Published in final edited form as:

Pediatr Diabetes. 2013 September ; 14(6): 417–421. doi:10.1111/pedi.12026.

Insulin Secretion Improves in Cystic Fibrosis Following Ivacaftor Correction of CFTR: A Small Pilot Study

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Abstract

Objective—To determine whether the cystic fibrosis transmembrane conductance regulator (CFTR) is involved in human insulin secretion by assessing the metabolic impact of the new CFTR corrector, ivacaftor.

Methods—This open-label pilot study was conducted in CF patients with the G551D mutation given new prescriptions for ivacaftor. At baseline and 4 weeks after daily ivacaftor therapy, intravenous (IVGTT) and oral glucose (OGTT) tolerance tests were performed.

Results—Five patients age 6–52 were studied. After 1 month on ivacaftor, the insulin response to oral glucose improved by 66–178% in all subjects except one with long-standing diabetes. OGTT glucose levels were not lower in the two individuals with diabetes or the two with normal glucose tolerance (NGT), but the glucose tolerance category in the subject with impaired glucose tolerance (IGT) improved to NGT after treatment. In response to intravenous glucose, the only patient whose acute insulin secretion did not improve had newly diagnosed, untreated CFRD. The others improved by 51–346%. Acute insulin secretion was partially restored in two subjects with no measurable acute insulin response at baseline, including the one with IGT and the one with long-standing diabetes.

Conclusions—This small pilot study suggests there is a direct role of CFTR in human insulin secretion. Larger, long-term longitudinal studies are necessary to determine whether early initiation of CFTR correction, particularly in young children with CF who have not yet lost considerable beta-cell mass, will delay or prevent development of diabetes in this high risk population.

Cystic fibrosis related diabetes (CFRD) is characterized by progressive insulin insufficiency. It is extraordinarily prevalent in the cystic fibrosis (CF) population, occurring in 15–20% of adolescents and, eventually, more than half of adults (1). Few of the remaining patients have completely normal glucose metabolism; even those with normal fasting and 2-hour oral glucose tolerance test (OGTT) glucose levels typically have mid-OGTT glucose elevation and have defective acute insulin secretion in response to intravenous glucose (2). While CFRD does not usually develop before puberty, it has its roots in childhood and glucose intolerance is common in 6–9 year old children with CF (3). It has not been studied in younger children, but ferret models of CF demonstrate insulin secretory abnormalities in the newborn period (4), suggesting that there may be an intrinsic defect in beta-cell function in CF.

CF is caused by abnormalities in the CF transmembrane conductance regulator (CFTR), an ATP-binding cassette transporter-class ion channel involved in chloride, sodium and water transport and absorption across cell membranes. CFTR defects lead to thick, viscous secretions with well-known chronic complications including obstructive lung disease associated with infection and inflammation, sinusitis, intestinal obstruction, liver disease and infertility. Pancreatic exocrine insufficiency develops as plugged ductules prevent digestive enzymes from reaching the gut; autodigestion of the pancreas by these trapped enzymes leads to fibrosis. It has long been debated whether insulin insufficiency in CF is merely a physical, “by-stander” consequence of this fibrotic destruction of the pancreatic architecture, or if CFTR defects per se impact insulin secretion (5). CFTR is expressed in human and mouse pancreatic alpha- and beta-cells (6; 7), but it is not known whether it is involved in hormone secretion. There has previously been no way to directly test this in a human model.

Ivacaftor (VX-770, Kalydeco™, Vertex Pharmaceuticals, Cambridge, MA) is the first of a group of “potentiator” molecules being developed to correct the CFTR defect. CFTR is made in the endoplasmic reticulum, processed in the Golgi apparatus, and secreted in vesicles which chaperone proteins carry to the cell membrane, where it must be inserted and then must function normally. Defects leading to CF may occur at any of these steps. In patients with the G551D mutation (about 4% of the CF population), CFTR is found in the cell membrane but is dysfunctional. Ivacaftor corrects this defect by restoring channel gating, through an as-yet unidentified mechanism (8). In clinical Phase 2 and 3 trials, ivacaftor produced dramatic improvements in skin sweat chloride levels and in lung function within just 3 weeks (9; 10), and the drug has recently been approved by the FDA in children down to age 6. The initiation of ivacaftor therapy offers a unique opportunity to test the role of CFTR in human insulin secretion, potentially opening the way for novel diabetes therapies and for prevention or at least amelioration of diabetes in CF.

Methods

Patients

This open-label pilot study was conducted in CF patients given new prescriptions for ivacaftor. Inclusion criteria were those required for clinical drug prescription: diagnosis of CF by standard sweat chloride testing, positive for at least one allele of the mutation G551D, and age 6 years or greater. The only exclusion criterion was current treatment with ivacaftor, as this study involved before and after assessment. Patients provided IRB-approved informed consent/assent.

Studies

A few days prior to drug initiation, a baseline intravenous glucose tolerance test (IVGTT) was performed on Day 1 and an OGTT on Day 2, and these were repeated in the same order 4 weeks later after daily oral treatment with ivacaftor. Subjects fasted for at least 8 hours before each test. For the 4 week assessment, the dose of ivacaftor was held until just after each test. The one subject with established diabetes was on an insulin pump; she continued to receive her usual basal insulin during testing but had no boluses for at least 8 hours prior to the tests.

For the IVGTT, an intravenous line was placed and used to rapidly push 0.5 grams/kg glucose (25% dextrose, 35 gram maximum) with time 0 being the end of the infusion. Insulin levels were measured at -10, -4, +1, +3, +5, +7 and +10 minutes. For the OGTT, 1.75 grams/kg (75g maximum) dextrose was given orally over 5 minutes, with time 0 being the beginning of beverage consumption. Glucose and insulin levels were measured at 0, 30, 60, 90 and 120 minutes.

Glucose and insulin measurements were performed at the Fairview University of Minnesota Laboratory. Insulin levels were measured by chemiluminescent immunoassay and glucose levels by glucose oxidase assay. Insulin secretion is presented as the area under the curve (AUC) during the 10 minute IVGTT and the 120 minute OGTT.

Data Analysis

Limited statistical analysis was performed using SAS 9.2 (Cary, NC, USA) to evaluate for trends in change from baseline in this small preliminary data set. Change in insulin secretion from pre to post-treatment were compared using paired student t-tests.

Results

Patients

Only 7 eligible patients had not yet been started on ivacaftor therapy at the time of this study; 5 agreed to participate (Table). Patient 1 was a 52 year old woman with a 16 year history of well-controlled CFRD, treated by insulin pump. Patient 2 was a 14 yr old boy not previously known to have diabetes who was diagnosed with early diabetes (CFRD without fasting hyperglycemia) during the screening OGTT for this study. He was not treated with insulin until after the one month study was completed. The remaining three patients included a 40 year old man with normal glucose tolerance (NGT), a 6 year old girl with NGT, and a 35 year old man with impaired glucose tolerance (IGT).

Oral Glucose Tolerance Testing

After 1 month of ivacaftor therapy, the insulin response to oral glucose improved by 66–178% in all subjects except the one with long standing diabetes ($p=0.07$) (Figure 1A). Glucose levels during the OGTT were not lower in the two individuals with diabetes or the two with NGT, but the glucose tolerance category in the subject with IGT at baseline improved to NGT after ivacaftor treatment, since his 2-hour OGTT glucose level dropped from 148 to 90 mg/dl (8.2 to 5.0 mmol/L). This patient also had the greatest improvement in insulin secretion in response to both oral and intravenous glucose stimulation. Insulin secretion in response to oral glucose increased from 1485 to 2955 mU/L*min (99%) in the 14 year old (patient 2), and 2235 to 5775 mU/L*min (158%) in the 6 year old (patient 4).

Intravenous Glucose Tolerance Testing

In response to intravenous glucose, the only patient who did not have improved acute insulin secretion with ivacaftor therapy was the 14 year old with newly diagnosed, untreated CFRD (Figure 1B). The others had a 51–346% improvement ($p=0.19$). Notably, acute insulin secretion was partially restored in two subjects who had no measurable acute insulin response at baseline, including the one with IGT and the one with long-standing diabetes.

Other Changes Associated with Ivacaftor

No changes in medical care other than the initiation of ivacaftor occurred during the study period. BMI increased an average of 0.5 kg/m² in the study participants, with individual increases of 0.3, 0.0, 0.8, 0.6 and 0.6 kg/m² in patients #1–5, respectively. There was a significant and positive correlation between the magnitude of change in the response to intravenous glucose and magnitude of change in BMI ($R^2=0.08$, $p=0.04$). There was no correlation between the change in BMI and the OGTT insulin response. PFT and sweat chloride values before and after are not available since these patients are being followed as part of a blinded study.

Conclusions

This pilot study shows proof-of-principal that correction of CFTR activity improves insulin secretion in persons with CF. Acute insulin secretion in response to intravenous glucose improved by 51–346% in all patients except one (who had untreated new-onset diabetes), including partial restoration in two subjects who previously had no measurable acute insulin response. The insulin response to oral glucose improved by 66–178% in everyone except the patient with established diabetes.

CFTR is expressed in human and mouse pancreatic alpha- and beta-cells, and CFTR conductance has been measured in mouse beta-cells (6; 7). Its role, if any, in hormone secretion is unknown. CFTR-knockout mice are more susceptible to streptozotocin-induced beta-cell damage than controls, implying an underlying role for CFTR in cell function (11). CFTR is involved in exocytosis, suggesting a mechanism by which it might play a role in insulin secretion (7). It may also influence secretion through alteration of membrane potentials, since, like the sulfonylurea receptor (SUR), CFTR is a member of the ATP-binding cassette transporter family of genes. The clinical significance of this relation with respect to insulin secretion is not clear, however. Sulfonylureas interact with CFTR on cell membranes to block the open state (keep the channels closed) (12); similarly, the effect of sulfonylureas on the beta cell is also to block (close) ATP-sensitive channels. In the case of CFTR, however, channel closure results in decreased function (decreased) chloride conductance, while in the case of the beta cell, channel closure leads to increased insulin secretion.

The three subjects with NGT or IGT all improved insulin secretion in response to both oral and intravenous glucose. Interestingly, the patient with long-standing well-treated diabetes improved her response to intravenous but not oral glucose, while the opposite was true in the adolescent with untreated new-onset diabetes. Acute insulin secretion is a marker of beta-cell health, representing secretion from a stored pool of readily-releasable insulin. The ability of the beta-cell to store insulin may be somewhat of a luxury—in patients with reduced beta-cell mass and chronic hyperglycemia, what insulin is present may need to be continually secreted. Thus, the restoration of the acute insulin response in two subjects including the one with long-standing well-treated diabetes is remarkable. The fact that this latter patient did not improve her response to oral glucose is perhaps not surprising, since the OGTT requires sustained first and second phase insulin secretion over a 2 hour period. In contrast, the patient with new, untreated, mild CFRD was not able to improve acute insulin secretion but ivacaftor increased the insulin response to oral glucose; this ability of the beta-cell to “rally” over the course of the two hour OGTT likely reflects better residual beta cell mass early in the course of diabetes in CF.

We postulate that CFTR plays a small but important role in insulin secretion. In childhood, CF patients are able to compensate for this defect because their beta-cell mass is largely intact. As islets are lost over time due to exocrine fibrosis and as chronic, unrelenting beta-cell stress occurs due to inflammation, oxidative stress and recurrent infection, the impact of CFTR on insulin secretion becomes more critical. Thus, childhood may be the ideal time to intervene, with the hope of establishing a healthy “bank” of fully functional beta cells which are better able to withstand the metabolic stresses of CF that escalate over time. Insulin secretion in the 6 year old child in this series improved by 158% and 67% in response to oral and intravenous stimulation, respectively. Longitudinal assessment of a greater number of young children with CF is necessary to determine whether early correction of CFTR could delay or even prevent diabetes in individuals with CF.

While CFTR has primarily been studied in the context of the “classic” CF phenotype, a role for this protein has also been documented in other conditions such as recurrent idiopathic pancreatitis, congenital bilateral absence of the vas deferens, allergic bronchopulmonary aspergillosis, chronic sinusitis, idiopathic bronchiectasis, and smoking-related lung disease (13). There is currently no reason to suspect deficiency of CFTR in persons with type 2 diabetes; however, documentation of a role for CFTR in insulin secretion may offer a novel treatment strategy for these patients with defective beta cell function.

The primary limitation of this study is the small sample size and the wide age range of subjects. Most patients with this gene mutation were already taking ivacaftor through involvement in the clinical trials. This was a cross-sectional study, and it will be important to assess the impact of this drug on insulin secretion over time. As new drugs designed to correct CFTR function go into trials, it will be important to add measures of pancreatic function before and after drug initiation.

In conclusion, this small pilot study provides the first evidence, in human studies that CFTR plays a direct role in insulin secretion. Drugs that correct CFTR function may improve glucose tolerance in CF. Further study is necessary to confirm this relation. Long-term longitudinal studies will determine whether early initiation of CFTR correction, particularly in young children with CF who still have the presence of considerable beta-cell mass, will delay or prevent development of diabetes in this high risk population.

Acknowledgments

This study was sponsored, in part, by a grant from Pennsylvania CF, Incorporated. There was no industry involvement in or sponsorship of this study. Drs. Dunitz, and Regelman received research support from Vertex Pharmaceuticals for the clinical trials which preceded this study. There were no other relevant conflicts of interest. MB and AM created the project, analyzed the data and wrote the manuscript; JL performed the studies; and TL, WR, JD, and JB contributed to the discussion and edited the manuscript.

Abbreviations

CF	cystic fibrosis
CFRD	cystic fibrosis related diabetes
CFTR	cystic fibrosis transmembrane conductance regulator
IGT	impaired glucose tolerance
IVGTT	intravenous glucose tolerance test
NGT	normal glucose tolerance
OGTT	oral glucose tolerance test

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Figure 1.

(A) Insulin secretion on oral glucose tolerance testing, displayed as the two hour area under the curve; and (B) insulin secretion on intravenous glucose tolerance testing, displayed as the acute insulin response to glucose measured from the area under the curve over 10 minutes following a dextrose bolus for 5 patients treated with ivacaftor. Open bars indicate pre-treatment values; checked bars indicate results while on ivacaftor.

Table**Patient Characteristics at Baseline.**

Patient Number	Gender	Age	Glucose Tolerance Status
1	F	52	CFRD with FH *
2	M	14	CFRD without FH **
3	M	40	NGT
4	F	6	NGT
5	M	35	IGT

* 16 year history of diabetes, treated by insulin pump

** newly diagnosed during study screening, no insulin treatment during study

CFRD=cystic fibrosis related diabetes. FH=fasting hyperglycemia. NGT=normal glucose tolerance. IGT=impaired glucose tolerance.