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Review

Update on cystic fibrosis-related diabetes

Andrea Kelly [a,*], Antoinette Moran [b,1]

[a] Division of Endocrinology & Diabetes, Children's Hospital of Philadelphia, Perelman School of Medicine at University of Pennsylvania, Room 1559, 3535 Market Street, Philadelphia, PA 19104, United States

[b] Pediatric Endocrinology, University of Minnesota, East Bldg Rm MB671, 2450 Riverside Ave, Minneapolis, MN 55455, United States

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Abstract

Diabetes mellitus has emerged as a common comorbidity in cystic fibrosis and is considered a clinical entity (cystic fibrosis-related diabetes, CFRD) distinct from that of type 1 diabetes (T1DM) and type 2 diabetes (T2DM). The relevance of this diagnosis extends not only from its imposition of additional medical burden but its association with worse health outcomes in individuals with CF. This paper will review the 2010 U.S. and other international guidelines for screening and treating CFRD. It will highlight newer data regarding early glucose and insulin secretion defects, mechanisms linking CFRD to worse outcomes, and recent advances in T2DM that may provide insights for CFRD; insulin secretion will be reviewed as background for these recent developments.

Keywords: Cystic fibrosis; Diabetes; Hyperglycemia; Cystic fibrosis-related diabetes

Contents

* Corresponding author. Tel.: +1 215 590 3174; fax: +1 215 590 3053.
E-mail addresses: kellya@email.chop.edu (A. Kelly), moran001@umn.edu (A. Moran).
[1] Tel.: +1 612 624 5409; fax: +1 612 626 5262.

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1. Introduction

1.1. Insulin physiology

Pancreatic β-cell insulin secretion strictly governs glucose, amino acid, and fat disposition. A highly anabolic agent, insulin targets these fuels for storage [1], stimulating glycogen synthesis and glucose uptake by fat and muscle while suppressing hepatic glycogenolysis and gluconeogenesis, lipolysis, and ketogenesis. In the absence of nutrient ingestion, insulin secretion is down-regulated and a catabolic state is invoked whereby glucose is accessed from glycogen and through conversion from amino acids. With more prolonged fasting, lipolysis and ketogenesis provide alternate fuels.

Insulin secretion is regulated by the availability of nutrients, other hormones, and neural factors. Following oral glucose ingestion, insulin levels normally rise within the first 30 min, peak at about 60 min, and return to baseline levels by 2–3 h. In contrast, following intravenous glucose bolus, insulin secretion occurs in a biphasic manner. An early rapid peak (acute insulin response, first phase insulin secretion) occurs within the first 10 min and then a more slow increase in insulin secretion (second phase insulin secretion) occurs over the next 20 min (reviewed in [2]). Insulin secretion in response to oral glucose is greater than insulin secretion in response to the same amount of glucose delivered intravenously. This augmented response arises from incretin secretion from gastrointestinal tract neuroendocrine cells in response to nutrient ingestion, Fig. 1. This "incretin" effect may account for 50–70% of total insulin response to an oral glucose load, with glucagon-like peptide (GLP-1) and gastric inhibitory peptide (GIP) accounting for ~90% of this response [3]. Fat also stimulates GLP-1 and GIP secretion — an effect that requires hydrolysis of fat [4].

1.2. Diabetes classification/clinical features

The pathophysiology of diabetes development, particularly in the setting of T2DM, is complex, but ultimately all diabetes arises as a result of either an absolute or relative insulin-deficient state. The American Diabetes Association (ADA) classifies diabetes mellitus based upon etiology [5], Table 1. T1DM arises from β-cell destruction, primarily of autoimmune origin. Insulin deficiency is severe, and provision of exogenous insulin is required to minimize hyperglycemia and prevent ketoacidosis. Insulin treatment in T1DM targets basal insulin needs and nutrient ingestion. Individuals with T1DM are at increased risk of other autoimmune diseases including hyper- and hypothyroidism, adrenal insufficiency, and Celiac disease.

Insulin secretory defects are now thought to underlie T2DM development. Frequently, obesity and an insulin resistant state place increased demands on β-cells. A compensatory increase in insulin secretion occurs. As β-cells are "over-worked," the secretory defect(s) is unmasked, β-cells can no longer meet the increased insulin requirements, and hyperglycemia ensues. Treatment approaches vary from diet and exercise to address obesity and insulin resistance, to use of medications that either improve insulin sensitivity or insulin secretion, to insulin replacement. Ketoacidosis is rare. Dyslipidemia, hypertension,

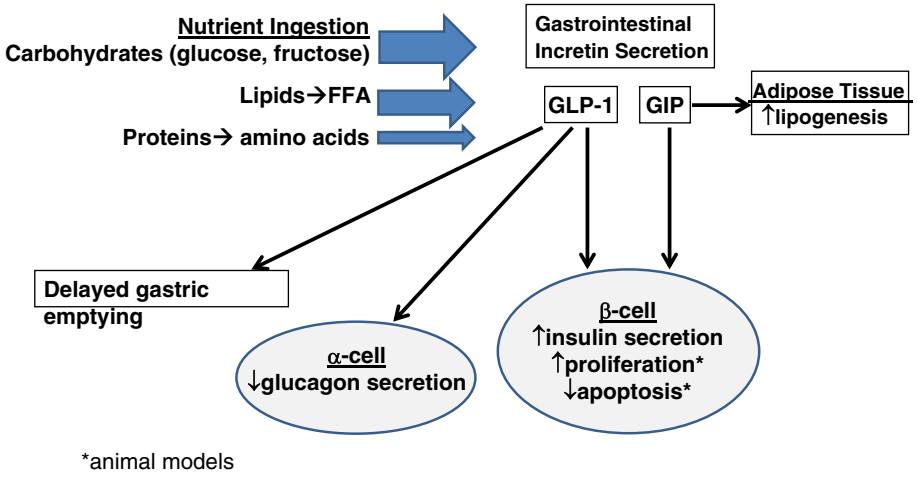

Fig. 1. Incretin secretion and action. Glucose, fructose, free fatty acids, and to a lesser extent amino acids stimulate GLP-1 and GIP secretions. GLP-1 and GIP augment glucose stimulated insulin secretion and in animal models inhibit β-cell apoptosis and promote β-cell proliferation. GIP also promotes lipogenesis. GLP-1 suppresses glucagon secretion and delays gastric emptying.

Table 1
Comparison of CFRD with T1DM and T2DM.

	T1DM	T2DM	CFRD
Clinical features			
Overweight	Low	High	Low
HTN	Low	High	Low
Dyslipidemia	Low	High	Low
Ketosis prone	Common	Uncommon	Uncommon
Microvascular complications	Common	Common	Common
Pathophysiology			
Islets	Autoimmune destruction	Inherent β-cell defect	Islet destruction due to exocrine tissue destruction Potential β-cell defect
Amyloid	Absent	Present	Present
Insulin status	Complete insulin deficiency	Insulin resistance Relative insulin deficiency	Partial insulin deficiency Episodes of insulin resistance
GLP-1	Normal	Normal or decreased secretion Efficacy normal	Decreased secretion Improved secretion with PERT [a]
GIP	Normal	Normal or decreased secretion	Near-normal secretion Decreased efficacy
Hyperglucagonemia	Absent	Present	Absent
Genetic predisposition	HLAD3 and D4	*TCF7L2*	*TCF7L2*

[a] PERT = pancreatic enzyme replacement.

inflammation, and cardiovascular disease are common additional metabolic conditions in T2DM.

Highlighting its complex nature, T2DM is considered a polygenic disorder. Inheritance of multiple common gene variants simultaneously increases the T2DM risk [6]. The repertoire of genes recognized as playing a role in the pathogenesis of T2DM has grown considerably as a result of recent genome wide association studies. The function of many such genes has yet to be established. Some appear to confer insulin resistance while others appear to impact insulin secretion including *TCF7L2*, *CAPN10*, *HNF1B*, *FOXO1*, *WFS1*, *SGK1*, and *KCNQ1* (reviewed by [7]).

The role of incretins in T2DM has received increased attention over the past decade. Reduced or absent GLP-1 responses [3,8] and partially reversible reductions in GLP-1 potency [9] have been described. Reductions in GIP have not been observed [8], but β-cell sensitivity to GIP may be reduced [10]. With continuous infusion of GLP-1 in subjects with T2DM, plasma glucose and insulin secretion improve [11,12]. Excess glucagon has also been invoked as a mediator of T2DM.

2. Cystic fibrosis related diabetes (CFRD)

Genetic defects of β-cell function, drug-induced diabetes including transplant diabetes, and exocrine pancreatic disorders, such as CFRD are classified by the ADA as "other forms of diabetes" [13]. CFRD occurs most commonly in the setting of severe CF mutations associated with exocrine pancreatic insufficiency and is considered an insulin insufficient state, although ketoacidosis is uncommon, Table 1.

Delayed and blunted insulin and C-peptide (product of proteolytic processing of pro-insulin) secretion typify the OGTT in CF patients even in the absence of CFRD [14–16], Fig. 2. Abnormalities are more pronounced with worsening glycemic status [14,16,17]. Intravenous challenges to glucose and other stimulatory agents reveal impaired first-phase insulin and C-peptide secretion in CF [16], a phenomenon also seen in T2DM. Basal insulin secretion is generally at least partially preserved.

Unlike T1DM, β-cell damage in CF does not appear to be of autoimmune origin [18]. Instead, according to the traditional "collateral damage" model of CFRD, abnormal chloride channel function results in thick viscous secretions that give rise to obstructive damage to the exocrine pancreas. Progressive fibrosis and fatty infiltration ensue and destroy islet architecture. Immunohistochemical studies of islets from patients with CFRD identified significantly reduced percentage of insulin-producing cells within islets when compared to islets of non-CFRD patients and controls [19–21] — this β-cell specific destruction characterizes T1DM. In contrast, decreased glucagon secretion has been found in response to OGTT and various other stimuli in subjects with CF and worsening glucose tolerance [14,16], suggesting islet cell destruction is not cell-selective and is linked to exocrine pancreas fibrosis. In fact, a subsequent post-mortem study found an overall decrease in islet number without specific reduction of β-cell content. Perhaps even more importantly, despite their limitations as retrospective studies, these post-mortem findings highlighted the variability in β-cell mass and its lack of correlation with the diagnosis of CFRD.

Given this lack of correlation between the quantification of β-cell mass and the presence or absence of diabetes, additional mechanisms for insulin secretion defects have been sought. Mouse models suggest CFTR (cystic fibrosis transmembrane regulator) may have a more direct role in β-cell dysfunction [22]. Islet amyloid deposition, a feature of T2DM but of neither T1DM nor pancreatitis [23], has been identified post-mortem in adults with CF but not those with NGT or controls [24]. The role of islet

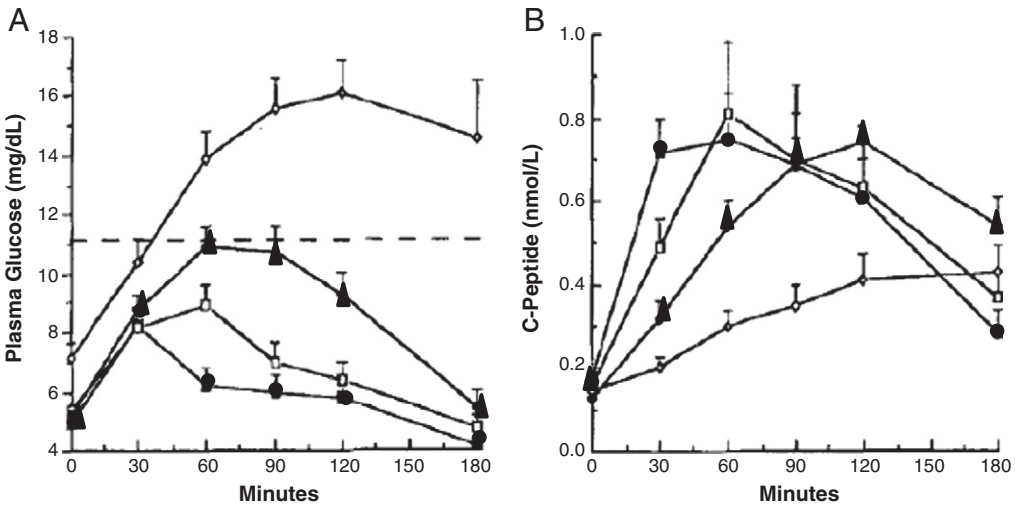

Fig. 2. Plasma glucose and C-peptide in healthy controls (●), pancreatic sufficient CF (O), pancreatic insufficient CF without CFRD (▲), and CFRD (◊), adapted from Moran et al. [16].

amyloid in β-cell dysfunction is not clear [25]. Amyloid may serve as a marker of endoplasmic reticulum stress or may play a direct role in this stress [26,27].

A possible link has been found between CFRD and T1DM genes associated with inflammation, such as tumor necrosis factor [28]. Twin studies have found that the most strong GWAS-implicated T2DM gene *TCF7L2* confers even more strongly the risk of CFRD [29].

Until recently, the role of incretins in CF has received limited attention. Initially, normal basal GLP-1 and GIP levels were observed across the spectrum of glucose tolerance in CF [14], but GIP hypersecretion during OGTT was found in adults without CFRD [30]. More recently, impaired GLP-1 and GIP secretions were described in five adults with CF without CFRD, although their glucose tolerance and peak insulin secretion were not well-characterized [31]. Another study reported no differences in GLP-1 or insulin responses to OGTT in adults with CF and NGT, IGT, and in newly diagnosed CFRD compared to healthy controls [32]. This study, however, had several methodological concerns: 1) they evaluated responses to an oral glucose load and not a mixed meal so impairments in fat- and protein-stimulated incretin secretion would not have been detected, 2) they may have missed peak incretin and insulin secretion — early measurements are critical since individuals with CF have delayed and blunted insulin secretion [33], and 3) they defined glucose tolerance by the two hour plasma glucose but peak glucose was 179 ± 30 mg/dL (9.9 + 1.7 mmol/L) in the NGT group suggesting that glucose excursion was not completely normal in at least a subset, and 4) they combined pancreatic exocrine sufficient and insufficient subjects in the analyses. Germane to clinical care, pancreatic enzyme replacement improves glucose excursion and GLP-1 secretion in response to a mixed meal (Fig. 3) [31].

As the CF population ages, the normal decline in β-cell function that occurs in everyone with aging may allow underlying β-cell abnormalities to become more prominent. This normal decline coupled with compromised insulin secretory capacity may then give rise to diabetes and in some cases may obscure the distinction between T2DM and CFRD.

2.1. Insulin deficiency vs. insulin resistance

Insulin deficiency is the primary defect in CFRD, but the potential contribution of insulin resistance in CF has also been explored. Insulin resistance may arise from decreased glucose uptake by muscle (peripheral insulin resistance) and through impaired suppression of hepatic glucose production (hepatic insulin resistance) [34,35]. Normal peripheral sensitivity in CFRD [36], increased peripheral but reduced hepatic insulin sensitivity [37], decreased hepatic sensitivity [38], and decreased peripheral insulin sensitivity [35] have all been observed in CF. These mixed results likely reflect differences in methodology, glucose categorization, and in the underlying state of health of the study populations. Overall, the data suggest that insulin sensitivity is preserved in CF patients who do not have diabetes [37], but modest insulin resistance is present in the setting of CFRD.

As with T2DM, insulin resistance may unmask underlying defects in insulin secretion in CF. Insulin resistance may worsen with acute pulmonary exacerbation, chronic severe lung disease, and glucocorticoid therapy [39]. Obesity (defined as BMI > 30 kg/m^2 in adults), common in T2DM, is now reported in CF and may place an additional burden on the CF endocrine pancreas. In the U.S. in 2011, median BMI among adult males and females with CF (age > 19 y) was 22.1. The University of Pittsburgh CF Center reported overweight in 13% and obesity in 7% of 233 children age 2–18 y followed at their center [40]. The 2008–2009 European Cystic Fibrosis Society Patient Registry reports maximum BMI > 30 in many countries in Europe [41]. According to the 2011 Australian CF Data Registry, nearly 43% of adult males with CF age > 30 years had BMI > 25; thus, nearly half of adult men with CF are overweight or obese [42].

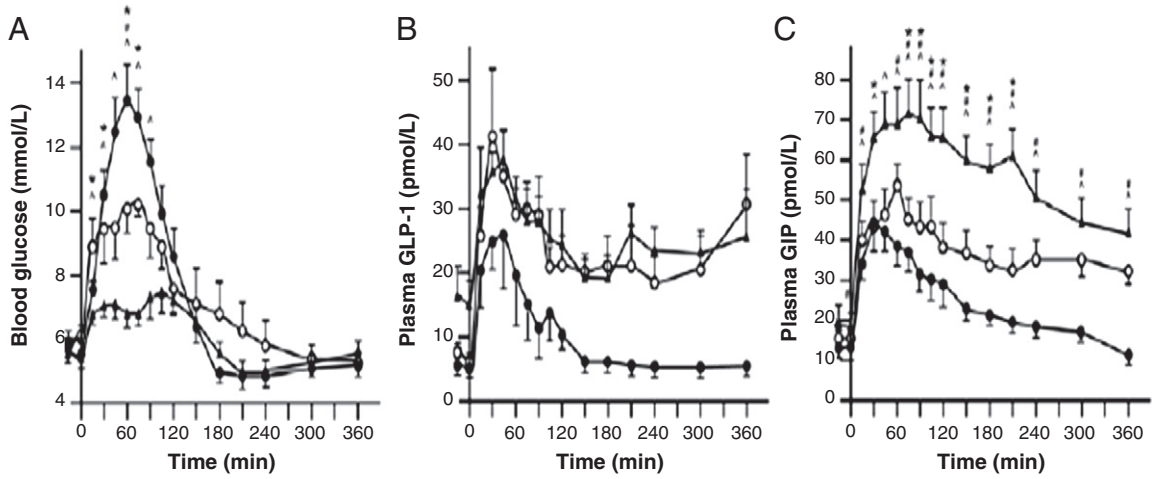

Fig. 3. Enzyme replacement improves glucose excursion and increases GLP-1 and GIP secretion in CF. Plasma glucose (A), GLP-1 (B), and GIP (C) following a mixed meal tolerance test in healthy controls (▲), CF without enzymes (O) CF with enzymes (●), adapted from Kuo et al. [31].

3. Implications and complications

3.1. Morbidity/mortality

CFRD has been associated with a nearly 6-fold greater mortality rate [43], and in the 1980's, only 25% of CFRD patients survived to age 30 years compared to 60% of the nondiabetic group [44]. Confirming data from the 1980's, CFRD has been associated with decreased survival even more recently [45–49]. Promising, however, are data associating improvements in survival with early identification and treatment of CFRD from the University of Minnesota where annual screening was initiated in the 1980's and more aggressive treatment was initiated in the following years [50], Fig. 4.

3.2. Nutritional status

Decreases in BMI have been found in the years prior to CFRD diagnosis [47], and lower BMI has been observed in CFRD patients older than 15 years with the greatest difference

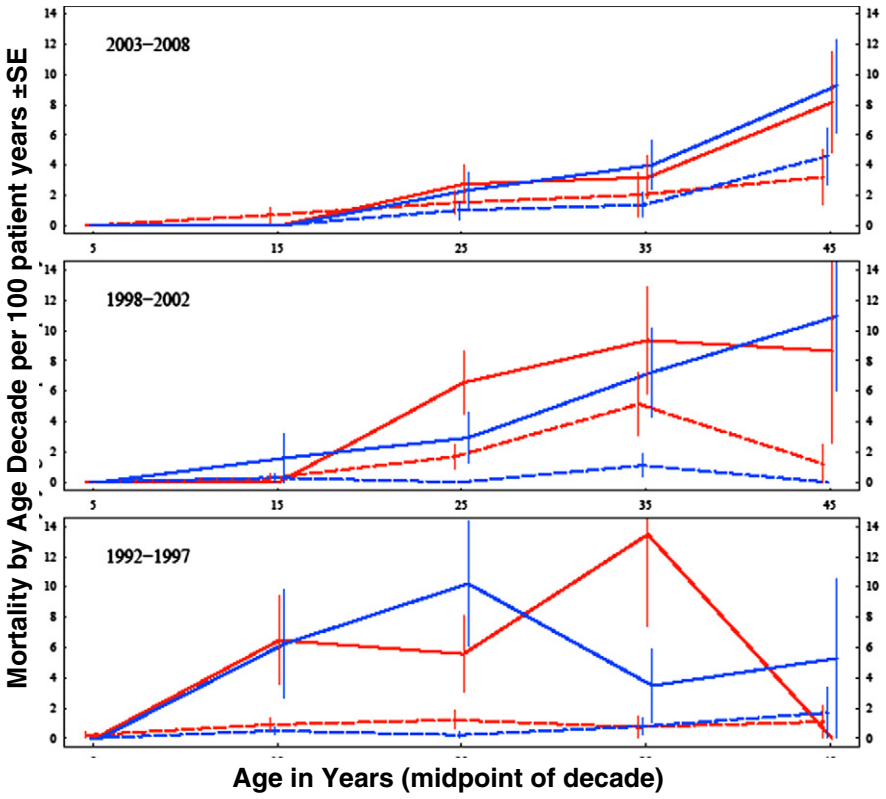

Fig. 4. Mortality in CF subjects with and without CFRD, from Moran et al. [50]. Blue line: males, red line: females; solid line: CFRD; dashed line: CFRD.

in adolescent patients aged 15–19 years [48]. In 2010, Hameed et al. found that having glucose > 140 mg/dL (>7.8 mmol/L) for ≥4.5% of the time during continuous glucose monitoring (CGM) (n = 15) predicted greater declines in weight-Z (change in weight-Z: −0.3 + 0.4 vs 0.1 + 0.2) and FEV1%-predicted (change in FEV1-percent predicted: −6 ± 7 vs −2 ± 11) over the previous year than a percentage time < 4.5% (n = 8) in adolescents defined as having NGT or IGT by OGTT [51]. These findings suggest more subtle glucose abnormalities may be clinically relevant in CF, but the extent to which these more subtle abnormalities predict future decline after adjusting for important factors such as baseline weight-Z, BMI-Z, FEV1%-predicted, and pubertal status is not yet known and the extent to which treatment of these glucose excursions impacts CF-relevant outcomes has yet to be delineated. Highlighting the role of insulin deficiency in nutritional status, a randomized control trial identified improved BMI in adults with CFRD without fasting *hyperglycemia* who were treated with insulin for a year [52]. Smaller studies have found insulin treatment improves weight in children with early insulin deficiency, even prior to development of CFRD [53–55].

3.3. Pulmonary function

The presence of CFRD is linked to worse pulmonary function regardless of age. The decline in clinical status can occur in several years before the diagnosis of CFRD is made [44,46,47]. The rate of pulmonary deterioration over a 4 year period has been correlated with the degree of insulin deficiency at baseline [46]. This finding reinforces the link between the loss of the potent anabolic effects of insulin, subsequent protein catabolism, and clinical deterioration [33], but hyperglycemia may also play a direct role in this deterioration potentially through oxidative stress. As found with nutritional status, studies of CGM have identified greater declines in pulmonary function in children with CF and greater daily glucose excursion even in the absence of CFRD as defined by the OGTT [51]. Underscoring the role of insulin in pulmonary function, insulin therapy may improve or stabilize pulmonary function in the setting of pre-diabetes and CFRD [56–58].

3.4. Microvascular complications

As in other forms of diabetes, microvascular complications occur in CFRD. The risk appears associated with the presence of fasting hyperglycemia: 16% of CFRD subjects with FH had retinopathy and 14% had microalbuminuria while none in the absence of fasting hyperglycemia had evidence of these complications [59]. Diabetic nephropathy has been confirmed histologically [60]. The prevalence is lower than with the other forms of diabetes which may stem from shorter duration of diabetes, better glycemic control, some persistence of endogenous insulin secretion, and absence of other metabolic risk factors, such as dyslipidemia and hypertension [59], although the landscape of CF is changing with both obesity [61,62] and hypertension being more commonly reported as the population ages [60]. In a much smaller group of 30 insulin treated CFRD subjects, nine of whom had history of lung transplant, Andersen et al., reported retinopathy in 27% [63]. Microalbuminuria in this group was not common although hypertension and renal impairment were found in the cyclosporine treated transplant group [63].

Autonomic neuropathy and gastropathy do occur in CFRD at similar rates to those found in T1DM [59]. Based upon the above findings, annual microvascular complication screening as occurs with T1DM is recommended in CFRD patients who have had fasting hyperglycemia for 5 years or at diagnosis if onset is not known [59]. Awareness should be heightened in groups receiving chronic nephrotoxic drugs in the setting of transplant.

3.5. Graft survival

Diabetes is also a well-recognized threat to overall survival after solid organ transplantation [64,65], but data with respect to transplant in CF and the pediatric population is limited and the extent to which diabetes impacts graft survival (liver or lung) in CF is not clear.

4. CFRD screening & diagnosis

Screening for CFRD has received increased attention over the past few years. The motivation for aggressive screening largely derives from the association of CFRD with negative outcomes. Screening is recommended because CFRD onset is usually insidious. Classical diabetes symptoms such as polyuria and polydipsia may not be evident, and other symptoms such as failure to gain or maintain weight, poor growth, and unexpected pulmonary function decline [66] are nonspecific.

4.1. Oral glucose tolerance testing (OGTT)

The majority of patients with CFRD do not have fasting hyperglycemia, and, in the absence of classic symptoms, the diagnosis of CFRD frequently relies on the oral glucose tolerance test (OGTT). As of 2010, annual screening for CFRD with an OGTT (1.75 g/kg glucose as advocated by the World Health Organization; maximum dose 75 g) starting at age 10 y was recommended by the U.S. Cystic Fibrosis Foundation (CFF) [67] and the International Society of Pediatric & Adolescent Diabetes (ISPAD) [68]. The OGTT should also be performed prior to transplant and during pregnancy. Based on the OGTT, four glucose tolerance categories are defined:

Normal glucose tolerance (NGT) = one hour plasma glucose (PG1) < 200 mg/dL (<11.1 mmol/L) and two hour plasma glucose (PG2) < 140 mg/dL (<7.8 mmol/L)

Impaired glucose tolerance (IGT) = PG2 ≥ 140 and <200 mg/dL (≥7.8 and <11.1 mmol/L)

CFRD = PG2 ≥ 200 mg/dL (≥11.1 mmol/L)

CFRD w/o fasting hyperglycemia (FH) = fasting PG < 126 mg/dL (<7 mmol/L)

Table 2
Screening & diagnostic criteria for CFRD.

OGTT	Interpretation of OGTT PG mg/dL (mmol/L)			
•Healthy outpatients (OGTT is test of choice)		Fasting PG	2-h PG	1-h PG
✓ Annually by age 10 y	NGT	<126 (<7)	<140 (<7.8)	
	IGT	<126 (<7)	140–199 (7.8–11)	
•Prior to transplant	CFRD	≥126 (≥7)	≥200 (≥11.1)	
•Prior to planned pregnancy	Indeterminate	<126 (<7)	<140 (<7.8)	≥200 (≥11.1)
•During pregnancy	Gestational diabetes	≥92 (≥5.1)	≥153 (≥8.5)	≥180 (≥10)
Fasting and 2-h post-prandial glucose (PPG) monitoring				
•During hospitalizations	CFRD	Fasting glucose ≥126 mg/dL (≥7 mmol/L)		
•Outpatient		PPG ≥ 200 mg/dL (≥11.1 mmol/L)		
•During intercurrent illness, intravenous antibiotic use, or systemic glucocorticoid use		Persisting >48 h during illness		
•Monthly during and after continuous overnight enteral feeds		≥200 mg/dL (≥11.1 mmol/L) during/after feed		
HbA1C	CFRD	≥6.5% (<6.5 does not exclude CFRD)		
Random glucose	CFRD	≥200 mg/dL (≥11.1 mmol/L) + polyuria & polydipsia		

ADAPTED FROM North American CF Consensus Committee 2010 [67].

CFRD with fasting hyperglycemia (FH) = fasting PG ≥ 126 mg/dL (<7 mmol/L)

Indeterminate glycemia (Ind-) = PG1 ≥ 200 mg/dL (≥11.1 mmol/L) but PG2 < 140 mg/dL (<7.8 mmol/L).

Few patients have completely normal glucose tolerance. Early glucose changes involve variable postprandial hyperglycemia, occurring earlier than 2 h as evidenced by frequent elevations in 30-, 60-, and 90-minute plasma glucose during OGTT [69], Fig. 2. Moreover, with respect to the "new" category of Indeterminate glycemia, recent data in non-CF suggests PG1 > 155 mg/dL (>8.6 mmol/L) may not be completely normal; PG1 at this level are a risk factor for T2DM development and are associated with early atherosclerosis [70]. The clinical relevance of PG1 in this lower range for CF is not known.

The CFF [67] and ISPAD [68] guidelines no longer differentiate whether FH is present or absent. This original distinction arose because at the time of the 1998 consensus [43], limited data were available relating mild to moderate hyperglycemia and risk of complications in CFRD and regarding appropriateness of using conventional thresholds derived from epidemiologic studies in non-CF patients [66] in whom glucose concentrations associated microvascular complications were used to define diabetes. Newer data targeting CF-relevant outcomes such as BMI and pulmonary function have provided evidence supporting treatment of CFRD even in the absence of fasting hyperglycemia [52]. Contrary to what one might expect, impaired fasting glucose is not associated with worse survival, nutritional status, pulmonary function, or progression to CFRD [71].

4.2. Random glucose monitoring

Measurement of fasting and postprandial glucose during hospitalizations for acute illness is recommended [67,68]. Hyperglycemia persisting beyond 48 h in this setting is consistent with the diagnosis of CFRD. The utility of formal OGTT over these measures during hospitalization has not been evaluated. In the outpatient setting, glucose should be measured periodically during and after continuous overnight G-tube feeds and should also be measured during intercurrent illnesses requiring intravenous antibiotics or glucocorticoid treatment [39].

Implementation of annual CFRD screening with the OGTT has been problematic for some individuals and centers, and the utility of random or post-prandial glucose monitoring as potentially more practical approach has been broached. The current guidelines combine random plasma glucose > 200 mg/dL (11.1 mmol/L) with the presence of symptoms (or during hospitalization). Extending the use of random glucose to individuals in the well state is problematic: glucose ≥ 200 mg/dL (11.1 mmol/L) is not uncommonly found at times earlier than 2 h during the OGTT but is <200 mg/dL (11.1 mmol/L) by 2 h and during continuous glucose monitoring. While these early glucose increases are likely both abnormal and reflective of defective insulin secretion, they are not synonymous with diabetes. Insufficient evidence pairing random glucose concentrations with either the OGTT or long-term outcomes is currently available to extend the current diagnostic guidelines to include random/post-prandial glucose > 200 mg/dL (11.1 mmol/L) in the absence of symptoms. A similar issue arises in the diagnosis of Type 2 diabetes but in T2DM HbA1C and fasting glucose [5] are much more useful alternatives than in CF.

Screening strategies for inpatient and outpatient care are outlined in Table 2.

4.3. Hemoglobin A1c

The majority of studies find HbA1c underestimates overall glycemic control in CF patients compared with the non-CF population. For instance, in one study, HbA1c was normal in about 70% of CFRD cases diagnosed by OGTT [34]. Thus, HbA1c is not recommended as a tool for CFRD screening. Importantly, however, while a normal HbA1C does not exclude CFRD, an HbA1C ≥ 6.5% is consistent with diabetes. A good HbA1c may also be falsely reassuring in the management of

patients with CFRD [72]. Nonetheless, while HbA1C may be spuriously low, it may still be useful for monitoring diabetes control since an elevated HbA1C is consistent with increased blood glucose and trends in HbA1c may still be followed.

4.4. Continuous glucose monitoring

CGM measures interstitial glucose which is then "translated" as blood glucose. It has been validated in both CF and non-CF patients and is frequently used to evaluate glucose trends in T1DM. In CF, mean glucose levels higher than age-matched controls have been identified by CGM [73], and postprandial glucose peaks above 200 mg/dL (11.1 mmol/L) have been observed in a third of CF subjects with NGT, half of IGT subjects, and all patients with CFRD [42]. In 2010, Hameed et al. found glucose > 140 mg/dL (>7.8 mmol/L) 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 [51]. O'Riordan reported CGM results in over 100 children with CF and found it to agree well with OGTT and to be reproducible [74]. In an abstract presented at the 2012 North American CF Conference, CGM has been identified as a useful tool in diagnosing and managing CFRD in adults with CF [75]. While CGM was not recommended by the U.S. Cystic Fibrosis Foundation as a diagnostic test for CFRD, it was considered a complementary tool in the management of CFRD. ISPAD extended the use of CGM as a potential adjunct to OGTT in diagnosing CFRD [68]. Use of CGM as a diagnostic tool for CFRD is receiving increasing attention. Glucose excursions ≥200 mg/dL (≥11.1 mmol/L) are well recognized in individuals with CF in the absence of OGTT-defined CFRD just as these same excursions are commonly found at 30-, 60-, and 90-min but not at 120 min during OGTT. While these glucose excursions are not normal, may explain declines in CF-relevant outcomes, and may be worthy of treatment, the extent to which they can be defined as CFRD has not been the subject of rigorous investigation.

5. Prevalence/incidence

The number of patients diagnosed with CFRD is rapidly increasing, possibly reflecting better surveillance and improved survival. In fact, an Australian study identified a 10 times higher incidence of CFRD (22.1 cases/1000 children and adolescents with CF) following the introduction of annual screening [76]. Data from the University of Minnesota where annual OGTT screening is recommended for all patients ≥ 6 years, find CFRD affects 2% of children, 19% of adolescents, and 40–50% of adults [50]. A study that included 24 young Italian children (age 2–5.9 years) with CF found 33% had varying degrees of glucose intolerance ranging from Indeterminate-GT to CFRD [77]. A 15 year study of 775 patients ≥ 6 years identified CFRD diagnosed by OGTT in over a third [59]. Within a 10 year period, 60% of patients with CFRD without FH progressed to CFRD with FH [59]. The annual incidence of CFRD is reported to increase with age at 5.0%/year in patients 10 + years and 9.3%/year in patients 20 + years [34]. At least in children, increased plasma glucose at 1 h during an oral glucose tolerance test predicts increased risk of progression to CFRD [78]. Other risk factors include pancreatic insufficiency and family history of diabetes.

Post-transplant diabetes is considered a distinct clinical entity, but, in the setting of CF, the etiology blurs. Stresses related to transplant, including glucocorticoids and immunosuppression with tacrolimus and cyclosporine [79–81], likely unmask the underlying β-cell defects and diabetes becomes evident. In one study, the diagnosis of CF increased the likelihood of diabetes post-transplant three times and over 50% of transplant recipients with CF developed diabetes post-transplant [82].

Gestational diabetes is not uncommon in the otherwise healthy population, and women with CF appear to be at increased for developing diabetes during pregnancy. The data regarding incidence and maternal and fetal outcomes with respect to CFRD, however, is limited.

Autoimmune T1DM can occur in the setting of cystic fibrosis. In fact, in the study by Rana et al. reporting the incidence of CFRD in Australian children and adolescents, two children were identified as having T1DM over an eight year period (an additional 49 were diagnosed with CFRD) [76]. The presence of diabetes autoantibodies and higher insulin requirements were distinguishing features. Distinguishing T1DM from CFRD is clinically relevant; T1DM greatly increases the risk of diabetic ketoacidosis and is associated with other autoimmune disease (thyroid, primary adrenal insufficiency) which may impact management.

6. Treatment

Prior to the 2009 ISPAD and 2010 CFF guidelines, the treatment of CFRD *with* FH was recommended and treatment of CFRD *without* FH was recommended only in the presence of symptoms. With newer data identifying a nutritional benefit, treatment of CFRD *without* hyperglycemia is now recommended. The role of treating pre-diabetes is now receiving increasing attention [53,54,77]. The CFRD treatment of choice is insulin.

The insulin regimen is tailored to fit the individual patient. Combinations of basal (long-acting) and bolus (rapid-acting) insulins are used in the setting of fasting hyperglycemia. Pre-meal rapid-acting insulin is the primary approach to the treatment of CFRD *without* FH.

Basal insulin formulations such as glargine and detemir last typically 18–24 h, are generally peakless, and are frequently given once daily. NPH is also long-acting but the duration of action is about 12 h, and a peak occurs around 6 h following administration; this peak can be used to address food intake that is normally planned for that time but can lead to hypoglycemia if food is not ingested. Onset of action for rapid acting insulins (aspart, lispro, apidra) is approximately 5 min with a peak action at 90 min and a duration of action of 2–3 h making it an appropriate insulin to target food intake [83,84]. Carbohydrate coverage is typically started at 0.5–1 units of rapid-acting insulin for every 15 g of carbohydrates consumed; this dose is refined to achieve postprandial blood glucose goals [39]. Extra rapid-acting insulin, the so-called "touch up" or "correction" dose may be given pre-meal if hyperglycemia is present. Frequent meals are

typical in CF and can translate into frequent injections making an insulin pump often an ideal option [85,86].

With overnight continuous enteral feeds, a single injection of NPH and regular insulin can be used to cover the ~8 h "meal" [39]; with the initiation of this regimen blood glucose is monitored periodically in the middle and at the end of the enteral feeding to help with titration of insulin doses. During intercurrent illness and systemic glucocorticoid use, insulin needs can increase dramatically — frequently doubling and even tripling.

Multiple daily injections may be rejected by some patients, as demonstrated by the drop-out rate in a recent trial [52]. Once daily detemir was associated with improved nutritional status in six newly diagnosed children/adolescents with CFRD [53], but no study has directly compared the risks and benefits of once daily vs. bolus insulin regimens in either the early stages of CFRD or as CFRD progresses. As highlighted by Hameed et al. [53], these treatment burden considerations are extremely important: insulin injections, blood glucose monitoring, and even carbohydrate counting are additional medical burdens for a population already undertaking multiple medical therapies. Such interventions may be rejected or may impact adherence with other therapies. Thus, in discussions with patients and their families regarding treatment options, the lifestyle, eating habits, physical activity, and potential barriers to insulin administration and glucose monitoring must be considered. For individuals who "graze," who decline insulin injections with meals, in whom adherence is an issue, or in whom a very simple approach is desired, a combination 70/30 insulin may be useful. Some individuals may only require insulin during overnight continuous feeds, when the majority of carbohydrates are delivered. For individuals who have minimal caloric intake at breakfast, insulin therapy is delayed until the first meal of the day. Carbohydrate counting, the mainstay of T1DM management, may be cumbersome in the setting of CF, and set insulin doses may achieve good glucose control, especially if the individual has consistent food intake at meals when insulin is delivered. In the absence of an insulin pump, insulin injections beyond 3 times per day can be excessive, and the team might focus on insulin delivery at the three largest meals of the day.

Education regarding the etiology and implications of CFRD, insulin therapy, blood glucose monitoring, treatment of hypo- and hyperglycemia, and the effects of food intake, stress, illness, and physical activity is crucial for successful partnership in the management of CFRD. "Managing Cystic-Fibrosis-Related Diabetes: An Instruction Guide for Parents and Families" is available online from the CFF (http://www.cff.org/UploadedFiles/LivingWithCF/StayingHealthy/Diet/Diabetes/CFRD-Manual-5th%20Edition-05-2012.pdf).

Oral hypoglycemic agents are currently not recommended for the treatment of CFRD [87] based upon limited data and concerns about potential side effects such as diarrhea and appetite changes (metformin, acarbose), osteoporosis and liver dysfunction (thiazolidinediones), hypoglycemia (sulfonylureas, glinides), and theoretical acceleration of β-cell loss (sulfonylureas, glinides).

Nutritional therapy is an integral part of both CF and CFRD management. Individuals with CF often require 120–150% or more of normal caloric intake for age and gender to maintain body weight, and caloric restriction is not an option in the treatment of CFRD. While carbohydrate ingestion in general is not discouraged, avoidance of specific food items high in simple sugars and low in nutritional value such as soda or sugar confection is useful to decrease the glucose excursion. Consuming such foods in combination with complex carbohydrates, protein, and fats may "soften" this excursion. Glucose excursion also appears improved when pancreatic enzymes are taken with the meal [31].

7. Hypoglycemia

The major barrier to achieving near-perfect blood glucose control in the setting of diabetes is the risk of hypoglycemia. This risk was clearly demonstrated in the Diabetes Control and Complications Trial [88], and despite newer insulin formulations and glucose monitoring tools hypoglycemia remains a reality for individuals with diabetes. Occasional, mild hypoglycemia (symptoms of hypoglycemia that do not interfere with normal activities) is anticipated in the setting of good diabetes control. This hypoglycemia generally develops as a result of 1) excess insulin — as a result of erratic absorption, increased sensitivity, or just absolute excessive administration, 2) inadequate food intake or absorption for amount of insulin administered, 3) exercise without adequate reduction in insulin dose or increase in carbohydrate intake or 4) alcohol consumption.

As with T1DM, hypoglycemia can occur in the setting of treated CFRD. CF patients have normal hypoglycemia awareness, and thus the risk of hypoglycemia is no greater in patients with CFRD than in other patients receiving insulin therapy. In the first three months of the "Cystic Fibrosis Related Diabetes Trial" mild hypoglycemia was reported in 16% of subjects randomized to pre-prandial lispro insulin [52]. Education reduced the frequency of these episodes, but curiously over the course of the study, mild hypoglycemia was also reported in the placebo group. Moreover, fasting and reactive hypoglycemia have been reported in approximately 6–15% of CF patients undergoing routine OGTT [89,90], although the frequency may be less if the strict definition of hypoglycemia (PG < 50 mg/dL, <2.8 mmol/L) is used [91,92]. In otherwise healthy individuals undergoing OGTT, the average nadir glucose is 63 mg/dL (3.5 mmol/L) and 25% of subjects have a nadir glucose of 55 mg/dL (3 mmol/L) or less; the majority of the nadir blood glucose occurring at 3–4 h of the OGTT [93]. Thus while hypoglycemia is reported in CF during OGTT, the frequency does not appear more common than occurs in individuals without CF. Moreover, PG < 60 mg/dL (<3.3 mmol/L) at 2 h during the OGTT did not predict subsequent development of IGT or diabetes in individuals with CF [90].

Glucagon is the body's major defense against insulin-induced hypoglycemia. It stimulates glycogenolysis and gluconeogenesis. In T1DM, glucagon secretion is generally lost after a few years; in a subset of patients, epinephrine is also lost after 10–15 years of T1DM. Loss of these counter-regulatory hormones in T1DM as well as resetting of normal responses due to repeated hypoglycemia can lead to hypoglycemia unawareness and severe hypoglycemia. Glucagon secretion is also impaired in CFRD [16]. While not yet reported, loss of epinephrine secretion after

long-standing CFRD and hypoglycemia unawareness with frequent hypoglycemia are not unexpected in CF.

Other causes of hypoglycemia might also be considered. With fundoplication-related late dumping syndrome, hypoglycemia arises from exaggerated insulin secretion after a bolus feed. Early hyperglycemia is a common finding, and, thus the insulin and glycemic pattern can resemble that of a subject with CF. Excessive secretion of GLP-1 has been implicated in the excessive insulin secretion [94].

Fasting hypoglycemia can also occur in the setting of adrenal insufficiency. This adrenal insufficiency might arise following withdraw of a prolonged glucocorticoid use. Additionally, adrenal crisis and hypoglycemia have been reported with inhaled corticosteroid use [95–97]. Suppression of the hypothalamic–pituitary–adrenal axis may be more common with the combination of inhaled and nasal corticosteroids [98]. The combination of inhaled corticosteroids and fluconazole, a CYP3A4 inhibitor, has been reported to cause Cushing syndrome in a child with CF [99].

8. Psychosocial impact

The diagnosis of CFRD places additional treatment burden upon an already cumbersome daily regimen for patients with CF. Limited data is available on how individuals with CF cope with the diagnosis of a second chronic illness, how CFRD affects quality of life, or how the medical team can facilitate the acceptance of the diagnosis and its intervention. As one might imagine, initial reactions range from shock to relief [100]. Several key messages from the interviews conducted by Collins and Reynolds of adults diagnosed with CFRD are worth noting for healthcare providers: the lack of awareness that diabetes develops in CF was stressful for interviewees and better diabetes support and education are desirable [100].

Given the attention now being paid to CFRD and recommendations for annual screening, awareness of CFRD as a disease entity is likely to have increased among patients with CF and their families. Parent and family education events that include sessions on CFRD may help improve this awareness. Availability of a clinical team with expertise in CFRD, a CFRD-specific educational program, and educational materials (like those available through the CFF) may also facilitate adapting to the diagnosis of CFRD. Misconceptions that the diagnosis of CFRD translates into caloric restriction are also common. Assuring patients that the diabetes team does not seek to restrict calories is a key; calories may need to be more evenly distributed through the day and sugared-soda and pure sugar candies avoided or consumed in the context of complex carbohydrate, protein and fat intake. Moreover, the management of diabetes (as with T1DM) needs to be placed into the context of one's daily life. A flexible approach to CFRD is desirable; conforming one's daily activities around insulin dosing is less than ideal.

9. Future perspectives

The mechanisms underlying insulin secretion defects and the relationships of hyperglycemia and insulin deficiency to CF status are the subject of intense investigation as are diabetes screening and the role of earlier treatment in β-cell preservation, nutritional status, and pulmonary function.

CFRD and impaired glucose tolerance are defined by the two-hour plasma glucose during the OGTT. The standard 75 g OGTT is performed in the fasting state and requires blood draws at 0 and 120 min, although many centers also obtain a glucose level at 1 h. Adherence to recommendations to obtain an OGTT yearly starting at 10 years has not been an idea — raising concerns that the fasting requirement and time commitment are prohibitive for some patients. An alternate test, such as the 50 g glucose challenge test (GCT) may be more acceptable for some patients. This test 1) has been used to screen for gestational diabetes and more recently has been found to be useful in identifying pre-diabetes and T2DM [101], 2) does not require fasting, and 3) relies on a single blood draw at 1 h. Such a test might be used to identify the subset of individuals at greater risk of CFRD and IGT and in whom the standard OGTT should be performed. A multi-center study funded by the CF Foundation to address this question is now being conducted (PI: Phillips at Emory). Additional questions regarding screening include feasibility of identifying a subset of subjects in whom performing OGTT at less frequent intervals might be safe and appropriate.

The role of the earlier treatment of insulin deficiency and glucose intolerance in CF is receiving increasing attention with the main outcomes of interest, pulmonary function and BMI. A one-year study of short acting-insulin at meals found no benefit to BMI or pulmonary function in adults with CF and impaired glucose tolerance [52], but was likely underpowered. In a subsequent study that pre-selected a less healthy CF population, glargine insulin at a dose of 0.15 units/kg/day did not impact CF-relevant outcomes, but this dose of insulin has been considered too low to provide anabolic benefit [102]. Hameed's uncontrolled study of detemir insulin, 0.1 units/kg/day, however, did identify improvements in nutritional status and pulmonary function in children with pre-diabetes [53]. A follow-up randomized trial of once daily detemir in children and adolescents by this same group is ongoing (PI: Verge, Clinical Trials.gov NCT01100892). Additional studies will hopefully better define the role of earlier treatment. Such trials include an ongoing study of sitagliptin, a medication that inhibits catabolism of incretins, that is being trialed in CF-IGT (PI: Stecenko; ClinicalTrials.gov NCT00967798). This treatment modality is particularly attractive since incretin based therapy restores first phase insulin secretion in T2DM [103] and increases β-cell number in animal models [104–106]. Until the results of these or other definitive studies are available, the routine use of insulin or other diabetes therapy for the preservation of lung function, nutritional status, and β-cell function in individuals with CF and early glucose abnormalities cannot be recommended. However, in patients with deteriorating pulmonary status who do not meet the current criteria for CFRD but in whom glucose ≥ 200 mg/dL (11.1 mmol/L) has been observed either post-prandially or during CGM, consideration may be given to insulin therapy. This consideration should include a frank discussion with the patient/family regarding the limited and conflicting data that are available, additional burden, and risk for hypoglycemia. The choice of insulin therapy, once-daily

long-acting vs. multiple rapid-acting insulin injections with meals, will require input from the patient and CF team members. The dose of insulin required to secure an anabolic state without inducing hypoglycemia is not known. The Diabetes Prevention Trial, a study that aimed to prevent T1DM development in high-risk individuals, used ultralente 0.125 units/kg BID (total daily dose 0.25 units/kg/day) without causing severe hypoglycemia [107]; weight gain over the course of the study was not described.

An extension of this question is how one defines early glucose abnormalities in CF. A one hour plasma glucose > 200 mg/dL (11.1 mmol/L) during the OGTT is defined as abnormal. Values in the 140–200 mg/dL (7.8–11.1 mmol/L) range may not be "normal," but the clinical relevance of these values has yet to be established. The one-hour plasma glucose has been associated with lower FEV1%-predicted after adjustment for BMI, but the relationship of the one-hour plasma glucose value to longitudinal outcomes has not been established [108]. Hameed et al. identified a correlation between the peak OGTT in non-CFRD children and decline in pulmonary function in the previous year [51], but this study did not adjust for potentially important covariates such as age, baseline BMI, baseline FEV1%-predicted and the extent to which this greater decline reflects higher plasma glucose vs increasing age is not clear. In the otherwise healthy population, a one hour plasma glucose > 150–155 mg/dL (>8.3–8.6 mmol/L) during the OGTT is associated with increased likelihood of progression and evidence of carotid atherosclerosis compared to individuals with NGT and one hour plasma glucose less than this threshold [70,109,110] — suggesting even those lower glucose concentrations may be relevant.

The mechanisms underlying CFRD are also being further explored. A direct role of the CF transmembrane conductance regulator (CFTR, the site of the CF chloride channel defect) in the development of CFRD has been posited. CFTR is expressed in rat and pancreatic α- and β-cells [111,112], although it is much more highly expressed in α-cells [112]. Unlike the CF knock-out mouse, the ferret CF model displays early glucose and insulin secretory abnormalities [113]. The finding of dysregulated insulin secretion in the newborn ferret suggests a primary defect in insulin secretion is operative that goes beyond the collateral damage model. These and other animal models will serve as tools for understanding the pathophysiology of CFRD.

10. Conclusions

As the CF population ages and maintains good health, the prevalence of CFRD is expected to increase and complications such as micro and macrovascular disease may become more evident. Understanding the impact of hyperglycemia and insulin deficiency on these outcomes the impact of interrupting progression diabetes on CF nutritional status, lung function and survival are goals for the near future.

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