



## Original research

# Clinical practice versus guidelines for the screening of cystic fibrosis-related diabetes: A French survey from the 47 centers

Laurence Weiss<sup>a</sup>, Olivia Ronsin<sup>b</sup>, Quitterie Reynaud<sup>c</sup>, Michel Abely<sup>d</sup>, Laurent Mely<sup>e</sup>,  
Pierre-Régis Burgel<sup>f,g</sup>, Jacques Beltrand<sup>h,i</sup>, Laurence Kessler<sup>j,k,\*</sup>,<sup>1</sup>

<sup>a</sup> Pediatric Cystic Fibrosis Center, University Hospital of Strasbourg, France

<sup>b</sup> Adult Cystic Fibrosis Center, University Hospital Timone, Marseille, France

<sup>c</sup> Adult Cystic Fibrosis Center, Department of Internal Medicine Hospices Civils Lyon, France

<sup>d</sup> Pediatric Cystic Fibrosis Center, American Memorial Hospital, Reims, France

<sup>e</sup> Cystic Fibrosis Center, René Sabran Hospital, Giens, France

<sup>f</sup> Respiratory Medicine and Cystic Fibrosis National Reference Center, Cochin Hospital, Assistance Publique Hôpitaux de Paris, Paris, France

<sup>g</sup> Université de Paris, Institut Cochin, Inserm U1016, Paris, France

<sup>h</sup> Pediatric Endocrinology, Gynecology and Diabetes, Hôpital Necker Enfants-Malades, Assistance Publique Hôpitaux de Paris, Université de Paris, Paris, France

<sup>i</sup> Inserm U1016, Institut Cochin, Paris, France

<sup>j</sup> Department of Diabetology, Adult Cystic Fibrosis Center, University Hospital Strasbourg, France

<sup>k</sup> Inserm UMR 1260, Regenerative Nanomedicine, University of Strasbourg, France



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## ABSTRACT

This study aimed to analyze clinical practices concerning cystic fibrosis-related diabetes (CFRD) screening in France. A web-based questionnaire was distributed between December 1, 2020 and January 31, 2021 among 47 cystic fibrosis centers including pediatric, adult, and mixed units. In accordance with guidelines, 92.8% of CF centers performed annual oral glucose tolerance tests (OGTT). Overall, 86.3% of CF centers performed 1- and 2-hour blood glucose determinations following OGTT. The OGTT was conducted before 10 years of age in 73% of pediatric centers. Continuous glucose monitoring (CGM) and laboratory glycated hemoglobin were employed for CFRD screening in 86.5% and 50% of centers, respectively. CGM was carried out in 69% of centers after glucose tolerance abnormalities had been detected in OGTT. Most CF centers used OGTT and CGM for CFRD screening. Studies are required to assess CGM usefulness as a validated tool in CFRD screening.

## Background

The prevalence of cystic fibrosis-related diabetes (CFRD) increases with age [1]. In many studies, CFRD was shown to be associated with increased mortality and morbidity, including poorer nutritional status and lower respiratory function [2–4]. Clinically, the significance of early glucose abnormalities in people with CF (pwCF) is being evaluated [5]. Glucose intolerance may go unrecognized justifying screening before symptom onset.

In 2010, the American Diabetes Association proposed definitions of glucose tolerance abnormalities in pwCF based on 2-hour plasma glucose levels following oral glucose tolerance testing (OGTT) performed annually at age 10 years old [6]. In 2018, Clinical Practice

Consensus Guidelines from the International Society for Pediatric and Adolescent Diabetes (ISPAD) recommended to evaluate for glucose tolerance abnormalities in CF children and adolescents annually, starting at the age of 10 years, and may be considered in younger children with severe forms of CF [7].

Currently other CFRD screening tests are being investigated. Several studies reported the usefulness of determining 1-hour (T1) plasma glucose levels following OGTT, enabling earlier hyperglycemia to be detected [8]. T1 hyperglycemia in OGTT appeared correlated more strongly with continuous glucose monitoring (CGM) data than T2 hyperglycemia [9]. Currently, CGM is increasingly used by multiple CF centers for the detection of abnormal glucose trends. CGM can detect hyperglycemia that is undetected with OGTT. While several studies

\* Corresponding author at: Service d'Endocrinologie, Diabète et Nutrition, Hôpitaux Universitaires de Strasbourg, Hôpital Civil, UMR Inserm 1260, Nano medicine Regenerative, 1 place de l'Hôpital, Fr-67000 Strasbourg, France.

E-mail address: [laurence.kessler@chru-strasbourg.fr](mailto:laurence.kessler@chru-strasbourg.fr) (L. Kessler).

<sup>1</sup> on behalf of the Diabetes study group of French Cystic Fibrosis Society.

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reported a link between CGM abnormalities and clinical deterioration, whether such undetected hyperglycemia impacts with pwCF is unclear [4,9,10]. Moreover, CGM lacks standardization, with glucose intolerance threshold and CFRD criteria still undefined [11]. Further studies are required to determine CGM's precise usefulness in CFRD screening, and its place in guidelines.

In this survey, we sought to analyze current CFRD screening practices in French CF centers in light of international recommendations.

## Methods

A web-based questionnaire was distributed between December 1, 2020 and January 31, 2021 to coordinators of the 47 French CF centers. The authors formulated the questionnaire, they were all members of the Diabetes study group of the French Cystic Fibrosis Society. Questionnaire was sent online following by two reminders and a telephone call for the centers who had not responded. There was no incentive for survey participation. Single choice, multiple choices, and descriptive answers to 20 questions in fixed order were requested. Questions covered relevant topics pertaining to CFRD screening, including screening tests, OGTT and CGM modalities, their advantages and disadvantages, and patients targeted for screening. (Supplementary materials: S1).

### Statistical analysis

Descriptive analysis of responses was performed and results were expressed as percentage. The data were collected through a Google forms questionnaire and analyzed with the Google spreadsheets. Only one survey per CF center, adult, pediatric and mixt, was allowed. Answers to the survey were anonymous. We only collected the location (city) of the CF center. Data cleaning and coding ensured data quality: entries were checked to eliminate nonsense values and confirm that all values were within appropriate ranges. Open-ended responses were coded thematically.

## Results

### CFRD screening

All 47 CF centers participated in the survey and 52 responses were analyzed. Among the 16 mixed centers, 5 centers gave a separate response for the adult population and the paediatric population. The guidelines recommending annual 2-hour plasma glucose – 75 g–1.75 g/kg OGTT for CFRD screening were applied in 92.8% of all centers, 95% of pediatric centers, and 100% of adult centers. The other CFRD screening methods were CGM and laboratory glycated hemoglobin (HbA1C) in 86.5% and 50% of all centers, 90% and 55% of pediatric centers, and 82% and 53% of adult centers, respectively. The glycemic cycle including pre and postprandial blood glucose (fingerstick glucometer measurement) before and after each meal for a day, was performed in 41% of adult centers (Fig. 1). These screening methods are often used in combination.

### OGTt

CF center conducted OGTT screening in and in private laboratory in 82.4% and 29.4% of all centers, 89.5% and 15.8% of pediatric centers, and 88% and 12% of adult centers, respectively. Lying down at rest during OGTT is required in 73.1% of all centers, 70% of pediatric centers and 76.5% of adult centers. French CF centers reported that this requirement during OGTT was a challenge in 34% of all centers, 26.7% of adult centers and 35.3% of pediatric centers. At T0, T1 hour, and T2 hours laboratory plasma glucose levels were measured in 86.3% of all centers, 89% of pediatric centers, and 82% of adult centers (Table 2 A). OGTT was performed before 10 years of age in 73% of pediatric centers,

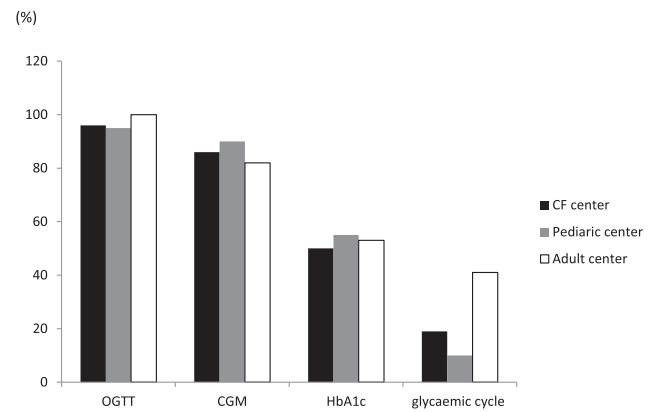


Fig. 1. Modalities of CFRD screenings in French cystic fibrosis centers (black column), pediatric centers (gray column), and adult centers (white column).

and in younger children with advanced lung disease (low FEV1 or rapid decline in pulmonary function, diffuse bronchiectasis, frequent pulmonary exacerbations), undernutrition, and growth retardation in 100%, 85.7%, and 71.4% of centers. In patients without exocrine pancreatic insufficiency, OGTT was performed in 29.5 % of all centers, 26% of pediatric centers, and 53% of adult centers. For patients with exocrine pancreatic insufficiency, OGTT was conducted in 62.7% of all centers, 68% of pediatric centers, and 82% of adult centers (Fig. 2B). The main

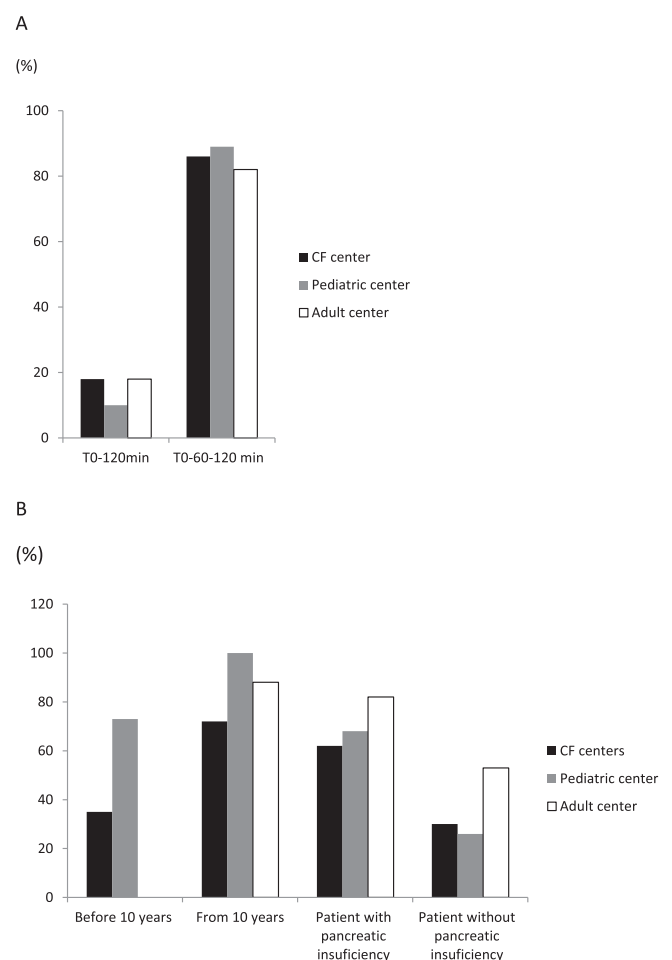


Fig. 2. OGTT with and without T-1 h glucose (A) and targeted populations (B) in French cystic fibrosis centers (black column), pediatric centers (gray column), and adult centers (white column).

difficulties encountered in OGTT included patient refusal (fasting; multiple venous samplings), poor test acceptability (length; poor digestive tolerance), not lying down at rest during the test and non-availability of healthcare teams (lack of time for nurse to do venipuncture and to take blood samples in satisfactory conditions).

### Continuous glucose monitoring

CGM for CFRD screening was performed in 92.8% of all centers, 92.8% of pediatric centers, and 88% of adult centers. CGM devices included I-Pro (Medtronic), Free Style Libre 1, and Pro (Abbott). These were implemented in CF centers, diabetology departments, and at home in 60%, 10%, and 35%, respectively, for pediatric centers; the corresponding figures were 50%, 34%, and 31% for adult centers.

CGM was performed in those with glucose tolerance abnormalities identified by OGTT in 69% of all centers, 75% of pediatric centers, and 60% of adult centers (Fig. 3A). Abnormal glucose tolerance categories included indeterminate glucose tolerance (INDET), impaired glucose tolerance, and CFRD without fasting hyperglycemia (Table 3B). INDET was defined as a 1-hour glucose level on OGTT > 200 mg/dL and occurred in 56%, 73%, and 40% of all centers, pediatric, and adult centers, respectively. CGM was performed annually versus occasionally in 33% and 57% of all CF centers, 40% and 40% of pediatric centers, and 37% and 69% of adult centers. The main difficulties encountered with CGM were device financing and lack of training for care teams; for patients, difficulties included refusal of external device wearing and the need to complete dietary records. Overall, 90% and 88% of pediatric and adult CF centers had a referent diabetologist for the management of CFRD. Only 45% and 65% of diabetologists were involved in the CFRD

screening whatever the used screening test, OGTT or CGM.

### Discussion

Based on this survey, most pediatric and adult French CF centers performed annual OGTT for CFRD screening based on 1- and 2-hour OGTT glucose levels. Additionally, 86% of CF centers proposed CGM for CFRD screening. French CF centers complied with international American Diabetes Association guidelines [6,7]. Indeed, OGTT establishes thresholds enabling patient categorization based on increasing severity of glucose intolerance, a valid predictor of CFRD, which is associated with increased morbidity and mortality [2,3]. In 2019, CF Foundation registry reported a median diabetes screening rate with OGTT of only 36.9% in adult CF centers and 66.6% in pediatric centers in the United States [12]. This low screening rate is likely explained by OGTT's limitations like poor patient acceptability, not lying down at rest during the test and lack of availability in CF centers. Centers are also increasingly using CGM for CFRD screening due to its higher acceptability and its ease to use. As in the USA, we found substantial variation across French CF centers practices.

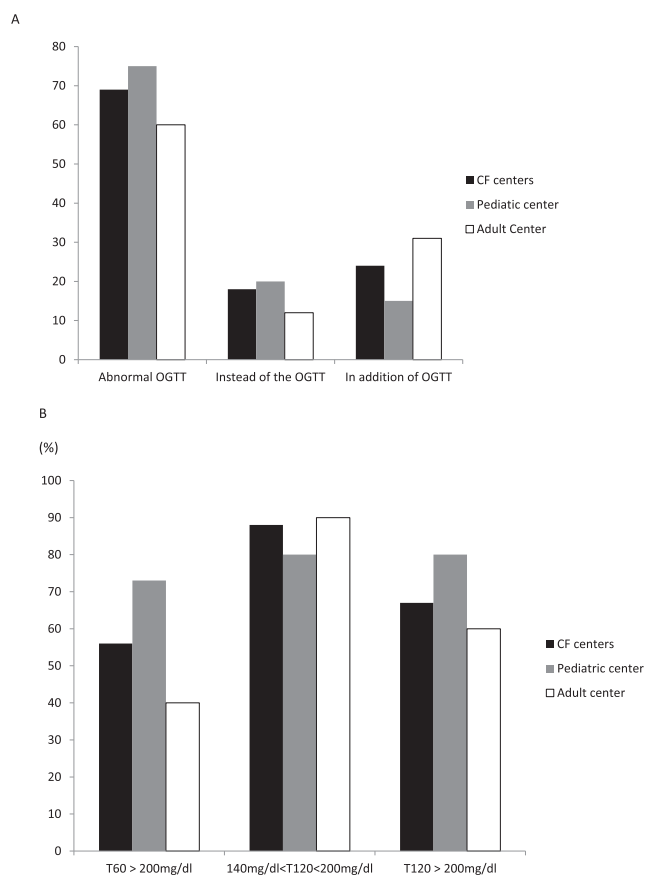
Several studies revealed early glucose tolerance abnormalities in CF patients based on 1-hour glucose on OGTT and on CGM [8–10]. In our survey, 86.3% of CF centers performed 1-hour and 2-hour plasma glucose levels on OGTT, though the usefulness of 1-hour value remains controversial [8,13,14]. Overall, 92.8% of CF centers proposed CGM for CFRD screening, but in 69% of centers, CGM was proposed only upon abnormal OGTT including 1-hour glucose on OGTT exceeding 200 mg/dL. For a third of centers, CGM was performed annually and at home. The impact of these new screening modalities is still being explored. Advantage of CGM over OGTT is to analyze the glucose profile in real live at home. CGM does not require a diet period of fasting, physical activity is free with better representation of everyday glucose profile, thereby explaining the wide CGM use in CF centers. CGM is often proposed after OGTT but substantial variation across CF centers exist calling into question the role of CGM in CFRD screening. Laboratory HbA1c was used for CFRD screening in 50% of centers but most often in combination with other tests due to the inability to detect early abnormalities in glucose tolerance. International guidelines do not recommend laboratory HbA1c for CFRD screening [6,7] and its interest as screening test is controversial [15,16].

Little differences in CFRD screening exist between pediatric and adult centers. However, pediatric centers use CGM for screening more often than adult centers in detecting early glucose tolerance abnormalities in patients with INDET.

Currently, CFRD screening is recommended every year from 10 years. Most centers followed this recommendation [6,7]. Overall, 72.5% of the centers offer OGTT from the age of 10 years, and 35.3% before this age. OGTT and CGM may be considered in young with specific clinical findings, as our study found that CF centers were utilizing them at high rates for pediatric patients with advanced pulmonary disease (80% and 73.3%), undernutrition (85% and 73.3%), and poor growth curve (65% and 40%). Although the significance of early glucose abnormalities remains controversial, several studies reported glucose intolerance occurring at earlier stages likely associated with poorer respiratory status [2–4,8].

Glucose intolerance and CFRD risk are likely higher in certain phenotypes, including those with exocrine pancreatic insufficiency [1]. In French centers, CFRD screening differs depending on the patient's pancreatic status. Overall, 62.5% of centers propose OGTT to patients with exocrine pancreatic insufficiency and 29.4% in those without exocrine pancreatic insufficiency. Likewise, CGM offered more frequently to patients with pancreatic insufficiency (97%) versus those without (51.4%). In the latter, CFRD screening is less commonly proposed because of lower risks of glucose intolerance [17].

Our study displays several limitations. First, the use of an unvalidated survey. Some of these questions may appear as guiding questions,



**Fig. 3.** Role of CGM for CFRD screening according to the OGTT (A) and the glucose values (B) of OGTT in French cystic fibrosis centers (black column), pediatric centers (gray column), and adult centers (white column).

with forced-choice answers. However, free comments were collected to limit this bias (Supplementary Materials S2). Second, a survey based on self-reporting is still scientifically questionable and the self-reported responses of centers may differ from the actual data. Answers to this survey represent the respondent's understanding of CF center recommendations, and not actual practice, nor actual rates of screening with OGTT or CGM across centers.

Third, the invitation to participate was sent to the CF center coordinators who then returned the information on behalf of the entire CF center team. Yet, as all French CF centers participated with a 100% response rate, this allowed for a sound national evaluation of clinical practices.

In conclusion, most French CF centers used OGTT and CGM in CFRD screening. However, the heterogeneity of practices highlights the difficulties of centers in using screening tests, in particular the CGM. Further studies are required to determine CGM's precise usefulness in CFRD screening, and its place in guidelines.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jcte.2022.100298>.

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