

Cystic fibrosis-related diabetes: links, challenges, and future directions

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Abstract: Cystic fibrosis-related diabetes (CFRD) is a common comorbidity in cystic fibrosis (CF) and portends worse clinical outcomes including lower lung function and nutritional status, and decreased survival. CFRD is distinct from other forms of diabetes, but relative insulin deficiency is a predominant feature. The catabolic effects of insulin deficiency coupled with the pro-inflammatory effects of hyperglycemia likely affect clinical outcomes. Posited mechanisms of CFRD development include collateral damage from pancreatic exocrine destruction, inherent β -cell defect, CFTR dysfunction, and incretin deficiency or unresponsiveness. Even though CF clinical care teams are increasingly aware of its implications, CFRD screening and management remain a challenge. Promising clinical and basic research in the fields of diabetes and CF and the advent of novel therapeutics targeting the protein defect in CF have potential to change CFRD care. This review presents newer data on insulin defects and glucose derangements and highlights continuing challenges and unanswered questions.

Keywords: cystic fibrosis, insulin, glucose intolerance

Background

With medical advances in the field of cystic fibrosis (CF), individuals with CF are now surviving into adulthood. This improved survival is accompanied by an increasing prevalence of non-pulmonary comorbidities that have the potential to threaten pulmonary health. Affecting 40%–50% of adults age >30 years, cystic fibrosis-related diabetes (CFRD) is particularly problematic.¹ It is associated with worse pulmonary function, greater nutritional decline, and increased mortality.² The relationship between CFRD and adverse clinical outcomes highlights the importance of an improved understanding of insulin deficiency and hyperglycemia in CF, with the ultimate goals of either slowing the progression or altogether preventing diabetes development and mitigating the negative effects in the setting of established diabetes. CF caregivers now recognize the importance of CFRD and great strides have been made in developing an understanding of the disease but many questions with respect to pathophysiology, screening including frequency and timing, and even nature of intervention remain unanswered.

Clinical significance

Since the 1980s, the CF community has recognized that diabetes portends worse survival in CF.³ Only 25% of individuals with CFRD survived to age 30 years compared to the 60% without CFRD.³ What remained unresolved, however, was the extent to which diabetes directly contributed to premature death versus (vs) represented a surrogate for worse CF disease. Indeed, *CFTR* mutation severity impacts not only the risk of

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diabetes development but mortality as well.⁴ Subsequently, early identification and treatment with insulin were associated with improved survival in CFRD.² Despite this improvement, mortality remains over three times higher in patients with CFRD than in individuals without CFRD (1.8 vs 0.5 per 100 person-years).⁴ Moreover, although CFRD prevalence is higher at every age in females than in males, CFRD has been associated with worse survival to a greater degree in males than females.⁴ The mechanism underlying this sex difference is unknown. Recent work identifying greater lean body mass deficits in males than females with CF may represent one avenue by which CFRD differentially affects CF outcomes.⁵

CFRD is identified as a preventable cause of the decline in forced expiratory volume in 1 second (FEV_1), a marker of pulmonary function.⁶ Lower percent predicted FEV_1 ($FEV_1\%$ -predicted) is seen in all age groups with CFRD.⁷ The rate of decline in FEV_1 is higher in CFRD compared to CF patients with normal glucose tolerance (NGT),⁸ can begin several years before CFRD is diagnosed,^{3,9} and is correlated with degree of insulin deficiency.⁸ Time to next exacerbation is a health outcome often used in clinical trials in CF, and CFRD is associated with shortened duration between CF exacerbations, although older age may be an important confounder in this relationship.¹⁰ Not surprisingly, CFRD is also associated with earlier age at lung transplantation.¹¹ Post-transplant diabetes is common in CF, but the impact of pre-transplant CFRD upon graft survival is not well defined.¹² The mechanisms linking CFRD with inflammation and pulmonary decline have yet to be resolved. In vitro studies identifying increased growth of *Staphylococcus aureus* and *Pseudomonas aeruginosa* with increasing airway surface liquid glucose concentration^{13,14} support a direct role for hyperglycemia promoting pathogens. However, sputum glucose values are not elevated in CFRD patients.¹⁵ This lower glucose may represent increased substrate uptake by a higher concentration of airway bacteria; alternatively, mechanisms other than the pro-infectious nature of chronic hyperglycemia may be operative. Treatment of CFRD at least partially reverses the pulmonary decline experienced by CF patients,^{16–18} but the direct pulmonary effects of insulin treatment vs lower glucose have yet to be resolved.

Since insulin is an anabolic hormone, insulin deficiency in CFRD can worsen nutritional status. Lower body mass index (BMI) has been observed in CFRD.⁷ CFRD at a young age reveals trends in shorter adult height;^{19,20} target adult height is not achieved despite treatment with insulin.²⁰ Lower BMI can be observed before the CFRD diagnosis is

made,^{16,21} but early insulin treatment has not consistently been associated with improved nutritional status in the setting of pre-diabetes.^{22–24} The inconsistent findings may be related to suboptimal insulin dosing and are likely hampered by the injections required for insulin administration.

Aggressive diabetes treatment in the non-CF population is routed in preventing microvascular (and macrovascular) complications, but the shortened life expectancy in CF previously obviated these concerns. These complications, however, are a reality in CF especially in the presence of fasting hyperglycemia (FH).²⁵ In individuals with CFRD with $FH \geq 10$ years, 14% had microalbuminuria and 16% retinopathy. In a separate study in which presence of FH was not clearly defined, subjects with CFRD were more likely than subjects with type 1 diabetes mellitus (T1DM) to have microalbuminuria, whereas retinopathy was less common.²⁶ People with CF already have multiple risk factors for renal dysfunction, including chronic inflammation and frequent usage of nephrotoxic drugs, and CFRD can compound this risk. Individuals with CFRD for 1–4 years vs CF individuals without CFRD were greater than two times more likely to have chronic kidney disease (hazard ratio 2.40, 95% confidence interval 1.74–3.32), and those who had disease >5 years were more than five times more likely to have chronic kidney disease (hazard ratio 4.56, 95% confidence interval 2.84–7.31).²⁷ The impact of aggressive CFRD treatment upon these outcomes has yet to be elucidated.

Pathophysiology

The American Diabetes Association classifies diabetes based on etiology, with CFRD categorized under “other form of diabetes” or pancreatogenic diabetes.²⁸ The primary defect in CF is that of insulin deficiency. The prevailing hypothesis for insulin deficiency in CF is that exocrine pancreatic damage incurred from viscous secretions spills over to damage the endocrine pancreas. As such, islet function is affected globally and not limited to β -cells.^{29–31} In support of this hypothesis, CFRD occurs more commonly in the presence of the severe CF mutations associated with pancreatic exocrine insufficiency.³² However, while autopsy studies of CF pancreas do reveal loss of β -cell mass, the extent of β -cell mass loss does not completely agree with presence or absence of diabetes – suggesting additional mechanisms are at play.

This insulin deficiency largely manifests as post-prandial hyperglycemia due to delayed early insulin secretion,³³ but basal insulin secretion is largely preserved until late in the course of CFRD. In non-diabetic CF individuals, despite NGT, β -cell secretory capacity is reduced.³⁴ In response to oral or intravenous glucose challenge, CF individuals with

NGT have delayed and blunted insulin secretion compared to controls,³⁵ and further differences can be elicited in these individuals based on pancreatic insufficiency status; whereas NGT-CF individuals who are pancreatic sufficient show normal insulin secretion, it is delayed and blunted in those who are pancreatic insufficient.³⁶ As glucose tolerance worsens, time to peak insulin increases and peak values decrease.^{36,37} During intravenous glucose tolerance testing and hyperglycemic clamp, acute insulin responses in subjects with CFRD were found to be dampened compared to controls.³⁸ Serial oral glucose tolerance tests (OGTTs) performed on CF individuals demonstrate that over time insulinopenia and glucose intolerance worsens.^{39,40} Incretin hormones are released from neuroendocrine cells in the gut and augment insulin secretion in response to nutrients. Defects in their secretion have been reported in chronic pancreatitis,⁴¹ and may also be operative in pancreatic insufficient CF. Studies of incretins, GIP, and GLP-1, have reported a spectrum of results, from normal basal secretion, to elevation in response to an oral glucose challenge to no change with a glucose challenge.⁴² Dietary constituents, including fatty acids, modulate insulin secretion, and, thus, a mixed meal tolerance test is likely a more physiologic test. Indeed, pancreatic enzyme replacement appears to improve GIP secretion and glucose excursion in individuals with pancreatic insufficient CF.⁴³ The role of incretin-based therapy in CF is the subject of active investigation (principal investigator: Stecenko – <https://clinicaltrials.gov/ct2/show/NCT00967798>; Kelly/Rickels – NCT01879228).

Insulin resistance is not considered a pronounced feature of CF.^{33,44} Studies using oral and intravenous glucose challenges have reported normal insulin sensitivity, which does not worsen over time.^{39,40,45} There is emerging evidence for insulin resistance in CF; a decrease in gluconeogenesis due to insulin signal transduction defect caused by reduction of the transcription factor, FOXO1, was recently discovered by Smerieri et al.⁴⁶ Insulin resistance emerges during periods of stress and is evident in the impaired insulin-mediated suppression of proteolysis in CF.^{47,48} The degree of suppression of proteolysis is linked to the degree of glucose intolerance with worsening glucose tolerance correlating with greater impairments in suppression of proteolysis.⁴⁸ Obesity is now reported in CF patients and may confer an insulin resistant state to confound underlying insulin secretion defects in CF;⁴⁹ the contribution of obesity to CFRD development will be an important consideration.

Amyloid deposition features in both type 2 diabetes mellitus (T2DM) and CF and, while not well understood, may be a marker of endoplasmic reticulum (ER) stress. Normal ER

function is essential for protein folding in all eukaryotic cells; misfolding triggers an adaptive response, failure of which results in β -cell apoptosis. Post-mortem studies in T2DM identify decreased β -cell mass and markers of apoptosis.^{50,51} Excessive insulin demand imposed by insulin resistance, obesity-related inflammation – so called “metainflammation”,⁵² lipotoxicity arising from excess free fatty acids, and hypoxia are all thought to give rise to ER stress that contributes to T2DM. Their role in CF has not been delineated but given that individuals with worse CF lung disease are more likely to have CFRD, it is reasonable to hypothesize that the inflammation of CF lung disease may also contribute directly to β -cell dysfunction and insulin deficiency. Also leading to inflammation and insulin resistance in CF may be the presence of impaired autophagy, a key process in clearing misfolded proteins which is hypothesized to be deficient in CF epithelial cells.⁵³ Autophagy may avert β -cell dysfunction and apoptosis in T2DM, and its loss in murine models of T2DM can lead to insulin resistance and inflammation.⁵⁴

Additional studies find similarities between CFRD and T2DM. Twin studies suggest that the risk of CFRD closely correlates with certain genes associated with T2DM, such as *TCF7L2*.⁵⁵ Genome-wide association studies have identified four more novel genetic modifiers of CFRD: *SLC26A9*, *CDKAL1*, *CDKN2A/B*, and *IGF2BP2*, all of which are known susceptibility alleles for T2DM.⁵⁶ Given the variable development of CFRD in CF patients with DF508 and genes associated with T2DM, epigenetic factors may play a yet unknown role in the pathogenesis of CFRD. Histone modification and DNA methylation causing altered gene expression and impaired insulin secretion in animal studies suggest presence of epigenetic factors in T2DM development.^{57,58} Differential DNA methylation of CpG sites within *TCF7L2* gene loci and its effect on insulin secretion in T2DM,⁵⁹ may be of interest in CFRD as well.

Finally, the direct role of defective CFTR function in CF is not known. Animal models are providing important insights. In rats, CFTR is expressed in pancreatic islet α -cells and to a lesser extent β -cells.⁶⁰ The CF ferret model reveals early dysregulated insulin secretion that appears to pre-date extensive pancreatic exocrine damage.⁶¹ Glucose stimulated insulin secretion is attenuated in CFTR mutant (DF508) mice compared with wild-type mice, and VX-809 a corrector of DF508 mutation helps reverse this dampened response.⁶² The CF pig model similarly reveals glucose and insulin secretion abnormalities in the absence of loss of islet mass.⁶³ Together these data support a direct role of CFTR in pancreatic islet function. Reports of improved glucose status in patients

with at least one of ten rare mutations, who are treated with the CFTR modulator, ivacaftor,^{64,65} are prompting human investigations of the underlying mechanisms.

Screening and diagnosis

Glucose tolerance tests

The onset of glucose abnormalities in CF is insidious and glucose derangements should be suspected with declining clinical status not amenable to direct pulmonary care and improved nutrition. The Cystic Fibrosis Foundation (CFF) and International Society of Pediatric and Adolescent Diabetes have recommended annual screening with an OGTT (1.75 g/kg glucose; maximum dose 75 g) starting by age 10 years.⁶⁶ Glucose tolerance fluctuates over a wide spectrum and can be characterized by an OGTT. Four categories of glucose tolerance are currently defined by the OGTT: NGT, indeterminate, impaired glucose tolerance (IGT) and CFRD, Table 1. CFRD with and without FH may be distinguished to communicate degree of insulin deficiency and microvascular disease risk, but both are treated based upon their negative impact upon nutritional status.⁶⁷ CFF guidelines have adopted the same cutoffs for diagnosis as those used for T2DM. However, glucose thresholds for defining T2DM have been developed largely based on the risk of microvascular complications. In CF, since pulmonary complications prevail, the relevance of lower thresholds for pulmonary, nutritional, and progression to diabetes risk are important considerations.

Variability in OGTT results is also of concern; the coefficient of variation for 2-hour blood glucose was as high as

25.3% in a German study of 1,128 subjects who underwent two OGTTs.⁶⁸ Annual screening in CF patients also identifies large variability over time, and abnormal OGTT results can revert in the subsequent year.^{69,70} Additionally mid-OGTT glucose values at 30, 60, and 90 minutes and the glucose area under the curve for OGTT differ significantly between non-CF controls and CF patients with NGT.⁷¹ Moreover, clinicians frequently observe a discrepancy between OGTT and post-prandial glucose: 2-hour post-prandial glucose may be relatively normal in the context of eating mixed meals, Figure 1. The best approach to address this apparent insulin deficiency is not clear.

The presence of DF508 mutation is probably the most important factor influencing OGTT results.^{72,73} Homozygosity of DF508 is closely linked to abnormalities in glucose tolerance seen on OGTT. While the clinical severity of CF disease assessed using Shwachman-Kulczycki scores did not appear to be linked to this observation,^{72,73} CFRD is associated with worse pulmonary status.⁷⁴ and severe CF mutations may increase pancreatic damage. Factors such as sex and anthropometric features have less of an impact on glucose tolerance.⁷⁵

Particularly problematic, adherence to screening recommendations is generally poor,⁷⁶ and from clinical experience, the OGTT is an unpopular test – it involves fasting and two to three blood draws. Lee et al⁷⁷ tested the non-fasting 1-hour 50 g glucose challenge test in adults and suggested a plasma glucose >140 mg/dL (7.8 mmol/L) could identify individuals at increased risk for glucose abnormalities. A CFF-funded multi-center trial assessing the glucose challenge test is ongoing.

Table 1 Screening and diagnosis of CFRD

OGTT	Annually ≥ 10 years		
	Glucose tolerance category	1-hour PG	2-hour PG
Normal (NGT)	<140 mg/dL	<140 mg/dL	<140 mg/dL
Impaired (IGT)	NA	>140 and <200 mg/dL	>140 and <200 mg/dL
Indeterminate (INDET)	>200 mg/dL	<140 mg/dL	<140 mg/dL
CFRD	NA	>200 mg/dL	>200 mg/dL
HbA_{1c}	≥6.5% for diagnosis <6.5% does not exclude diagnosis		
Fasting and 2-hour post-prandial glucose	During hospitalizations or intercurrent illnesses, systemic glucocorticoid use monthly during and after continuous overnight feeds		
Random glucose	CFRD ≥200 mg/dL + polyuria and polydipsia		

Abbreviations: CFRD, cystic fibrosis-related diabetes; HbA_{1c}, hemoglobin; A_{1c}; IGT, impaired glucose tolerance; INDET, indeterminate glucose tolerance; NA, not applicable; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; PG, plasma glucose.

Continuous glucose monitoring (CGM)

With these limitations of an OGTT, the utility of CGM in CF has been the subject of investigation. CGM, which is validated in diabetic populations,⁷⁸ measures interstitial glucose that is then translated into blood glucose. CGM has identified higher peak glucose levels in NGT CF people than healthy controls.⁷¹ Franzese et al⁷⁹ observed discordance between OGTT and CGM results; the OGTT underestimated the degree of glucose intolerance. Figure 1 highlights the discordance in OGTT and CGM results in an adult CF female. In one study of 22 CF subjects with NGT, a peak CGM glucose level of 182 mg/dL was identified, and observed post-prandial glucose peaks >200 mg/dL in one-third of CF subjects with NGT, half of IGT subjects, and all patients with CFRD.⁸⁰ Glucose excursions >200 mg/dL on CGM successfully predicted the development of IGT or CFRD as diagnosed by OGTT in a 2.5-year period.⁸¹ Hameed

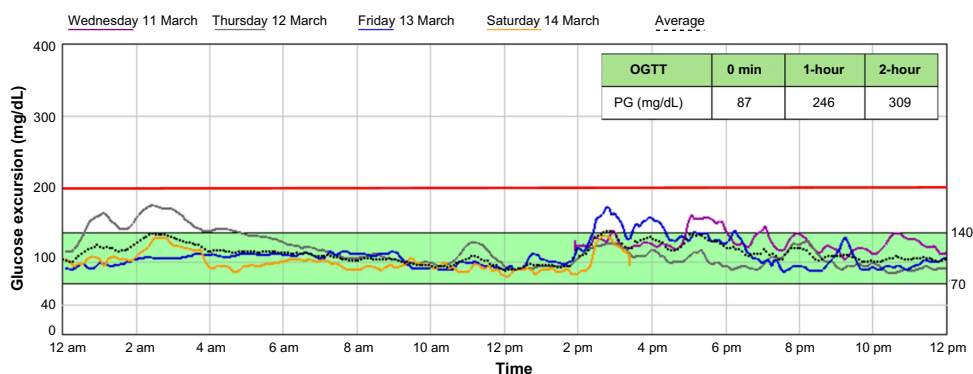


Figure 1 Patient 1 is an 18 years and 4 months old female who underwent CGM and OGTT testing during a 2 week period.

Note: Glucose excursions on CGM are milder compared to those seen on OGTT.

Abbreviations: CGM, continuous glucose monitoring; min, minute; OGTT, oral glucose tolerance test; PG, plasma glucose.

et al²¹ found glucose >140 mg/dL during CGM was correlated with greater declines in weight-Z and pulmonary function over the previous year in children defined as having NGT or IGT by OGTT. O’Riordan et al⁸² confirmed the validity and reproducibility of CGM in over 100 children with CF.

The major disadvantage of performing CGM is placement of a subcutaneous probe that monitors glucose over 3–5 days; blood glucose by finger stick must also be performed multiple times per day for calibration of the CGM. CGM is presently not recommended as a diagnostic tool for CFRD by the US CFF. Instead, it is considered a complementary tool in the management of CFRD.⁶⁶ The glucose excursions on CGM while not diagnostic of CFRD may be important in individual patients in whom clinical decline may be suspected and in whom early insulin treatment can improve clinical status.¹⁸

Glycosylated hemoglobin

Hemoglobin A_{1c} (HbA_{1c}) closely correlates with mean plasma glucose in T1DM but a similar correlation does not seem to exist for CF.⁸³ Despite higher mean HbA_{1c} values in CF patients with diabetes than in those with NGT,¹¹ a large proportion of diabetic CF individuals have normal HbA_{1c}.^{11,70,84} Thus, the CFF does not recommend use of HbA_{1c} for diabetes screening due to its poor sensitivity in the CF population.⁶⁶ The utility of a lower HbA_{1c} threshold to identify the subset of patients at greatest risk for CFRD and who, therefore, should undergo an OGTT has recently been addressed by Burgess et al.⁸⁵ Their study identified a threshold of $\geq 5.8\%$ as compared to ≥ 6.5 for T1DM and T2DM as sufficiently sensitive to screen for CFRD and to identify individuals whose “elevated” HbA_{1c} should be followed by a diagnostic OGTT.

Random blood glucose monitoring

Using only random blood glucose for the diagnosis of CFRD is challenging. An isolated elevated glucose level (>200 mg/dL) occurring within 2 hours post-meal (as evident by CGM) suggests an insulin defect but does not translate into diabetes. Random blood glucose checks – fasting and 2-hour post-prandial, are recommended for CF patients within the first 48 hours of an acute illness requiring intravenous antibiotics or glucocorticoids based on expert consensus.⁶⁶ These elevations require confirmation by serum glucose measurements but can identify individuals who are at risk for diabetes. In the outpatient setting, glucose should be measured periodically during and after continuous overnight gastrostomy tube (G-tube) feeds.⁶⁶ Figure 2 shows two CF subjects with NGT on OGTT followed at our CF center who experienced worsening BMI despite optimum nutrition and pulmonary care but who demonstrated hyperglycemia associated with G-tube feeds. On initiation of insulin, the nutritional status of both patients improved. Since G-tube feeds are routinely instituted in CF patients with low BMI, of particular interest in this population is whether continuous overnight feeds “overburden” the pancreas.

Significance of early glucose abnormalities

While the significance of CFRD and the treatment recommendations are relatively clear, early glucose abnormalities pose a challenge. During this “pre-diabetic” state, clinical decline has already ensued.^{9,18} This pre-diabetic state is based on conventional OGTT criteria and may be the byproduct of non-CF specific diagnostic cutoffs. The lag in CFRD diagnosis from clinical decline could suggest an inappropriate delay in treatment as clinical decline has already started. Given this consideration, some investigators have focused on the impact

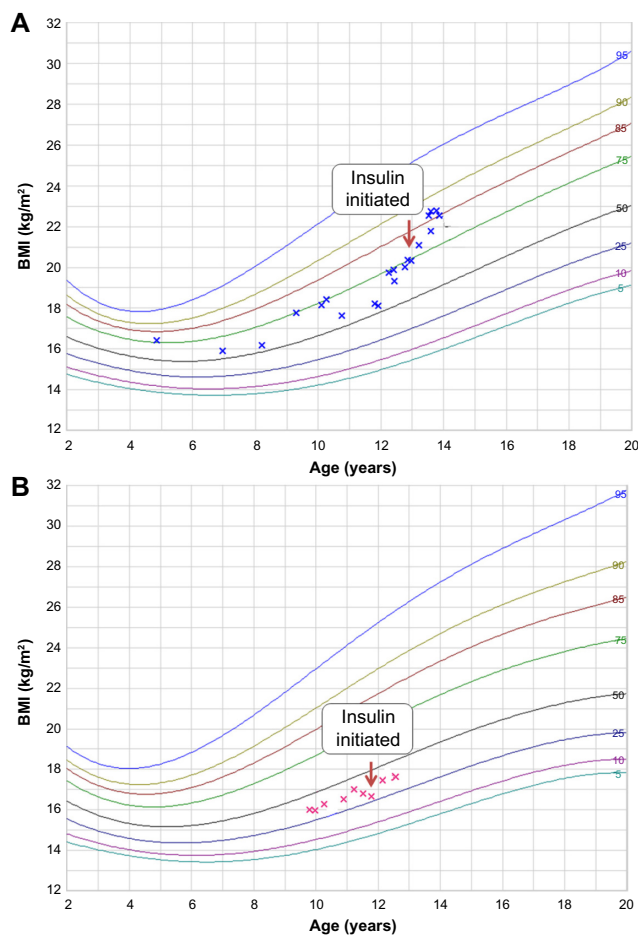


Figure 2 Improvements in BMI on insulin treatment among two individuals with normal OGTT but elevated random post-prandial blood glucose (BG) monitoring. **Notes:** Patient 1 (A) is a male, 13 years and 4 months old with pancreatic insufficient CF on long-term G-tube supplementation who showed BG results in the mid-300s mg/dL on overnight feeds. Patient 2 (B) is a female, 11 years and 6 months old who demonstrated BG >200 mg/dL immediately during overnight feeds. **Abbreviations:** BMI, body mass index; OGTT, oral glucose tolerance test; CF, cystic fibrosis; G-tube, gastrostomy tube.

of pre-CFRD glucose abnormalities on clinical outcomes and early treatment to prevent the associated decline.

Recent evidence suggests mild glucose derangements are not benign and are associated with clinical deterioration – pulmonary function and nutritional status worsen in pre-diabetics.^{3,9} The CFF has recognized that IGT may be important, but its consequences are unclear and therefore no specific guidelines for management have been recommended.⁸⁶ Tofe et al⁸⁷ evaluated lung function and nutrition in patients with IGT and demonstrated significantly lower FEV₁ and BMI values compared to CF patients with NGT. Diminished insulin secretion and increased insulin resistance were present in patients with IGT compared to those with NGT.⁸⁷ Therefore, insulin treatment may be beneficial in the pre-diabetic state, and a few small studies lend support to this approach.²² Bizzarri et al²² reported improvements in BMI and FEV₁%

with glargine treatment in a small population of CF patients with IGT. Moran et al⁶⁷ treated 20 patients with IGT with rapid acting insulin three times per day with meals and found no improvements in BMI. Minicucci et al⁸⁸ treated 16 patients with glargine and did not demonstrate improvements in BMI and FEV₁%. These studies are small, with a high proportion of dropouts, and also differed in the insulin dosages used. CF-IDEA, a larger randomized controlled trial using once-daily insulin determined to evaluate the benefits of treatment of early insulin deficiency is currently in progress (clinicaltrials.gov identifier: NCT01100892).

Treatment

The treatment of choice in CFRD is insulin; insulin administration has an established benefit for CF patients. Nutritional outcomes in patients diagnosed with CFRD improve with the initiation of insulin.^{16,67,89} as does pulmonary function.^{16,23} The decline in BMI and FEV₁%-predicted that is present in CFRD patients pre-treatment and likely also in the pre-diabetic phase is reversed with insulin.^{16,89,90} Insulin treatment may also decrease the frequency of pulmonary exacerbations.²⁴

However, CFRD treatment is an additional burden on patients with CF, who are already on complex medical regimens for maintenance of pulmonary and nutritional health. Management of CFRD with insulin can be demanding, requiring frequent blood glucose checks, subcutaneous injections, and carbohydrate counting.

Oral hypoglycemic agents are not recommended for treatment of CFRD as data on efficacy are limited. A recent Cochrane review noted that there is no established advantage of oral hypoglycemics over insulin and further studies are needed to establish benefit.⁹¹ A single trial was identified where 12-month treatment with repaglinide, an oral insulin secretagogue, did not improve BMI or FEV₁. The side effects of insulin sensitizers too may be problematic in CF individuals. Metformin favors weight loss in diabetes, can cause metabolic acidosis and gastrointestinal symptoms, and is contraindicated in renal impairment whereas thiazolidinedione causes osteoporosis. Based on their case report of a 48-year old female with CFRD who benefited from islet cell transplantation, Spijker et al⁹² have recommended islet transplantation after lung transplantation as an option for CFRD treatment in certain patients.

Novel therapeutic options include medications that target the incretin system. Incretin hormones, GLP-1 and GIP induce insulin release from the pancreas but have a short half-life as they are inactivated by enzyme DPP4. DPP4 inhibitors such as sitagliptin are a new class of

anti-hyperglycemic drugs that reduce degradation of incretins, enhance insulin secretion, and limit post-prandial hyperglycemia. GLP-1 agonists used in the treatment of T2DM may help avoid the hypoglycemic effects of insulin therapy.⁹³ These agents also induce weight loss,⁹⁴ which can be a potential drawback in CF subjects. However, with the reported increase in obesity among CF subjects,⁴⁹ GLP-1 agonists and DPP4 inhibitors may have an added role in the obese sub-group of CF subjects. Concern has arisen regarding GLP-1 analogs and cases of drug-induced pancreatitis, but the extent to which these analogs cause pancreatitis is still debated. Until more data are available, incretin-based therapies should be avoided in pancreatogenic diabetes.⁹⁵ In pancreatic insufficient CF, pancreatitis is not expected. Other agents yet to be explored in CFRD include SGLT2 inhibitors and IGF-I. There is limited experience using SGLT2 inhibitors in T2DM but they are promising agents.⁹⁶ IGF-I, which complements insulin action, has been used for treatment in combination with insulin.⁹⁷ IGF-I treatment in vitro and in vivo in CF mouse skeletal muscles improves insulin signaling.⁴⁶

CF-causing mutations may lead to: 1) defective production of CFTR, 2) failure of the CFTR to be presented to and

function at the plasma membrane or 3) defective CFTR conductance – ie, the probability of the chloride channel being open to transport chloride is decreased. Drugs that improve CFTR production and transit to the apical membrane, so-called correctors, and those that improve conductance, referred to as potentiators, may modulate pancreatic β -cell function as well. CFTR potentiator, ivacaftor, is available for a small subset of CF patients, those with one of ten rare mutations, and the treatment of this subset's defective CFTR conductance with ivacaftor results in clinically significant improvements in pulmonary function, weight, and BMI.⁹⁸ Interestingly, improvements in insulin secretion during OGTT and acute glucose infusion were found in a subset of five patients following ivacaftor treatment,⁶⁴ leading the authors to speculate whether initiation of a potentiator prior to β -cell failure can delay or prevent CFRD. Hayes et al⁶⁵ reported a case in which ivacaftor treatment resulted in resolution of diabetes, suggesting that ivacaftor may in fact also treat CFRD. Figure 3 shows improvements in BMI and normalization of OGTT after initiation of ivacaftor in a 13-year-old female with G551D mutation and CFRD without FH. The impact of these CF-specific therapies may extend beyond pulmonary function and nutrition and further investigation on the impact

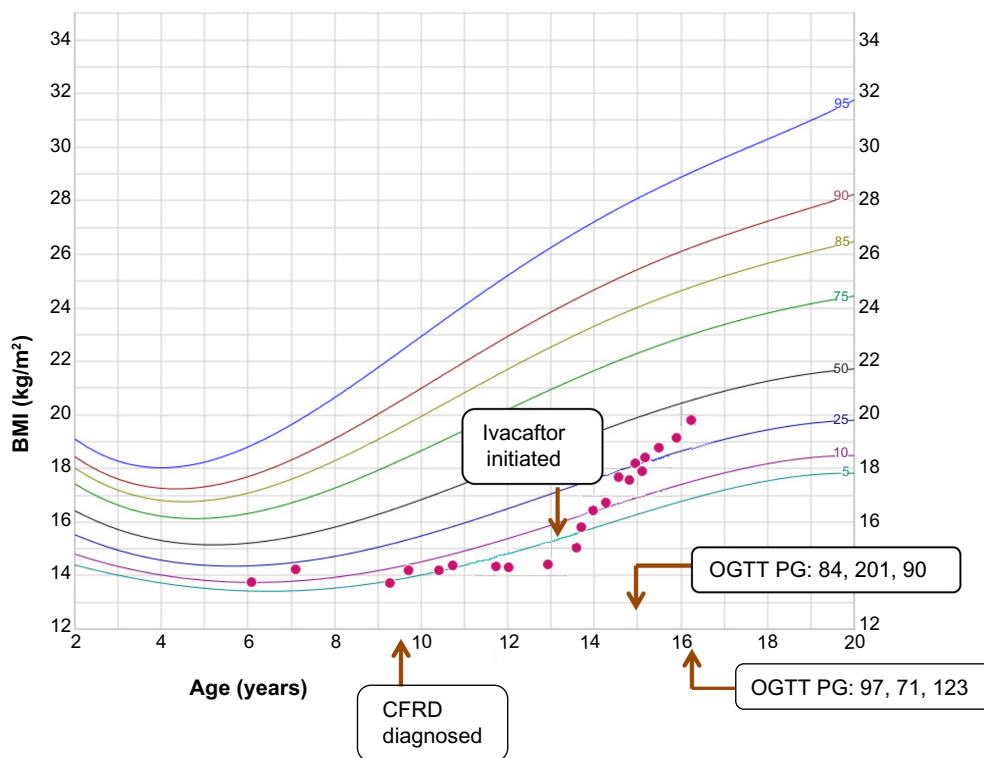


Figure 3 Patient with one G551D mutation, diagnosed with CFRD at 9 years and 5 months who initiated ivacaftor at 13 years 4 months old.

Note: The patient's BMI and BG on home glucose monitoring improved and CFRD treatment was stopped; the individual subsequently has remained off CFRD treatment with improvements in OGTT plasma glucose (PG; fasting, 1- and 2-hours).

Abbreviations: CFRD, cystic fibrosis-related diabetes; BMI, body mass index; BG, blood glucose; OGTT, oral glucose tolerance test.

of ivacaftor upon insulin secretion and glucose tolerance in CF patients with G551D mutation is underway (clinicaltrials.gov identifier: NCT02039986).

Quality of life

The diagnosis of diabetes places an additional burden on patients already managing the complexities of CF care. Adding to the difficulty is the observation that approximately half of CF individuals are not aware of the possibility of developing CFRD as a complication of CF.^{97,99} To avoid patients feeling blind-sighted by the diagnosis of CFRD, CF caregivers might introduce the possibility of CFRD development as a common complication in CF at an earlier age. This can be achieved through educational materials, family/patient education events, and interaction with experts in CFRD.

The diagnosis of CFRD can be especially challenging in the pediatric population; CFRD is often diagnosed in the adolescent ages, a time during which children are learning to deal with the burdens of a chronic disease and exercising autonomy. The management of CFRD can significantly disrupt the lives of these individuals, more so during acute illnesses when CF disease treatment is already taxing. However, some individuals take on greater responsibility and ownership of diabetes and are able to incorporate CFRD into CF care. Managing CFRD can help encourage adolescents to participate more in routine CF care.

Treatment recommendations can be rejected or poorly followed by the patient, and therefore a close partnership between the CF care team including an endocrinologist and the patient must be developed to overcome individual barriers to CFRD care. Education regarding the etiology and implications of CFRD, insulin therapy, blood glucose monitoring, treatment of hypo- and hyperglycemia, the effects of food intake, stress, illness, and physical activity is crucial for successful partnership in the management of CFRD. Along with the pain of insulin injections, frequent blood glucose monitoring is cumbersome. Patients are most likely to avoid blood glucose checks, erroneously assuming (especially during illnesses) that an estimated insulin dose is sufficient. The importance of glucose monitoring needs to be repeatedly emphasized at CFRD visits. The most prevalent misconception regarding CFRD is that calories should be restricted. This is in conflict with CF care but reflects what is common knowledge regarding care of T2DM. Therefore, a nutritional plan should be discussed by the CFRD team and the patient educated regarding caloric intake with a focus on healthy calories.

Future directions

The mechanisms underlying insulin secretion defects, diabetes screening, and the role of earlier treatment on nutritional status, and pulmonary function are presently under further investigation.

Important areas where further study is crucial and would address management concerns include:

1. the mechanistic links between insulin secretion defects, glucose intolerance, and worse clinical outcomes are still vague. Hyperglycemia is postulated to increase infection susceptibility and to perpetuate the inflammatory cascade while insulin deficiency results in increased proteolysis and presumably loss of muscle mass.
2. Optimal screening practices remain a challenge, and the intervals at which screening should occur with respect to CF status, age, and previous glucose tolerance have yet to be assessed.
3. Earlier treatment of glucose abnormalities either in the IGT or indeterminate phase may have implications for progression of not only CF lung disease but insulin secretion abnormalities.
4. With the advent of ivacaftor therapy, assessment of insulin secretion and improvements in glucose tolerance related to ivacaftor are also exciting areas of research. As other disease modifying agents become available, their impact upon glucose intolerance and insulin secretion will need formal consideration.

Conclusion

Improved survival in CF has brought CFRD to the forefront of CF care. The CF community recognizes the negative effects of CFRD on pulmonary health and efforts are underway on both the research and clinical fronts to understand and manage CFRD. With further characterization of insulin defects and the mechanisms by which hyperglycemia adversely affects clinical status, improved screening practices, and novel therapeutics, the threat CFRD poses can be countered.

Disclosure

The authors do not have any conflicts of interest.

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