95% CI: 21.3–31.7)
5.6	48	101	189	7	87.3 (95% CI: 74.9–94.3)	34.8 (95% CI: 29.4–40.6)
5.7	44	122	168	11	80.0 (95% CI: 66.6–89.1)	42.1 (95% CI: 36.4–48.0)
5.8	42	153	137	13	76.4 (95% CI: 62.7–86.3)	52.8 (95% CI: 46.8–58.6)
5.9	40	189	101	15	72.7 (95% CI: 58.8–83.5)	65.2 (95% CI: 59.3–70.6)

A1C, glycated hemoglobin; *CFRD,* cystic fibrosis-related diabetes.
Notes: Number of results obtained to screen for CFRD in 345 adult patients with cystic fibrosis according to differing A1C thresholds. Sensitivity and specificity are presented as percentages (%), and 95% confidence intervals were calculated using the Clopper-Pearson method.

numerous issues related to CFRD screening (e.g. usefulness of continuous glucose monitoring, possible CF-specific diagnosis thresholds, etc.), this new approach should translate into a simplification of CF management and cost reductions.

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Author Disclosures

Dr. Rabasa-Lhoret reports a grant from Cystic Fibrosis Circle of Care (Vertex). No other authors have any conflicts of interest to disclose. This study was supported by a grant from Cystic Fibrosis Canada.

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