Letter to the Editor

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Sensitivity and specificity of cystic fibrosis-related diabetes screening methods: which test should be the reference method?

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To the Editor,

We have read with interest the original article by Mainguy et al. [1] on the evaluation of the sensitivity and specificity of some methods to screen for diabetes in a cystic fibrosis (CF) population. This work evaluates the efficacy of the oral glucose tolerance test (OGTT with 1-h and 2-h glucose values), intravenous glucose tolerance test (IGTT), glycated hemoglobin (HbA_{1c}), an index of insulin resistance (HOMA-IR) and an index of pancreatic β cell function (HOMA-%β) to screen for CF-related diabetes (CFRD) in comparison with a continuous glucose monitoring system (CGM) worn for 3 days in 29 patients with CF aged 13.1 ± 2.2 years. They conclude that the OGTT is not sensitive enough to identify CFRD and propose a two-step approach using the HOMA-%β to identify patients who need to be screened by OGTT. Although we found it very interesting to investigate simpler tools to screen for CFRD, we have concerns with the use of CGM as the reference screening method because there is no consensus on how to diagnose CFRD with this system [2]. We believe that it is not possible to affirm that the OGTT is not sensitive enough, based on glycemic excursions measured with CGM in the absence of CGM-based criteria known to be clinically relevant for CF patients.

CFRD is the second most common complication after pulmonary complications, and the prevalence increases with age, reaching up to 50% of adults with CF. CFRD is mainly caused by a reduced insulin secretion secondary to CF-associated chronic pancreatitis. This highly frequent complication is associated with an increased risk of clinical decline including accelerated weight loss, reduced lung function as well as early mortality. An annual OGTT for CFRD screening is thus recommended from the age of 10. Patients drink a glucose solution of 1.5 g per kg of body weight up to a maximum of 75 g after an 8-h fasting. Diagnosis is made either by fasting glucose ≥7.0 mmol/L (which is rare in CF) or a 2-h glucose value ≥11.1 mmol/L [2]. However, many CF clinical teams have criticized this standard screening method for several reasons: it is perceived as invasive and inconvenient, which translates into a low adherence rate (between 25% and 50% of patients actually take the test annually) [1, 3] and thresholds used to diagnose CFRD are those used in patients with type 2 diabetes validated based on the risk of retinopathy, which could be different than the ones capturing the increased risk of accelerated CF clinical decline. Indeed, rather than fasting and 2-h glucose values, a high 1-h OGTT value is more strongly associated with early clinical deterioration [4]. Moreover, simple alternative methods validated for type 2 diabetes (e.g. fasting blood glucose or HbA_{1c}) have a low sensitivity in CF and, thus, cannot be used [3, 4].

Thus, as mentioned by Mainguy et al. there is an important need to find an alternative screening method

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that would not only identify de novo CRFD but also the risk of accelerated weight loss and pulmonary function deterioration, while being more acceptable for patients and CF teams. Such alternative screening methods should be validated prospectively against current clinical standard (OGTT) as well as clinical outcomes relevant to CF.

CGM is more and more accessible, painless, does not require fasting and allows a detailed glucose profile in real life conditions, which cannot be observed during the OGTT and might, thus, be used as a screening test in populations at high risk for diabetes [4]. However, unlike the well-accepted criteria to evaluate glucose control in patients with established diabetes, there is no consensus on diagnosis criteria for diabetes using CGM [2].

For patients with CF, several research groups have compared the CGM glucose profile with glucose excursion during a standard OGTT [5]. These studies conducted on small groups of patients reported that one-third of the patients with normal OGTT present CGM glucose excursions above the usual threshold used to diagnose diabetes (≥11.1 mmol/L), a threshold that can be associated with reduced pulmonary function [6]. Prospective studies are needed to confirm the association between glycemic excursions on CGM and clinical deterioration. It is now well described that even CF patients with normal glucose tolerance experience early glucose excursions followed by rapid glucose normalization. Thus, a single or even a few CGM-glucose values ≥11.1 mmol/L does not necessary represent a diabetes diagnosis, but probably better reflect the importance of a high glycemic excursion which is present in most CF patients. As such, glucose excursions are more frequent in adult patients [6], and the reported OGTT sensitivity by Mainguy et al. could have been even lower in older patients.

It was, thus, expected that fasting and 2 h-OGTT values would have less sensitivity when compared to values of CGM as reported by Mainguy et al. a conclusion that is, however, not based on validated thresholds to diagnose diabetes with CGMS. Establishing the most accurate CGM-based criteria to diagnose CFRD and/or the risk of accelerated clinical deterioration will require large cohorts with prospective follow-up assessing clinically relevant outcomes. These studies will have to answer numerous questions, including CF-specific glucose criteria (thresholds, number and length of episodes), how long CGM testing should last (most published data used 3 days but current devices offer up to 2 weeks of values with a single sensor), specific CGM accuracy, screening for aberrant values and minimal requirement for CGM calibration as well as for carbohydrate intake. CGM represents a promising way to simplify CFRD screening both from a clinical and a practical point of view, but it is too early to recommend its use for CFRD screening. Although the standard OGTT has significant shortcomings, it remains the recommended standard test [2].

Furthermore, we found it very interesting that Mainguy et al. investigated other simpler methods to screen for CFRD including HbA_{1c}, IGTT, homeostatic model assessment-infra red (HOMA-IR) and HOMA-%β. These are simple formulas as only fasting insulin and glucose values are needed. We have already shown that even if decreased insulin secretion remains the first cause of CFRD, variations in insulin resistance (probably caused by exacerbations of the disease) may influence glucose tolerance in CF patients. When comparing these indices to CGM, Mainguy et al. obtained a sensitivity of 91% to identify de novo diabetic patients with a reduced HOMA-β% index (using 100% to define a normal β cell function). Thus, if confirmed in larger cohorts, it could be possible to reduce OGTT-associated burden for several patients by identifying patients at risk. We investigated the accuracy of this measure in the Montreal CF adult cohort in which an OGTT with plasma glucose and insulin values are measured (every 30 min). Values are available in 261 adult patients (Table 1). All analyses were made by analysis of variance (ANOVA) except for sex difference (χ^2-analysis for categorical variables) and were all performed using SPSS Software v24 for Windows (IBM, Chicago, IL, USA). Using the same criteria as Mainguy et al. to define a normal β cell function, we observed a 69% sensitivity of the HOMA-β% index to identify patients at risk of de novo CFRD. This sensitivity is far less than the one reported by Mainguy et al. but also far higher than the one observed using an HbA_{1c} threshold ≥6.5% (39%). For HOMA-IR, representing insulin resistance, we did not use the value of 1 to estimate insulin-resistant patients as proposed by Mainguy et al. because 96% of adult patients of the Montreal CF cohort have a value ≥1. As some authors recommended using a value ≥2.5 for insulin resistance, we lowered this value because our patients frequently present a value ≥2.5 even with a normal glucose tolerance and, thus, the sensitivity would be very low. We, thus, used a lower threshold of 2.0, which provided a sensitivity of 75%. However, the specificity was 32%, which was expected by reducing the threshold to have a better sensitivity. This is an interesting sensitivity (75%), but by using this approach, we would still miss one-quarter of CFRD patients, which, in association with the low specificity, probably make this approach unacceptable in clinical practice. In addition, the absence of standardization of plasma insulin dosage will prevent establishing a threshold with external validity. However, it could be very interesting to elaborate a tool using different

Table 1: Characteristics of CF patients according to glucose tolerance groups and performance of indices to screen for CFRD vs. the OGTT.

	NGT	IGT	De novo CFRD	p-Value	Sensitivity for CFRD, %	Specificity for CFRD, %	PPV, %	NPV, %
n (%)	148 (56.7)	75 (28.7)	38 (14.6)	–	–	–	–	–
Sex, % women	41.9	55.7	38.5	0.087[a]	–	–	–	–
Age, years	25.5±8.2	25.4±7.4	26.5±7.1	0.741	–	–	–	–
FEV1, %	73.9±21.0	74.2±22.1	68.1±24.4	0.307	–	–	–	–
BMI, kg/m^2	21.8±2.8	21.8±3.1	21.4±3.1	0.687	–	–	–	–
HOMA-%β	130±86	131±109	105±90	0.332	69	57	22	91
HOMA-IR	2.5±1.3	2.4±1.0	3.07±1.6	**0.040**	75	32	16	88
HbA_{1c}, %	5.6±0.4	5.7±0.5	6.3±0.8	**<0.001**	39	98	75	90

NGT, normal glucose tolerance (fasting glucose value <7.0 mmol/L and 2-h glucose value <7.8 mmol/L); IGT, impaired glucose tolerance (2-h glucose value ≥7.8 mmol/L but <11.1); CFRD, cystic fibrosis-related diabetes (fasting glucose value ≥7.0 mmol/L or 2-h glucose value ≥11.1 mmol/L); PPV, positive predictive value; NPV, negative predictive value. [a]χ^2-analysis. Bold values represent significant p-values.

parameters and clinical values to screen for patients at risk of CFRD and target patients who need to do the OGTT.

Although it is important to screen for CFRD, many scientists and clinical teams criticized the current OGTT screening test. We agree that more simple and convenient screening methods should be investigated. CGM is one promising emerging method. However, we believe that with current evidence, CGM may help in the early diagnosis of CFRD when considered with the OGTT but should not be used as a substitute. Another option could be to combine indices from fasting values and clinical data (inexplicable weight or pulmonary function loss) to create a sensitive and easy-to-use screening tool.

Finding the optimal way to diagnose CFRD based on criteria more relevant for the CF population (e.g. risk of lung function decline) rather than diabetes-specific complications (e.g. retinopathy) is an important goal for the CF population.

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References

1. Mainguy C, Bellon G, Delaup V, Ginoux T, Kassai-Koupai B, et al. Sensitivity and specificity of different methods for cystic fibrosis-related diabetes screening: is the oral glucose tolerance test still the standard? J Pediatr Endocrinol Metab 2017;30:27–35.
2. Moran A, Brunzell C, Cohen RC, Katz M, Marshall BC, et al. Clinical care guidelines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. Diabetes Care 2010;33:2697–708.
3. Boudreau V, Coriati A, Desjardins K, Rabasa-Lhoret R. Glycated hemoglobin cannot yet be proposed as a screening tool for cystic fibrosis related diabetes. J Cyst Fibros 2016;15:258–60.
4. Boudreau V, Reynaud Q, Dubois CL, Coriati A, Desjardins K, et al. Screening for cystic fibrosis-related diabetes: matching pathophysiology and addressing current challenges. Can J Diabetes 2016;40:466–70.
5. Taylor-Cousar JL, Janssen JS, Wilson A, Clair CG, Pickard KM, et al. Glucose >200 mg/dL during continuous glucose monitoring identifies adult patients at risk for development of cystic fibrosis related diabetes. J Diabetes Res 2016;2016:1527932.
6. Coriati A, Ziai S, Azar M, Berthiaume Y, Rabasa-Lhoret R. Characterization of patients with cystic fibrosis presenting an indeterminate glucose tolerance (INDET). J Cyst Fibros 2016;15:127–32.