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Insulin Responses to Intravenous Glucose and the Hyperglycemic Clamp in Cystic Fibrosis Patients with Different Degrees of Glucose Tolerance

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ABSTRACT

The relationship between altered insulin secretion and impaired glucose tolerance was studied in 32 cystic fibrosis patients, 16 men and 16 women, aged 8–26 y, using oral and i.v. glucose tolerance tests and a hyperglycemic glucose clamp (10 mmol/L). Seven of these subjects were already being treated with insulin; seven had fasting blood glucose levels below 7.2 mmol/L but satisfied diabetic criteria at the oral glucose tolerance test; glucose tolerance was impaired in 13 subjects and normal in five. The insulin responses to the two i.v. glucose stimuli were inversely correlated with the plasma glucose levels (60 and 120 min) and the area under the curve of the oral glucose tolerance test. However, the acute insulin response to i.v. glucose was severely altered in patients with impaired glucose tolerance, whereas plasma insulin levels during the hyperglycemic clamp did not differ from those of healthy subjects. The responses to the two stimuli were dramatically low in the diabetic patients. These results suggest that cystic fibrosis patients with normal or impaired glucose tolerance retain their capacity to secrete insulin. Alterations in the acute phase of glucose-stimulated insulin secretion seem to be principally responsible for the early impairment in glucose tolerance. (***Pediatr Res* 36: 667–671, 1994**)

Abbreviations

AIR, acute insulin response
CF, cystic fibrosis
IDDM, insulin-dependent diabetes mellitus
IVGTT, i.v. glucose tolerance test
OGTT, oral glucose tolerance test
BMI, body mass index
IGT, impaired glucose tolerance
NT, normal glucose tolerance

CF causes alterations of both the exocrine and the endocrine pancreas. About 20–30% of CF patients show IGT (1–5) and the percentage of those who develop diabetes mellitus increases with their extending life expectancy (4). The onset of diabetes may cause a decline in the clinical status of CF patients (6, 7). In addition, hyperglycemia often occurs during the intensive enteral feeding needed by undernourished patients (8) or with the immunosuppressive therapies used after lung transplantation. Thus, diabetes mellitus is a growing concern in the follow-up of CF patients.

The pathophysiologic mechanisms responsible for glucose intolerance and diabetes in CF differ from those of autoimmune type 1 IDDM. The immunologic (5, 9, 10) and genetic (5, 11) markers of IDDM are not generally linked with CF diabetes. Histologic studies (12–14) have shown no insulitis. Studies with the OGTT show low plasma insulin levels (1, 3, 15–22) and delayed insulin peaks (5, 9, 10, 16–18, 21) in CF patients. However, the IGT was correlated with the degree of insulinopenia in only a few studies (16, 17, 19). Because the insulin response to the OGTT is a poor estimate of insulin secretion, other tests [the IVGTT (9, 15, 16, 22, 23), i.v. arginine (15, 21, 24, 25), i.v. glucagon (26), or i.v. tolbutamide (16, 17, 22)] have been used, but they have not fully explored the relationship between insulin secretion and glucose tolerance in CF patients.

This study was designed to evaluate the insulin response of CF patients with diverse degrees of glucose tolerance to the IVGTT and the hyperglycemic glucose clamp. CF patients with IGT retained their capacity to secrete insulin. The early impairment in glucose tolerance was mainly correlated with alterations in the acute phase of glucose-stimulated insulin secretion.

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METHODS

Patients. Thirty-two CF patients, 16 men and 16 women, aged 7.6 to 25.9 y (mean ± SD, 16.6 ± 5.0 y) were studied. They had BMI of 12.3 to 23.0 (16.1 ± 2.7), with normalized, age-corrected *z* scores (27) of −4.86 to 2.29 (−1.83 ± 1.54). None of them had a known family history of IDDM. Seven patients had been treated with insulin for 1 mo to 4.5 y (1.7 ± 2.0 y). The insulin doses were 12 to 58 U/d and mean HbA1C was 8.2 ± 2.1% (6.0–12.0%; normal values, 4.2–5.6%). Four of the seven insulin-treated patients and 23 of the 25 other patients were registered on the waiting list for lung transplantation. The tests were performed at intervals from acute infectious episodes, but most of the patients were taking various antibiotics. All patients were regularly taking exocrine pancreatic enzymes. Their liver and kidney functions were normal. None were treated with oral hypoglycemic agents, corticosteroids, or other medication known to influence glucose metabolism.

The same investigations were conducted in healthy subjects, six men and two women, aged 22 to 32 y (26.5 ± 2.9 y), with no diabetic relatives. Their BMI were 20.2 to 24.6 (22.0 ± 1.6).

The patients and their parents were fully informed of the purpose and potential risks of the study, and they gave informed consent before participating. The protocol was approved by the ethical committee of Necker-Enfants Malades Hospital.

Metabolic studies. Two metabolic tests were performed at a few days' interval, after an overnight fast, with the subjects remaining fasting and supine. The patients remained on their usual diet in the days preceding the tests, but were advised to consume at least 250 g of carbohydrate. For the OGTT, 1.75 g/kg glucose (maximum 75 g) in 300 mL water were ingested in 5 min. Blood samples were taken at 0, 30, 60, and 120 min.

The insulin responses to IVGTT and the hyperglycemic glucose clamp were measured consecutively in a single 2-h protocol. The IVGTT represents approximately twice the priming dose of glucose regularly used for the hyperglycemic clamp (28), but performing the two tests on the same day was judged of interest for such patients and did not alter the results of the clamp. Two indwelling catheters were inserted into forearm or antecubital veins for substrate infusion and blood sampling. A blood sample was taken and 0.5 g/kg glucose was injected i.v. over exactly 2 min, as for a standard IVGTT. Venous blood samples were collected exactly 1 and 3 min after the end of the injection. From 10 to 120 min after the i.v. glucose bolus injection, the plasma glucose was measured every 5 min and clamped at 10 mmol/L, using established algorithms (28) calculated on a microcomputer, which also automatically controlled a 30% dextrose infusion. Blood samples were taken every 20 min during the clamp to measure plasma immunoreactive insulin and C-peptide.

Patients on insulin were not given intermediate insulin injections the night before the test; blood glucose was controlled overnight by i.v. insulin infusion. The hyperglycemic clamp could not be performed in two normotolerant, one intolerant, and one diabetic patient; these patients underwent only the IVGTT.

Analytical procedures for plasma samples. Plasma glucose was measured on a 10-μL aliquot by the glucose oxidase technique (Glucose Autoanalyzer Beckman, Fullerton, CA). Blood samples for hormone assays were centrifuged at 4°C, and the plasma was kept at −20°C. Insulin (SB-INSI 5 kit, CIS Bio International, Gif sur Yvette, France) and C-peptide (C-PEP kit, CIS Bio International) were measured in duplicate by RIA. Free insulin was determined, in insulin-treated patients, after separation with polyethylene glycol. Intraassay coefficients of variation were 4 and 6%, interassay coefficients of variation 3 and 8%, and detection limits 4 pmol/L and 0.05 nmol/L for insulin and C-peptide, respectively.

Data analysis. Values are means ± SEM unless otherwise stated. The AIR to IVGTT is the sum of 1 + 3 min plasma insulin or C-peptide values, and the response to the hyperglycemic clamp is the mean of two values (100 and 120 min). Correlations with glucose tolerance were calculated after logarithmic transformation of the insulin secretion responses to obtain a normal distribution (29). The insulin responses to the different metabolic tests were compared between the groups of subjects by repeated-measures analysis of variance. Factorial analysis of variance was used to compare each time point of the tests when required.

Because the insulin responses of normal children differ from those of postpubertal and adult subjects (29), statistical analyses were made for all the subjects and then repeated with the postpubertal subjects only. The conclusions in the two cases were similar, and values are given for the postpubertal subjects unless otherwise stated. The postpubertal group included 12 men and 10 women; their mean age was 19.2 ± 3.8 y and mean BMI 16.6 ± 2.7.

RESULTS

OGTT (Fig. 1). Twenty-five patients were not treated with insulin. Seven of them had biologic criteria of diabetes (plasma glucose ≥ 11 mmol/L at 120 min of the OGTT); 13 showed IGT (plasma glucose 7.8–11 mmol/L at 120 min); and five had NT (plasma glucose < 11 mmol/L at 30 and 60 min, < 7.8 mmol/L at 120 min). Six postpubertal patients were treated with insulin, five had preclinical diabetes, nine were IGT and two were NT. The fasting plasma glucose levels of the non–insulin-treated diabetic were below 7.2 mmol/L, but higher (5.7 ± 0.6 mmol/L, $p < 0.01$) than those of the other CF patients (4.8 ± 0.2 mmol/L). The plasma glucose levels were higher ($p < 0.01$) in the diabetic and IGT than in the NT CF patients at 30 min; the values for all the groups differed at 60 min ($p < 0.001$), but there were no differences between the NT and IGT CF patients at 120 min of the OGTT. The plasma insulin levels at 30 min and the

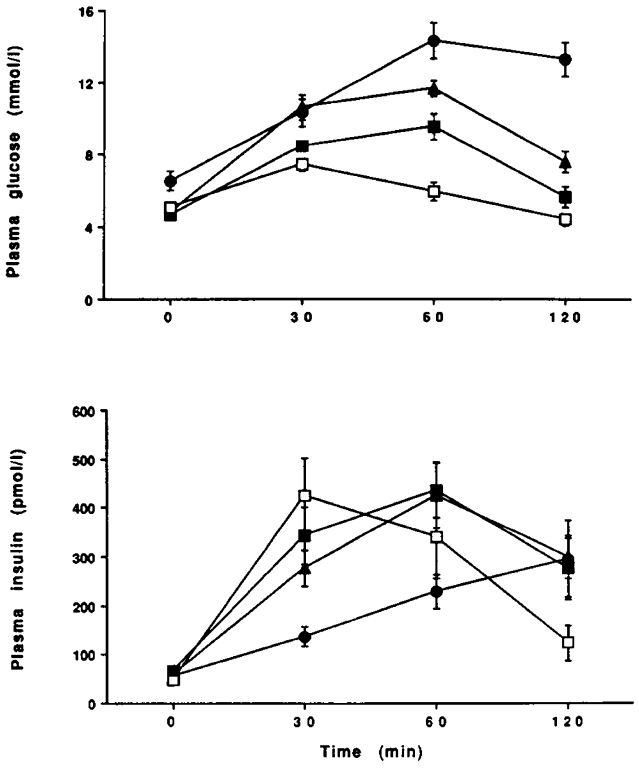

Figure 1. Mean ± SEM plasma glucose and insulin values during the OGTT in 25 (pre- and postpubertal) CF patients with normal (■, n = 5), impaired (▲, n = 13), or diabetic (●, n = 7) glucose tolerance and in eight healthy young adult subjects (□).

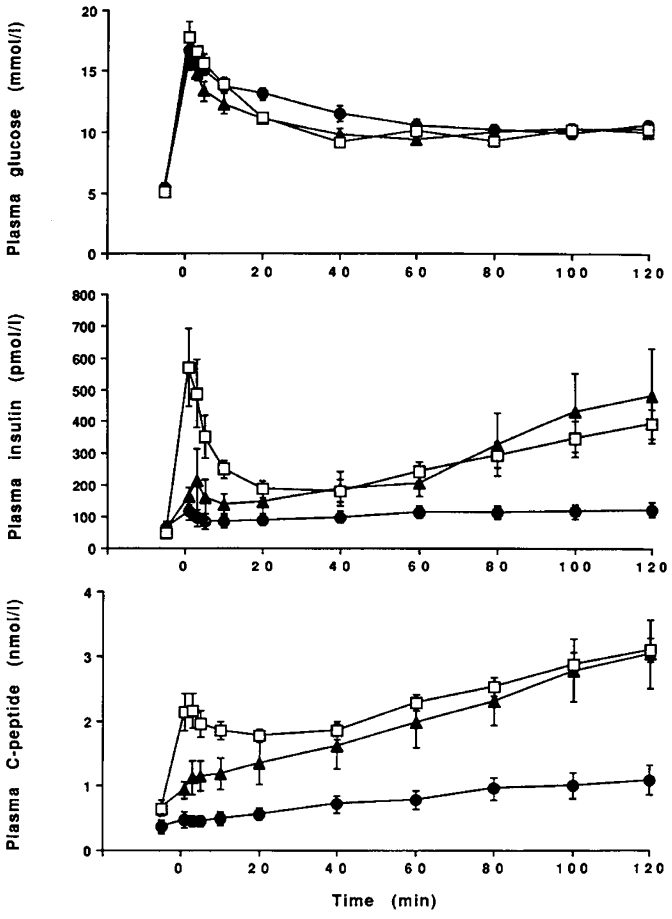

Figure 2. Mean ± SEM plasma glucose, insulin, and C-peptide values during the IVGTT and the hyperglycemic clamp in 18 postpubertal CF patients with IGT (▲, n = 9) or diabetes (●, n = 11) and in eight healthy young adult subjects (□).

area under the curve of plasma insulin were lower (p < 0.01) in the diabetic CF patients than in the other groups.

IVGTT and hyperglycemic clamp. For the tests measuring insulin secretion (Fig. 2), the results of the NT CF patients are not shown, inasmuch as only three (prepubertal) patients completed the hyperglycemic clamp; the insulin-treated and non–insulin-treated diabetic CF patients are pooled. The plasma glucose decay after the IVGTT was delayed in the diabetic CF patients: plasma glucose levels decreased approximately 10 mmol/L after approximately 60 min, compared with 20 min in the IGT CF and healthy subjects. However, the mean plasma glucose levels during the last 60 min of the hyperglycemic clamp (Fig. 2) in the diabetic (10.3 ± 0.2), the IGT (10.1 ± 0.2) CF patients and the healthy subjects (9.8 ± 0.2 mmol/L) were similar.

The mean AIR to IVGTT (1 + 3 min) of the diabetic (treated plus untreated, 218 ± 217 pmol/L) and the IGT (373 ± 100 pmol/L) CF patients were lower (Fig. 2, p < 0.01) than those in the healthy subjects (1061 ± 229 pmol/L). There were no significant differences between the diabetic CF patients, treated or untreated, and the IGT CF patients (Table 1). The AIR to IVGTT of the NT CF patients (pre- and postpubertal, n = 5: 731 ± 269 pmol/L) did not differ significantly from the values for the healthy subjects.

The plasma insulin and C-peptide levels in response to the hyperglycemic clamp were similar in the IGT CF

Table 1. *Plasma insulin and C-peptide values during IVGTT and hyperglycemic glucose clamp in 20 postpubertal CF patients with IGT* (n = 9), *diabetic glucose tolerance* (n = 5), *or IDDM* (n = 6) *and in eight healthy young adult subjects**

	Healthy adults	IGT	Untreated diabetes	Insulin-treated diabetes
IVGTT				
Insulin (pmol/L)	1061 ± 229	373 ± 100†	229 ± 65†	210 ± 115†
C-peptide (nmol/L)	4.30 ± 0.55	2.05 ± 0.35†	1.49 ± 0.36†	0.42 ± 0.08†
Hyperglycemic clamp				
Insulin (pmol/L)	373 ± 143	459 ± 136	158 ± 29‡	79 ± 29‡
C-peptide (nmol/L)	2.99 ± 0.18	2.92 ± 0.50	1.63 ± 0.27‡	0.44 ± 0.08‡

* Values are means ± SEM. Untreated diabetes, diabetic criteria at the OGTT.

† Significantly different from the healthy subjects (p < 0.01).

‡ Significantly different from the healthy (p < 0.001) and the IGT (p < 0.01) subjects.

patients and the healthy subjects (Fig. 2, Table 1). They were much lower in the diabetic (Fig. 2) insulin-treated or untreated CF patients (Table 1) than in the IGT CF patients ($p < 0.01$) or the healthy subjects ($p < 0.001$). The plasma insulin and C-peptide responses to the hyperglycemic clamp were lower in the insulin-treated than in the non–insulin-treated diabetic CF patients (Table 1); the difference was significant for the C-peptide values only ($p < 0.001$).

Correlations between parameters of insulin secretion and glucose tolerance. Although the subjects were assigned to a group according to their glucose tolerance, the plasma glucose values followed a continuous distribution from normal to diabetic levels. HbA1C ($p < 0.01$), plasma glucose at 60 ($p < 0.01$) and 120 min ($p < 0.05$) of the OGTT, and the area under the curve of the OGTT ($p < 0.05$) were inversely correlated with the AIR to IVGTT and with the plasma insulin and C-peptide levels during the hyperglycemic clamp. The C-peptide response to the IVGTT was inversely correlated only with HbA1C ($p < 0.01$), and fasting plasma glucose was inversely correlated only with the AIR to IVGTT ($p < 0.01$). The plasma glucose at 30 min of the OGTT correlated with none of the tests of insulin secretion.

DISCUSSION

The alterations in the islets of Langerhans produced by CF gradually impair glucose tolerance and may cause diabetes. Only one third of the patients who are alive at the age of 25 y have NT, and one third have diabetes (4). The pulmonary manifestations of CF may still be life threatening in the pediatric age, but the life expectancy is increasing, and sufferers of this common genetic disease might account for a fair number of adult insulin-treated diabetic patients in the future.

The metabolic changes in CF patients seem to develop very slowly. Young children may have IGT (1, 5), whereas diabetes declares much later (4, 6). This seems to differ from pre–type 1 diabetes, in which IGT often precedes IDDM by only a few years (30). If IGT in CF has a different course, specific therapeutic approaches (31) might be attempted. Moreover, many patients are readily accessible and complex screening is not needed. Thus, CF might be of particular importance for studies on a long insulin-deficient prediabetic phase.

Many studies have shown that insulin secretion is reduced (1, 3, 15–22) and delayed (5, 9, 10, 16–18, 21) in CF patients, but only a few (16, 17, 19) established a correlation with the state of glucose tolerance. The present study shows that the glucose intolerance of CF patients is correlated with the decrease in the insulin responses to the IVGTT and the hyperglycemic glucose clamp.

Insulin secretion in response to the two stimuli was dramatically reduced in diabetic CF patients, whether treated with insulin or untreated. Thus, when the diabetic stage is reached, the β-cell mass seems so much reduced that insulin is low in response to the two stimuli.

Conversely, the insulin responses to the two tests differ in CF patients with IGT. The mean AIR to IVGTT was reduced to 35% of control values, whereas the response to the hyperglycemic clamp was comparable to that of the healthy subjects. These results might initially suggest that the alterations of insulin secretion in CF patients do not markedly differ from those of autoimmune pre–type 1 diabetes, in which the AIR to IVGTT might be altered more severely than the responses to other stimuli (32). However, other studies (33–35) have suggested that the decreased AIR to i.v. glucose is a late sign of altered insulin secretion. Our study of islet cell antibody–positive subjects has shown that the changes in the responses to the IVGTT and the hyperglycemic clamp are comparable at different degrees of glucose intolerance (36), which is in contrast with the present results in CF patients.

Although the reduced insulin secretion in islet cell antibody–positive subjects seems mainly due to the progressive loss of β-cell mass (33), the present results suggest that functional alterations of insulin secretion determine the impairment of glucose tolerance in CF patients. Histologic studies have shown that the number of islets of Langerhans is reduced and is correlated with the degree of glucose intolerance (12, 14), but it is not as low as in type 1 diabetes (13, 17). This has suggested that functional changes in insulin release caused by the disorganization of the islets' structure by fibrosis (12, 17) might worsen the consequences of the simple reduction of the β-cell mass, which is in agreement with our findings. It is noteworthy that the insulin secretion in our CF patients was correlated only with plasma glucose values at 60 and 120 min of the OGTT, such as in type 2 diabetes mellitus (37) or after exogenous somatostatin (38), two conditions in which the impairment of glucose tolerance is correlated with the loss of the early phase of insulin secretion.

Our study included few CF patients with NT. This is because we selected patients registered for lung transplantation. Our initial purpose was to investigate metabolic changes after transplantation. The majority of these patients had abnormal glucose tolerance, which suggests that the preterminal pulmonary stage is associated with factors aggravating glucose metabolism. Insulin resistance does not seem to be one of these factors, inasmuch as insulin action was not different from control values, whether it was estimated by the glucose infusion rate–plasma insulin ratio during the hyperglycemic clamp (39) or by euglycemic clamps in five of the subjects (unpublished data). The mean AIR to IVGTT of the five NT CF patients was within the normal range, although it was slightly lower than in normal subjects, but three subjects were prepubertal, and normal values are lower at this age (29). The results of earlier reports have been contradictory, showing normal (15, 16) or decreased (9) AIR to IVGTT in NT CF patients. This particular point should thus be further clarified. Only three prepubertal NT patients had a hyperglycemic clamp; unsurprisingly, these insulin responses were preserved, as in IGT CF patients.

In conclusion, CF alters the islets of Langerhans, and the reduction of β-cell mass may cause diabetes. In agreement with the histologic studies (12, 17), our results suggest that the impairment of glucose tolerance is mainly due to functional changes in insulin secretion, whereas the β cells can still secrete insulin in response to sustained hyperglycemia.

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