Cystic Fibrosis–Related Diabetes: Pathophysiology and Therapeutic Challenges

Ryan Kelsey[1], Fiona N Manderson Koivula[1], Neville H McClenaghan[2] and Catriona Kelly[1]

[1]Northern Ireland Centre for Stratified Medicine, School of Biomedical Sciences, University of Ulster, Derry/Londonderry, UK. [2]School of Biomedical Sciences, University of Ulster, Derry/Londonderry, UK.

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ABSTRACT: Cystic fibrosis–related diabetes (CFRD) is among the most common extrapulmonary co-morbidity associated with cystic fibrosis (CF), affecting an estimated 50% of adults with the condition. Cystic fibrosis is prevalent in 1 in every 2500 Caucasian live births and is caused by a mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. Mutated CFTR leads to dehydrated epithelial surfaces and a build-up of mucus in a variety of tissues including the lungs and pancreas. The leading cause of mortality in CF is repeated respiratory bacterial infections, which prompts a decline in lung function. Co-morbid diabetes promotes bacterial colonisation of the airways and exacerbates the deterioration in respiratory health. Cystic fibrosis–related diabetes is associated with a 6-fold higher mortality rate compared with those with CF alone. The management of CFRD adds a further burden for the patient and creates new therapeutic challenges for the clinical team. Several proposed hypotheses on how CFRD develops have emerged, including exocrine-driven fibrosis and destruction of the entire pancreas and contrasting theories on the direct or indirect impact of CFTR mutation on islet function. The current review outlines recent data on the impact of CFTR on endocrine pancreatic function and discusses the use of conventional diabetic therapies and new CFTR-correcting drugs on the treatment of CFRD.

KEYWORDS: cystic fibrosis–related diabetes, cystic fibrosis, CFTR, islet, exocrine pancreas

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CORRESPONDING AUTHOR: Catriona Kelly, Northern Ireland Centre for Stratified Medicine, School of Biomedical Sciences, University of Ulster, C-TRIC Building, Altnagelvin Hospital Campus, Glenshane Road, Derry/Londonderry, Northern Ireland, UK. Email: c.kelly@ulster.ac.uk.

Cystic Fibrosis

Cystic fibrosis (CF) is the most common autosomal recessive condition in Caucasian populations with an incidence of 1 in 2500 live births. Globally, CF is estimated to affect between 70 000 and 100 000 people.[1] The condition is caused by a mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, which is found on the long arm of chromosome 7 and spans 230 kb with 27 coding exons. The *CFTR* gene codes for a cyclic adenosine monophosphate (cAMP)–regulated chloride channel of the same name. The membrane-bound CFTR glycoprotein was first identified in 1989 by Riordan et al[2] and is a member of the ATP-binding cassette membrane transporter gene superfamily – a class of transporters that also includes the sulfonylurea receptor. CFTR is responsible for the outward movement of Cl^- and the linear movement of water across cell membranes.[3] CFTR also regulates the activity of other membrane proteins, including the epithelial sodium channel ENaC, the outwardly rectifying chloride channel ORCC, and a Cl^-/HCO_3^- exchanger.[4]

CFTR is a large protein of more than 1400 amino acids separated into 2 homologous halves, each containing 6 membrane-spanning segments and a nucleotide-binding domain. The 2 halves are linked by a regulatory (R) domain.[2] Functional imaging studies suggest that the CFTR pore resembles an asymmetrical hourglass with a deep wide intracellular vestibule and a shallow extracellular vestibule separated by a narrow channel.[5] Most of the CFTR protein resides in the cytoplasm (77%), with 19% in the membrane and only 4% is extracellular.[6] Channel gating is controlled by conformational changes in the cytoplasmic domains and requires a 2-step process involving phosphorylation and binding/hydrolysis of ATP.[2] There exists a structure-function relationship, whereby the more extensive the phosphorylation, the greater the probability of channel opening.[7]

Since the discovery of the *CFTR* gene in 1989, close to 2000 different variants have been identified, of which approximately 440 are disease-causing.[8] Furthermore, ~97% of all CFTR mutations are caused by a mutation in between 1 and 3 nucleotides. Among these, missense mutations are the most common, accounting for 40% of all reported mutations.[9] CFTR mutations are categorised into 5 groups, depending on the amount of protein present at the cell surface membrane and the degree of functionality.[10] Broadly speaking, class I mutations are associated with more severe phenotypes and class V mutations with milder phenotypes.[11] The F508del mutation accounts for approximately 90% of the prevalence of disease-causing CFTR mutations in Caucasian populations and is characterised by a deletion of phenylalanine at position 508. This results in defective folding of the protein and subsequent degradation via the ubiquitin proteasome pathway.[12] Therefore, minimal functional CFTR reaches the cell surface membrane and is characteristic of a class II mutation.

Cystic fibrosis is associated with a build-up of thick, viscous secretions in epithelial tissues, leading to bacterial colonisation

and subsequent fibrosis and destruction of a number of organs, including the respiratory, gastrointestinal, hepatobiliary, and reproductive systems in particular.[13] Lung disease driven by recurrent infections and bacterial colonisation is the most common cause of mortality in CF. CFTR is readily detected in the airways,[6] and structural changes in the airways of patients with CF are present from birth.[14] Inflammation occurs rapidly, is severe, and is aided by a decrease in surface fluid pH (approximately 8-fold lower compared with non-CF patients[15]), which leads to impaired host-pathogen defences.[15] The CF lung is at increased risk of bacterial colonisation from *Staphylococcus aureus* and/or *Pseudomonas aeruginosa* in particular, leading to excessive airway and systemic inflammation and an eventual loss of pulmonary function.[15] The CF lung disease represents a significant clinical challenge and is difficult to manage. Although lung disease is the primary cause of mortality, CF is a systemic condition with almost all organ systems affected.

Patients with CF are at increased risk of a number of side effects, including inadequate weight maintenance,[16] in addition to obstruction of the bowel and musculoskeletal disorders which are relatively common in CF, affecting up to 15% of patients.[17] Cystic fibrosis also results in reproductive problems and infertility, with 95% of men infertile due to azoospermia caused by complications with the vas deferens.[18] In addition, patients with CF may also suffer from renal disease, metabolic bone disease, cancer, adverse drug reactions, and complications associated with lung transplants.[18] Emerging evidence suggests that CFTR mutation may also impair neurological function.[19] Cystic fibrosis–related diabetes (CFRD) is the most prevalent extrapulmonary co-morbidity in CF and is the focus of the current report.

Cystic Fibrosis–Related Diabetes

Cystic fibrosis–related diabetes affects approximately 50% of CF adults over the age of 30 and results in a significantly worsened prognosis and 6-fold higher mortality rate in comparison with CF patients without diabetes.[13] Cystic fibrosis–related diabetes is associated with lower lung function[20] caused in part by increased colonisation of the lungs by bacteria such as *Psuedomonas aeruginosa, S aureus*, and *Stenotrophomonas maltophilia.*[21] Patients with CFRD have been shown to have up to double the pulmonary exacerbations compared with CF patients without diabetes.[22] Increased glucose levels induce airway surface liquid acidification in CFTR-deficient airway epithlia.[23] This results in an increase in lactate production and is further exacerbated by *P aeruginosa* colonisation. *Psuedomonas aeruginosa* has been shown to favour lactate as a growth source over traditional growth media,[23] meaning the environment in the airway epithelia of someone with CFRD is better suited to bacterial colonisation.

Cystic fibrosis–related diabetes shares clinical features of both type 1 and type 2 diabetes mellitus (T1D and T2D, respectively) but is considered a distinct classification of diabetes. Consistent with T1D, patients are insulin deficient, lean, and adolescents or young adults at the time of diagnosis[24]; however, CFRD is not an autoimmune condition, and modest insulin resistance has been reported consistent with a T2D phenotype.[24] Currently, the American Diabetes Association reccommends the 2-hour OGTT (1.75 g/kg body weight) for the diagnosis of CFRD. A 2-hour OGTT glucose greater than 200 mg/dL in a patient with CF leads to a diagnosis of CFRD.[24] However, routine CFRD screens are not performed on patients under the age of 10. The UK Cystic Fibrosis Trust[25] recommends routine OGTT for CF patients over the age of 12, which should also be performed if there is an unexplained deterioration in lung function or unexpected weight loss.

Islet Function and Insulin Secretion in CF

A consistent observation in human tissues and animal models is that the CF disease is associated with reductions in islet size and beta cell area.[26–33] This is often accompanied with glucose responsiveness abnormalities and insulin secretory defects.[34–38] Reports dating back to the 1980s showed marked reductions in beta cell area in the pancreata of patients with CF irrespective of whether diabetes was present or not.[27,28] Consistently, altered islet morphology and function was reported at birth in the CF ferret model, with a notable increase in the number of small islets present in this model.[29] Reductions in islet mass or beta cell area have repeatedly been shown in animal models of CF[30–32] and in postmortem tissue from children[33] and adults with CF.[26] Bogdani et al[33] examined pancreatic tissue from CF children under the age of 4 and reported reductions in beta cell area of up to 50% compared with age-matched controls. Decreases in islet and/or beta cell area, therefore, appear to occur early in the development of CF disease. However, much debate exists as to the mechanisms leading to islet dysfunction in CF. Several studies show CFTR channel activity in cells isolated from mouse[34–37] and human islet cells[34,35] and report insulin and glucagon secretory defects in the absence of functional CFTR.[34–38] In contrast, others report minimal or absent expression of CFTR in human pancreatic endocrine cells[26,39,40] and suggest that any insulin secretory defect likely results from reductions in islet mass, from intra-islet inflammation, or from the paracrine influences of exocrine-derived inflammatory mediators.[26,39] In the CF pig model, an activated inflammatory response that appears largely confined to the pancreas of newborns and which is associated with exocrine destruction at birth has been reported.[40,41] Thus, the theories surrounding the development of CFRD can largely be grouped into 3 categories, which are discussed below and summarised in Figure 1.

First, the bystander hypothesis suggests that islets are lost as a consequence of fibrotic progression in the pancreas. CFTR is highly expressed in pancreatic ductal cells, and pancreatitis linked to CFTR mutation is common. Early work by Sharer et al[42] reported that the risk of developing chronic pancreatitis was 2.5 times higher in those heterozygous for CFTR

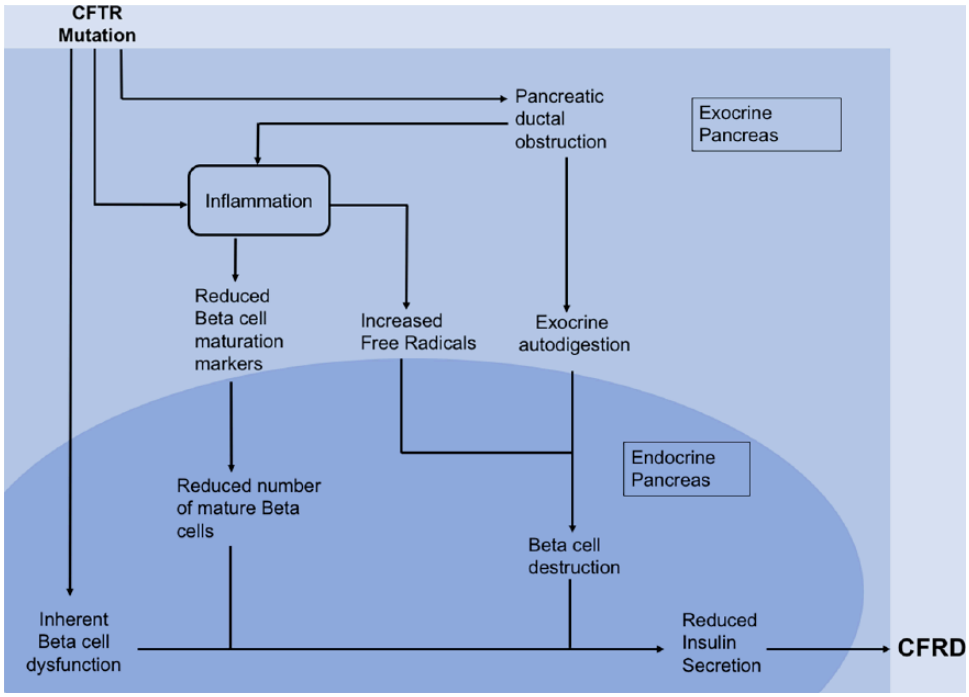

Figure 1. Summary of the different hypotheses behind the development of cystic fibrosis–related diabetes (CFRD), from initial cystic fibrosis transmembrane conductance regulator (CFTR) mutation to its proposed effects in both the endocrine and exocrine pancreas.

mutations. The suggestion that CFTR plays a role in the pathogenesis of pancreatitis is supported by several subsequent studies (summarised by Hegyi et al[43]). Indeed, known risk factors for the development of pancreatitis, including alcohol and smoking, strongly inhibit CFTR function.[43] In patients with CF, the reduction in chloride and bicarbonate secretion causes acidification of the pancreatic juices and increased production of mucins, leading to pancreatic ductal obstruction.[44] Cystic fibrosis exocrine pancreatic insufficiency predominantly affects patients with class I-III CFTR mutations.[44] Patients who are deemed pancreatic insufficient (PI) are unable to break down food correctly due to loss of digestive enzymes, and therefore require extensive dietary supplementation.[44] These processes ultimately lead to autodigestion of the pancreatic ducts and exocrine pancreatic fibrosis.[42,44] The information on the relationship between exocrine pancreatic status and insulin secretion is varied. A study of 146 patients with CF found insulin secretory defects on OGTT even in pancreatic-sufficient individuals.[45] A further report found impairments in functional islet mass, early-phase insulin secretion, and incretin responses in PI, but not pancreatic-sufficient patients with CF.[46] In both studies, subjects were glucose tolerant.

The second and third hypotheses on CFRD development are based on opposing views on whether CFTR is, or is not, expressed in the islet and whether mutations in CFTR therefore generate islet intrinsic or extrinsic defects that ultimately lead to reductions in insulin secretion. Early work by Boom et al[47] suggested that low-level CFTR messenger RNA could be detected in rat beta cells, with alpha cells showing higher abundance of the gene. Subsequent studies have shown CFTR expression and channel activity in mouse[34–37] and human islet cells.[34,35] Experimental data from isolated primary beta cells, beta cell lines, and transgenic animal models have identified potential mechanisms that surround the reduction in insulin secretion associated with CFTR deficiency.

Insulin secretion was shown to be reduced in studies using isolated beta cells exposed to CFTR inhibitors such as 3-[(3-triflouromethyl)phenyl]-5-[(4-carboxyphenyl) methylene]-2-thioxo-4 thiazolidinone (CFTRInh-172) and CFTR inhibitor II (GlyH-101),[35,37,38] in studies on CFTR-deficient cell lines,[38] and in studies on islets from F508del mutant mice.[37] In primary human beta cells, insulin granule exocytosis in response to the cAMP agonists forskolin and glucagon-like peptide 1 (which activate CFTR through the protein kinase A pathway) was significantly decreased following treatment with CFTRInh-172 and GlyH-101.[35] On measurement of membrane depolarisations, this effect was most prominent in the initial depolarisations, which is in line with the decreased first-phase insulin secretion reported in patients with CFRD.[34] This study also reported a novel role for CFTR as a regulator of ANO1. CFTR was shown to act upstream of ANO1. In addition to reductions in insulin secretion in response to cAMP activators, 2 independent studies have reported reductions in glucose-induced insulin secretion in models with CFTR interference.[37,39] The CFTR inhibitor CFTRInh-172 affected beta cell resting membrane potential and Ca^{2}+flux in RINmF5 cells.[36] Both CFTRInh-172 and GlyH101 are potent inhibitors of CFTR. However, as with all

inhibitors, when used at higher concentrations (ie, above 5-10 μM), off-target effects on volume-sensitive outwardly rectifying Cl^- conductance have been observed.[48] Most studies listed here used concentrations of 10 μM of each inhibitor and may have been subject to some off-target effects in addition to CFTR inhibition. Silencing of CFTR in the MIN6 beta cell line caused a significant reduction in the ATP:ADP ratio, and this was associated with reduced glucose-induced insulin secretion.[38] These results suggest that the first-phase insulin response to glucose observed in patients with CFRD may be partly attributable to responses mediated by membrane-bound voltage-dependent channels. In the CF pig model, glycaemic abnormalities and insulin secretory defects were observed in newborn animals that went on to develop spontaneous diabetes over time.[49] These changes took place despite sparing of islet mass, suggesting that early functional deficits within the islets may play a role in the development of CFRD in this model.

In addition to insulin secretion, CFTR has been reported to regulate glucagon release from the pancreatic alpha cell. Glucagon secretion was enhanced in response to glucose and forskolin following CFTR inhibition in human islets.[35] However, depolarization-induced glucagon secretion was unaffected. Using a mathematical model of alpha cell electrophysiology, the authors suggest that CFTR predominantly regulates alpha cell membrane potential.[35] Consistently, enhanced glucagon release was also observed in the islets from F508del mice.[37] Through overexpression studies in the alphaTC1-9 cell line, it was suggested that wild-type CFTR acts as a glucose-sensing negative regulator of glucagon release and that defects in this process may contribute to glucose intolerance.[37]

Further investigations into an F508del mouse model confirm a significant reduction in glucose-induced insulin secretion in islets studied ex vivo. However, in contrast to the findings of the above studies, the authors concluded that the observed reduction in insulin secretion was directly proportional to the reduction in insulin content and did not occur as a result of a CFTR-induced beta cell insulin secretory defect.[37] Furthermore, this study reports that as the mice aged, they developed insulin resistance. More recently, several studies have been published that suggest that the environment beyond the islet plays a significant role in islet dysfunction in CF. Using an inducible mouse model, Hart et al[26] report that beta cell–specific deletion of CFTR did not affect beta cell function, that CFTR was poorly detected in human beta cells, and that isolated islets from CF patients with and without CFRD displayed relatively normal insulin and glucagon release upon challenge. This study demonstrated significant intra-islet inflammation and a reduction in beta cell area of around 65% in CF and suggests that these are the primary factors driving the development of CFRD. Work in the CF ferret model revealed that insulin content was reduced in CF in comparison with wild-type ferrets.[30] Furthermore, perifusion studies showed that glucose-stimulated insulin secretion was reduced in CF neonates at all phases of secretion. However, it was shown that CF islets compensated for reductions in insulin content by secreting a higher proportion of insulin than wild-type animals under low glucose concentrations.[30] This observation was attributed to higher expression of *SLC2A1*, increased basal inhibition of the K_{ATP} channel, and increased basal intracellular calcium concentrations. Importantly, this study showed that interleukin 6 (IL-6) release from CF islets was higher than that of wild-type islets and that administration of recombinant IL-6 to wild-type islets resulted in a phenotype that was consistent with that of CF islets, including reductions in insulin content and an increase in the percentage of insulin release under basal glucose conditions.[30] Using single-molecule fluorescent in situ hybridization, on isolated ferret and human islets, the authors report that *CFTR* colocalised with *KRT7*-expressing ductal cells, but not with endocrine cells. The authors conclude that CFTR affects beta cell function via non-cell autonomous factors derived from islet-associated exocrine-derived cell types. Consistent with this theme, a recent report details increased interleukin 1β (IL-1β) concentrations in the islets of CF patients with and without diabetes, including young children under the age of 10.[50] In this study, a reduction in beta cell mass was not observed, but an increase in alpha cell area was evident in the islets of people with CF independent of the presence or absence of diabetes.[50]

Given the condition of the exocrine pancreas in CF, it seems unlikely that this environment will not exert a negative effect on the islet. The bystander hypothesis suggests that pancreatic islets are lost as a secondary consequence of pancreatic fibrosis and is a credible explanation of how diabetes might occur in older CF patients with long-standing established pancreatic disease. However, loss of beta cell mass (but not islet mass) has been reported in children, independent of the degree of pancreatic fibrosis,[33] suggesting that additional factors beyond fibrosis and autodigestion of the pancreas may play a role in regulating beta cell mass in CF. Furthermore, the conflicting data on the role of pancreatic sufficiency in glucose tolerance and insulin secretion, and the recent observation from a small cohort study that over half of children tested have glucose responsiveness abnormalities,[51] suggest that the bystander hypothesis may not fully explain the onset of diabetes in the CF population. The consensus from the literature suggests that CFTR is detectable in mouse islets and in rodent beta cell lines.[34,38,39] However the data from human islets and in other CF models including the ferret vary. Convincing and robust evidence has been presented on each side of the argument,[34–37] and further studies are emerging that seek to shed light on this issue. Nothwithstanding this debate, recent studies suggest that exocrine-derived paracrine signals are detrimental to islet function in CF. Further work on exocrine-endocrine interactions is needed to determine whether these signals are the sole cause of islet

Table 1. Summary of common changes in the endocrine and exocrine pancreas in models of cystic fibrosis–related diabetes.

OBSERVATION	MODEL
Reduction in islet area/mass	Human[26-28,30,33]/Cell/Mouse[31]/Ferret[29,30,32]
Reduction in beta cell area/mass	Human[26-28,30,33]/Cell/Mouse[31]/Ferret[29,30,32]
Impaired insulin secretion	Human[34,43,46]/Cell[36,38]/Mouse[31,34,36]/Ferret[29,39]
Enhanced glucagon secretion	Human[35]/Cell[37]/Mouse[35,37]/Ferret
Impaired glucose tolerance	Human/Cell/Mouse[36]/Ferret[29]
Inflammation	Human[26,33,50]/Cell[38]/Mouse/Ferret[29,32,39]
Exocrine pancreatic destruction/insufficiency	Human[33]/Cell/Mouse/Ferret[29,30,32]

The reported observations have been suggested to play a role in the overall occurrence of glucose abnormalities in cystic fibrosis as well as the development of diabetes.

dysfunction in CF or whether they compound already existing secretory defects within the islet (Table 1).

Implications for the Clinical Management of CFRD

Insulin therapy is the most commonly used treatment for CFRD. Clinical trials have demonstrated that patients with CF benefitted from treatment with insulin as they showed a beneficial reduction in weight loss and an increase in body fat.[52] Insulin therapy before a formal diagnosis of CFRD (but with impaired glucose tolerance) has been shown to improve clinical status and lung function.[53]

Several recent studies have examined insulin and islet hormone concentrations following administration of the CFTR corrector ivacaftor. Ivacaftor was designed to counter gating mutations such as G551D, found in approximately 5% of people with CF. Insulin response was found to be improved in a small 5-patient cohort following 1 month of Ivacaftor treatment. Each patient in this study had never been on ivacaftor therapy before and had varying levels of glucose tolerance, including CFRD with and without fasting hyperglycaemia as well as normal and impaired glucose tolerance. Insulin secretion in response to intravenous glucose improved by 51% to 346% in 4 of the patients and it was restored in 2 patients who had no response before the trial. Furthermore, insulin response to oral glucose improved by 66% to 178% in all patients except one with a diagnosis of CFRD.[54] A short 16-week study on 2 siblings with different glycaemic status showed that ivacaftor can improve insulin secretion. Following the completion of this study, one patient with indeterminate glycaemia reverted to normal glucose tolerance and one patient with CFRD reverted to indeterminate glycaemia.[55] An improvement in insulin secretion was also observed following 4 months of Ivacaftor treatment in a 12-person cohort who had not previously been on ivacaftor therapy. However, incretin concentrations were not altered in this study.[56] It should be noted that improvements in insulin secretion in response to ivacaftor treatment may result from overall improvements in metabolic health, rather than a direct impact on the insulin secretory machinery, and further study is required. Despite the promising data from preliminary trials with ivacaftor, most CF patients do not have any copies of an ivacaftor-targeting mutation. Thomassen et al[57] examined the effect of dual therapy with lumacaftor-ivacaftor (marketed as Orkambi and targeted towards those homozygous for F508del mutation), but reported no improvement in glucose metabolism and insulin secretion after 6 to 8 weeks of treatment. However, in a long-term 1-year study, glucose tolerance was found to be improved in patients homozygous for the F508del mutation.[58]

Due to the ever-increasing life expectancy in patients with CF, CFRD is becoming more prevalent, adding a further burden to patients with CF and creating new challenges for treatment. Different treatment programmes have tried to address both restoration of CFTR and insulin levels with varying degrees of success. There is increasing evidence that factors beyond the endocrine pancreas have a significant role to play in the development of CFRD. An ongoing clinical trial is currently exploring the utility of the dipeptidyl peptidase-4 inhibitor sitagliptin for the treatment of CFRD.[59] Increasing incretin concentrations may well help maintain beta cell mass and improve insulin secretion in CF.

It is likely that no single hypothesis is sufficient to explain the complexity of islet dysfunction in CF, and there is much to be learned about how islets function in the inhospitable enviroment of the CF pancreas and how secretory defects may be restored or prevented. Evidence from young children shows reductions in islet size and glucose abnormalities even in the absence of overt exocrine damage. It is possible that early intervention with drugs designed to maintain beta cell mass and to restore CFTR function may aid in slowing the onset of CFRD.

Author Contributions

RK and FMK wrote the initial draft of the manuscript, which was revised by NMcC and CK. All authors reviewed and approved the final manuscript.

ORCID iD
Ryan Kelsey https://orcid.org/0000-0002-6555-4990

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