CLINICAL STUDY

Spontaneous hypoglycemia in patients with cystic fibrosis

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Abstract

Objective: Diabetes frequently complicates cystic fibrosis (CF) without fasting hyperglycemia or despite spontaneous hypoglycemia (anecdotally ascribed to malnutrition), whose prevalence, clinical meaning, and relationship with glucose tolerance and clinical/nutritional status were not previously investigated. The relationship of CF genotype with insulin secretion control is also unclear.

Design and methods: A total of 129 CF patients without stable diabetes received 188 oral glucose tolerance tests. Distribution of fasting plasma glucose (FPG), glucose, insulin and C-peptide responses, clinical/nutritional variables, and their relationships were analyzed.

Results: FPG < 60 mg/dl (3.3 mmo/l) was detected in 14% of studies and reactive hypoglycemia (PG < 50 mg/dl (2.8 mmo/l)) in 15%.

OGTT-based diabetes frequency was similar in the lowest quartile (Q1) and Q2–3 for FPG (10 and 8%), with higher glucose increment and area under the curve in Q1.

Insulin and C-peptide levels were similar among FPG quartiles. Class I cystic fibrosis transmembrane conductance regulator mutation carriers had higher insulin concentrations than class II, especially in Q1 for FPG. Age, sex, nutritional, and anthropometric parameters including fat and lean body mass were unrelated to FPG. Lower FPG was associated with more frequent hospitalization rates (P < 0.002) and lower Shwachman scores (P = 0.041).

Conclusions/interpretation: Fasting asymptomatic hypoglycemia is frequent and possibly related to inappropriate insulin secretion control in class I mutation carriers. Low FPG does not exclude impaired glucose tolerance (IGT) and diabetes in CF and reflects worse clinical status.

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Introduction

Growth failure and diabetes (CFRD) are attributed to anabolic defects in patients with cystic fibrosis (CF) (1). Insulin secretory defects and insulin resistance impair glucose tolerance in an increasing proportion of CF patients with advancing age (2–5). A recent study suggests that metabolic derangements in CFRD originate from an islet dysfunction inherent to the cystic fibrosis transmembrane conductance regulator (CFTR) state (6), but this hypothesis remains to be extensively demonstrated in humans. CFRD has a burden of complications, chiefly the deterioration of pulmonary function (7–9), but also classic diabetes complications, as recently shown (10, 11).

Overall, CFRD increases the mortality risk, particularly in females (12).

A unique feature of CFRD is that, postabsorptively, so many patients are normoglycemic (13) that the most recent diagnostic criteria for diabetes based on fasting plasma glucose (FPG) are not sensitive enough (14). The association of diabetic glucose tolerance with such low FPG is unusual in other forms of diabetes (15). We recently noticed that several CF patients are spontaneously hypoglycemic and, despite that, a subgroup of them has CFRD (16). In addition, reactive hypoglycemia has been described after OGTT (17, 18). The reason why FPG is often lower than expected, despite a high prevalence of CFRD is presently unknown. It is unclear whether this reflects an inappropriate insulin secretory control or an anabolic defect of undernourished patients. Insulin is choice therapy in CFRD (19) and early treatment is also proposed to counteract nutritional decay, progression to CFRD, and pulmonary deterioration (20–24) in patients with intermittent CFRD or impaired glucose tolerance (IGT), but hypoglycemia could be a limiting factor. To our knowledge, this issue was not clarified by studies relating low FPG to glucose tolerance and clinical status.

We therefore investigated, in a large cohort of CF patients followed at a single center in Milan where glucose tolerance status is yearly assessed after the age of 8 years, whether spontaneous and reactive hypoglycemia are frequent, they are related to inappropriate insulin concentrations and to glucose tolerance, genotype, nutritional, and clinical status.
Subjects and methods

Subjects

Between 2003 and 2005, all patients followed at the CF, Center of the University of Milan aged ≥8 years were offered to enter this study during their annual routine care visits if they had been clinically stable in the previous 3 weeks (neither major clinical events including pulmonary exacerbations nor changes in antibiotic or other drugs). Patients were excluded if they had a stable CFRD diagnosis or had received insulin or oral hypoglycemic agents in the previous 6 months. We enrolled 129 patients, who received 188 evaluations because 45 of them could be seen more than once. Table 1 reports their demographic features.

The CF diagnosis was based on the 1998 consensus conference criteria (25). Patients were examined for a panel of 34 CF mutations (Cystic Fibrosis Assay V.3.0, Abbott) and when necessary denaturing high performance liquid chromatography (DHPLC) (26) technique followed by sequencing analysis. The CFTR gene mutations were identified on both alleles in 96 patients (74%). Unknown mutations were present in one allele in 24 patients (19%) and in both alleles in 4 (3%). Genotype remained not evaluated in five (4%) cases.

Genotype classification

Mutations were classified according to their basic molecular mechanisms using the six-class functional classification system (27).

Except for homozygotes for ΔF508 (n=38), G542X (n=1), 1717-1G->A (n=1), most patients were compound heterozygotes with mutations belonging to different classes. Patients, who did not carry ΔF508 but were compound heterozygous for mutations in different classes were excluded and we used the functional class of the second mutation on a ΔF508 background. On this basis, we could classify 81 patients. There were no differences in the distribution of the main clinical features, FPG, or variables related to nutritional status at entry (Tables 1 and 2) between patients who could or could not be classified according to functional class mutations.

Clinical assessment

Table 1 reports the main clinical features at entry. Pancreatic insufficiency, defined by means of fecal elastase (28), was present in 115 (89%) patients, who were receiving pancreatic enzyme replacement therapy; doses were established on the basis of meal fat content, clinical symptoms, and steatocrit determinations (29). A high-fat diet was prescribed to achieve a daily caloric intake of 120–150% of recommended dietary allowances.

At the time of each study, patients underwent clinical evaluation with anthropometric measurements and determination of the Shwachman score (30). Weight and height were expressed as z-scores using published population means and s.d. (31). Ideal body weight for age and height were also calculated (32). Pulmonary function tests (FEV1 and FVC) were determined by spirometry and expressed as percentage of predicted for age (33). Chest X-ray, sputum culture, and abdominal ultrasound were also performed.

Biochemical and metabolic evaluation

Blood samples were drawn after overnight fast to evaluate FPG, blood counts, inflammatory status, hemoglobin A1c, serum free-insulin and C-peptide, plasma lipid profile, liver function tests, then a standard 3-h oral glucose tolerance test (OGTT, 1.75 g/kg, max 75 g) was performed, sampling every 30 min plasma

Table 1 Clinical features of patients according to the quartile of fasting plasma glucose levels at baseline determinations.

<table>
<thead>
<tr>
<th>Quartile of FPG a</th>
<th>No. of patients</th>
<th>Any FPG level (mg/dl)</th>
<th>1 (&lt;68 mg/dl)</th>
<th>2 (68–83 mg/dl)</th>
<th>3 (&gt;83 mg/dl)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>129</td>
<td>34</td>
<td>64</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>74 (57%)</td>
<td></td>
<td>17 (50%)</td>
<td>38 (59%)</td>
<td>19 (61%)</td>
<td>0.590</td>
<td></td>
</tr>
<tr>
<td>No. of patients with &gt;1 study</td>
<td>45 (35%)</td>
<td>13 (38%)</td>
<td>21 (33%)</td>
<td>11 (35%)</td>
<td>0.760</td>
<td></td>
</tr>
<tr>
<td>Age at time of study (years)</td>
<td>17 (8–32)</td>
<td>15 (8–24)</td>
<td>17 (8–31)</td>
<td>17 (8–24)</td>
<td>0.073</td>
<td></td>
</tr>
<tr>
<td>Age at time of CF diagnosis</td>
<td>4 mo (0–23 years)</td>
<td>3 mo (0–14 years)</td>
<td>4 mo (0–23 years)</td>
<td>4 mo (0–16 years)</td>
<td>0.177</td>
<td></td>
</tr>
<tr>
<td>Functional mutations b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>30 (37%)</td>
<td>7 (33%)</td>
<td>16 (42%)</td>
<td>7 (32%)</td>
<td>0.400</td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td>47 (58%)</td>
<td>12 (57%)</td>
<td>21 (55%)</td>
<td>14 (64%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class IV</td>
<td>1 (1%)</td>
<td>0</td>
<td>0</td>
<td>1 (4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class V</td>
<td>3 (4%)</td>
<td>2 (10%)</td>
<td>1 (3%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of homozygous for ΔF508 mutation</td>
<td>38 (31%)</td>
<td>11 (34%)</td>
<td>16 (26%)</td>
<td>11 (35%)</td>
<td>0.574</td>
<td></td>
</tr>
<tr>
<td>No. of with history of meconium ileus</td>
<td>18 (14%)</td>
<td>6 (18%)</td>
<td>8 (13%)</td>
<td>4 (13%)</td>
<td>0.782</td>
<td></td>
</tr>
<tr>
<td>No. of with liver cirrhosis</td>
<td>14 (11%)</td>
<td>5 (15%)</td>
<td>4 (6%)</td>
<td>5 (16%)</td>
<td>0.257</td>
<td></td>
</tr>
</tbody>
</table>

Median and range of values are reported for continuous variables. To express FPG values in mmol/l multiply by 0.05551.

aFPG values are the average of baseline determinations carried out in each patient during the different studies.

bFunctional class could be determined in 81 patients.
Table 2 Clinical and nutritional state according to the quartile of fasting plasma glucose levels at baseline determination in 186 OGTTs.

<table>
<thead>
<tr>
<th>Quartile of FPG</th>
<th>Any FPG level</th>
<th>1 (&lt;67 mg/dl)</th>
<th>2 and 3 (67–84 mg/dl)</th>
<th>4 (&gt;84 mg/dl)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of studies</td>
<td>186 (100%)</td>
<td>50 (100%)</td>
<td>89 (100%)</td>
<td>47 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

Medians and range of values are reported for continuous variables. To express FPG concentrations in mmol/l multiply by 0.05551, to express insulin concentrations in mmol/ml multiply by 6, and to express C-peptide concentrations in ng/ml multiply by 0.331. Two studies that resulted in incomplete collection of OGTT data are excluded.

aPseudomonas aeruginosa or Burkholderia cepacia species.
bDXA was assessed in 63 patients (11 patients in Q1 for FPG, 35 in Q2–3, 17 in the highest quartile) P, are Bonferroni-adjusted P values to control for multiple testing.

glucose, serum insulin, and C-peptide concentrations. Based on fasting and 2-h plasma glucose after OGTT, patients were assigned to one category of glucose tolerance (13); normal, impaired, diabetes without fasting hyperglycemia, and diabetes with fasting hyperglycemia. Specifically, plasma glucose was measured on fluoride plasma samples (Gluco-quant; Roche/Hitachi analyzer; Roche Diagnostics) and the other analytes were measured by commercial kit assays.

**DXA**

In 63 patients, a dual energy X-ray absorptiometry (DXA) total body scan was performed to determine body composition (percent fat mass, lean body mass, bone mineral density), using Hologic QDR 2000 as previously described (34).

**Data analysis**

The study sample was divided into quartiles (Q) according to the distribution of baseline FPG or serum insulin levels. Accordingly, the studies were classified into categories of low (Q1), medium (Q2–3) or high (Q4) levels for each variable. To avoid possible bias originating from preferential replication of studies in certain patients, we did alternative analyses using the average value of serial determinations of baseline FPG, or serum insulin, from the different studies carried out in each patient, rather than using individual values from each study. Therefore, we performed analyses based on individual patients in addition to those based on individual studies. Such alternative analyses were favored in the assessment of associations with demographic, genotype, or comorbidity data. Since mutation classes other than I and II were underrepresented in our population, patients harboring such mutations were excluded from the analyses concerning genotype.

Differences in proportions were tested using Fisher’s exact test or χ² statistics. Continuous variables are summarized as median values and range; significance of their differences was assessed using the Mann–Whitney test to compare two groups and the Kruskal–Wallis test to compare more than two groups. If the latter analysis gave a significant result (P<0.05), pairwise comparisons were carried out using Mann–Whitney tests to assess which group differed from the others. For each comparison, the significance value was multiplied for the number of comparisons made (Bonferroni inequality method) to control for multiple testing. In the analyses showing P<0.10 for the comparison among FPG quartiles, the relationship was further studied by regression analysis using individual FPG values after the appropriate transformations were applied to the variables under study to normalize their distributions.

Multiple regression analysis or logistic regression analysis were used to assess relationships between two variables while simultaneously adjusting for other pertinent variables within the framework of multivariate analysis. Likelihood ratio tests were used to test whether adding new variables to a logistic regression model significantly improved its predictive ability. Odds ratios, their 95% confidence intervals (CI), and P values were calculated with logistic regression analysis or the Mantel–Haenszel method.

Statistical analyses were two sided and were performed using Stata statistical software (Version 8.0, Stata Corporation, College Station, TX, USA).
Results

Frequency of fasting hypoglycemia

Figure 1 shows the FPG distribution. In 6 studies (3%) FPG was < 50 mg/dl (2.8 mmol/l), in 13 (7%) it was < 55 (3.1), and in 24 (13%) it was < 60 mg/dl (3.3 mmol/l). None of the patients spontaneously reported symptoms or had signs of hypoglycemia at study time. Only 13 subjects (7%) had FPG ≥ 100 mg/dl (5.6 mmol/l) and 7 (4%) had FPG ≥ 126 mg/dl (7.0 mmol/l), diagnostic for CFRD with fasting hyperglycemia. Sex and age had no effect on FPG distribution.

Relationship of FPG with insulin, C-peptide, glucose tolerance, and reactive hypoglycemia

FPG, insulin and C-peptide concentrations are shown in Table 3 and Fig. 2A. Fasting insulin and C-peptide concentrations in Q1 were similar to the other quartiles, showing no suppression of insulin secretion by hypoglycemia.

The relationship between FPG and glucose tolerance is shown in Table 3. Diabetes with fasting hyperglycemia was observed in seven male patients: of these, four were participating in their first study; two had presented with diabetes without fasting hyperglycemia and IGT respectively in the earlier studies: their baseline FPG consistently clustered into the highest quartile; the last patient had undergone an earlier test that showed a FPG of 43 mg/dl in basal conditions and disclosed diabetes during the test. Compared with patients in Q2–3 for FPG, those in the highest quartile were 4.4 times (95% CI: 1.6–12.0; P < 0.001) more likely to have diabetes identified by OGTT. Being in the lowest quartile was not associated with reduced risk and, actually, the risk of diabetes was the same in tests with a FPG value in Q1 or in Q2–3 (odds ratio: 1.3, 95% CI: 0.4–4.3, P = 0.668). We also found reactive hypoglycemia (FPG < 50 mg/dl (2.8 mmol/l)) in 28 tests (15%), with similar frequency in Q1 and Q2–3. As expected, patients with fasting glucose in the fourth quartile (Q4) and insulin in Q1 (Fig. 2B) have the maximum odds ratio for IGT and diabetes. Interestingly, among tests in Q1 for FPG, those with the highest fasting insulin levels tended to be associated with increased frequency of IGT or diabetes.

Both maximum glucose increment during OGTT and the area under glucose curve were higher in the extreme than in the central FPG quartiles (Table 3). Maximum glucose increment in Q2–3 was significantly different from Q1 (P<0.054) and Q4 (P<0.002), according to a significant quadratic relationship (P=0.007) with FPG in a regression analysis. Likewise, the area under glucose curve significantly differed.

Figure 1  Distribution of fasting plasma glucose values at baseline evaluation in 188 studies. Number of studies with a baseline FPG falling into each class is reported between parentheses. To express FPG values in mmol/l multiply by 0.05551. Median levels of FPG were: 75 mg/dl (range, 45–121) in female and 76 mg/dl (37–162) in male patients (P = 0.534), and 74 mg/dl (range, 45–140) in patients aged < 17 years and 76 mg/dl (37–162) in those aged 17 years or older (P = 0.253).
between Q2–3 and Q4 ($P_c=0.002$), and a significant quadratic relationship with FPG ($P=0.011$) again emerged in the regression analysis.

### Effect of genotype

Distribution of functional mutation classes was similar among different FPG quartiles (Table 1). Patients with class II mutations had lower insulin concentrations than class I mutation carriers for any given level of FPG (Fig. 2C and D).

### Clinical and nutritional status

Shwachman score distribution (Table 2) showed a significant quadratic relationship with FPG in a regression analysis, with the lowest scores clustering both in the lowest and the highest quartiles for FPG values ($P=0.041$). In addition, tests in Q1 for FPG were associated with higher hospitalization rates in the preceding year, mainly due to pulmonary exacerbation, compared with both Q2–3 ($P_c=0.003$) and Q4 ($P_c=0.035$). In addition, frequency of at least one hospital admission in the tests in Q1 was higher than frequencies in Q2–3 ($P_c=0.003$) and Q4 ($P_c=0.036$); specifically, tests in Q1 were associated with a 3.5-fold higher frequency (95% CI: 1.6–7.6; $P=0.001$) of at least one hospital admission compared with tests in Q2–3. Steroids were being administered at time of nine studies, of which four (8%) were in the lowest, two (2%) in the medium, and three (6%) in the highest FPG quartile. Of the six subjects with FPG < 50 mg/dl, five had not taken steroids in the previous 6 months, and one was on oral steroids (prednisone 5 mg every other day for more than 1 month). Anthropometric variables, including BMI, weight and height z-score, weight for height, and pulmonary function (FEV-1 and FVC) were similar among FPG quartiles. Body composition parameters, evaluated by DXA, were not associated with FPG levels (Table 2). Strong relationships of age with Shwachman score, FEV-1, FVC, lean body mass, and total bone mineral density, but not FPG, were observed at regression analysis ($P<0.001$).

### Discussion

This study evaluated the frequency of hypoglycemia in CF using plasma glucose concentrations collected during OGTT routinely performed in clinically stable patients, not receiving hypoglycemic agents and without established CFRD. Overall, 13% of studies had FPG < 60 mg/dl (3.9 mmol/l), considered the lower threshold for normoglycemia by most laboratories, including ours, because in healthy individuals counter-regulatory responses take place between 70 and 60 mg/dl (3.3–3.9 mmol/l) (35, 36). Nobody reported symptoms or had signs of hypoglycemia at the time of blood drawing, despite glucose concentrations as low as 35–55 mg/dl (1.9–3.1 mmol/l; usually symptomatic in healthy subjects), nor had previously reported hypoglycemic coma or severe hypoglycemia requiring outside help to treat the occurrence (37). Reactive hypoglycemia (PG < 50 mg/dl (2.8 mmol/l)) after OGTT (38), detected in 15% of the studies, was asymptomatic as well. It is thus improbable that in CF hypoglycemia becomes clinically manifest because of related symptoms or neuroglucopenia, although studies of glucose counter-regulation and

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*Table 3 Altered glucose tolerance and clinical and nutritional state according to the quartile of fasting plasma glucose levels at baseline determination in 186 OGTTs.*

<table>
<thead>
<tr>
<th>Quartile of FPG</th>
<th>Any FPG level</th>
<th>1 (&lt;67 mg/dl)</th>
<th>2 and 3 (67–84 mg/dl)</th>
<th>4 (&gt;84 mg/dl)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of studies</td>
<td>186 (100%)</td>
<td>50 (100%)</td>
<td>89 (100%)</td>
<td>47 (100%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes and impaired glucose tolerance</td>
<td>Normal glucose tolerance</td>
<td>125 (67%)</td>
<td>41 (82%)</td>
<td>68 (76%)</td>
<td>16 (34%)</td>
</tr>
<tr>
<td></td>
<td>Impaired glucose tolerance</td>
<td>31 (17%)</td>
<td>4 (8%)</td>
<td>14 (16%)</td>
<td>13 (28%)</td>
</tr>
<tr>
<td></td>
<td>Diabetes without fasting hyperglycemia</td>
<td>23 (12%)</td>
<td>5 (10%)</td>
<td>7 (8%)</td>
<td>11 (23%)</td>
</tr>
<tr>
<td></td>
<td>Diabetes with fasting hyperglycemia</td>
<td>7 (4%)</td>
<td>0</td>
<td>0</td>
<td>7 (15%)a</td>
</tr>
<tr>
<td>Reactive hypoglycemia</td>
<td>28 (15%)</td>
<td>11 (22%)</td>
<td>14 (16%)</td>
<td>3 (6%)</td>
<td>0.088</td>
</tr>
<tr>
<td>Maximum glucose increment (mg/dl)</td>
<td>111 (9–352)</td>
<td>112 (32–244)</td>
<td>101 (9–255)</td>
<td>141 (33–352)</td>
<td>0.002</td>
</tr>
<tr>
<td>Area under glucose curve</td>
<td>8332 (296–22 440)</td>
<td>8565 (1992–22 440)</td>
<td>7260 (296–20 295)</td>
<td>10 800 (1059–21 945)</td>
<td>0.002</td>
</tr>
<tr>
<td>Serum insulin (mU/ml)</td>
<td>5.5 (0.2–29.2)</td>
<td>5.6 (0.2–28.9)</td>
<td>5.4 (0.2–29.2)</td>
<td>5.9 (0.2–24.9)</td>
<td>0.965</td>
</tr>
<tr>
<td>Serum C-peptide (ng/ml)</td>
<td>1.3 (0.4–4.1)</td>
<td>1.1 (0.4–2.7)</td>
<td>1.3 (0.4–4.1)</td>
<td>1.1 (0.4–3.4)</td>
<td>0.643</td>
</tr>
</tbody>
</table>

Median and range of values are reported for continuous variables. To express FPG concentrations in mmol/l multiply by 0.05551, to express insulin concentrations in mmol/ml multiply by 6, and to express C-peptide concentrations in ng/ml multiply by 0.331. Two studies that resulted in incomplete collection of OGTT data are excluded.

aStudies showing diabetes with fasting hyperglycemia, that, by definition, could only be found in the highest quartile for FPG, were not included into this analysis. $P_c$ are Bonferroni-adjusted $P$ values to control for multiple testing.
hypoglycemia awareness thresholds would be advisable to better clarify this issue. In this respect, neither younger age nor female gender, known to predispose to reduced hypoglycemia responsiveness (39), were determinants of hypoglycemic values. After the analysis reported in this study, we decided to administer a structured questionnaire to detect symptoms of hypoglycemia (autonomic and neuroglucopenic) at the time of the basal drawing of each new OGTT during the follow-up. That study is presently under way.

In general, the relationship to insulin secretion is critical to understand the pathogenesis of hypoglycemia. The suppression of insulin secretion is the primary factor preventing glucose concentrations to fall below the physiologic range and consequently trigger counter-regulatory hormone responses (40). In many CF patients, we found that insulin and C-peptide concentrations were not reduced with decreasing FPG, suggesting a lack of insulin suppression by hypoglycemia. When subjects with the lowest FPG were stratified for insulinemia, a strong association with genotype emerged, as carriers of class I mutations (no CFTR synthesis) had higher insulin concentrations than carriers of class II (defective protein maturation and premature degradation) (41). The mechanism underlying this difference is difficult to explain. In fact, although CFTR mutations belonging to class I, II, and III have variable effects on gene transcription, mRNA translation or intracellular trafficking of the nascent protein, they would all be expected to confer complete loss of cAMP-regulated chloride channel function. However, several studies suggest that homozygotes for ΔF508 mutations (the most frequent class II genotype) retain in some tissues a residual functional protein expression on the cell membrane (42–44). Unfortunately, not enough class IV and V mutations carriers (confering residual function) could be evaluated.

Figure 2 Distribution of baseline fasting plasma glucose and serum insulin values, and their relationship with impaired glucose regulation and functional mutation class. To express FPG values in mmol/l, multiply by 0.05551 and to express insulin concentrations in mmol/ml, multiply by 6. (A) Lines denote boundaries for the lowest and highest quartiles of the distribution of FPG (vertical lines, 67 and 84 mg/dl) and serum insulin determinations (horizontal lines, 3.9 and 7.6 μU/ml) in 188 studies. (B) For the calculation of risks of impaired glucose tolerance or diabetes without fasting hyperglycemia, odds ratios were obtained by logistic regression analysis; the tests in quartiles 2 and 3 for FPG and quartiles 2 and 3 for serum insulin, i.e., the largest group of tests, were considered the reference class (dark column, odds ratio = 1). Seven OGTTs showing diabetes with fasting hyperglycemia are not included. (C) Vertical lines denote boundaries for the lowest and highest quartiles of the distribution of average FPG (68 and 83 mg/dl) from each patient. The corresponding boundaries for the distribution of average serum insulin values from each patient are 4.3 and 7.9 μU/ml (not indicated). The regression lines for the relationship between serum insulin and FPG in patients with class I (straight line, n = 30; median insulin value: 6.5 μU/ml, range: 1.7–13.3) or class II functional mutations (dotted line, n = 45; 4.6 μU/ml, range: 0.2–13.2) differ significantly (P = 0.015, multiple regression analysis). (D) Odds ratios for the association with class I functional mutations were obtained by logistic regression analysis; the patients in quartiles 2 and 3 for FPG and quartiles 2 and 3 for serum insulin, i.e., the largest group of patients, were considered the reference class (dark column, odds ratio = 1). Overall, patients in the lowest quartile for serum insulin were less likely (OR 0.25, 95% CI: 0.07–0.84; P = 0.025) to harbor a class I mutation than those in quartiles 2 and 3 after correction for FPG.
To our knowledge, a dysregulation of basal insulin secretion related to the CFTR genotype and possibly leading to hypoglycemia was not previously reported. Persistent hyperinsulinemic hypoglycemia of infancy (45) is a condition caused by potassium channel defects produced by mechanisms similar to those impairing CFTR in CF. It is presently unknown whether the defects causing CFTR dysfunction could also affect potassium channels involved in insulin secretion: alternatively, CFTR defects themselves may change ion fluxes across β-cell membrane and affect insulin secretion, glucose transport and sensing. Our study had not enough statistical power to evaluate whether the genotype also affects glucose tolerance and insulin response in the subjects with low FPG. Nonetheless, the subjects showing low glucose and high insulin concentrations at baseline (more frequently harboring class I mutations) were more liable to IGT or diabetes than subjects with low concentrations of both glucose and insulin. Our results therefore suggest that the simultaneous occurrence of fasting hypoglycemia and diabetes is not accidental and may be related to insulin secretory dysfunction and CF genotype.

The maximum glucose increment during OGTT and the area under glucose curve were higher in the lowest than in the central FPG quartiles, but glucose tolerance was similar. Notably, a low FPG did not predict lower chance of being diabetic. According to an European meta-analysis of type 2 diabetes, the diabetes diagnoses based on 2 h-OGTT glucose concentrations without fasting hyperglycemia were frequent (46), but median FPG (109 mg/dl (6.0 mmol/l)) was much higher than in our CF patients (87 mg/dl (4.8 mmol/l)). These results strengthen the notion that the diagnosis of CFRD should rely upon yearly OGTT (14), since low FPG levels do not exclude it.

CF patients with exocrine pancreatic insufficiency have a defective glucagon secretion leading to hypoglycemia (47). It is unlikely, however, that isolated glucagon response defects could cause fasting hypoglycemia (35). Although advanced exocrine pancreatic disease may induce endocrine dysfunction in CF patients by involving the islet components, the hypothesis that a common pathogenic process simultaneously and independently impairs exocrine and endocrine function seems more attractive (47).

Limitation of gluconeogenic amino acid supply by depleted muscular mass could lead to hypoglycemia in patients with severe nutritional imbalance (48), but typical signs of severe malnutrition were lacking in the subjects with the lowest FPG and, specifically, anthropometric parameters were not different from the other patients. To further clarify this issue, a side investigation was performed using DXA to relate FPG and the fat, lean, and bone mineral components of body weight. Again, these parameters were not related to hypoglycemia, indicating that impaired nutritional status in CF cannot explain hypoglycemia.

Finally, we found that low FPG reflects some clinical disadvantage like lower Shwachman scores and higher hospitalization rates. Corticosteroid withdrawal could cause hypoglycemia and it was anecdotally reported that hypoglycemia can occur also during inhaled corticosteroid treatment (49). Only oral and not inhaled steroids were being administered in few (10) studies, which were performed at least 3 weeks from the last change in dosage. Therefore, corticosteroids are unlikely to have a role in inducing hypoglycemia.

In conclusion, low FPG are frequent in CF patients, they do not exclude diabetes diagnosis and may imply a worse clinical status. Further, pathogenetic investigations should address the role of altered regulation of insulin secretion and its possible link with CF genotype.

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