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Sensitivity and specificity of different methods for cystic fibrosis-related diabetes screening: is the oral glucose tolerance test still the standard?

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Abstract

Background: Cystic fibrosis-related diabetes (CFRD) is a late cystic fibrosis (CF)-associated comorbidity whose prevalence is increasing sharply lifelong. Guidelines for glucose metabolism (GM) monitoring rely on the oral glucose tolerance test (OGTT). However, this test is neither sensitive nor specific. The aim of this study was to compare sensitivity and specificity of different methods for GM monitoring in children and adolescents with CF.
Methods: Continuous glucose monitoring system (CGMS), used as the reference method, was compared with the OGTT, intravenous glucose tolerance test (IGTT), homeostasis model assessment index of insulin resistance (HOMA-IR), homeostasis model assessment index of β-cell function (HOMA-%B) and glycated haemoglobin A_{1C}. Patients were classified into three groups according to CGMS: normal glucose tolerance (NGT), impaired glucose tolerance (IGT) and diabetes mellitus (DM).
Results: Twenty-nine patients (median age: 13.1 years) were recruited. According to CGMS, 11 had DM, 12 IGT and six NGT, whereas OGTT identified three patients with DM and five with IGT. While 13 of 27 had insulin deficiency according to IGTT, there was 19 of 28 according to HOMA-%B. According to HOMA-IR, 12 of 28 had insulin resistance. HOMA-%B was the most sensitive method for CFRD screening [sensitivity 91% (95% CI), specificity 47% (95% CI) and negative predictive value 89% (95% CI)].
Conclusions: OGTT showed the weak capacity to diagnose DM in CF and should no longer be considered as the reference method for CFRD screening in patients with CF. In our study, HOMA-%B showed promising metrics for CFRD screening. Finally, CGMS revealed that pathological glucose excursions were frequent even early in life.

Keywords: continuous glucose monitoring system; cystic fibrosis-related diabetes; glucose metabolism; homeostasis model assessment index of β-cell function; homeostasis model assessment index of insulin resistance; intravenous glucose tolerance test; oral glucose tolerance test.

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Introduction

The increasing lifespan of patients with cystic fibrosis (CF) is accompanied by an increase in comorbidities such as cystic fibrosis-related diabetes (CFRD). The French CF registry reported an increasing prevalence of CFRD with increasing age, with a rise from less than 5% before 10 years of age to 45% between 35 and 39 years of age [1].

Our understanding of the pathophysiological process of CFRD is far from complete. Insulin insufficiency, characterised by a lower quantity and a delay of insulin secretion, is a major constant component. Insulin resistance is another factor mainly related to the patient's inflammatory status [2]. Recent data obtained in animal models have shown that glucose abnormalities may occur earlier than initially believed [3]. Furthermore, in vitro data

indicate that the cystic fibrosis transmembrane regulator (CFTR), as a chloride channel, is directly involved in both phases of insulin secretion by inducing membrane cell hyperpolarisation and rapid insulin release as well as the increase in intracytoplasmic calcium concentration involved in the late phase of insulin release [4].

From a clinical point of view, the consequences of CFRD have been well documented: increased mortality especially in the female population [5], accelerated lung function decline, poor nutritional status and finally microvascular complications [6]. As such, insulin replacement has shown benefits in diabetic patients with CF with nutritional status and lung function improvement [7].

International guidelines recommend CFRD to be screened as early as 10 years of age using the oral glucose tolerance test (OGTT) [8, 9]. The World Health Organization (WHO) criteria are used to classify patients depending on fasting glycaemia (T0) and the 2-h glycaemia after glucose intake (T120). For over 10 years now, several studies have shown that T120 underestimates glucose abnormalities in patients with CF, T60 being a more promising outcome that better correlates with lung function decline [10–13]. Furthermore, data from our own group have shown that the OGTT prospectively and annually performed over 3 years varied from 1 year to another (over half of patients changed glucose tolerance status at least once during the study period) [14].

In this setting, having a better and robust test to monitor glucose metabolism (GM) status in patients with CF is critically needed. Experts in diabetes have used different outcomes and methods to monitor GM in other conditions, mainly type 2 diabetes [15–17]. We wondered if some of these tests would have the capacity to appropriately monitor GM in a paediatric cohort with CF. We hypothesised that the OGTT was not the test of choice because of its lack of sensitivity to diabetes mellitus (DM) diagnosis and its capacity to properly explore insulin resistance or β-cell function. Consequently, we designed a monocentric, prospective study that aimed to compare the OGTT with the intravenous glucose tolerance test (IGTT), the homeostasis model assessment index of insulin resistance (HOMA-IR), the homeostasis model assessment index of β-cell function (HOMA-IR) and glycated haemoglobin A_{1c} (HbA_{1c}), using the continuous glucose monitoring system (CGMS) as the reference method.

Materials and methods

Patients

This prospective monocentric study was conducted between June 2009 and April 2012. All patients more than 10 years old and followed in the paediatric CF centre of Lyon University Hospital (France) were systematically asked to participate. Eighty patients were approached and 51 declined to participate mainly because of the need for CGMS implantation for several days (Figure 1). Participants' consent was collected before enrolment. The study was approved by our Local Institutional Review Board (Comité de protection des personnes SUD-EST IV; No. 2008-038).

Inclusion criteria were as follows: confirmed CF patients bearing at least one class I, II or III *CFTR* mutation and being pancreatic insufficient, aged between 10 and 18 years and lung function assessed by forced expiratory volume in 1 s (FEV_1) > 40% of predicted values. Exclusion criteria were: previous documented glucose

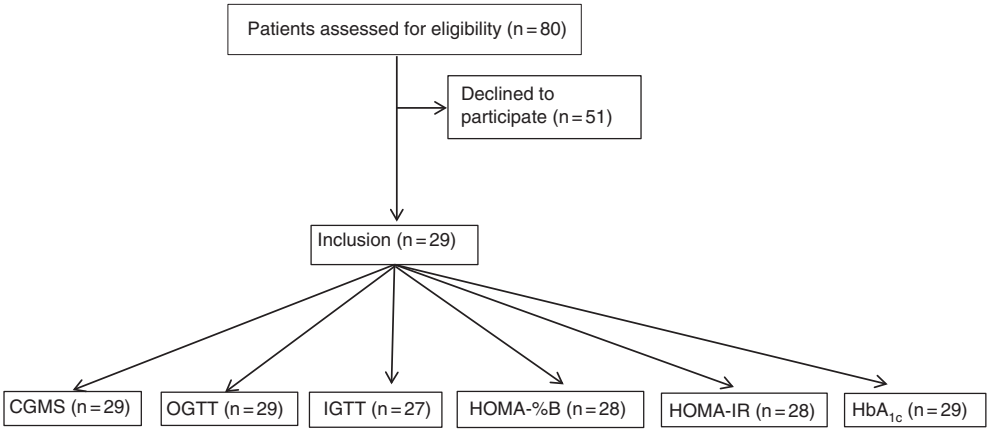

Figure 1: Flow chart of the study participants.
CGMS, continuous glucose monitoring system; OGTT, oral glucose tolerance test; IGTT, intravenous glucose tolerance test; HOMA-%B, homeostasis model assessment index of β-cell function; HOMA-IR, homeostasis model assessment index of insulin resistance HbA_{1c}, glycated haemoglobin A_{1c}.

tolerance abnormalities; pulmonary exacerbation occurrence in the 4 weeks before investigations, oral glucocorticoid intake in the 2 months prior to inclusion, impossibility keeping the CGMS in place with predictable monitoring difficulties, patients having undergone lung transplantation or awaiting transplantation, parenteral nutrition or participation in another research protocol.

Study design

Patients were seen twice within 4 days. At the first visit at day 1 (V1), a complete clinical examination was performed (including Tanner Staging for pubertal status), followed by the OGTT and pulmonary function tests. Finally, the CGMS was implanted and patients and their parents were educated for capillary glycaemia to be taken four times a day to set up the CGMS. A second visit (V2) was scheduled at day 4, where the IGTT was performed as well as the HbA_{1C} level.

Glucose metabolism exploration tests

Oral glucose tolerance test: The OGTT was performed as recommended after an 8-h fasting [18]. In the previous 48 h, patients were asked to have their regular diet and physical activity.

Briefly, blood glucose and insulin were measured immediately before (T0) and 30 (T30), 60 (T60), 90 (T90) and 120 (T120) min after drinking a glucose solution at a dose of 1.75 g/kg (up to a maximum of 75 g). The patients' GM status was classified as determined by the WHO: normal glucose tolerance (NGT) if blood glucose was strictly less than 6.1 mmol/L at T0 and strictly less than 7.8 mmol/L at T120; DM when blood glucose was greater than or equal to 7 mmol/L at T0 or strictly greater than 11 mmol/L at T120; impaired glucose tolerance (IGT) if the blood glucose was greater than or equal 6.1 mmol/L and strictly less than 7 mmol/L at T0 or greater than or equal 7.8 mmol/L and less than or equal to 11 mmol/L at T120 [8].

Intravenous glucose tolerance test: The test was performed in patients who had fasted for at least 8 h. Two venous lines were placed. A glucose solution at a dose of 0.5 g/kg (up to a maximum of 35 g) was injected in 2.5–3 min. T0 corresponds to the end of glucose injection. Blood was sampled 5 min before injection (T−5), 1 min (T1), 3 min (T3), 7 min (T7) and 15 min (T15) after the end of injection in order to measure venous glycaemia and insulin.

Insulin secretion capacity was evaluated using the sum of insulin levels at 1 and 3 min (T1 + T3). Insulin deficiency was defined by a T1 + T3 insulin level of less than 40 mIU/L.

Homeostasis model assessment index of insulin resistance: The HOMA-IR is an index derived from glucose (expressed in mmol/L) and insulin (expressed in mIU/L) levels at T0 on the OGTT and at T−5 on the IGTT prior to any glucose administration. The following formula was used as previously described: [(fasting insulinaemia × fasting plasma glucose)/22.5]. This index has been used in other studies investigating GM in other conditions such as type II diabetes [16, 17]. The HOMA-IR normal value is 1. Values strictly higher than 1 reflect insulin resistance.

Currently, there is no strict definition for insulin resistance in children or adolescents. According to different studies, different insulin resistance thresholds (using HOMA-IR) have been used for normal weight adolescents: >4.39 [19], 3.29 [20], >3.99 [21], 3.16 [22].

Homeostasis model assessment index of β-cell function: Similarly, HOMA-%B is an index derived from fasting glucose and insulin levels measured during the OGTT and IGTT. It evaluates residual insulin secretion. It was calculated using the following formula: [(fasting insulinaemia (in mIU/L) × 20)/(fasting plasma glucose (in mmol/L) − 3.5)]. The HOMA-%B normal value is 100%. Values lower than 100% reflect insulin secretion deficiency.

HbA_{1c}: HbA_{1c} was tested using the Varian 2 - HbA_{1c} – "Dual Program kit" to be determined. A pathological level was considered when strictly higher than 6.5% [23].

The reference standard: the continuous glucose monitoring system: The CGMS (Medtronic MiniMed®) was considered as the reference test with which other tests were compared. It allows continuous interstitial glucose monitoring for 3 days in patients' usual and actual lifestyle conditions. The system is connected to a glucose sensor inserted under the skin. Patients and their parents are trained and asked to enter four capillary glucose results collected over a day during the 3 days of monitoring (i.e. device calibration). During the recording, the patient keeps a log indicating meals, activities and all relevant events. The device records interstitial glucose every 10 s whose values are averaged every 5 min. Two periods were defined during the CGMS: fasting period (any period of a minimum of 6 h since the last meal) and non-fasting period (any period less than 6 h since the last food intake). The patient's GM status was defined as NGT, IGT or DM according to the WHO criteria for the CGMS [8]: NGT, if blood glucose was strictly less than 6.1 mmol/L during the fasting period and strictly less than 7.8 mmol/L during the non-fasting period; DM, if blood glucose was greater than or equal to 7 mmol/L during the fasting period or strictly greater than 11.1 mmol/L during the non-fasting period and IGT, if blood glucose was greater than or equal 6.1 mmol/L and strictly less than 7 mmol/L during the fasting period or greater than or equal to 7.8 mmol/L and less than or equal to 11 mmol/L during the non-fasting period. The status is set from 5 points minimum in the most pathological zone.

The same person read all the tests according to the reference standard results.

Statistical analysis

Initially, the inclusion ability was estimated at 60 patients with an expected proportion of patients with a GM abnormality of 50%. This sample size would allow obtaining a precision of 15% of the estimation of the sensitivity (specificity) of the different tests for an expected value of 80%. It would also allow concluding in a significant difference between the sensitivities (specificities) of two tests with a power of 80% for an expected absolute difference of 25% and a proportion of discordant pairs around 26%. The patients' quantitative characteristics were described by the mean, the standard deviation and the minimum and maximum values. The qualitative characteristics were described by the absolute and relative frequency in each category.

The patients' characteristics were compared between the group with DM and the group without DM as defined by the reference test. Quantitative characteristics were compared using the Student t-test.

Qualitative characteristics were compared using the Fisher exact test. A p-value <0.05 was considered as statistically significant.

The performance of the different tests for distinguishing the patients with DM from the patients without DM was assessed by the estimation of their sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). The 95% confidence intervals (CIs) of the estimations were built using the Clopper-Pearson exact method based on the binomial distribution. PPVs and NPVs were estimated for a DM prevalence corresponding to the prevalence observed on the studied sample.

All the analyses were carried out using the software S-Plus version 7.0 (Software edited by Tibco, Palo Alto, CA, USA).

Results

Patient characteristics

Data from 29 patients (15 males) whose mean age was 13.1 ± 2.22 (range, aged 10–17 years) were analysed for the CGMS and the OGTT (Table 1). Two patients did not complete the IGTT: one declined to participate on the day of V2 (no sample was taken), the second after several unsuccessful blood sampling attempts. The main patient demographic data are given in Table 1. Patients had an overall good nutritional status [mean body mass index (BMI) was 17.1 ± 2.21 (range, 13.7–21.5)]. One patient out of 29 had enteral feeding. The mean pubertal Tanner stage was 2.5. Thirteen patients were prepubescent (Tanner stage I), while seven of 29 were postpubescent (Tanner stage V). The patients' mean FEV_1 and forced vital capacity (FVC) were 86.6% ± 14.9% (range, 63%–126%) and 91% ± 13.24% (range, 67%–120%), respectively.

Table 1: Participants' clinical and demographic characteristics.

Total number of patients included, n	29
Age during the study, years	13.1 ± 2.22 (range, 10–17)
Male/female	15/14
Body mass index, kg/m²	17.1 ± 2.21 (range, 13.7–21.5)
Enteral feeding, n	1
Number of patients with pubertal status 1 (according to the Tanner scale)	12
Number of patients with pubertal status 5 (according to the Tanner scale)	7
FEV_1, %	86.6% ± 14.9 (range, 63%–126%)
FVC (%)	91% ± 13.24 (range, 67%–120%)

Results are presented as mean ±SD. FEV_1, force expiratory volume in 1 s; FVC, forced vital capacity.

Patients' GM status determined by the CGMS

Using the WHO criteria, of our 29 patients, 11 were classified as having DM, 12 as having IGT and six as having NGT. This gave a 38% prevalence of DM in this study population. Ten out of 11 diabetic patients had at least one T0 ≥7 mmol/L during the 3-day recording period.

There was a higher proportion of boys in the DM group (nine of 11) than in the non-DM group (six of 18) (p = 0.02). Diabetic patients tended to be older (aged 13.6 years vs. 12.9 years), had a worse nutritional status in terms of BMI (16.4 vs. 17.6) and poorer lung function measured by FEV_1 (82.4% vs. 89.3%), but differences did not reach statistical significance.

Patients' GM status determined by the OGTT and IGTT

According to the OGTT results, three patients had DM, whereas five patients had IGT and 21 had NGT (Figure 2). All patients had glucose blood below 7 mmol/L at T0. Eight patients with DM according to the CGMS were misclassified by the OGTT (they were in the NGT category). Similarly, eight patients were classified as having IGT with the CGMS had a normal GM profile on the OGTT, and one patient was classified as having NGT by the CGMS had IGT on the OGTT.

Twenty-seven out of 29 patients had IGTT. Among them, 11 were classified as having DM on the CGMS and 16 as not having DM. Using 40 mIU/L as the cut-off for defining insulinopaenia (see Methods), 13 patients (48%) were classified as insulinopaenic. Eight of them had a DM profile and five had a non-DM on the CGMS (Table 2).

HOMA indexes

The HOMA-%B explores the β-cell insulin secretion capacity. For one patient, data on the HOMA-%B could not be calculated (this patient refused the test). Nineteen were considered to be insulinopaenic with a mean HOMA-%B of 64.6% ± 21.8%. In these patients, ten out of 11 (91%) were diabetic, while nine of 17 (53%) were not in the DM category (Table 2).

The HOMA-IR explores insulin resistance. Twelve out of 28 patients were considered as having insulin resistance, with a mean HOMA-IR of 1.9 ± 1.2. Out of the 11 DM patients, four (36%) had insulin resistance according to the HOMA-IR value (1.4 ± 0.3). Out of the 17 non-DM patients, eight (47%) had insulin resistance (Table 2).

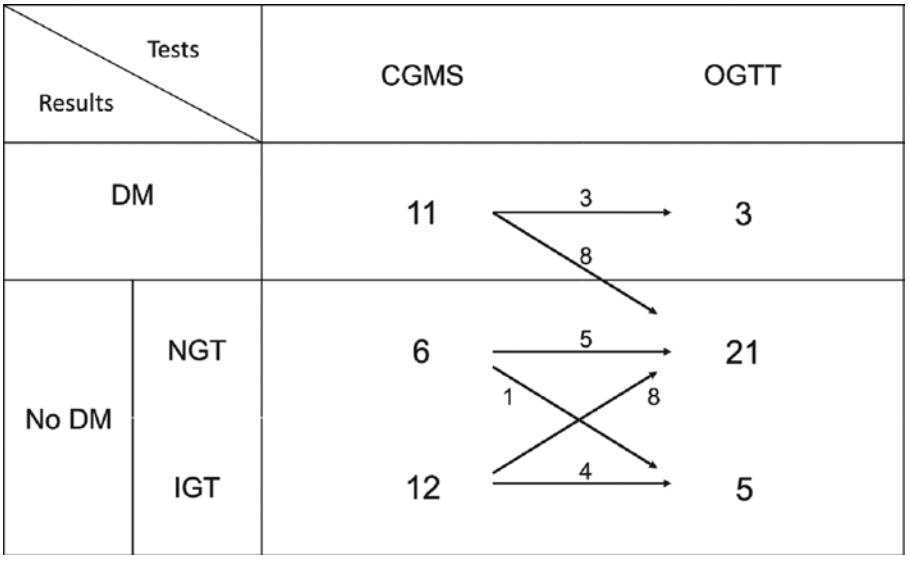

Figure 2: Distribution of the patients' glucose metabolism status according to the CGMS and OGTT.
CGMS, continuous glucose monitoring system; OGTT, oral glucose tolerance test; DM, diabetes mellitus; NGT, normal glucose tolerance; IGT, impaired glucose tolerance.

Table 2: Results of IGTT, HOMA-%B and HOMA-IR according to CGMS status.

		CGMS	
		DM	No DM
IGTT (n = 27)	<40 mIU/L	8	5
	>40 mIU/L	3	11
HOMA-%B (n = 28)	<100%	10	9
	>100%	1	8
HOMA-IR (n = 28)	>1	4	8
	<1	7	9

IGTT, intravenous glucose tolerance test; HOMA-%B, homeostasis model assessment index of β-cell function; HOMA-IR, homeostasis model assessment index of insulin resistance; CGMS, continuous glucose monitoring system; DM, diabetes mellitus.

When coupling HOMA-%B and HOMA-IR results, four of 28 patients had both HOMA-%B <100% and HOMA-IR >1. Three patients had DM and one had IGT.

GM test sensitivity, specificity and predictive values

Test performance was evaluated with regard to their capacity to properly diagnose DM patients (Table 3). Both the OGTT at T60 and T120 had low sensitivity (36% and 27%, respectively). However, the OGTT at T120 had good specificity and positive predictive value. The best sensitivity was obtained with the HOMA-%B index (91%), but its

Table 3: Performance indices of the different tests in reference to the standard (CGMS).

TEST	Se, %	Sp, %	PPV	NPV
OGTT T60	36 (11–69)	83 (59–96)	57 (18–90)	68 (45–86)
OGTT T120	27 (6–61)	100 (81–100)	100 (29–100)	69 (48–86)
IGTT	73 (39–94)	69 (41–89)	62 (32–86)	79 (49–95)
HOMA-%B	91 (59–100)	47 (23–72)	53 (29–76)	89 (52–100)
HOMA-IR	36 (11–69)	53 (28–77)	33 (10–65)	56 (30–80)
HbA_{1c}	36 (11–69)	83 (59–96)	57 (18–90)	68 (45–86)

Confidence interval is between brackets. Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value.

specificity was low (53%). The IGTT, HOMA-IR and HbA_{1c} did not provide useful results.

There was no adverse event from performing the index test or the reference standard.

Discussion

This study prospectively compared different GM evaluation methods in children and adolescents with a classical form of CF and exocrine pancreatic insufficiency: the CGMS, OGTT, IGTT, HOMA-%B, HOMA-IR and HbA_{1c}. When comparing the results with the CGMS as the reference method, we found that 1) the OGTT frequently missed IGT patients, 2) the HOMA-%B seemed to have the best sensitivity but low specificity, 3) GM abnormalities were more frequent on the CGMS than believed and 4) insulinopaenia and insulin resistance were frequent as measured by the IGTT and the HOMA index.

Glucose abnormalities are associated with greater declines in pulmonary function, nutritional status worsening and increased mortality [24]. In this context, making the DM diagnosis earlier is of crucial importance, particularly in the setting of the patient's increasing lifespan.

In this study, the prevalence of diabetes suggested by the CGMS was much higher than usually reported in the literature, affecting 38% of the study population with a mean age of 13.1 years. These discrepancies are to a large extent related to differences in DM diagnosis modalities, as the OGTT is the most frequent test used to screen CFRD as recommended by international guidelines [8]. Therefore, according to the OGTT (T120), the prevalence of diabetes in the present study would have been 10%. For comparison, recent data indicate that DM prevalence in adolescents with CF was between 15% and 20% according to the OGTT [9]. In France, according to the 2013 data from the French Cystic Fibrosis Registry, 4.7% of the patients with CF were reported to have DM between 10 and 14 years of age, reaching 15.8% between 15 and 19 years of age.

The OGTT is the standard test for CFRD screening in the current recommendations [8, 9]. Test performance was evaluated using the T60 and T120 results because both times have been recognised as either better correlated with DM occurrence or considered as the reference time for DM diagnosis in international guidelines [8, 9, 20]. This study has confirmed the shortcomings of these tests pointed out by various authors over the last 10 years [10, 25, 26]. We found that T120 only identified three patients with DM and five with IGT (including one whose CGMS results remained within the limits of normal). Thus, the OGTT did not detect eight cases of DM and seven IGT patients detected by CGMS.

Several authors have shown that the intermediate times of the OGTT, mostly T60, were more frequently abnormal than T120 [10, 27–29]. Brodsky et al. [11] identified 14 diabetic patients according to T60 but only two according to the T120 value (total, 101 patients). They also showed that elevated T60 on the OGTT was negatively associated with percent predicted FEV_1, even after adjustment for BMI percentile. The present study was not designed to address the question of whether T60 was a better predictor of DM.

Malabsorption and high variability of blood glucose are two reasons to explain the weakness of OGTT in patients with CF. The early loss of insulin secretion peak causes a rise in blood glucose especially during the intermediate times of the OGTT (including T60) but may be normal thereafter (at T120) [28, 29].

In patients with CF, fasting hyperglycaemia is classically described as being late and rare in glucose manifestation [24]. In our study, ten of the 11 diabetics according to the CGMS had abnormal fasting blood glucose at least once, whereas glycaemia at T0 on the OGTT was normal for all the patients. Thus, time fasting capillary measured or at T0 on the OGTT underestimated abnormalities.

It has been well demonstrated that women with CF had a higher risk of developing diabetes [30]. Contrastingly, in our study, there were more boys diagnosed with CFRD. This result was, however, not of statistical significance, and likely a consequence of the small number of patients included.

The CGMS has already been used in children and adolescents with CF [31, 32]. Some centres have already administered it to patients for GM monitoring.

As in our study, Leclercq et al. identified 12 of 38 patients with blood glucose > 11 mmol/L (diabetic zone) according to the CGMS, who were not detected by the OGTT [13].

Our study is one of the rare studies [33–35] to report HOMA indexes in the context of CFRD. The HOMA-IR index and HOMA-%B have mostly been used in type 2 diabetes [16, 17] but have not to date been sufficiently evaluated in patients with CF. They were developed by Matthew [15] and they have the advantage of being simply calculated from insulin and fasting glucose measured prior to glucose intake for the OGTT and IGTT. These indexes have been validated using invasive techniques (the hyperglycaemic clamp for HOMA-%B and the hyperinsulinaemic euglycaemic clamp for HOMA-IR) such that they are good surrogate outcomes of both these pathophysiological CFRD characteristics [15]. This study confirmed the high prevalence (13 of 27 patients according to the IGTT

and 19 of 28 patients according to the HOMA-%B) and the precocity of insulinopaenia that may precede the onset of glucose abnormalities in CF patients [33, 36, 37]. Insulinopaenia is more relative than absolute during CFRD: this is partly related to the decrease in the overall β-cell numbers related to the progressive destruction of pancreatic islet architecture [33]. In addition, the defect of the early phase of insulin secretion is well documented, even in patients with NGT [38]. Animal models (particularly the ferret mode) have shed new light on the relationship between structural pancreatic damage and GM. It was shown that a deficit in insulin secretion could be detected long before pancreatic fibrosis and acinar reduction [3]. For instance, ferrets with CF challenged with intraperitoneal glucose load already have GM abnormalities between 6 and 12 h of life, despite no or minor structural damage. The authors showed that ferrets with CF have a more pronounced decrease in the early phase of insulin secretion when challenged with L-arginine, which stimulates insulin release from zymogen granules. In vitro, pancreatic islets from CF ferrets have 1.5 times more insulin and are able to secrete 5.3 times more insulin than non-CF islets. Taken together, the results obtained from these models showed that insulin deficiency occurs earlier in the course of the disease, prior to structural pancreatic damage, and is more pronounced at the early secretion phase of insulin despite the greater capacity of β-cells to secrete insulin. GM investigations conducted in young children with CF have also reported early GM abnormalities [39]. More than half of the patients had insulinopaenia according to the IGTT and two-thirds of patients had insulinopenia according to the HOMA-%B.

The present study also confirmed the high proportion of patients with insulin resistance, as suggested by a high HOMA-IR ratio (12 of 28 patients). As mentioned above, our study was one of the first to investigate the usefulness of this type of index in the context of CFRD. Previous studies on CF have shown the fluctuating nature of insulin resistance, mainly because of the wax and wane of patients' inflammatory status and because of the definition of insulin resistance, which is still a matter of debate [38, 30, 40]. In the present study, the abnormalities of this index were present in 43% (12 of 28 patients), while patients were clinically stable and sometimes very young. Insulin resistance could contribute to the depletion of residual insulin secretion [41, 42].

Finally, this study confirmed that HbA_{1c} level has a very limited value in screening patients for CFRD because it remains within the normal ranges even in patients showing a DM profile on the CGMS [43, 44]. Consequently, it is not a good indicator of GM abnormalities in CF and should not, as such, be considered as a screening tool. This was shown recently in a study that included 204 patients with CF. The study showed that the HbA_{1C} threshold at 5.8% had weak sensitivity (68.5%) and specificity (60%) [45]. This can be explained by the large variations in blood glucose over time for the same person [45]. Another explanation is related to the reduced lifespan of red blood cells in CF patients [44].

When looking at GM test performance, we found that none of them combined high sensitivity and specificity for DM diagnosis as we defined it on the CGMS. This means that rather than a single test, a combination of two tests could be used in order to diagnose CFRD. We propose that the HOMA-%B could be used at a first-line screening procedure (it is easy to perform in fasted patients with only the required insulin and glycaemia measurements). In the case of insulin secretion deficiency (i.e. the HOMA-%B value lower than 100%), the OGTT could be scheduled secondarily. Using this two-step approach, we estimate that out of the 100 patients tested, nine DM patients would be missed, while with the OGTT alone, 73 would be missed.

Finally, this study had strengths and limitations. The main strength is that the study investigated GM abnormalities by comparing results from several and/or original tests or indexes. Some of them are easy to use in today's clinical setting (index calculation during the OGTT for instance). We concluded that the OGTT may miss DM patients and thereby delay patient management.

This study would deserve to be reproduced with adult patients.

The study's limitations are that DM was defined based on a CGMS profile, which is not a universally accepted method for DM diagnosis. However, given the weak performance of the OGTT, we strongly believe that real-life continuous GM monitoring is more pertinent than a single, high-glucose-load test. However, adopting CGMS as a screening method may lead to DM and GM metabolism abnormalities over-diagnosed. More robust parameters should be used to define GM abnormalities with CGMS. For instance, the hyperglycemic area under the CGMS curve per day, whose value is generally better correlated with HbA_{1c} in diabetes type 1 or 2, would be pertinent. This parameter would be a relevant indicator of both metabolic degradation and long-term microvascular complications. It will thus help clinicians make better therapeutic decisions. Unfortunately, our current CGMS system does not allow us to analyse this parameter. Also, because we did not reach the intended sample size, the statistical uncertainty around estimates of sensitivity and specificity are important. The high burden for CF patients of not being screened by index and reference tests was the main cause

of lower enrollment. The same person read all the tests so there was no information bias.

Conclusions

This study confirmed the relatively high frequency, early onset and complexity of glucose abnormalities in patients with CF that involve insulinopaenia and insulin resistance mechanisms. The current recommendation for CFRD screening using the 2-h glycaemia during the OGTT shows poor sensitivity because the CGMS revealed glucose abnormalities not seen by the OGTT. However, a two-step CFRD screening procedure, including the HOMA-%B measurement followed by the OGTT in case of abnormal results, could be a good screening strategy.

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