Tolbutamide Causes a Modest Increase in Insulin Secretion in Cystic Fibrosis Patients With Impaired Glucose Tolerance

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We examined the effect of intravenous (IV) tolbutamide administration on glucose and hormone levels in cystic fibrosis (CF) patients with impaired first-phase insulin secretion and oral glucose tolerance (oral glucose tolerance test [OGTT]) and compared them with CF patients with only an impaired first-phase insulin secretion and healthy control subjects. Five CF patients with an impaired OGTT, ie, a serum glucose value of 7.8 mmol/L or greater 120 minutes after an oral glucose load (group I), five CF patients with a normal OGTT, ie, a serum glucose not exceeding 7.8 mmol/L 120 minutes after oral glucose (group II), and five healthy control (CON) subjects underwent IV glucose tolerance tests with glucose alone (IVGTT) and glucose administered in conjunction with tolbutamide ([IVTTT] 25 mg/kg; maximum dose, 1 g). Serum glucose levels were measured using the glucose oxidase method; insulin, C-peptide, and glucagon levels were measured by the double-antibody radioimmunoassay (RIA) technique. Serum immunoreactive trypsin (IRT) and hemoglobin A_1 (HbA_1) levels and height and weight were measured for each subject, and in addition, pulmonary function was assessed in those with CF. There were no significant differences in the area under the curve (AUC) for glucose or glucagon levels or the serum glucose disappearance rate (k value) between group I, group II, or CON subjects during the IVGTT. First-phase insulin and C-peptide secretion was abnormal during IVGTT and IVTTT in the CF groups: in group I it was severely impaired, whereas in group II it was between group I and CON values. During the IVTTT serum glucose levels and glucose k values were not significantly altered in any of the three groups as compared with the IVGTT. Tolbutamide administration significantly increased the AUC for serum insulin in group II and CON subjects as compared with IVGTT values (67% and 135%, respectively, $P < .05$), with a modest ($P > .05$) increase in group I levels (28%). Likewise, there were significant increases in the AUC for C-peptide with IVTTT in group II (49%, $P < .05$) and CON subjects (58%, $P < .01$), with a lesser increase in group I (21%). The glucagon AUC was not significantly altered in IVTTT as compared with IVGTT in any group. These observations suggest that endocrine function in CF subjects is a continuous spectrum from those with diabetes mellitus to normals. Only long-term studies will determine if the residual secretion of insulin in response to oral sulfonylurea is of clinical importance.

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CYSTIC FIBROSIS (CF) is the most common fatal autosomal recessive disease in whites. At the cellular level, electrolyte transport is impaired, resulting in abnormal exocrine secretions mainly affecting the lungs, pancreas, and sweat glands.[1] Improved therapy for the pulmonary and digestive complications of this disease has led to increased life expectancy, but this has been accompanied by other complications, which include abnormal carbohydrate metabolism and diabetes mellitus. Recent studies by us[2] and other investigators[3-7] report that diabetes mellitus was diagnosed in 2% to 11% of CF patients who underwent oral glucose tolerance tests (OGTTs) and that 6% to 33% were glucose-intolerant. The decline in glucose tolerance in CF has been attributed to a number of factors such as disorganization and strangulation of islet cells,[8,9] an increased rate of jejunal glucose absorption,[10] and decreased exocrine pancreatic function.[11]

Although carbohydrate intolerance as defined by a standard OGTT is well recognized in CF patients and is associated with decreased plasma insulin levels,[12,13] the treatment has received little attention. It is still not clear whether hypoglycemic agents such as tolbutamide, a sulfonylurea that stimulates β cells to secrete insulin, would be of some value in this population. We provide evidence in this report that intravenous (IV) tolbutamide is not particularly effective in increasing insulin secretion in CF patients with impaired glucose tolerance. Instead of administering tolbutamide alone as in previous studies,[8,14,15] a combination of IV tolbutamide and glucose was used. This novel approach allows direct comparison of glucose and hormone levels with the results of IV glucose tolerance tests (IVGTT) from each patient, and circumvents the risk of severe hypoglycemia induced by tolbutamide alone.

SUBJECTS AND METHODS

Study Population

Patients attending CF outpatient clinics at the Alberta Children's Hospital and Foothills Hospital who were at least 5 years of age (to facilitate compliance) were contacted by letter and telephone. The purpose of the study was explained and patients were invited to participate. Fifty patients with CF as diagnosed by elevated sweat electrolytes and clinical signs agreed to take part. The study was approved by the conjoint ethical committee of the University of Calgary and the Alberta Children's Hospital, and informed consent was obtained from all subjects and/or their legal guardians. Only patients who were judged to be clinically stable, ie, not undergoing pulmonary exacerbation, were entered into the study. Those with known diabetes mellitus as defined by National Diabetes Data Group criteria[16] (fasting serum glucose ≥7.8 mmol/L and 2-hour post-OGTT ≥11.1 mmol/L) were excluded from the study. Table 1 shows subject characteristics.

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Table 1. Characteristics of Study Subjects (mean ± SEM)

	Group I (n = 5)	Group II (n = 5)	CON (n = 5)
Age (yr)	22.8 ± 4.47	18.4 ± 2.6	20.6 ± 2.8
Range	14-39	18-24	19-28
Gender	3F/4M	2F/3M	2F/3M
%IBW	93 ± 4.96	85 ± 6.2	101 ± 6.8
PF	29 ± 4.49	52 ± 11.8	NM
IRT (μg/L)	7.1 ± 1.88*	15.4 ± 8.96	28.1 ± 3.92
HbA_1 (%)	6.0 ± 0.50	6.0 ± 0.24*	5.3 ± 0.1
Baseline glucose (mmol/L)			
IVGTT	5.2 ± 0.38	4.5 ± 0.21	4.2 ± 0.09
IVTTT	4.9 ± 0.42	4.2 ± 0.23	4.5 ± 0.13
Baseline insulin (pmol/L)			
IVGTT	44.9 ± 5.5	67.7 ± 13.6	48.5 ± 4.3
IVTTT	33.2 ± 8.4	44.5 ± 5.5	49.7 ± 11.9

*Significantly different from CON group, $P \leq .05$.

Abbreviations: %IBW, % of expected ideal body weight for height; PF, pulmonary function, forced expiratory flow between 25% and 75% of expired vital capacity; NM, not measured.

Glucose Tolerance Tests

Each glucose tolerance test took place on separate days at the Alberta Children's Hospital after a 12-hour overnight fast and a high-carbohydrate intake 3 days (>50% of daily caloric intake provided by carbohydrate) before the test. During the studies, subjects were resting and an IV catheter was inserted into the forearm for blood sampling.

OGTT. OGTTs were performed according to National Diabetes Data Group criteria,[16] as described previously.[2] Subjects ingested an oral glucose load of 1.75 g/kg (maximal dose, 100 g; Glucodex, Rougier Laboratories, Chambly, Quebec, Canada), and blood samples were drawn at 0, 30, 60, 120, and 180 minutes after glucose administration for measurement of serum glucose concentration.

Of the 50 CF patients who underwent an OGTT, six had impaired glucose tolerance, ie, a serum glucose value of at least 7.8 mmol/L 120 minutes after an oral glucose load. Five of these patients (group I) then completed an IVGTT and an IV tolbutamide test (IVTTT) together with five CF patients with a nonimpaired OGTT, ie, a 120-minute OGTT serum glucose not exceeding 7.8 mmol/L (group II), and five healthy control (CON) subjects.

IVGTT. Following collection of a fasting blood sample, subjects received an infusion of 0.5 g/kg dextrose (Abbojet, maximum dose 25 g, Abbott Laboratories, Montreal, Quebec, Canada) over a 3-minute period. Serial blood samples were drawn at 2, 4, 10, 20, and 40 minutes after dextrose administration for measurement of serum glucose, insulin, and C-peptide and plasma glucagon concentrations.

IVTTT. Subjects underwent an IVTTT within 6 months of completing an IVGTT. The procedure for the IVTTT was identical to that for the IVGTT, with each subject receiving an infusion of 0.5 g/kg dextrose (maximum dose, 25 g together with sodium tolbutamide 25 mg/kg (Rastinon, maximum dose 1 g, Hoechst, Frankfurt, Germany) over 3 minutes. Blood samples were drawn and glucose and hormone levels measured in the same way as during the IVGTT.

Analytical Methods

Serum glucose concentrations were determined by the glucose oxidase method using a Kodak Ektachem Autoanalyzer (Eastman Kodak, Rochester, NY). Insulin and C-peptide concentrations were measured by the standard double-antibody radioimmunoassay (RIA) technique (Intermedico, DPC, Los Angeles, CA) using serum separated from whole blood at room temperature and kept frozen at −20°C until assay.[17] Blood samples for glucagon determination were anticoagulated with EDTA, and aprotinin was added to minimize enzymatic degradation (500 KIE U/mL) before separation at 4°C and storage at −20°C until the double-antibody RIA.[18] Intraassay and interassay coefficients of variation for hormone RIAs were as follows: insulin, 7.2% and 7.3%; C-peptide, 3.4% and 6.8%; and glucagon, 9.3% and 8.1%. Hemoglobin A_1 (HbA_1) levels were determined using an affinity chromatography Glyc-Affin GHb Kit (Iso Lab, Akron, OH). Normal reference values in our laboratory were 4% to 8%).

Other Measurements

Weight (in kilograms) and height (in centimeters) were measured and expressed as a percentage of ideal body weight (expected weight for height) using height-for-age tables for children and adults.[19,20] Pulmonary function was measured by spirometry, and the results were expressed as a percentage of the predicted value for age. Exocrine pancreatic function was assessed in CF patients and CON subjects by measuring the serum immunoreactive trypsin (IRT)[21] level using a double-antibody RIA kit (ICN Biomedicals, Quebec City, Quebec, Canada). The normal range for serum IRT in our laboratory was 16.7 to 39.1 μg/L (standard limits, mean ± 2 SD from control data).[21,22] Fecal fat excretion was quantified from a 3-day stool collection and expressed as the percentage of fat intake while off enzymes. Fecal fat was measured by the method of Maission and McNeely.[23]

Statistics

Data are expressed as the mean ± SEM unless otherwise stated. Statistical differences were calculated using ANOVA and Student's *t* test for paired data ($P \leq .05$ were considered significant). The incremental integrated areas under the glucose and hormone curves (AUCs) were determined by the trapezoidal rule. The glucose disappearance rate (*k* value) from the blood was calculated from the IVGTT and IVTTT using the method of Amatuzio et al.[22] The first-phase insulin and C-peptide response to IV glucose or IV glucose and tolbutamide was analyzed as the change between the 2- and 4-minute stimulated values.

RESULTS

Subject Characteristics

Subject age, gender, percentage ideal body weight, pulmonary function, serum IRT and HbA_1, and baseline IVGTT and IVTTT serum glucose and insulin levels are shown in Table 1. There was no significant difference in age between the two CF groups and the CON group, although the age range was broader in group I (14 to 39 years). There were no significant differences between groups for the percentage of expected ideal body weight for height. Although pulmonary function (forced expiratory flow between 25% and 75% of expired vital capacity as a % of expected values) was only 29% in group I, there was no significant difference between groups I and II (pulmonary function was not measured in the CON subjects). Serum IRT, a measure of pancreatic exocrine function, was significantly lower in group I as compared with CON subjects ($P < .005$), and serum IRT concentrations in groups I and II were below the normal range. All CF patients who underwent the IVGTT and IVTTT had steatorrhea and therefore were

taking pancreatic enzyme replacement capsules with meals. There was no significant difference in HbA_1 levels between groups I and II, but HbA_1 was significantly higher in group II as compared with CON subjects ($P < .05$). Fasting serum glucose levels before the IVGTT and IVTTT were within the normal range in CF and CON subjects, with no significant differences between groups (Table 1). Fasting insulin, C-peptide, and glucagon in groups I and II were not significantly different from CON values. There was no significant difference in the fasting insulin to glucose ratio between groups. Likewise, C-peptide and glucagon baseline levels were not significantly different between groups.

OGTT

The mean AUC for serum glucose in group I (CF patients with impaired glucose tolerance) was significantly greater than in group II (CF patients with a nonimpaired OGTT) and CON subjects ($P < .005$). There was no significant difference between AUC values for group II and CON subjects. The insulin AUC was significantly greater in the CON group versus groups I and II and significantly greater in group II as compared with group I ($P < .05$).

IVGTT and IVTTT

Glucose. Changes in serum glucose during the IVGTT and IVTTT are shown in Fig 1. There were no significant differences between glucose concentrations with either IVGTT or IVTTT at any time point in groups I or II. The glucose level was significantly reduced at 40 minutes ($P \leq .05$) after the IVTTT in the CON group as compared with the IVGTT values. There were no significant differences in the total mean AUC for glucose and the glucose disappearance rate from plasma between the IVGTT and IVTTT in any of the three groups (Table 2).

Insulin. When tolbutamide was administered with glucose (IVTTT), serum insulin increased significantly in group II and CON subjects as compared with glucose alone (IVGTT); Fig 2). In those patients with an impaired OGTT (group I), serum insulin levels, although modestly increased in all patients, were not significantly greater with tolbutamide administration at any time point as compared with IVGTT values. The serum insulin concentration was significantly greater at 10 minutes after glucose and tolbutamide loading (IVTTT) in group II and CON subjects ($P < .05$) as compared with IVGTT values. Tolbutamide administration significantly increased the AUC for insulin in group II and CON subjects ($P < .05$; Table 2). For group I, the insulin AUC was 28% greater upon tolbutamide stimulation, as compared with 67% and 135% in group II and the CON group, respectively. The AUC for insulin in group I during the IVTTT was 23% of the value for the CON subjects, and during tolbutamide administration, it was 55% of the measurement for CON subjects administered glucose alone (IVGTT).

The first-phase insulin response to IV glucose in group I was severely impaired, whereas in group II it was between CON and group I levels. The first-phase insulin response to IV glucose plus tolbutamide was absent, whereas in group II it was between control and group I levels (Fig 2). The

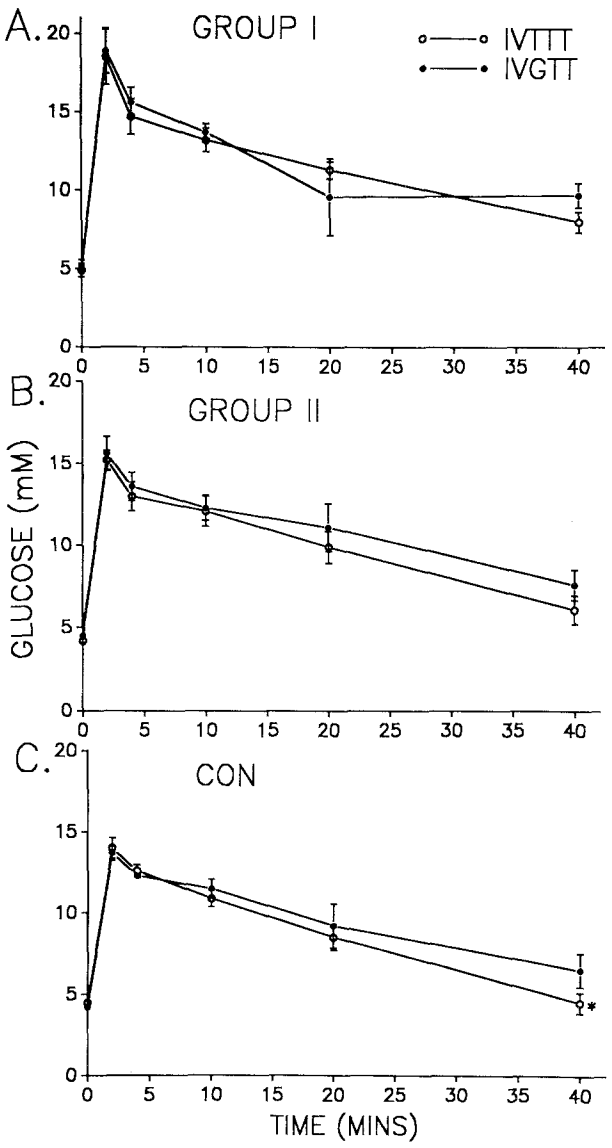

Fig 1. Changes in serum glucose in (A) CF group I with an impaired OGTT (n = 5), (B) CF group II without an impaired OGTT (n = 5), and (C) CON group (n = 5) in response to an IV glucose load alone or glucose loaded simultaneously with tolbutamide at time zero. Data are expressed as the mean ± SEM. *$P \leq .05$.

plasma insulin response to IV glucose at 2 minutes was approximately two, five, and eight times baseline levels for CF groups I and II and CON subjects, respectively.

C-peptide and glucagon. Basal C-peptide levels in the two CF groups were not significantly different from CON levels. The first-phase C-peptide response to IV glucose (IVGTT) mirrors the insulin response for the CF groups and CON subjects. Likewise, the first-phase C-peptide response to IVTTT was absent in group I and severely impaired in group II as compared with CON subjects.

The AUC for C-peptide was significantly increased in group II ($P < .005$) and CON subjects ($P < .01$; Table 2). The AUC for C-peptide in group I during the IVTTT was 47% of the value for CON subjects. There were no

Table 2. Mean ± SEM AUC for Serum Glucose, Insulin, and C-peptide and Plasma Glucagon in IVGTT and IVTTT

	Group I (n = 5)	Group II (n = 5)	CON (n = 5)
Glucose (mmol/min/L)			
IVGTT	498.9 ± 43.4	500.6 ± 51.9	456.3 ± 38.1
IVTTT	522.6 ± 25.2 (↑ 5%)	470.1 ± 39.8 (↓ 6%)	439.7 ± 25.0 (↓ 4%)
Serum glucose disappearance rate (*k* value)			
IVGTT	3.0 ± 0.04	2.9 ± 0.26	3.2 ± 0.41
IVTTT	3.1 ± 0.09	3.2 ± 0.27	3.6 ± 0.30
Insulin (pmol/min/L)			
IVGTT	3,192.0 ± 672	6,084 ± 1,698	7,440 ± 1,734
IVTTT	4,098.0 ± 1,008 (↑ 28%)	10,152 ± 2,100* (↑ 67%)	17,502 ± 3,960* (↑ 135%)
C-peptide (nmol/min/L)			
IVGTT	25.5 ± 4.45	35.9 ± 7.19	41.0 ± 6.9
IVTTT	30.8 ± 4.43 (↑ 21%)	53.7 ± 8.3* (↑ 49%)	64.9 ± 5.9* (↑ 58%)

*Significantly different from IVGTT, $P \leq .05$.

significant differences in plasma glucagon levels at any time point during the IVTTT as compared with the IVGTT in group I, group II, or the CON group, and the glucagon AUC was not significantly altered with tolbutamide administration in any group.

DISCUSSION

Of the 50 CF patients who underwent an OGTT, six (12%) had a 120-minute serum glucose concentration of at least 7.8 mmol/L, which is defined as an impaired response by the National Diabetes Data Group[16] (group I). None of these individuals were overtly diabetic. Five of these patients completed an IVGTT and IVTTT, together with five healthy CON subjects and five CF patients with a nonimpaired OGTT (group II). There were no significant differences in mean age, percent ideal body weight, HBA_1, or pulmonary function between the two CF groups. Baseline levels of glucose, insulin, C-peptide, and glucagon in those subjects with CF did not differ from CON values. Our studies were designed to allow direct comparison of serum glucose and hormone levels in response to a glucose load with and without the addition of tolbutamide. Tolbutamide is a hypoglycemic sulfonylurea, a class of drugs routinely used in the treatment of non–insulin-dependent diabetes mellitus. At the pancreatic β-cell level, sulfonylureas are thought to initiate their effect by interacting with high-affinity receptors on the cell membrane.[24] Potassium ion (K^+) conductance through adenosine triphosphate–sensitive K^+ channels is thus reduced, causing depolarization and producing an increase in conductance of voltage-dependent calcium ion (Ca^{2+}) channels and hence stimulating insulin secretion. Residual β-cell function has been considered by some as a prerequisite for a beneficial effect of sulfonylurea.[25] Others have stated that sulfonylurea may decrease blood glucose by mechanisms other than stimulation of insulin secretion.[26]

The glucose disappearance rate and AUC for serum glucose during the IVGTT were similar in groups I and II despite marked differences in insulin responses. IV glucose disposal in CF patients with impaired oral glucose tolerance was therefore as effective as in the group II CF patients with a more normal insulin response, as previously demonstrated by Geffner et al,[14] using tolbutamide administration without glucose. This suggests an enhanced peripheral tissue insulin sensitivity[8,11] or a surplus of insulin in

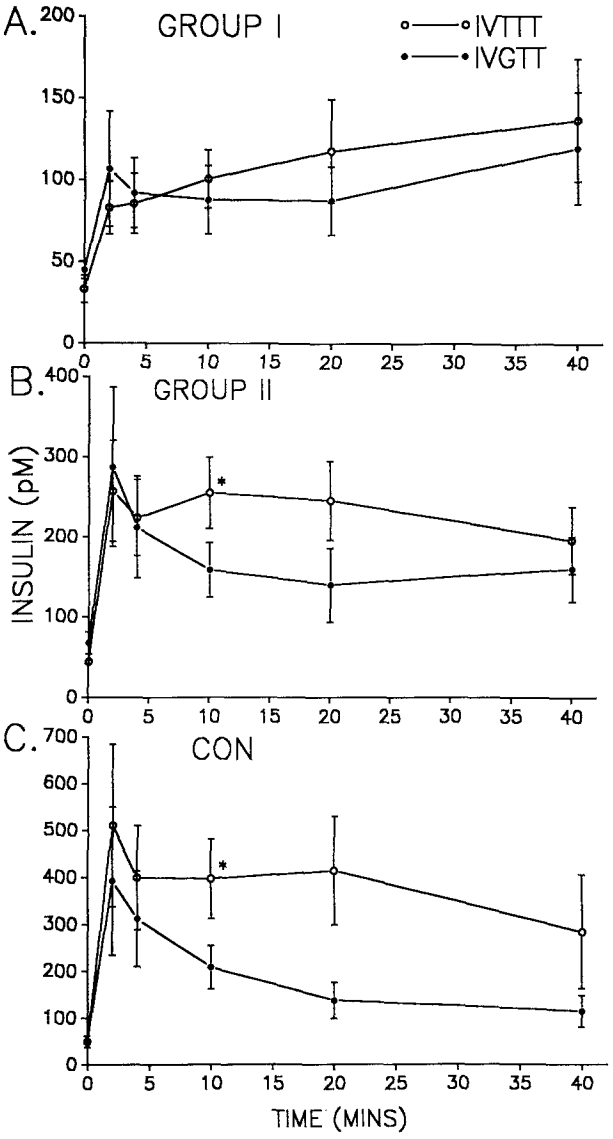

Fig 2. Changes in serum insulin in (A) CF group I with an impaired OGTT (n = 5), (B) CF group II without an impaired OGTT (n = 5), and (C) CON group (n = 5) in response to an IV glucose load alone or glucose loaded simultaneously with tolbutamide at time zero. Data are expressed as the mean ± SEM. *$P \leq .05$.

group II and CON subjects. In a recent study by Cucinotta et al,[27] no difference was found in insulin sensitivity between CF and weight-matched CON subjects using the euglycemic clamp technique, although the CF patients who participated had normal glucose tolerance. Upon tolbutamide administration, the AUC for insulin was increased by 28% in group I as compared with IVGTT values, suggesting limited residual insulin secretory capacity, whereas the insulin AUC was augmented by 67% with tolbutamide in group II as compared with glucose alone, suggesting greater insulin reserve. Simultaneous measurement of insulin and C-peptide concentrations showed lower levels in CF patients in comparison to CON subjects. This result indicates β-cell hypofunction rather than increased liver degradation of insulin and is in agreement with the data of Mohan et al.[12] Despite an increased insulin output, glucose disposal was largely unaffected in any of the three groups. Although the cellular mechanism through which sulfonylureas potentiate insulin action remains to be elucidated, it has been reported to increase insulin receptor binding in vivo.[28] Insulin secretion appears to be adequate to control glucose metabolism under normal circumstances, so that an increase via tolbutamide stimulation on one occasion is possibly not sufficient to upregulate insulin receptor binding and hence alter glucose clearance.

The IVGTT results were also consistent with previously described impaired early or first-phase insulin and C-peptide responses to IV glucose.[11,15] The first-phase response to IV glucose or other agonist, which occurs 2 to 5 minutes after stimulation, is considered a sensitive index of β-cell function.[29,30] The absence of a first-phase response to IV glucose plus tolbutamide in group I and the very limited response in group II suggest a general impairment of β-cell function that is graded in severity. The blunted first-phase response to glucose and tolbutamide argues for a reduction in islet cell numbers rather than an insensitivity to glucose; a decreased β-cell number[31] may be coupled with a reduced blood supply to islet cells due to fibrosis.[32] There is also a possibility that specific mutations in the CF gene could account for pancreatic endocrine abnormalities, as has already been demonstrated with pancreatic exocrine function.[33,34] The AUCs for insulin and C-peptide likewise suggest that β-cell function in the CF patient is a continuum. Tolbutamide is capable of marginally increasing insulin and C-peptide secretion in CF patients with an impaired response to oral glucose. In those without impaired glucose tolerance, tolbutamide stimulated insulin and C-peptide levels between group I and CON subjects. For those with impaired glucose tolerance, the increase in the release of insulin with tolbutamide, although only 28% above that with glucose alone, may be clinically significant. Zipf et al[35] administered tolbutamide orally to children with CF for the purpose of improving linear growth and most specifically glucose homeostasis. In their study, tolbutamide decreased blood glucose during a meal stimulation test, but had no effect on the insulin concentration during the meal stimulation or 24-hour insulin secretion before or after 4 months of tolbutamide therapy. Future studies will need to address the efficacy of long-term sulfonylurea therapy in those CF patients with impaired glucose tolerance.

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