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Original Article

Early assessment of glucose abnormalities during continuous glucose monitoring associated with lung function impairment in cystic fibrosis patients

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Abstract

Background: Cystic fibrosis-related diabetes (CFRD) is correlated with a decline in lung function. Under certain circumstances, oral glucose tolerance test (OGTT) screening, used to diagnose CFRD, fails to reveal early glucose tolerance abnormalities. In this situation, continuous glucose monitoring (CGM) could be a useful tool for evaluating early abnormalities of glucose tolerance in CF patients. We aimed to study the CGM glucose profile in CF patients with normal OGTT screening results and to evaluate lung function and nutritional status according to the CGM glucose profile.

Methods: We assessed glycemic control, the CGM glucose profile, nutritional status, lung function antibiotic courses and colonization (*P. aeruginosa* and *S. aureus*) in CF patients, aged 10 years and over, with normal screening OGTT results (blood glucose at T120 min < 7.8 mmol/l). Two groups were identified according to the max CGM glucose value: Group 1 < 11 mmol/l and Group 2 ≥ 11 mmol/l.

Results: Among the 38 patients with normal OGTT, 12 (31.6%) were in Group 2. Compared to Group 1, Group 2 patients exhibited a significant impairment in lung function: FEV_1, 68.2 ± 25.6% vs. 87.3 ± 17%, p = 0.01 and FVC, 86.1% ± 19.4% vs. 99.3% ± 13.4%, p = 0.021, as well as a higher rate of colonization by *P. aeruginosa*: 83.3% vs. 44%, p = 0.024. Nevertheless, there were no differences in nutritional status (BMI standard deviation score: p = 0.079; prealbumin: p = 0.364).

Conclusions: CGM reveals early abnormalities of glucose tolerance that remain undiagnosed by OGTT screening and are associated with worse lung function and a higher prevalence of *P. aeruginosa* colonization in patients with CF.

Clinical trial registration number: NCT00476281.

Keywords: Cystic fibrosis; OGTT; CGM; Lung function; Early glucose tolerance abnormalities

1. Background

Because the life expectancy of cystic fibrosis (CF) patients has increased over the past few decades, cystic fibrosis-related diabetes (CFRD) has become a common complication of CF

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(50% of patients over 30 years old) [1]. CFRD is also known to be associated with an impairment of lung function [2,3] and weight loss [4]; both are associated with higher mortality rates [5–7].

For the early detection of CFRD and improvements in its treatment, OGTT is recommended in the North American Cystic Fibrosis Foundation criteria [1] to be performed yearly on patients older than 10 years of age. However, some authors have shown that the standard methods of glycemic assessment, random or fasting glucose concentrations, and/or OGTT underdiagnosed CFRD [8–10]. Consequently, early glucose abnormalities remained undetected. Moreover, it is known that patients who will later develop CFRD present a decrease in their lung function and weight standard deviation score (SDS) during the preceding 12 months [11].

CGM is a new method that can be used to evaluate the blood glucose profile over several days. It was used to control the efficiency of insulin pump therapy or the self-management of type 1 diabetic patients at home [12–14]. It has also been evaluated in children, adolescents and adults with CF [15,16], and its use has been proposed to study early glucose tolerance abnormalities [17–19]. As a result, it could be a useful tool to diagnose early glucose abnormalities that are not revealed by OGTT.

We designed this study to assess CGM glucose profiles in CF patients with normal OGTT. Nutritional status, lung function and infection parameters were studied in CF patients according to their CGM glucose profile.

2. Methods

2.1. Study design and patients

A total of 83 CF patients (42 males and 41 females) with fasting glycemia < 6.9 mmol/l who were at least 10 years old (age range: 12.4–57.3 years) were followed at the CF center of Strasbourg University Hospital (France) and enrolled in a prospective monocentric cross-sectional cohort study between March 2009 and September 2012. The CF diagnosis in these patients was based on clinical features and on positive CF genotype. The subjects were excluded if they had been diagnosed with diabetes or liver disease, had undergone a lung transplant or were taking steroids. Each patient underwent blood tests (HbA1c and prealbumin), OGTT, CGM, respiratory and nutritional evaluation. The evaluations were performed while the patients were in a clinically stable state, with at least 1 month having passed since any respiratory exacerbation and in the absence of a restricted-calorie diet. The protocol was approved by the local ethics committee (n.2007/09), and each patient or their legal representative provided written informed consent. The study protocol was conducted in accordance with the Declaration of Helsinki.

2.2. Metabolic evaluation

The OGTT screening was performed at the CF center on the morning after an unrestricted diet and typical physical activity. As recommended by the World Health Organization criteria [20] and the North American Cystic Fibrosis Foundation criteria [1], plasma glucose and C-peptide levels were measured at 0 and 120 min after drinking a glucose solution at a dose of 1.75 g/kg (up to a maximum of 75 g). The patients were classified according to the level of glycemia they presented at 2 h: normal glucose tolerance (NGT), glycemia at 2 h < 7.8 mmol/l; impaired glucose tolerance (IGT), 7.8 mmol/l ≤ glycemia at 2 h < 11 mmol/l; and CFRD, glycemia at 2 h ≥ 11 mmol/l.

The HbA1c (hemoglobin A1c) level was determined before performing the OGTT (%) using high-performance liquid chromatography (Variant 2, Bio-Rad, Marnes-La-Coquette, France).

Within three months after the OGTT was performed, patients remained stable in terms of weight, did not show pulmonary exacerbations requiring steroid intake, and had the CGM device installed at the outpatient clinic (Medtronic, and Sylmar, CA, USA). This device remained in situ in the home environment for 72 h for all of the subjects. They consumed their typical diet and entered a minimum of four self-monitored blood glucose values for daily CGM calibration. Various parameters were assessed: average glucose (mmol/l), maximum glucose (mmol/l), AUC of glucose values ≥ 7.8 mmol/l (mmol/l/day), duration of glucose values ≥ 7.8 mmol/l over the course of 72 h (%) and peak number of interstitial glucose values ≥ 11 mmol/l. We defined two groups based on the presence (Group 1) or absence (Group 2) of at least one interstitial glucose value higher than 11 mmol/l during the CGM recording.

2.3. Nutritional status

Patients were weighed and measured, and their BMI [weight in kilograms/height in meters squared] was calculated. The age- and gender-specific z-scores for BMI SDS (SD: standard deviation) were computed relative to the French reference population [21]. A blood sample was taken just before the OGTT to determine the prealbumin level (g/l).

2.4. Lung function

The patients performed spirometry with FEV_1 and FVC measurements (Vmax spirometer, VIASYS, Healthcare Respiratory Technologies, Canada), which was adjusted in percentage according to the age, gender, height and weight, as recommended by the ERS (European Respiratory Society) and the North American (American Thoracic Society) guidelines [22]. The number of intravenous antibiotic courses in one year was quantified for each subject. The bacterial species in sputum specimens (*P. aeruginosa* and *S. aureus*) were identified according to the North American guidelines [23].

2.5. Statistical analysis

All of the data were extracted from the CGM sensor to a personal computer with the aid of a communication device, which allowed downloading and reviewing (MiniMed Solutions Software, version 1.7a). The mean and SD of the interstitial glucose concentrations were derived for all of the CGM

recordings. Comparisons of categorical variables were made using chi-squared tests or Fisher's exact tests. Continuous variables were analyzed using the Student's t-tests or the Wilcoxon's test, as appropriate. Correlations among variables were calculated using the Pearson's correlation coefficient or Spearman's rank correlation. In multivariate analysis, variables found to be statistically significant in bivariate analyses (age, age at diagnosis, sex, genotype, exocrine pancreatic insufficiency, BMI SDS, and *P. aeruginosa* colonization) were included as potential covariates. Analyses were performed using GraphPad Prism, version 5.0 and the R statistical software, version 3.0.2. The data are expressed as the mean values with standard deviation where appropriate. Significance was set at the 5% level.

3. Results

3.1. Study design and patients

Of the 83 initially selected patients with CF, 15 were excluded: 6 were diabetic prior to inclusion, 7 were lost to follow-up, and 2 revoked their consent. Then, 16 of the 68 remaining patients underwent OGTT only. The remaining 52 (59.6% female) underwent both OGTT and CGM. The average age was 26.6 ± 9.76 years; the age upon diagnosis of CF was 9.38 ± 12.6 years (means ± SD), and 84.2% of the subjects presented exocrine pancreatic insufficiency. A total of 32.7% of the patients were homozygous F508Del, 34.6% were heterozygous for F508Del, and 32.7% presented other mutations. Of these 52 patients, 38 were NGT, and 14 had glucose tolerance abnormalities (IGT: n = 9, CFRD: n = 5). The study design is shown in Fig. 1.

In the 38 patients with normal OGTT (NGT), the BMI SDS was 0.88 ± 1.52 SD, and the prealbumin concentration was 0.25 ± 0.05 g/l. FEV_1 and FVC were 82% ± 22.2% (2.62 ± 0.89 l) and 96 ± 17.4% (3.64 ± 1.12 l), respectively. The characteristics of the NGT groups are described in Table 1. A total of the 38 patients with normal OGTT was evaluated. Of these, 12 patients (31.6%) had at least one interstitial glucose greater than 11 mmol/l (Group 2). The other 26 patients who had no interstitial glucose value ≥ 11 mmol/l composed Group 1.

The patients in Group 1 (n = 26) had a mean age of 27.2 ± 10.7 years and were predominantly female (57.7%). The age at diagnosis of CF was 12.25 ± 14.12 years old, and 76.9% had exocrine pancreatic insufficiency. With respect to mutations, 30.8% patients were homozygous for F508Del, 53.8% were heterozygous for F508Del, and 15.4% had other mutations. Group 2 (n = 12) was 66.7% female, and the mean age was 23.53 ± 6.9 years. With respect to the age at CF diagnosis, the patients in Group 2 were significantly younger than those in Group 1: 3.16 ± 4.75 vs. 12.25 ± 14.12 years, respectively (p = 0.037). All of the patients in Group 2 had exocrine pancreatic insufficiency. Additionally, 50% of the patients were homozygous for F508Del, 25% were heterozygous for F508Del, and 25% had other mutations. There were no differences with respect to age, sex ratio, genetic status or exocrine pancreatic insufficiency (p = 0.07) between the two groups. The characteristics of the patients are summarized in Table 1.

3.2. Metabolic evaluation

Analyses of the OGTT between these two groups revealed no significant differences in the C peptide plasma levels at T0 min or at T120 min. There was a tendency toward a higher HbA1c in Group 2 compared with Group 1 (p = 0.055). In Group 2, the CGM revealed a significantly higher AUC ≥ 7.8 mmol/l (3.42 ± 2.27 vs. 0.39 ± 0.57 mmol/l/day, p < 0.0001) and a longer percentage of time with interstitial glucose ≥ 7.8 mmol/l: (14.17% ± 10.38% vs. 3.54% ± 3.99%, p < 0.0001). However, the average interstitial glucose did not differ between the two groups (p = 0.067).

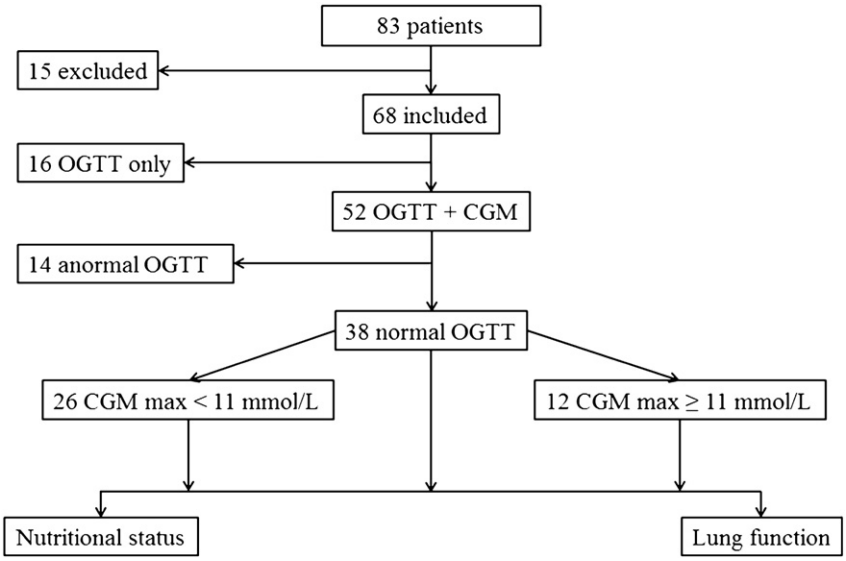

Fig. 1. Study design.

Table 1
Baseline characteristics of the patients. Group 1: CGM max < 11 mmol/l, Group 2: CGM max ≥ 11 mmol/l. p values refer to the comparison between Group 1 and Group 2. NS: Not significant. ND: Not done.

	Total	Group 1	Group 2	p
No. of patients (%)	38	26	12	
Female	23 (60.5%)	15 (57.7%)	8 (66.7%)	NS
Age at evaluation (years)	26.05 ± 9.76	27.21 ± 10.7	23.53 ± 6.9	NS
Age at diagnosis of CF (years)	9.38 ± 12.6	12.25 ± 14.12	3.16 ± 4.75	0.037
Genotype (% of patients)				
-Homozygous F508Del	36.8	30.8	50	NS
-Heterozygous F508Del	44.8	53.8	25	NS
-Other mutations	18.4	15.4	25	NS
Exocrine pancreatic insufficiency	32 (84.2%)	20 (76.9%)	12 (100%)	0.07
OGTT				
Glycemia T0 min (mmol/l)	4.73 ± 0.44	4.67 ± 0.33	4.73 ± 0.44	NS
Glycemia T120 min (mmol/l)	5.01 ± 1.43	5.66 ± 1.15	5.94 ± 1.1	NS
C-peptide plasma level T0 min (μg/l)	1.67 ± 0.57	1.77 ± 0.55	1.46 ± 0.60	NS
C-peptide plasma level T120 min (μg/l)	6.92 ± 2.34	6.85 ± 1.90	7.07 ± 3.12	NS
HbA1c (%)	5.66 ± 0.33	5.58 ± 0.35	5.81 ± 0.24	0.055
CGM				
Average interstitial glucose (mmol/l)	5.79 ± 0.80	5.61 ± 0.82	6.10 ± 0.60	NS
AUC ≥ 7.8 mmol/l/day	1.34 ± 1.94	0.39 ± 0.57	3.42 ± 2.27	<0.0001
% time ≥ 7.8 mmol/l	6.89 ± 8.24	3.54 ± 3.99	14.17 ± 10.38	<0.0001
No. of peaks with interstitial glucose ≥ 11 mmol/l	0.42 ± 0.76	0	1.08 ± 0.2	ND
No. of IV antibiotic courses/year	0.82 ± 1.16	0.68 ± 1.14	1.17 ± 1.27	NS
Prevalence (%)				
P. aeruginosa	55.3	44	83.3	0.024
S. aureus	76.3	84.6	58.3	0.076

An example of a CGM recording of a patient with normal OGTT is shown in Fig. 2. Glucose peaks higher than 7.8 mmol/l were present after each meal for 3 days. This patient was classified into Group 2 because he had one glucose peak that was higher than 11 mmol/l on Sunday evening. The average glycemia was 6.1 mmol/l, and the maximal glycemia was 20.6 mmol/l.

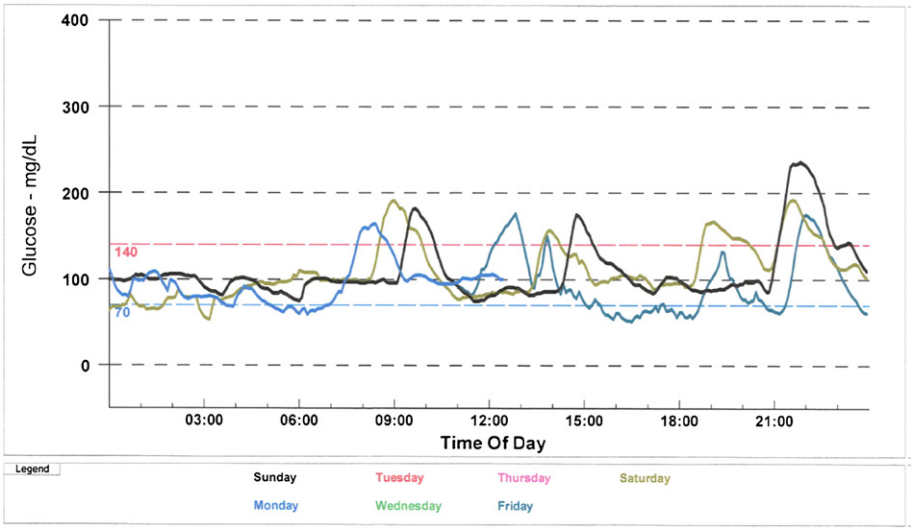

Fig. 2. CGM recording in a patient with normal OGTT results. Pathological CGM recordings over the course of three days (Saturday: brown; Sunday: black; Monday: blue) in a patient with normal OGTT results. Several interstitial glucose peaks higher than 140 mg/dl (7.8 mmol/l) are present after each meal. One peak of interstitial glucose higher than 200 mg/dl (11 mmol/l) was present on Sunday evening.

The duration of interstitial glucose greater than 7.8 mmol/l was 16% of 72 h (i.e., 11.52 h), and the AUC ≥ 7.8 mmol/l was 22 mmol/l/day.

3.3. Nutritional status

There was no difference between the patients in Groups 1 and 2 with respect to the BMI SDS (1.75 ± 2.17 SD vs. 0.34 ± 1.06 SD, p = 0.079) or prealbumin concentration (0.256 ± 0.044 g/l vs. 0.239 ± 0.052 g/l, NS; Fig. 3A and B, respectively).

3.4. Lung function and bronchopulmonary infections

FEV_1 and FVC were significantly lower in the Group 2 patients compared to the Group 1 patients independent of age, age at diagnosis, sex, genotype, exocrine pancreatic insufficiency, BMI SDS, and *P. aeruginosa* colonization: 68.2% ± 25.6% (2.20 ± 0.88 l) vs. 87.3% ± 17% (2.82 ± 0.84 l) (p = 0.01) and 86.1% ± 19.4% (3.26 ± 1.08 l) vs. 99.3% ± 13.4% (3.82 ± 1.11 l) (p = 0.021), respectively (Fig. 3C and D). There was no difference in the number of intravenous antibiotic courses (p = 0.24) between the two groups. With respect to bacterial colonization, Group 2 patients were more frequently colonized by *P. aeruginosa* (83.3% vs. 44%, p = 0.024) independent of age, age at diagnosis, sex, genotype, exocrine pancreatic insufficiency, and BMI SDS. *S. aureus* colonization appeared to be less common in Group 2 (p = 0.076).

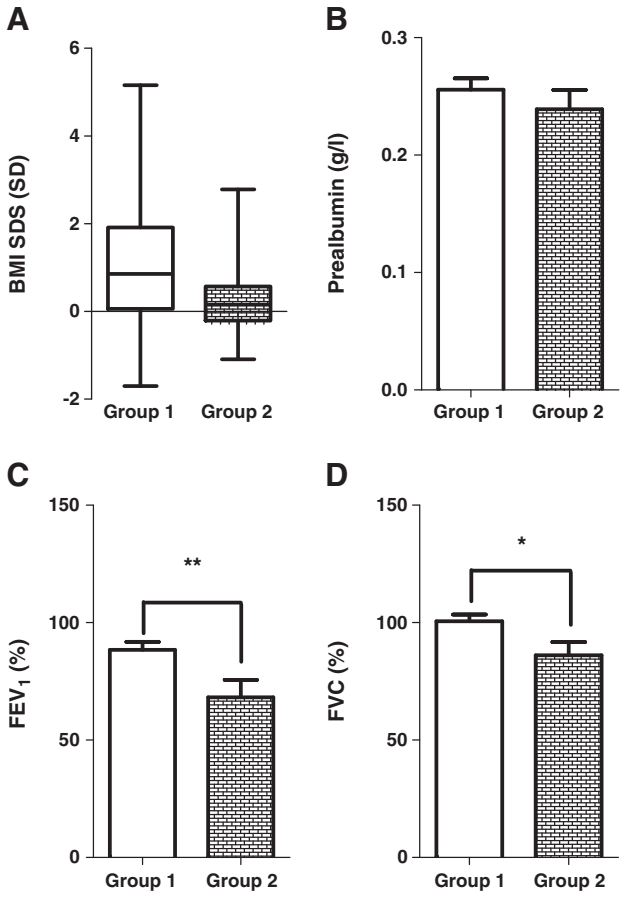

Fig. 3. BMI SDS (A.), prealbumin (B.), FEV_1 (C.), and FVC (D.) in cystic fibrosis patients with normal OGTT and CGM glucose values < 11 mmol/l (Group 1) □ or ≥ 11 mmol/l (Group 2) ▨ *p < 0.05; **p < 0.001.

4. Discussion

We have shown that early abnormalities in glucose tolerance, which were detected by CGM but not conventional OGTT, were associated with lung function impairment in CF patients.

In agreement with other studies [16,17,19], we observed that approximately one third of the patients with normal OGTT results, according to the WHO criteria [20], presented early abnormalities according to a CGM glucose profile (glucose value above 11 mmol/l).

The explanation of why OGTT screening underdiagnosed these early abnormalities in glucose tolerance has previously been studied. Dobson et al. have shown that, despite having similar fasting and 120-min glucose values, non-diabetic CF patients reach higher glucose values at the intermediate point during OGTT and exhibit an increased AUC in blood glucose values compared to non-diabetic non-CF patients [8]. No significant difference was observed between NGT patients and CFRD patients. Furthermore, glucagon-like peptide 1 (GLP-1), an incretin hormone released from intestinal L-cells in response to eating, is known to induce insulin secretion. Hillman et al. have shown that the GLP-1 level is lower in non-diabetic CF patients compared to normal patients, but no difference has been observed in CFRD patients [24]. Additionally, early glucose abnormalities in CF patients are due to beta-cell dysfunction and reduced early insulin secretion rather than insulin resistance [25]. Secondary to this alteration in early insulin secretion, CF patients with no known glucose abnormalities exhibit blood glucose peaks that are higher than those of CF patients without glucose abnormalities during OGTT screening. In our study, this reduced early insulin secretion was also responsible for the postprandial glucose peak greater than 7.8 mmol/l that was observed in the CGM glucose profile. The durations of these two types of glucose peak profiles (OGTT, post-prandial) were similar (approximately 90 min). Finally, in contrast to OGTT screening (which was typically not associated with the intermediate glucose value), CGM, a more physiological tool, allowed the diagnosis of early abnormalities in glucose tolerance due to alterations in early insulin secretion.

Therefore, in our study, CGM revealed high glucose value excursions that were not observed in the OGTT, whereas there was no difference in the mean glucose values between the two groups. However, the AUCs above 7.8 mmol/l and the duration of the hyperglycemic period (%) were higher in patients with glucose values above 11 mmol/l. These two parameters have previously been reported to be higher in CFRD patients compared to those in NGT and IGT patients, although no difference has been reported between NGT and IGT [17]. Khammar et al. compared the CGM glucose profiles in non-CFRD patients

(blood glucose T120 min < 2 g/l at OGTT) according to the presence of high interstitial glucose values above 11 mmol/l. The duration of the hyperglycemic period was also significantly longer in patients with a high number of glucose values above 11 mmol/l [24]. Consequently, three CGM parameters (an AUC above 7.8 mmol/l, duration of the hyperglycemic period (%) and interstitial glucose values above 11 mmol/l) can be used to study the early abnormalities of glucose tolerance in CF patients.

In our study, HbA1c was comparable between the two groups, although it appeared to be higher in patients with a greater number of glucose values above 11 mmol/l. A few explanations regarding how HbA1C can remain normal for such a long time in CFRD patients have been discussed in the literature. First, the lifespan of red blood cells is reduced in CF patients [27]. Second, due to the effect on early insulin secretion, early glucose tolerance abnormalities may particularly affect postprandial glucose (PPG) in CF patients, with less effect on the mean glucose value according to CGM. Moreover, in type 2 diabetic patients, some authors have observed that the fasting plasma glucose (FPG) level is the strongest predictor of HbA1c [28]. In fact, Monnier et al. showed that in patients with type 2 diabetes, HbA1c was linked in different ways to PPG or FPG according to the severity of diabetes [29]. Indeed, PPG was the predominant contributor in patients who maintained satisfactory to good control of their diabetes, whereas the contribution of FPG increased as diabetes worsened. Furthermore, PPG was a better predictor of good or satisfactory control of diabetes (HbA1c < 7%) compared to FPG. Consequently, HbA1c appeared to be linked to PPG due to the early abnormalities of glucose tolerance. However, according to the recommendations regarding CFRD [1], HbA1c is not an appropriate parameter to identify CF subjects who present early abnormalities in glucose tolerance.

Because CFRD has been associated with impaired lung function and poor nutritional status, many studies have used CGM to detect early abnormalities in glucose tolerance in CF patients. Even if these studies have shown that patients with normal OGTT can exhibit early abnormalities in glucose tolerance using the CGM glucose profile [17–19,26], none have shown an association with lower FEV_1 and FVC values and a higher level of colonization with *P. aeruginosa*.

It is already known that overt CFRD is a potential risk factor for decreased lung function [3]. Our study demonstrates that even early abnormalities in glucose tolerance could also be a risk factor for impaired lung function. In a retrospective study, Alicandro et al. demonstrated that CF patients with normal OGTT and lower insulin secretion had worse lung function. Similar results were observed for CF patients with a higher AUC for the glucose concentration, but no difference was observed using the number of blood glucose peaks above 8.14 mmol/l (OGTT) [30].

The fact that the C peptide plasma level was not different between our two groups can be explained. For example, compared to Alicandro et al., the C peptide plasma level was only measured at T0 min and T120 min. These data agreed with the hypothesis that alterations of early insulin secretion, undetected by the OGTT, were associated with worse lung function.

Repeated infections by *P. aeruginosa* are also known to be a risk factor for poor lung function. The frequency of these infections is increased with CFRD [3]. Moreover, Brennan et al. have demonstrated in CF patients that airway glucose concentrations are dependent on the blood glucose and that *P. aeruginosa* growth increases if the airway glucose is above 1–4 mmol/l [31]. Consequently, these data can explain why CF patients with early abnormalities in glucose tolerance were more frequently colonized by *P. aeruginosa*.

Malnutrition is also a risk factor for worse lung function, and nutritional status is linked to glucose abnormalities. The nutritional status is generally worse in CF patients with CFRD [4]. According to the literature, during the preceding 12 months of CFRD, CF patients already exhibit a decline in the weight standard deviation score (SDS) [11]. Moreover, CF patients with normal OGTT results and lower insulin secretion had a lower BMI SDS [30]. However, in accordance with our study, Alicandro et al. failed to observe a difference in the BMI SDS using the AUC concentration of glucose or the blood glucose peak above 8.14 mmol/l. Consequently, early abnormalities in the glucose profile did not appear to be associated with impaired nutritional status. Indeed, Hameed et al. did not show a difference in the weight SDS during the preceding 12 months between NGT and IGT patients [11]. Our findings suggest that, contrary to the nutritional status, lung function might be more sensitive to early abnormalities in the glucose tolerance of CF patients.

Some interesting points can be made regarding our population. Even if there was no difference in age between the patients with and without glucose abnormalities, the age at diagnosis of CF was higher in patients without early abnormalities in glucose tolerance. Age at diagnosis has also been shown to significantly affect FEV_1 ($p < 0.0001$), but this result was not clinically relevant (under the 10% threshold after making adjustments for age, BMI, pancreatic status, chronic *P. aeruginosa* infection and CFRD) [3]. Therefore, CF patients diagnosed at a later age could have better lung function and develop the early abnormalities of glucose tolerance later than others.

Pancreatic insufficiency has also been shown to be a risk factor for poor lung function [3]. In our study, compared to three quarters of the patients with normal glucose tolerance, all of the patients with early abnormalities of glucose tolerance also exhibited pancreatic exocrine insufficiency, although there was no significant difference. These findings suggest an important role of global pancreatic cell dysfunction in lung function impairment and glucose abnormality.

According to our main hypothesis, alterations in pancreatic function (particularly early insulin secretion dysfunction) in CF patients with normal OGTT screening could be revealed using CGM, thanks to the early blood glucose peak present after a meal or glucose intake.

One limitation of our study is the relatively small number of patients in the cohort. The flow chart indicates that only half of the patients initially recruited were ultimately included in the

analysis. However, because these patients were thoroughly evaluated, it appears unlikely that increasing the number of patients could change the main findings of this study.

In conclusion, CGM revealed early abnormalities of glucose tolerance that had remained undiagnosed by OGTT screening and that were associated with impaired lung function and a higher prevalence of *P. aeruginosa* colonization in patients with CF. Further studies with a larger sample size are needed to confirm our results. Such studies may confirm the usefulness of CGM in the diagnosis of early glucose abnormalities and the prevention impaired lung function.

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