Cystic Fibrosis–Related Diabetes Workshop: Research Priorities Spanning Disease Pathophysiology, Diagnosis, and Outcomes

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Cystic fibrosis (CF) is a recessive disorder arising from mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein. CFTR is expressed in numerous tissues, with high expression in the airways, small and large intestine, pancreatic and hepatobiliary ducts, and male reproductive tract. CFTR loss in these tissues disrupts regulation of salt, bicarbonate, and water balance across their epithelia, resulting in a systemic disorder with progressive organ dysfunction and damage. Pancreatic exocrine damage ultimately manifests as pancreatic exocrine insufficiency that begins as early as infancy. Pancreatic remodeling accompanies this early damage, during which abnormal glucose tolerance can be observed in toddlers. With increasing age, however, insulin secretion defects progress such that CF-related diabetes (CFRD) occurs in 20% of teens and up to half of adults with CF. The relevance of CFRD is highlighted by its association with increased morbidity, mortality, and patient burden. While clinical research on CFRD has greatly assisted in the care of individuals with CFRD, key knowledge gaps on CFRD pathogenesis remain. Furthermore, the wide use of CFTR modulators to restore CFTR activity is changing the CFRD clinical landscape and the field's understanding of CFRD pathogenesis. For these reasons, the National Institute of Diabetes and Digestive and Kidney Diseases and the Cystic Fibrosis Foundation sponsored a CFRD Scientific Workshop, 23–25 June 2021, to define knowledge gaps and needed research areas. This article describes the findings from this workshop and plots a path for CFRD research that is needed over the next decade.

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Cystic fibrosis (CF) is a multisystem condition arising from recessive mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) channel. This protein is expressed in numerous tissues, with high expression in epithelia of the airways, small and large intestine, pancreatic and hepatobiliary ducts, and the male reproductive tract. Loss of CFTR in these tissues disrupts salt, bicarbonate, and water movement across epithelia, resulting in progressive organ dysfunction and damage. The lungs are a particularly vulnerable site, and CF largely manifests with recurrent infections and progressively worsening lung function that leads to early death or requires lung transplant. Malnutrition, liver disease, and pancreatic exocrine insufficiency (PI) also feature in CF. CF-related diabetes (CFRD) is common, occurring in 20% of teens and up to half of adults with CF (1), largely arises from insulin insufficiency (2,3), and has been associated with worse lung function and increased mortality (1,4–6).

Despite several decades of research describing the clinical manifestations of CFRD, a firm understanding of the underlying pathophysiology remains elusive, in part due to a longstanding absence of model systems for study that faithfully recapitulate the human disease phenotype. With the recent advent of novel animal models of CF that demonstrate unprovoked glucose intolerance/diabetes, new insights from human-derived pathology specimens with specialized tools and reagents, and organ-on-chip technologies, the research community is poised to examine the chain of events in CFRD pathogenesis with unprecedented granularity. Furthermore, CF care is currently undergoing a major transformation, with the availability of CFTR modulator therapies for many (but not all) in the CF community. These modulator therapies partially restore CFTR function. The most active of these modulators (considered highly effective modulator therapies, or HEMT) result in dramatic improvements in pulmonary function, CF symptoms, disease stability, and nutritional status (7–17), the last of which has been complicated by the emergence of overweight and obesity in some people with CF (18). Further details regarding the variety of CFTR mutations and HEMT are presented in the *Genetic Risk Factors* section. The impacts of HEMT on endocrine manifestations of CF, however, remain largely unknown.

The National Institute of Diabetes and Digestive and Kidney Diseases and the Cystic Fibrosis Foundation sponsored a CFRD Scientific Workshop, 23–25 June 2021, with the goal of sharing basic and clinical research data that highlight our understanding of CFRD disease mechanisms and treatment and identify key research questions and knowledge gaps that can be used to inform research priorities. A wide range of topics was covered during this 3-day workshop, including mechanisms of disease, localization of CFTR in the pancreas, the interaction between the exocrine and endocrine pancreas, prevention and treatment of CFRD, and the effect of CFTR modulator therapy on glucose and insulin homeostasis. The following sections provide a summary of the scientific presentations and discussion, updated with interim discoveries where appropriate, that highlights research priorities as well as perspectives from a person with CF who lives with CFRD and a parent of a person with CF, sharing their lived experiences and priorities for CFRD research.

GENETIC RISK FACTORS

Over 2,000 distinct *CFTR* variants have been identified—many playing a disease-causing role in CF and others of unknown consequence (19). These variants result in a spectrum of functional CFTR impairments. CF disease severity correlates with the degree of functional CFTR impairment (20). In many populations, the most common variants cause complete or near-complete loss of CFTR function, resulting in the classic manifestations of CF, including lung disease and PI. In contrast, some of the disease-causing variants produce a CFTR protein with a small amount of residual function, resulting in somewhat milder CF disease and pancreatic exocrine sufficiency. HEMT involves small-molecule pharmaceuticals that restore CFTR protein function, for example, by improving CFTR protein folding or channel function. The specific HEMT agents used must be matched to the *CFTR* variant present in each patient. In some cases, multiple compounds are needed to sufficiently restore CFTR function. Currently employed HEMT include ivacaftor (single-drug example) and elexacftor-tezacaftor-ivacaftor (triple-combination example). F508del is the most common CF-causing allele in people of Northern European descent and is a "severe" variant that causes both CFTR misfolding and impaired channel function, with triple-combination therapy being required to restore function. G551D is another severe *CFTR* variant, impairing channel function in a manner that can be robustly restored with ivacaftor alone. HEMT are, of course, not effective for persons with two *CFTR* null alleles, and HEMT have yet to be identified for various other *CFTR* variants. Readers interested in further details are referred to recent reviews on *CFTR* variants and HEMT (19,21).

The risk of CFRD depends in part on the degree of residual CFTR function produced by a person's two *CFTR* variants (i.e., the *CFTR* genotype). In general, genotypes that cause severe CFTR dysfunction and PI confer a high risk of developing diabetes over time (6,22). Milder *CFTR* genotypes associated with pancreatic exocrine sufficiency exhibit lower risk of CFRD (6,22). A survivor bias in the CFRD prevalence statistics should be acknowledged, as people with severe *CFTR* genotypes historically tended to have earlier mortality. Individuals with severe *CFTR* genotypes, such as F508del homozygotes, historically have had a risk of developing diabetes exceeding 80% by age 50 years (4) and approaching 100% by age 60 years.

Even though people with severe *CFTR* genotypes have a very high lifetime risk of CFRD, the age of onset of CFRD remains highly variable, ranging from younger than 10 years to greater than 60 years, even in people with identical *CFTR* genotypes (6,22). The genetic contribution to this diversity in CFRD risk is determined largely by genetic variations outside the *CFTR* locus—so-called genetic modifiers. Genetic

association studies, using both candidate gene and genome-wide approaches, have identified a number of genetic modifiers of CFRD risk (23). Some genetic modifiers of CFRD risk appear to also be associated with other aspects of CF disease (e.g., variants at *SLC26A9*, encoding an epithelial chloride channel, and *PRSS1*, encoding cationic trypsinogen) (24,25). These variants can provide insight into pathogenesis of CFRD and other aspects of CF disease and could lead to studies of novel therapies for CF. Other CFRD modifiers appear to affect the risk of CFRD but do not directly affect other aspects of CF (e.g., variants at *TCF7L2*, a risk variant for type 2 diabetes) (26). Modifier variants associated with CFRD overlap with variants that affect risk of type 2 diabetes and other glucose metabolic abnormalities in the general population (26). The biology that underlies this association is not clear but may represent β-cell susceptibility to stressful conditions. In contrast, risk alleles for type 1 diabetes have not shown strong evidence of association with CFRD risk (26,27).

Understanding the relationship between *CFTR* genotype and CFRD risk may provide insight into CFRD pathogenesis and could help inform possible outcomes in individuals whose CFTR is partially rescued by CFTR modulator medications. Understanding and identifying genetic modifiers of CFRD can aid in elucidating the mechanisms of CFRD pathogenesis and how CFRD relates to other complications of CF. Genetic modifiers might also be used to help predict risk of CFRD or related outcomes. Genetic modifiers may themselves provide novel CFTR-independent targets for new therapies, which might be of utility in people unable to benefit from CFTR modulator treatments.

Provocatively, genetic variations in the *CFTR* locus that do not cause CF, either by carrier status (heterozygosity) or nature of the mutation, have shown epidemiological or mechanistic association with type 1 diabetes (27,28).

Priority research opportunities to address knowledge gaps include the following:

- Expand knowledge on the genetic heterogeneity and diversity of CFTR variants and their relationship to CFRD risk.
- Obtain deeper understanding of those genes other than *CFTR* that modify risk of CFRD to further understanding of the pathophysiology of CFRD.
- Leverage in vitro cell and in vivo animal models to understand the insulin secretion defects that underlie clinical phenotypes of abnormal glucose tolerance.
- Determine if or how genetic information aids in risk stratification of CFRD and related outcomes.
- Evaluate if or how CFTR variant carriers are at increased risk of type 1 or type 2 diabetes.

RESEARCH PRIORITIES FOR UNDERSTANDING BIOLOGICAL UNDERPINNINGS OF CFRD

Several decades of human clinical investigation have consistently established that diminished insulin secretion is the dominant cause of CFRD (2,3). Insulin secretion is impaired even in CF subjects without diabetes, in whom diminished first/early-phase insulin secretion is chiefly affected (29). A degree of insulin resistance, especially hepatic insulin resistance, has been demonstrated by euglycemic hyperinsulinemic clamps (30), but this insulin resistance does not appear to be a major or essential feature in CFRD. Speculation has arisen that HEMT will alter the broad pathologic features of CFRD (31).

The presence of CFRD is tightly linked to PI (32). CF exocrine pancreatic disease is characterized by a near-total loss of acinar cells, ductal dilation, fibrosis, and fatty replacement. Histopathologic studies of human cadaveric CF pancreas suggest that the endocrine component is relatively spared compared with the extensive exocrine tissue loss, partial loss of β-cell mass, altered islet composition (increased non–β-cells), islet remodeling, and expression of inflammatory molecules are all evident (33–37). Emerging areas of research include studies that investigate perturbations of nonendocrine pancreatic cells, such as vascular cells, neural elements, and leukocytes.

Factors external to the pancreas may also impair β-cell function in CF. For example, incretin secretion and incretin responses are impaired in PI CF (38–40). How each of these components might be affected by HEMT is an important unanswered question. Another area of biological inquiry is the cellular localization of CFTR in the pancreas. *CFTR* is predominantly expressed in the epithelial cells of the small ducts. Studies using several approaches, including single-cell RNA sequencing and carefully validated CFTR protein staining, show that only a minority of β-cells (∼3%) express any *CFTR* message, all at low abundance, with <1% demonstrating CFTR protein staining (33,41,42). Likewise, CFTR mRNA expression is absent or minimal in all endocrine cell types of the islet (33,42). However, others have suggested that as much as 30% of β-cells express small amounts of *CFTR* transcript and protein (43). Functional studies evaluating CFTR-mediated current in β-cells and islet insulin secretion in response to a CFTR channel blocker (CFTR-inh172) have produced contradictory findings in favor (43,44) and against (33) a functional role for CFTR in β-cells. Whether important β-cell–intrinsic CFTR actions arise from a subpopulation of β-cells and/or from communication with neighboring ductal cells is the subject of ongoing debate.

Understanding the biology underlying CFRD may not only help identify targeted treatments and preventative strategies but also yield important knowledge regarding endocrine–exocrine interactions in the pancreas relevant to other forms of diabetes.

Priority research opportunities to address knowledge gaps include the following:

- Determine how CF exocrine pancreatic disease impairs islet function, including understanding of the relative roles of local factors, such as altered islet vasculature, innervation, inflammation, islet remodeling, and redox imbalance.

- Characterize how altered incretin secretion and incretin responsiveness affect CFRD development.
- Determine the CFTR-expressing cell types essential to maintain proper islet function and avoid diabetes.
- Identify the developmental stages during which CFTR function is critical for the long-term prevention of CFRD.

DEVELOPMENT OF MODEL SYSTEMS TO STUDY CFRD, PANCREATIC REMODELING, AND REGENERATION IN CF

The development of CFRD is multifactorial and may involve contributions from multiple organ systems, including nonpancreatic organs. The CF field has an array of models that recapitulate different aspects of CF disease (Table 1); however, models that reflect human pathophysiology in the pancreas and the development of CFRD are limited. Small-animal CF models, such as mice and rats, do not spontaneously develop exocrine pancreatic disease or a CFRD phenotype (45), and thus the number of studies evaluating glucose homeostasis in CF mice is limited. However, treatment with low-dose streptozotocin can result in abnormal glycemic control associated with the loss of islets, providing a model for studying the role for inflammation in β-cell injury and CF glucose homeostasis (46,47). There is significant debate about whether CFTR functions within endocrine cells of mice, and some evidence shows that CFTR impacts β-cell insulin (48) and α-cell glucagon (49) secretion in isolated CF mouse islets (48). Others have shown that β-cell–specific deletion of the *Cftr* gene in mice has no impact on glucose tolerance or islet insulin secretion (33). An additional study suggests that insulin-induced glucose transporter 4 translocation to the cell membrane of muscle fibers was abnormal in the *Cftr* knockout mice (50), suggesting that CF mouse models have utility in studying glucose homeostasis controlled by insulin responses in the periphery.

In contrast to the small-animal models, several large animals, including the CF ferret (51), CF pig (52), and CF sheep (53), develop spontaneous exocrine pancreas pathology similar to that of humans. However, only CF ferrets and pigs have been studied in the context of endocrine physiology and glucose regulation, which may uniquely position these models for studying mechanisms of CFRD pathogenesis. The CF pig model exhibits glycemic abnormalities, insulin secretion defects, and significant exocrine pancreatic pathology at birth (52,54), which is characteristic of the more extensive pancreatic damage seen in young human patients with CF. In contrast, the CF ferret presents with very mild pancreatic pathology at birth with progressive loss of endocrine and exocrine pancreas function during the first few months of life (51,55–57).

Pancreatic enzyme–secreting acinar cells compose the majority of the exocrine pancreas, and the destruction of this cell type leads to PI. The CF pancreas undergoes substantial remodeling associated with the clearance of the acinar cell compartment. CF ferret models have assisted

Table 1—CF organ phenotypes in mammalian animal models

Model species	Spontaneous lung infections	Lung mucus defects	Impaired growth	Intestinal pathology	Exocrine pancreas destruction	Endocrine pancreas dysfunction^	CFRD	Hepatic pathology	Gallbladder pathology	CFTR modulator responsive genotypes	References
Human	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Many	
Pig	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	G551D, F508del	54,130–133
Sheep	Unknown	Glands	Unknown	Yes	Yes	Unknown	Unknown	Yes	Yes	F508del	53,134
Ferret	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	G551D, F508del	42,51,55–57,60–62,135,136
Rabbit	No	No	Yes	Yes	No	Unknown	No	No	No	F508del†	137,138
Rat	No	Glands	Yes	Yes	No	Unknown	No	No	NA	Humanized G551D*	139–143
Mouse	No	No	Yes	Yes	No	Mild to none	No	No	No	Humanized G551D, F508del*	33,46–48,144–147

NA, not applicable since the organ does not exist in this species; glands, limited to submucosal gland mucus accumulation and/or obstruction; unknown, not yet studied; mild to none, some studies show certain abnormalities following β-cell injury with streptozotocin. ^Endocrine pancreatic dysfunction means alterations to glucose metabolism and insulin secretion. †F508del rabbit model has been generated, but it remains unknown if the rabbit mutant CFTR is responsive to CFTR modulators. *Mouse and rat CFTR mutants are not responsive to CFTR modulators, thus humanized models were generated that either randomly insert the human *CFTR* mutant gene locus into the mouse genome or insert a *CFTR* mutant cDNA into the rat *Ctfr* locus.

in defining phases of exocrine and endocrine pancreatic remodeling and how these events impact glycemic status. Juvenile, but not neonatal, *CFTR* knockout ferrets have spontaneous fasting and postprandial glucose excursions above 200 mg/dL between 1 and 2 months of age, a time when mRNA and protein markers of functional islets decline and inflammation and fibrosis peak (51,57). This phase is followed by rapid expansion of islets and a glycemic recovery at about 3 months of age, when adipose tissue begins to expand within the pancreas (55,57). As CF ferrets age into adulthood, islet dysfunction, insulin insufficiency, and glucose intolerance return.

Key questions pertain to the processes that control islet resurgence in juvenile CF ferrets and how these events may ultimately impact endocrine cell fate and function later in life. Two progenitor cell populations that could participate in islet expansion include dedifferentiated endocrine cells and/or ductal cells that adopt the phenotype of bipotent ductal progenitors formed during pancreatic development. In support of the latter hypothesis are changes in CF ductal cell phenotype that implicate upstream regulators known to participate in the specification of endocrine cells from ductal progenitors during pancreatic development (58). New transgenic ferret models capable of fate mapping these cellular compartments are being used to understand the origins of progenitors that participate in CF pancreatic remodeling (59). The recent creation of CFTR modulator-responsive CFTR-G551D ferrets is also enabling dissection of how the age of pancreatitis onset in CF impacts long-term islet function and the reversibility of these defects (60–62). Other CFTR modulator-responsive mutant animal models, including those for pig, sheep, and rabbit as well as humanized CFTR mutant models of mice and rats (Table 1), have been subject to fewer CFRD-focused studies.

In addition to in vivo studies of the development of CFRD and other pancreatic complications, CF ferrets and pigs have also proven to be valuable as in vitro models to study insulin secretion by islets isolated from CF and non-CF animals. Studies in CF pig islets have recently shown that oxidative stress may impair islet insulin secretion (63). Total insulin content was lower in CF ferret islets than in non–CF ferret islets, and perfused CF islets had impaired glucose-stimulated insulin secretion for all phases of section (first, second, and amplifying phases) (42). Under static low-glucose conditions, CF islets compensated for lower insulin content by secreting a greater fraction of total islet insulin than non-CF islets (42,51). CF islets also secreted higher levels of IL-6, which may be responsible for the elevated expression of glucose transporter SLC2A1 and higher basal intracellular Ca^{2+} compared with non-CF islets (42). Additional in vitro models using CF ferrets have included the development of polarized ductal epithelium to study paracrine mechanisms by which the exocrine compartment may influence endocrine function (58). These studies evaluated the secretome and cellular proteome of polarized non-CF ferret and CF ferret ductal epithelia using mass spectrometry. These studies demonstrate a number of signaling pathways are dysregulated in ductal epithelium in vitro, and these findings were confirmed in vivo (58). Notably, reconstitution experiments in isolated islets confirmed the impact of an altered CF secreted factor on islet insulin secretion, suggesting that this model is useful for dissecting paracrine exocrine/endocrine signaling abnormalities in CF and their impact on islet function and maintenance.

Research priorities include the following areas:

- Define the cellular origin of expanding endocrine cells following acinar cell clearance in the CF pancreas.
- Elucidate mechanisms of pancreatic acinar cell regeneration on HEMT and the developmental window in which this can occur.
- Define the endocrine cell–intrinsic and –extrinsic factors that lead to impaired islet function in CFRD.
- Identify blood-borne molecular biomarkers that report CF pancreatic disease states and predict clinical outcomes and responses to treatment.

DYSGLYCEMIA AND CFRD SCREENING AND DIAGNOSIS

How best to screen for and diagnose CFRD remains a challenge. At present, the recommended screening test for CFRD is the oral glucose tolerance test (OGTT) performed annually in all people with CF by age 10 years (22). Abnormal glucose tolerance (defined as impaired glucose tolerance [IGT] [2-h OGTT glucose 140–199 mg/dL], indeterminate glucose tolerance [1-h OGTT glucose ≥200 mg/dL with 2-h OGTT glucose <140 mg/dL], and the more recently defined early glucose intolerance [1-h OGTT glucose ≥155 mg/dL with 2-h OGTT glucose <140 mg/dL]) is common in CF (22,29). Rates of disease progression to frank CFRD vary (64,65), and studies are now examining the role of the 1-h OGTT glucose as well as peak glucose prior to 2-h glucose in predicting the subsequent emergence of CFRD (66). Data on the clinical relevance of early dysglycemia across the life span in people with CF are otherwise conflicting (67–70). Similarly, OGTT and continuous glucose monitoring (CGM) identify dysglycemia (glucose excursion to ≥200 mg/dL) even in very young children (67,71), but the clinical significance of insulin insufficiency and dysglycemia in toddlers is unknown.

Not unexpectedly, annual OGTTs are perceived as burdensome, and adherence to current CFRD screening guidelines is poor (72). Increasingly, CGM technology is being utilized to characterize dysglycemia in people with CF, but larger studies are needed to identify the appropriate CGM variables and thresholds for guiding clinical decision-making. As the landscape of CF continues to evolve, particularly with increasing use of HEMT, the identification of alternative CFRD screening approaches that will not only detect clinically meaningful outcomes but also be feasible and acceptable to providers and patients is needed. These alternative

approaches include considerations of frequency of OGTT given patient characteristics and previous OGTT results.

Research priorities include the following:

- Prospective, longitudinal studies to identify the clinical effects of early dysglycemia as well as optimal OGTT glucose thresholds that will predict CFRD and clinical outcomes relevant to people with CF.
- Studies to better understand the early pathophysiology of CFRD, including drivers of disease progression, and the timing and type of interventions needed to slow/prevent progression to CFRD. Questions to be addressed include the optimal age to start screening for CFRD, how best to identify subpopulations at highest risk for disease progression, and what impact the introduction of novel CF therapeutics at different ages may have on the natural history of CFRD.
- Investigation of *1*) alternatives to the traditional OGTT, including sampling from blood spots for at-home testing and CGM, which are less invasive and time-intensive methods and that are administered with more personalized frequency, and *2*) novel biomarkers (breath testing or sputum) for quantifying dysglycemia.

RESEARCH PRIORITIES TO ADDRESS THE IMPACT OF NUTRITION ON CFRD

Prevention of malnutrition, both undernutrition and overweight/obesity, and achievement of adequate nutritional status are major goals in the management of CF because of the strong links of nutritional status with both lung function and survival (73,74). Current dietary recommendations are to consume an unrestricted, high-calorie, high-fat diet to offset persistent fat malabsorption and increased energy expenditure and to achieve sex-specific BMI recommendations (75). The introduction and now-widespread use of HEMT have resulted in weight and BMI status improvements in many patients (76). The mechanisms responsible for weight gain with HEMT are not well defined but likely include decreasing resting energy expenditure, systemic and gut inflammation, and fat malabsorption (77).

Current research indicates that consumption of the typical or "legacy" CF diet translates to poor-quality diet patterns, evidenced by intakes of saturated fats and added sugars above recommendations for the general population (78). Motivated by increases in BMI, many CF centers have adopted recommendations from the World Health Organization, American Heart Association, and Dietary Guidelines for Americans to limit added sugars (79–81), while the Cystic Fibrosis Foundation has organized experts in the field to update current nutrition guidelines. Moreover, such poor-quality diets are known risk factors for glucose intolerance and diabetes in general non-CF populations (82).

However, CFRD is unique in its pathophysiology compared with more common types of diabetes (83), and the role that nutrition has in CFRD development, prevention, or management must be studied as such. Whether poor-quality diets contribute to onset or progression and severity of CFRD is unknown, as is the role of specific nutrients and diet patterns, whether positive or negative, on insulin secretion and sensitivity in individuals with CF. Further, with a small but rising prevalence of overweight and obesity among those with CF (84), the impact of increased adiposity, compounded with increasing age of survival on CFRD development and other age-related comorbidities, is an important area of study. It is critical to acknowledge, however, that underweight status in adults and growth faltering in children and adolescents remain prevalent in individuals with CF (72). The persistence of underweight status is especially evident in people with genotypes that are not eligible for currently approved HEMT. Malnutrition/underweight, as defined by BMI status, is a risk factor for CFRD, which is a further challenge to the recommendations (85). Thus, nutritional status assessment and dietary recommendations, including individualized caloric recommendations, must account for the need to prevent growth failure and malnutrition as well as prevent excess adiposity. The current CF landscape provides opportunities to shift nutrition research in CF from a focus solely on quantity of calories, macronutrients, and BMI to include the quality of calories and micronutrients and impacts on body composition, metabolic disease risk, and functional and quality-of-life outcomes. Such dietary components may include strategies to increase consumption of complex carbohydrates and unsaturated fats while individualizing nutritional recommendations and weight goals.

Priority research opportunities to address gaps in the role of nutrition on CFRD include the following:

- Determine effects of changes in diet quality of macronutrients (for example, glycemic index/load, saturated vs. unsaturated fatty acids, and plant vs. animal proteins) on risk for CFRD and management of CFRD.
- Define adequate nutritional status to include body composition assessment and novel biomarkers in people with CF.
- Determine caloric, macronutrient, and micronutrient needs in children and adults taking HEMT.
- Specify dietary recommendations, including calorie needs, and associated behavioral intervention strategies for individuals who are overweight/obese and those who are underweight or have growth failure.
- Determine the role of body fat distribution on CFRD-related outcomes.
- Assess long-term changes in nutritional status in children and adults taking HEMT.

EFFECTS OF HEMT ON CFRD

Advances in CF care, including use of HEMT, have contributed to improved health and survival, but the impacts of aging and better nutritional status, as well as overweight/obesity, on the emergence and progression of insulin secretion defects, insulin resistance, and glucose abnormalities remain unclear. Small studies have documented short-term improvements in insulin secretion and glucose excursion/

tolerance with ivacaftor (31,86), while U.S. and U.K. registry data demonstrate trends toward lower CFRD rates in the 4–5 years following the introduction of ivacaftor treatment (87). In contrast, glucose tolerance improved following 1 year of the CFTR modulator therapy combination lumacaftor-ivacaftor in a French multicenter study of 40 F508del homozygous individuals age >12 years with IGT or CFRD (88) but not in the U.S.-based PROSPECT (A Two-Part Multicenter Prospective Longitudinal Study of CFTR-Dependent Disease Profiling in Cystic Fibrosis) study of lumacaftor-ivacaftor (89) or in a more limited Italian study of six individuals with either dysglycemia or CFRD (90). More recent CGM data from adults with and without CFRD identified improvements in hyperglycemia and glycemic variability with the introduction of the triple HEMT combination elexacaftor-tezacaftor-ivacaftor (91).

The contributions of direct potentiation of insulin secretion by β-cell CFTR modulation versus indirect insulin secretion improvements secondary to reductions in systemic or peri-islet inflammation remain undefined. Nodding toward direct islet action, CFTR inhibition led to impaired glucagon-like peptide 1 (GLP-1) and forskolin-augmented glucose-potentiated insulin secretion in in vitro murine and human islet studies (44). In contrast, additional studies identified very low CFTR RNA expression in β-cells (24,33,92,93) and absent CFTR protein coexpression with insulin-positive, glucagon-positive, or somatostatin-positive cells in human islets. Moreover, CFTR modulators and inhibitors did not appear to impact in vitro insulin secretion in human islets even at high glucose concentrations (33). These inconsistencies may be attributed to the nonspecificity of CFTR inhibitors, since insulin secretion is similarly reduced by CFTR inhibitors in isolated human, wild-type ferret, and *CFTR* knockout ferret islets (42).

The Cystic Fibrosis Foundation-funded PROMISE (A Prospective Study to Evaluate Biological and Clinical Effects of Significantly Corrected CFTR Function) endocrine substudy has been organized to test the impact of elexacaftor-tezacaftor-ivacaftor on glucose excursion, insulin secretory rates, suppression of glucagon, and incretin secretion using 3-h OGTT performed at baseline and at 12–18 and 24–30 months after elexacaftor-tezacaftor-ivacaftor initiation (94). This study will also test the relationships of changes in OGTT outcomes with changes in BMI, body composition, pulmonary function, and, potentially, systemic inflammation, liver stiffness, and gastrointestinal health, including recovery of pancreatic insufficiency as measured by fecal elastase.

Priority research opportunities to address gaps regarding the relationships between HEMT and CFRD include the following:

- Determine the role of HEMT in improving glucose tolerance and delaying or altogether preventing CFRD development.
- Define mechanisms responsible for glucose tolerance and insulin secretion improvements produced by HEMT.
- Determine patient characteristics responsible for the variability in glucose tolerance and insulin secretion produced by HEMT.
- Explore the time frame for and durability of improvement in glucose excursion and insulin secretion/sensitivity produced by HEMT.
- Determine whether the underlying propensity to diabetes persists in people with CF receiving HEMT and whether this predisposition is unmasked with overweight/obesity and aging despite HEMT.
- Clarify whether initiation of HEMT at a young age, potentially even in infancy, impacts β-cell survival and diabetes progression.

CURRENT GAPS IN CFRD CARE AND USE OF NOVEL TREATMENT APPROACHES IN DISEASE MANAGEMENT

The diagnosis of CFRD has been associated with a decline in lung function, increase in pulmonary exacerbations, compromised nutritional status, and earlier mortality (22). Studies have found that elevated glucose concentrations in airway surfaces of people with CFRD promote bacterial growth and exaggerated but less effective inflammatory responses (95–98). Concomitantly, pulmonary exacerbations often cause increased insulin resistance and worsen hyperglycemia. Further studies are needed to understand the impact of hyperglycemia on pulmonary exacerbations as well as the most effective approach to glycemic management during acute illness.

CFRD management, including insulin administration, carbohydrate counting, and glucose monitoring, adds a significant burden to the medical care of people with CF. The recommended glycemic targets for CFRD are based on those developed for type 1 and type 2 diabetes for the prevention of microvascular complications (22). Whether achieving these targets leads to beneficial effects on CF-specific outcomes, such as pulmonary function and nutritional status, is unknown.

Recent advances in diabetes technology have shown promise in improving glycemic control and quality of life in people with type 1 diabetes (99–111), but studies are limited in CFRD. A recent survey of adults with CFRD and parents of children with CFRD suggested that sustained use of diabetes technology, including CGM and insulin pumps, was low and that strategies are needed to improve insurance coverage and patient education along with research to confirm efficacy and acceptability (112). Although CGM-guided insulin initiation was associated with slowing of the annual rate of pulmonary decline over 12 months (113), no published studies have investigated the effect of CGM on glycemic control or quality of life in people with CFRD managed with insulin. A retrospective multicenter study of 13 adolescents and adults with CFRD found that transition to a hybrid closed-loop pump, an artificial pancreas device that automatically modulates insulin administration based on real-time CGM data, increased time spent in the target glucose range (114);

however, prospective studies with patient-reported outcomes are not available. After promising results were noted in a small pilot study (115), studies investigating a fully automated artificial pancreas device with or without coadministration of glucagon are currently underway in children and adults with CFRD (NCT03258853).

At present, insulin is the only recommended treatment for CFRD, as it has an established anabolic effect of improving BMI, which has not been observed with other therapies (1). Whether initiating insulin in those with abnormal glucose tolerance leads to metabolic improvements is currently under study (NCT02496780). However, with the advent of HEMT, many patients with CF no longer struggle with undernutrition, and rates of overweight and obesity are increasing (84,116). The emergence of overweight/obesity and the overall improved health of people with CF have led to rising interest in the role of nutritional interventions and noninsulin therapies, including medications used for the management of type 2 diabetes, as alternative strategies to prevent or delay the need for insulin therapy. Oral agents currently used to treat type 2 diabetes tested to date have not demonstrated efficacy in CFRD (117,118). However, limited studies that examine the benefits of glucagon-like peptide agonists or dipeptidyl peptidase-4 inhibitors as treatment alternatives to insulin show promise (118,119).

Key research priorities include the following:

- Understand how glycemia affects pulmonary exacerbations and determine the best approach for managing hyperglycemia in the setting of acute illness in people with CF.
- Investigate the impact of diabetes technology, including CGM and artificial pancreas devices, on glycemic control, quality of life, and other important patient-reported outcomes in CFRD.
- Identify CFRD-specific glycemic targets not only to optimize pulmonary and nutritional outcomes but also to prevent microvascular complications.
- Clarify whether early initiation of insulin during the stage of abnormal glucose tolerance (prediabetes) has beneficial effects on nutritional and pulmonary outcomes.
- Explore the potential role for noninsulin therapies in the management of abnormal glucose tolerance and CFRD, particularly in those who are overweight or obese.

CFRD HEALTH CARE DELIVERY AND PATIENT OUTCOMES

Chronic complications in CFRD, other than the detrimental impacts on lung function and nutrition, are rarely addressed. Microvascular and macrovascular complications pose a large disease burden for individuals living with type 1 diabetes and type 2 diabetes (120,121). Historically, vascular complications related to CFRD were rarely observed, and this was thought to be due to the shortened life span (122,123). With advances in CF care, individuals are living longer, and theoretically the toll associated with vascular complications of CFRD could increase (122). Microvascular complications in CFRD have appeared to be less severe than those in other forms of diabetes (122), and macrovascular complications generally have been thought to be nonexistent. With the introduction of HEMT, we soon will have an aging CF population with increasing BMI and less malabsorption. This aging of the population and emergence of overweight/obesity will necessitate closer surveillance for the development of microvascular and macrovascular disease in CFRD. Also incumbent upon all CF diabetes providers is the education of patients about chronic complications in CFRD. Coordinated care from a multidisciplinary team with expertise in CF and diabetes may bridge this gap and provide anticipatory guidance around the treatment course of diabetes and its possible complications.

Disease burden from diabetes is understudied in the CF community, particularly as it impacts communities of color. Non-White individuals with CF tend to have a later diagnosis of CF and significantly lower BMI than their White counterparts (124). Furthermore, they are more likely to have rare *CFTR* variants that are not amenable to HEMT. In other forms of diabetes, non-Hispanic Black and Hispanic individuals tend to have higher rates of morbidity and mortality than non-Hispanic White individuals (125–129). The impact of race and ethnicity on CFRD course has not been explored. Understanding the disease burden could inform providers, address equity gaps, and provide preventive and tertiary care that strives to achieve equitable outcomes.

Finally, the complexity of CFRD and the differences from other forms of diabetes point to the need for endocrinologists with specific training in CFRD. Ideally, such individuals would become integral members of the interdisciplinary CF health care team. The Cystic Fibrosis Foundation established the EnVision CF program with the goal of providing mentored CF clinical and research training to adult and pediatric junior faculty endocrinologists to expand the pool of physicians with expertise in CF endocrinology and diabetes. Thirty-six physicians have completed or are enrolled in the program, with a new cohort of twenty physicians starting in July 2023.

Key research priorities include the following:

- Determine the incidence and prevalence of macrovascular and microvascular disease in CFRD with a particular emphasis on understanding racial, ethnic, and social determinants contributing to health outcomes and disparities.
- Examine the impact of social determinants of health, race, and ethnicity on CFRD and relevant outcomes.
- Continue the development of endocrinologists with training in CFRD and new programs to provide this training to nurse and dietitian certified diabetes educators to provide diabetes multidisciplinary care to the pediatric and growing adult CF population.

PATIENT AND FAMILY PERSPECTIVES

Including the voice of patients and families currently living with CFRD is critical for prioritizing research opportunities. A young adult with CFRD and a mother of an adult

with CFRD joined the workshop to discuss daily life experiences with CFRD as well as to propose research priorities from the perspective of a patient and caregiver.

CFRD adds a substantial burden to an already onerous disease. The burden of a comorbidity that demands daily glucose monitoring, multiple daily injections or use of an insulin pump, physical discomfort from hypoglycemia and hyperglycemia, and risk of diabetes complications can negatively impact quality of life.

The speakers highlighted the mental and emotional toll of dealing with two demanding chronic diseases that are interdependent: when diabetes is not controlled, lung function suffers, and during a CF pulmonary exacerbation, blood glucose levels are often unstable. In addition, some medications used to treat CF, such as corticosteroids, make blood glucose control endlessly challenging.

Both speakers emphasized the lack of access to practitioners knowledgeable of CFRD. Many endocrinologists are not familiar with treatment guidelines for CFRD or how CFRD differs from type 1 or 2 diabetes. Since endocrinologists are often not included in the CF care team, diabetes care plans are often written without consideration of current treatment plans for CF, ignore possible medication interactions, and overlook added treatment burden. In addition, the separately scheduled visits result in more missed time from work or school.

As the CF population ages due to the advent of HEMT, long-term effects of CFRD should become a vital area of research focus. The addition of these long-term complications of CFRD to the already daunting complications of CF significantly increases the physical and mental health burden on patients.

Potential research opportunities and priorities include the following:

- Education and training of additional multidisciplinary practitioners familiar with CFRD and integration of these professionals into the CF care team.
- Prevention and treatment of long-term complications of CFRD.
- Advancement in treatments such as
  - Artificial pancreas technology
  - Optimization in the presence of frequent illness and CF medications
  - Noninsulin therapies to treat CFRD
- Prevention or delayed onset of CFRD and treatment options during prediabetes stage.

CONCLUSION

While the pathophysiology of CF lung disease has received significant attention over time and has resulted in significant improvements in patient outcomes, many of the extrapulmonary manifestations of the disease, including CFRD, are still understudied. As people with CF are living longer, the number of people who develop CFRD is expected to increase. However, many unanswered questions remain regarding CFRD pathogenesis, risk factors for developing CFRD, the impact of CFRD on CF outcomes as well as on more traditional diabetes outcomes such as microvascular disease, and optimal strategies for diagnosis and treatment. In addition, how the introduction of HEMT into clinical care may affect the development and/or progression of CFRD remains unknown. This workshop focused on the latest scientific research regarding CFRD disease pathophysiology as well as critical basic and clinical research gaps that should be prioritized. Addressing these priorities has the potential to produce meaningful change in our understanding of CFRD and its diagnosis, management, and long-term impacts on health outcomes. Further, including the voice of CF community members is critical to ensuring that these priorities speak to the needs of people with CF, including treatments that are feasible and positively impact their quality of life.

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