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Dichotomy between postprandial glucose and lipid profiles in adults with cystic fibrosis: A pilot study

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Abstract

Background: Cystic fibrosis (CF) patients present a high incidence of glucose tolerance abnormalities. Altered insulin secretion combined with recommended high-fat intake could be associated with dysregulation of glucose and lipid metabolism. We examined postprandial glucose and lipid profiles during an oral glucose tolerance test (OGTT) and following a standardized high-fat test meal (TM).
Methods: Sixteen CF patients with normal glucose tolerance (NGT) or CF-related diabetes (CFRD) and 16 controls underwent a 4 h OGTT and a TM. We then measured plasma glucose, insulin, free fatty acid (FFA) and triglyceride (TG) concentrations.
Results: CF patients presented higher glucose excursion compared to controls after the OGTT and TM. However, in CF patients, this excursion was significantly reduced in both amplitude and length after the TM. The TM provoked a comparable increase in TG levels in both groups whereas they remained stable during the OGTT. FFAs were suppressed similarly in both groups after both challenges.
Conclusion: CF is associated with abnormal glucose excursion in the presence of relatively normal lipid excursion. The rapid normalization of glucose values after a mixed meal should be further explored and, if confirmed, might have significant implications for CFRD diagnostic.

Keywords: Cystic fibrosis; Diabetes; Insulin; Lipid metabolism; Meal test

1. Introduction

The cystic fibrosis (CF) adult population is characterized by a very high incidence of glucose intolerance states [1]. Previous studies by our group and others have documented decreased insulin secretion with a possible contribution of altered insulin sensitivity as the cause of glucose tolerance abnormalities in CF patients [2,3]. Insulin also plays an important role in lipid metabolism, tightly regulating plasma free fatty acid (FFA) levels by reducing adipose tissue mobilization and enhancing FFA clearance [4]. Thus, abnormal insulin secretion in CF patients could be associated with abnormal postprandial glucose and lipid excursion.

CF is characterized by exocrine pancreatic insufficiency, which leads to fat malabsorption [5,6]. To prevent malnutrition, current guidelines recommend that CF patients have a higher energy diet and fat intake (40% of total calories as fat) than healthy peers [5,7], along with appropriate pancreatic enzyme supplementation. Despite these recommendations, data on the postprandial metabolic profile of CF patients are scarce, and most glucose values are derived from the oral glucose tolerance test (OGTT) rather than post-meal. To our knowledge there is few available data about lipid excursion.

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Table 1
Physical characteristics of CF patients and control subjects

	Controls $N=16$	CF-NGT $N=10$	CFRD $N=6$
Age (years)	24.8±4.2	28.5±10.5	27.0±8.6
Sex ratio (M/F)	9/7	6/4	4/2
Weight (kg)	66.7±9.1	64.6±11.6	56.±10.6*
BMI (kg/m2)	22.4±1.6	23.5±2.2	20.7±3.5*
Pancreatic enzyme supplementation	0%	50%	100%
A_{1c}	0.050±0.002	0.052±0.005	0.066±0.007+†
Fasting glucose (TM) (mmol/L)	5.0±0.3	5.3±0.4	6.4±0.8+†
Fasting glucose (OGTT) (mmol/L)	5.0±0.5	5.3±0.3	6.1±0.9*+
Insulin AUC 120 min (TM) (μU/ml)	4,804±2,229	4,351±2,314	3,731±1,824
Insulin AUC 120 min (OGTT) (μU/ml)	6,632±2,766	5,379±2,346	4,142±2,412*
Total cholesterol (mmol/L)	3.84±0.46	3.78±1.13	3.74±0.09
HDL-cholesterol (mmol/L)	1.35±0.38	1.20±0.22	1.41±0.48
LDL-cholesterol (mmol/L)	2.13±0.37	2.12±0.82	1.74±0.51
Fasting TG (mg/dl)	0.98±0.34	1.05±0.46	1.15±0.41
Fasting FFA (mEq/L)	0.35±0.12	0.32±0.16	0.46±0.22

CF-NGT: cystic fibrosis patients with normal glucose tolerance, CFRD: cystic fibrosis-related diabetes, BMI: body mass index, A1c: glycated hemoglobin, OGTT: oral glucose tolerance test, TM: test meal, AUC: area under the curve; HDL: high-density lipoprotein, LDL: low-density lipoprotein, TG: triglyceride, FFA: free fatty acids.
+$P<0.001$ CFRD vs CF-NGT; †$P<0.001$ CFRD vs Controls; *$P<0.05$ CFRD vs Controls.

Because of reduced insulin secretion in CF patients along with the recommended high-fat dietary intake, it is not known (i) whether the high-glucose excursion observed after an OGTT correctly represent that observed after a test meal (TM), and (ii) whether CF patients present abnormal lipid excursion, i.e. the inability to suppress FFA. The aim of this pilot study was to examine postprandial glucose and lipid profiles during an OGTT and a standardized high-fat TM in CF patients with or without CF-related diabetes (CFRD) compared to a paired control group.

2. Methods

2.1. Subjects

Sixteen adult CF patients (>18 years of age) and 16 controls with normal glucose tolerance (NGT) matched for age and sex participated in this study. CF patients had either normal glucose tolerance (CF-NGT) ($N=10$) or CFRD (diabetes duration 1–3 years; $N=6$). The diagnosis of CFRD was based on 2 consecutive abnormal OGTT values (fasting values>7.0 mmol/L or 2 h>11.0 mmol/L). To minimize the confounding effect of chronic hyperglycemia, CFRD patients were included in the study only if they were controlled by diet alone or if they could discontinue hypoglycemic agents for at least 24 h without significant short-term impact on diabetes control (fasting glycemia<8.0 mmol/L).

Subjects were enrolled in the study if they met the following criteria: 1) no antibiotic treatment in the previous 8 weeks, 2) no weight fluctuation in the past 2 months (±2 kg), 3) no medications or conditions that could affect glucose metabolism such as oral or intravenous steroids, growth hormone, Megace, or pregnancy, 4) no clinical signs of dyspepsia or medication known to alter gastric motility, 5) absence of liver disease, and 6) appropriate enzyme and vitamin supplementation. The exclusion criteria were respiratory exacerbation in the previous month, according to criteria published by the 1994 Cystic Fibrosis Foundation Microbiology and Infectious Disease Consensus Conference [8]. Exacerbation was identified by a trained CF pneumologist on the day of the study. The protocol was approved by the Research Ethics Committee of the Centre Hospitalier de l'Université de Montréal (CHUM), and all subjects signed a written consent form.

2.2. CF status

Pulmonary function was measured on the day of the OGTT, using force expiratory volume $(FEV)_1$ (L/sec) and predicted % FEV_1 (Medgraphic 1870, St. Paul, MN) as variables. Pancreatic insufficiency was defined by current enzyme supplementation. Five CF-NGT and all CFRD subjects were on pancreatic enzyme replacement therapy (Table 1). The patients took pancreatic enzymes only with the TM respecting their usual dosage for a comparable meal. The dose was within recommended values for all subjects [9].

2.3. Oral Glucose Tolerance Test (OGTT)

All subjects underwent a 4 h OGTT. After at least a 10 h fast, they ingested a glucose solution in less than 5 min: 1.75 g/kg of body weight to a maximum of 75 g according to American Diabetes Association guidelines [10].

2.4. High fat test-meal

A standardized high-fat TM was given after at least a 10 h fast. The objective was to obtain a high-fat mixed meal with comparable carbohydrate content as provided by the OGTT. Subjects ingested a high-fat meal consisting of a 500 ml milk

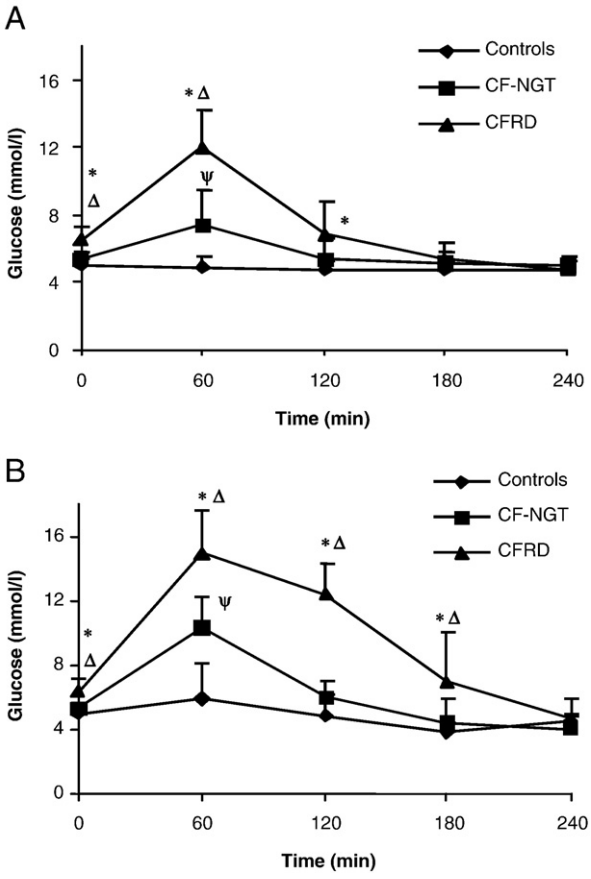

Fig. 1. Plasma glucose profile in response to a TM (A) and an OGTT (B) in CF patients and controls. CF-normal glucose tolerance (CF-NGT); CF-related diabetes (CFRD). $^{*}P<0.05$ CFRD vs. Controls; $^{\Delta}P<0.05$ CFRD vs. NGT; $^{\Psi}P<0.05$ NGT vs. Controls.

shake (whole milk, ice cream and egg), 50 g cheddar cheese and a slice of bread, in 10 min. The energy density of the meal was 940 Kcal and comprised 40 g proteins (17% of energy), 71 g carbohydrates (30%) and 55 g lipids (53%).

2.5. Biochemical dosages

Blood samples were taken at times (T) 0, 60, 120, 180 and 240 min of the OGTT and the TM to measure plasma glucose, insulin, FFA and triglyceride (TG) concentrations, while cholesterol and high density lipoprotein (HDL) cholesterol were measured only at T0 min. Glucose, insulin and FFA levels were measured in duplicate. Plasma glucose was assessed at the time of sampling with a Glucose Analyser (Beckman, Fullerton, CA). Insulin levels were measured by radioimmunoassay (Linco Research Inc., St. Charles, MO) while glycated hemoglobin (A_1c), an index of blood glucose control in the previous month, was analyzed by immunoturbidimetric assay with ADVIA1650 (Bayer Health Care Diagnostics, Toronto, ON, Canada). Plasma fatty acids levels were measured by an enzymatic colorimetric method (Wako Chemical, USA, Inc., Richmond, VA). Inter- and intra-assay percent coefficients of variation were under 0.2 and 0.68%, respectively. Plasma total

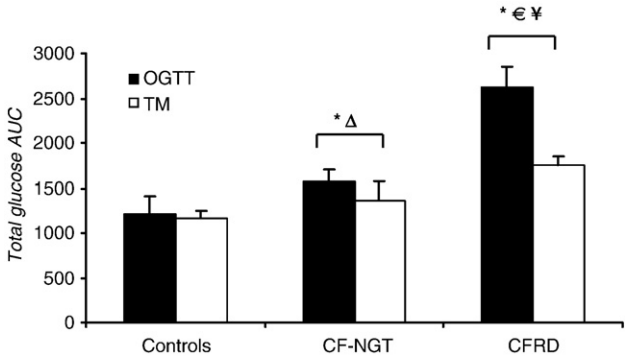

Fig. 2. Total glucose area under the curve (AUC) of the OGTT and TM. $^{*}P<0.005$ TM vs OGTT; $^{\Delta}P<0.0001$ NGT vs Controls for TM and OGTT; $^{€}P<0.0001$ CFRD vs Controls for the TM and OGTT; $^{¥}P<0.0001$ CFRD vs NGT for TM and OGTT.

cholesterol, HDL-cholesterol, triglyceride and glucose were analyzed on the COBAS INTEGRA 400 (Roche Diagnostic, Montreal, QC, Canada). Low-density lipoprotein cholesterol was calculated according to the Friedewald equation.

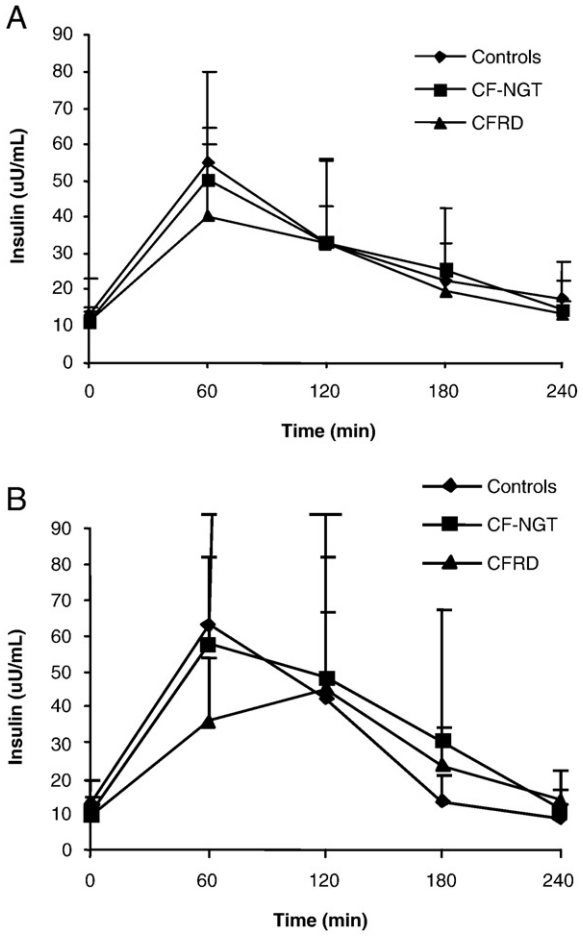

Fig. 3. Insulin profile in response to a TM (A) and an OGTT (B) in CF patients and controls. CF-normal glucose tolerance (CF-NGT); CF-related diabetes (CFRD).

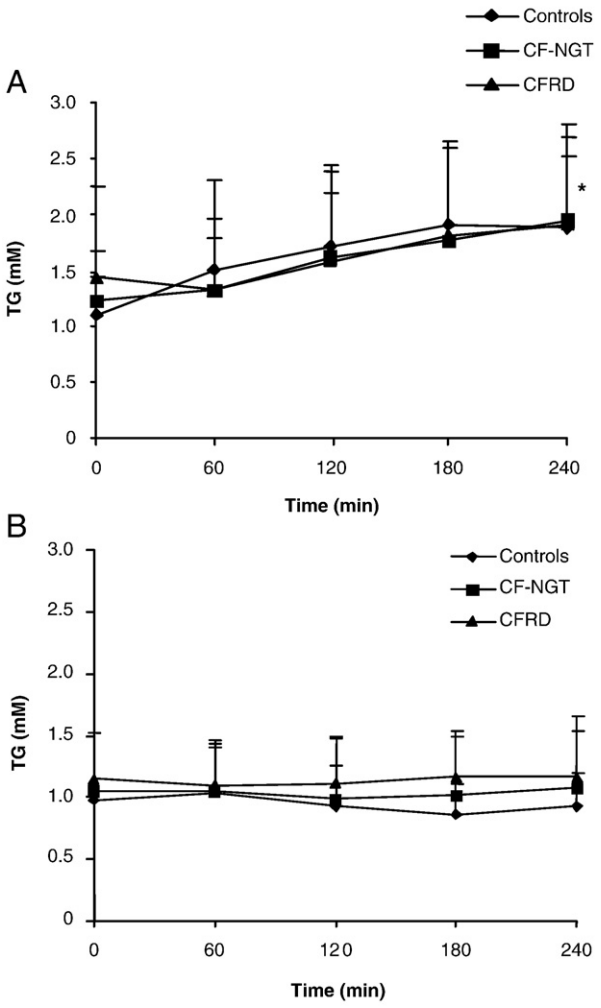

Fig. 4. Triglyceride levels in response to a TM (A) and an OGTT (B) in CF-patients and controls. CF-normal glucose tolerance (CF-NGT); CF-related diabetes (CFRD). *$P<0.01$ versus basal condition (time 0).

2.6. Statistical analysis

The data are presented as means±SE. Both plasma glucose and insulin area under the curve (AUC) were calculated by the trapezoidal method. One-way ANOVA was performed to analyze mean differences between the groups. When significant differences were found, Fisher's post hoc test was used to identify group differences. Significance was accepted at $P<0.05$.

3. Results

3.1. Subject characteristics

Basic demographic data on the 16 control subjects and 16 CF patients, 10 CF-NGT and 6 CFRD, are reported in Table 1. All control subjects had NGT. CFRD patients showed higher A_1c and lower body weight as well as body mass index compared to the controls ($P<0.05$) and CF-NGT subjects ($P<0.05$).

3.2. Plasma glucose during the TM and the OGTT

As reported in Table 1, CFRD patients presented significantly higher fasting plasma glucose levels compared to the controls and CF-NGT ($P<0.05$). Irrespective of their glucose tolerance status, both groups of CF patients showed significantly higher glucose excursion compared to the controls (Fig. 1A and B). In CF patients, glucose excursion had a similar profile after both the OGTT and TM. However, despite similar glucose intake, the magnitude of this excursion was reduced during the TM both for peak values ($p<0.05$; Fig. 1A and B) and the glucose AUC (Fig. 2). This was especially striking for CFRD patients, who showed a 33% decrease of the glucose AUC after the TM compared to the OGTT. Furthermore, and as illustrated in Fig. 1, CFRD patients normalized their glucose value more rapidly after the TM (T120 min) than after the OGTT (T180 min). At T120 min, the post-challenge time determining glucose tolerance status, there was a striking difference between OGTT (12.40±1.85 mmol/L) and TM glucose values (6.83±1.89 mmol/L; $P<0.001$).

3.3. Insulin profile in response to the TM and OGTT

There was no significant difference in fasting insulin levels between the 3 groups studied (Table 1) as well as between the test days (data not shown). As illustrated in Fig. 3A and B, administration of the OGTT or ingestion of a high fat meal induced a time dependent increase in plasma insulin levels ($p<0.05$), which followed a similar profile for both tests in both groups of patients while the insulin AUC tended to be lower during the TM than during the OGTT (Table 1).

3.4. Triglyceride levels in response to the TM and OGTT

In the fasting state, TG concentrations were similar in all groups on both tests (Fig. 4A and B and Table 1). The standardized high-fat TM provoked a progressive and comparable increase in TG in all groups, resulting in significantly higher levels at 4 h compared to fasting values (controls 1.91±0.65 mmol/L; CF-NGT 1.94±0.74 mmol/L; CFRD 1.91±0.89 mmol/L; $P<0.01$). On the other hand, and as reported in Fig. 1B, TG levels were not significantly modified during the OGTT in any of the groups studied.

3.5. FFA levels in response to the TM and OGTT

Fasting plasma FFA concentrations were not significantly different between control subjects and either CF-NGT or CFRD patients, whether they were measured on the day of the TM or the OGTT (Fig. 5A and B). The OGTT and TM ingestion provoked a time-dependent decrease in plasma FFA levels, which followed a similar pattern in all 3 groups. This reduction was followed by normalization of FFA levels by the end of the 4 h TM. However, differences were noted in the FFA profile between the 2 tests. A maximum reduction of FFA levels was reached at 60 min during the TM while it occurred between 120 and 180 min during the OGTT. Thus, the time to nadir seems to

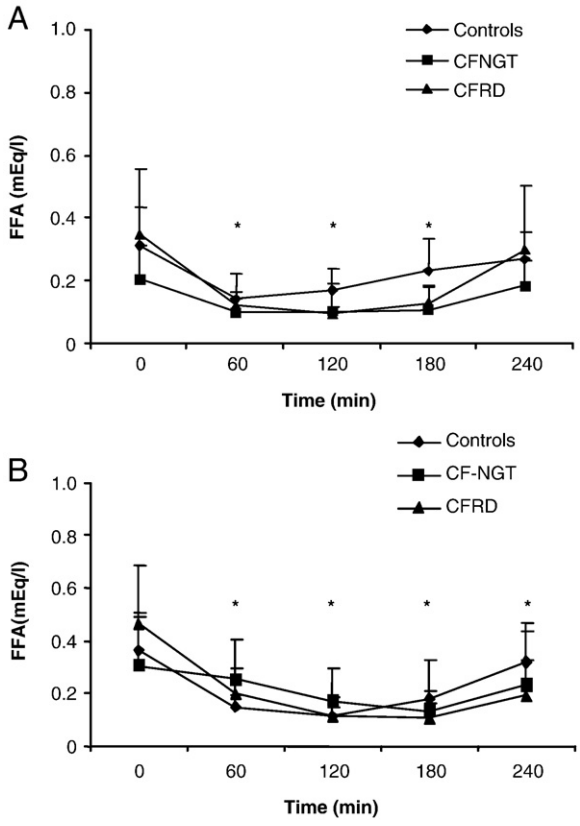

Fig. 5. FFA levels in response to a TM (A) and an OGTT (B) in CF patients and controls. CF-normal glucose tolerance (CF-NGT); CF-related diabetes (CFRD). *$P<0.05$ versus basal condition (time 0).

be prolonged after the OGTT compared to the TM. This is surprising since insulin levels peak at 60 min on both tests.

4. Discussion

Because CF subjects present decreased insulin secretion and have a recommended high dietary fat intake, we explored postprandial glucose and lipid profiles after a glucose load or a TM in CF patients with and without diabetes. The results of our pilot study indicate that CF patients present exaggerated glucose excursions after both a TM and a glucose load. Despite comparable glucose intake during both challenges, glucose excursion was significantly reduced after the TM. Surprisingly, and despite lower insulin levels, we were unable to document any abnormalities in FFA and TG responses between CF patients and controls even after a high-fat TM. These results highlighted the dichotomy between glucose and lipid profiles in CF patients.

Excessive postprandial glucose excursion is well-documented in CF patients [1,3]. The main reason is believed to be the significant reduction of early insulin secretion already apparent in CF-NGT patients [3]. While Moran et al. examined glucose and insulin levels after a TM in CFRD patients [11], to our knowledge, no study has directly compared glucose and FFA profiles after an OGTT and a TM in CF patients. Interestingly, and despite similar glucose loads during both challenges, CF patients presented reduced glucose excursion (peak and AUC) after the TM. This is especially striking for CFRD patients, who showed a decrease of glucose AUC and plasma glucose levels at 120 min of the TM compared to the OGTT. It also contrasts with type 2 diabetic patients who remain hyperglycemic at 120 min of the TM [12].

The different amplitudes of glucose excursion between the 2 conditions are probably multifactorial. It is well-known that a high fat meal can delay gastric emptying, leading to a shallower rise in plasma glucose after the TM compared to the OGTT [13]. This could be important since severely affected CF individuals have a higher rate of delayed gastric emptying [14,15] while the opposite has been reported in less affected patients [16]. Alternatively, it could be due to differential incretin secretion between the 2 conditions. Incretins play an important role in glucose homeostasis, especially in the postprandial state. Since the TM is a better stimulus than the OGTT, it leads to increased gastric inhibitory peptide (GIP) and glucagons-like peptide (GLP)-1 concentration after the meal [17]. CF patients present lower GLP-1 and GIP plasma concentrations compared to controls during an OGTT and these alterations may participate in the exaggerated glucose excursion observed in these subjects [18]. The relative contributions of abnormal gastric emptying and/or hormonal responses to glucose excursion after the TM require further exploration.

Blunted glucose excursion after the TM could also be explained by better suppression of postprandial hepatic glucose production. This process is a major determinant of glucose excursion [19] and is mainly regulated by early insulin secretion and glucagon suppression [20]. Recently, Hardin et al. reported reduced insulin-mediated suppression of gluconeogenesis in CF patients with abnormal glucose tolerance compared to those with NGT [21,22]. Furthermore, in CF patients, the deterioration of glucose tolerance status is also paralleled by a reduction of glucose-mediated glucagon suppression [18,23]. Together, these results indicate that alteration of glucagon secretion may contribute to the rapid rise of postprandial glucose in CF patients. Our results demonstrated reduced glucose excursion in CF patients after the TM. Since insulin secretion was reduced to a similar extent in all groups, it suggests that CF patients have better suppression of hepatic glucose production after the TM than after the isolated glucose challenge. This could be due to the potent stimulatory effects of nutrients on GLP-1, a major inhibitor of glucagon secretion [20]. Better glucagon suppression could also explain the more rapid decrease in postprandial glucose after the TM compared to the OGTT.

The postprandial glucose profile of CF patients is characterized by an abrupt rise in plasma glucose followed by rapid normalization [3,24], a pattern widely different than that usually seen in type 2 diabetic patients [25]. The present pilot study extends this observation to a mixed meal, a condition in which postprandial glucose excursion is blunted and normalization rapid (Fig. 1). Our finding has major implications if random postprandial glucose values are used to screen for diabetes and it probably explains the very low sensitivity of random blood glucose measurement to detect new cases of CFRD [26]. This observation suggests that the OGTT should be maintained as the key

test to detect new cases of CFRD [1,3]. Recently, continuous glucose monitoring revealed pathological glucose excursion, even in CF-NGT patients [27]. Because of their unique postprandial glucose profile, continuous glucose monitoring may provide an additional tool to more precisely investigate CF patients [27].

As already reported, CF patients have normal fasting plasma FFA concentration [28]. Importantly, FFA suppression after the OGTT and the TM was comparable to that in control subjects. This contrasts with type 2 diabetic subjects who present reduced insulin-mediated FFA suppression during the OGTT [29]. Furthermore, and in contrast to glucose metabolism, we could not observe any difference in FFA profile between CF-NGT and CFRD after the TM or the OGTT, which is somewhat surprising considering that CF patients showed reduced insulin secretion. These findings do not preclude abnormalities that could have been detected either with a longer study period after the TM or a more detailed fatty acid profile [30]. They suggest, however, that insulin levels remain sufficiently high to inhibit lipolysis and stimulate lipogenesis (Fig. 5A and B). The postprandial lipid profile also suggests that, in contrast to type 2 diabetes, in whom lipotoxicity could be involved in both beta-cell failure and insulin resistance [31,32], there is a low probability that such a phenomenon is implicated in the development of CFRD. Thus, in CF patients, deterioration of glucose metabolism does not seem to be associated with a parallel deterioration of insulin-mediated FFA suppression.

We investigated a limited number of stable patients to avoid various confounding factors. However, it remains possible that, in more severely affected subjects, glucose and FFA metabolism may be regulated differently. Furthermore, CF patients present significant lipid malabsorption, which is not totally palliated by pancreatic enzyme supplementation, and we cannot rule out that it may have affected our results. Insulin is also the primary regulator of protein metabolism, controlling both anabolic and catabolic pathways. Thus, the reduced insulin secretion seen in CF patients might have its most clinically significant impact on fat free mass maintenance [30,33].

In conclusion, the present pilot study indicates that CF patients show abnormal postprandial glucose (but not lipid) excursion. Despite the overall similarity of blood glucose and insulin profiles after the OGTT and TM, we noted intriguing differences, with a better glucose profile after the mixed meal, indicating better suppression of hepatic glucose production. Postprandial glucose homeostasis should be further characterized in a larger group of CF patients.

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