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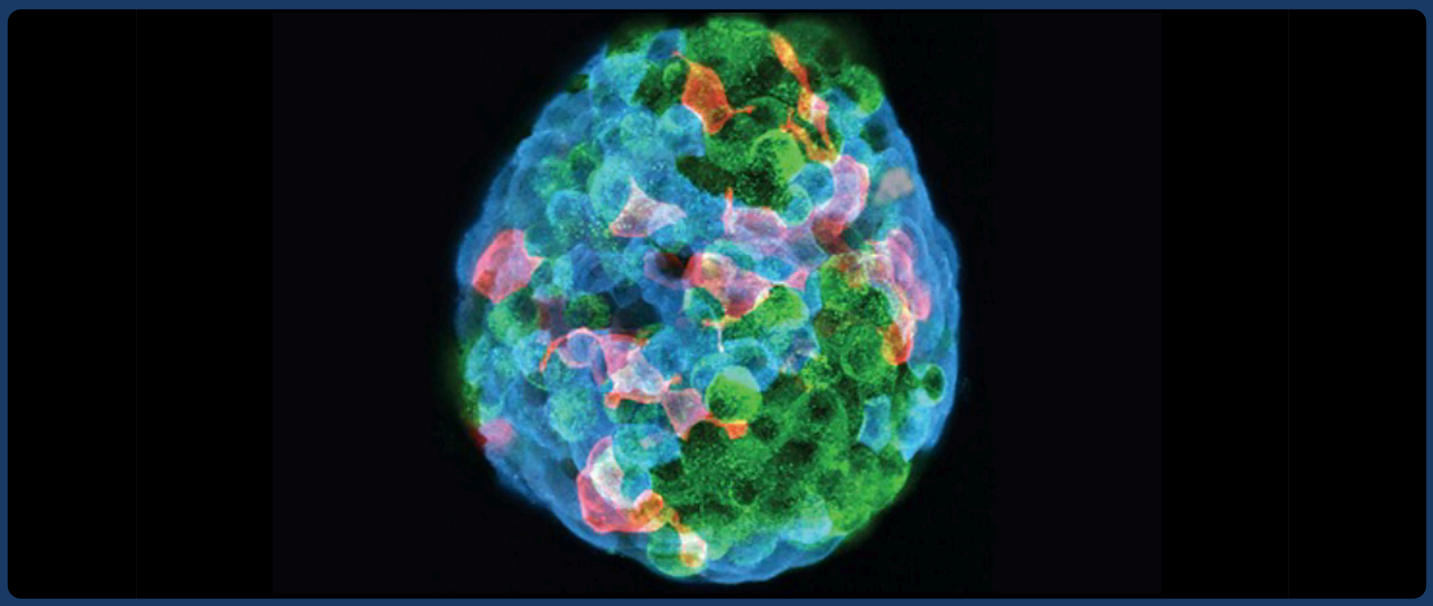

Topic: **Diabetes Mellitus**

Guest Editor: **Melena Bellin, MD**

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(pancrelipase) DELAYED-RELEASE CAPSULES

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When your patients' mealtimes seem like a gamble,

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- Clinically proven to relieve EPI (Exocrine Pancreatic Insufficiency) symptoms such as abdominal pain, bloating, and diarrhea.[1]
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Choose PANCREAZE — a trusted enzyme replacement therapy for over 15 years

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Indication

PANCREAZE is indicated for the treatment of exocrine pancreatic insufficiency in adult and pediatric patients.

Important Safety Information

Fibrosing Colonopathy: Associated with high doses, usually over prolonged use and in pediatric patients with cystic fibrosis. Colonic stricture reported in pediatric patients less than 12 years of age with dosages exceeding 6,000 lipase units/kg/meal. Monitor during treatment for progression of preexisting disease. Do not exceed the recommended dosage, unless clinically indicated.

Hyperuricemia has been reported with high dosages; consider monitoring blood uric acid levels in patients with gout, renal impairment, or hyperuricemia.

Irritation of the oral mucosa may occur due to loss of protective enteric coating on the capsule contents.

The presence of porcine viruses that might infect humans cannot be definitely excluded.

Monitor patients with known reactions to proteins of porcine origin. If symptoms occur, initiate appropriate medical management; consider the risks and benefits of continued treatment.

Please see the **Summary of Information about PANCREAZE** on the following page.

*Terms and conditions apply. See **HCP.PANCREAZE.com/save** for more information.

References: 1. Trapnell BC, et al. Efficacy and safety of PANCREAZE® for treatment of exocrine pancreatic insufficiency due to cystic fibrosis. *J Cyst Fibros.* 2011;10(5):350–356.

500447.02-USP 05/2026

VIVUS

Summary of Information about PANCREAZE® (pancrelipase) delayed-release capsules

Initial U.S. Approval: 2010

These highlights do not include all the information needed to use PANCREAZE safely and effectively. **See Full Prescribing Information for PANCREAZE at PANCREAZE.com.**

INDICATIONS AND USAGE

PANCREAZE is indicated for the treatment of exocrine pancreatic insufficiency in adult and pediatric patients.

DOSAGE AND ADMINISTRATION

PANCREAZE is a mixture of enzymes including lipases, proteases, and amylases. PANCREAZE dosing is based on lipase units.

Use either an actual body weight or fat ingestion-based dosing scheme.

Start at the lowest recommended dosage and individualize the dosage based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet. Changes in dosage may require an adjustment period of several days.

Do not exceed 2,500 lipase units/kg/meal, 10,000 lipase units/kg/day, or 4,000 lipase units/g fat ingested/day in adult and pediatric patients greater than 12 months of age without further investigation.

The total daily dosage in adult and pediatric patients greater than 12 months of age should reflect approximately three meals plus two or three snacks per day. With each snack, administer approximately half the prescribed PANCREAZE dose for a meal.

Do not substitute other pancreatic enzyme products for PANCREAZE. When switching from another pancreatic enzyme product to PANCREAZE, monitor patients for clinical symptoms of exocrine pancreatic insufficiency and titrate the dosage as needed.

Recommended Dosage

Adult and Pediatric Patients Greater than 12 Months of Age

The recommended oral initial starting dosage is:

500 lipase units/kg/meal for adult and pediatric patients 4 years of age and older.

1,000 lipase units/kg/meal for pediatric patients greater than 12 months to less than 4 years of age.

If signs and symptoms of malabsorption persist, increase the dosage. Titrate to either 2,500 lipase units/kg/meal, 10,000 lipase units/kg/day, or less than 4,000 lipase units/grams of fat ingested/day.

Higher dosages may be administered if they are documented to be effective by fecal fat measures or an improvement in signs and symptoms of malabsorption including measures of nutritional status.

Pediatric Patients Birth to 12 Months of Age

The recommended oral dosage is 2,600 lipase units per 120 mL of formula or per breast-feeding.

Preparation and Administration Instructions

Instruct adult and pediatric patients greater than 12 months of age, or their caregivers, of the following:

Take PANCREAZE with meals or snacks. If a dose is missed, take the next dose with the next meal or snack.

Swallow capsules whole.

For patients who are unable to swallow intact capsules, carefully open the capsules and sprinkle the entire contents on a small amount of acidic soft food with a pH of 4.5 or less (e.g., applesauce). Consume the entire mixture immediately.

Do not crush or chew PANCREAZE capsules or capsule contents.

Consume sufficient liquids (water or juice) to ensure complete swallowing of PANCREAZE capsules.

Instruct caregivers of pediatric patients birth to 12 months of age of the following:

Immediately prior to each breast-feeding session or each administration of 120 mL of formula, carefully open one PANCREAZE capsule (containing 2,600 USP units of lipase) and administer the entire contents using one of the following two methods:

- Sprinkle on a small amount of acidic soft food with a pH of 4.5 or less (e.g., applesauce) being careful not to crush the capsule contents. The entire mixture should be given to the infant immediately.
- Sprinkle the capsule contents directly into the infant's mouth.

Immediately administer additional breast milk or formula after PANCREAZE to ensure complete swallowing of the capsule contents.

Do not mix PANCREAZE capsule contents directly into a bottle of breast milk or formula.

Do not crush PANCREAZE capsule contents, and visually inspect the infant's mouth to ensure that no drug is retained in the mouth.

If a dose is missed, administer the next dose with the next feeding.

WARNINGS AND PRECAUTIONS

Fibrosing Colonopathy

Fibrosing colonopathy has been reported following treatment with pancreatic enzyme products. Fibrosing colonopathy is a rare, serious adverse reaction initially described in association with use of high-dose pancreatic enzyme products, usually over a prolonged period of time and most commonly reported in pediatric patients with cystic fibrosis. Pancreatic enzyme products exceeding 6,000 lipase units/kg/meal have been associated with colonic strictures, a complication of fibrosing colonopathy, in pediatric patients less than 12 years of age. The underlying mechanism of fibrosing colonopathy remains unknown.

If there is a history of fibrosing colonopathy, monitor patients during treatment with PANCREAZE because some patients may be at risk of progressing to colonic stricture formation. It is uncertain whether regression of fibrosing colonopathy occurs. Do not exceed the recommended dosage of either 2,500 lipase units/kg/meal, 10,000 lipase units/kg/day, or 4,000 lipase units/g fat ingested/day in adult and pediatric patients greater than 12 months of age without further investigation. Higher dosages may be administered if they are documented to be effective by fecal fat measures or an improvement in signs and symptoms of malabsorption including measures of nutritional status. Patients receiving dosages higher than 6,000 lipase units/kg/meal should be frequently monitored for symptoms of fibrosing colonopathy and the dosage decreased or titrated downward to a lower range if clinically appropriate.

Irritation of the Oral Mucosa

Crushing or chewing PANCREAZE capsules or mixing the capsule contents in foods having a pH greater than 4.5 can disrupt the protective enteric coating on the capsule contents and result in early release of enzymes, irritation of the oral mucosa, and/or loss of enzyme activity.

Instruct the patient or caregiver of the following:

Swallow capsules whole. For patients who cannot swallow the capsules whole, the capsules can be opened, and the contents sprinkled on a small amount of acidic soft food with a pH of 4.5 or less (e.g., applesauce).

Do not crush or chew PANCREAZE capsules or capsule contents.

Consume sufficient liquids (juice, water, breast milk, or formula) immediately following administration of PANCREAZE to ensure complete swallowing.

Visually inspect the mouth of pediatric patients less than 12 months of age and of patients who are unable to swallow intact capsules to ensure that no drug is retained in the mouth and irritation of the oral mucosa has not occurred.

Hyperuricemia

Pancreatic enzyme products contain purines that may increase blood uric acid levels. High dosages have been associated with hyperuricosuria and hyperuricemia. Consider monitoring blood uric acid levels in patients with gout, renal impairment, or hyperuricemia during treatment with PANCREAZE.

Risk of Viral Transmission

PANCREAZE is sourced from pancreatic tissue from swine used for food consumption. Although the risk that PANCREAZE will transmit an infectious agent to humans has been reduced by testing for certain viruses during manufacturing and by inactivating certain viruses during manufacturing, there is a theoretical risk for transmission of viral disease, including diseases caused by novel or unidentified viruses. Thus, the presence of porcine viruses that might infect humans cannot be definitely excluded. However, no cases of transmission of an infectious illness associated with the use of porcine pancreatic extracts have been reported.

Hypersensitivity Reactions

Serious hypersensitivity reactions including anaphylaxis, asthma, hives, and pruritus have been reported with pancreatic enzyme products. If symptoms occur, initiate appropriate medical management.

Monitor patients with a known hypersensitivity reaction to proteins of porcine origin for hypersensitivity reactions during treatment with PANCREAZE. The risks and benefits of continued PANCREAZE treatment in patients with serious hypersensitivity reactions should be taken into consideration with the overall clinical needs of the patient.

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ADVERSE REACTIONS

The data described below reflect exposure to PANCREAZE in 57 adult and pediatric patients with exocrine pancreatic insufficiency due to cystic fibrosis in two clinical trials. The most common adverse reactions were gastrointestinal, including diarrhea and vomiting.

The following adverse reactions have been identified during post-approval use of PANCREAZE or other pancreatic enzyme products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Eye Disorders: blurred vision Gastrointestinal Disorders: fibrosing colonopathy, distal intestinal obstruction syndrome, abdominal pain, flatulence, constipation, and nausea Immune System Disorders: anaphylaxis, asthma, hives, and pruritus Investigations: asymptomatic elevations of liver enzymes Musculoskeletal System: myalgia, muscle spasm Skin and Subcutaneous Tissue Disorders: urticaria and rash.

USE IN SPECIFIC POPULATIONS

Pregnancy

Published data from case reports with pancrelipase use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Pancrelipase is minimally absorbed systematically; therefore, maternal use is not expected to result in fetal exposure to the drug. Animal reproduction studies have not been conducted with pancrelipase.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Lactation

There are no data on the presence of pancrelipase in either human or animal milk, the effects on the breastfed infant or the effects on milk production. Pancrelipase is minimally absorbed systemically following oral administration, therefore maternal use is not expected to result in clinically relevant exposure of breastfed infants to the drug. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PANCREAZE and any potential adverse effects on the breastfed infant from PANCREAZE or from the underlying maternal condition.

Pediatric Use

The safety and effectiveness of PANCREAZE for the treatment of exocrine pancreatic insufficiency have been established in pediatric patients.

Geriatric Use

Clinical studies of PANCREAZE did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients.

OVERDOSAGE

In Study 1, a 10 year-old patient was administered a PANCREAZE dose of 12,399 lipase units/kg/day for the duration of the open-label and randomized withdrawal periods (21 days).

The patient experienced mild abdominal pain throughout both study periods. Abnormal chemistry data at the end of the study included mild elevations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and serum phosphate. Abnormal hematology data at the end of the study included mild elevations of hematocrit. No abnormalities from analyses of urinalysis or uric acid were noted.

Chronic high dosages of pancreatic enzyme products have been associated with fibrosing colonopathy and colonic strictures. High dosages of pancreatic enzyme products have been associated with hyperuricosuria and hyperuricemia.

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SMART Medical Review

Cystic Fibrosis-Related Diabetes: A Practical Guide for Endocrinologists

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Abstract: Cystic fibrosis-related diabetes (CFRD) is an increasingly prevalent complication of cystic fibrosis (CF), as people with CF live longer, particularly in the era of cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapies. Though our understanding of the underlying pathophysiology of CFRD continues to evolve, the primary defect is relative insulin deficiency resulting from reduced pancreatic beta-cell mass and impaired beta-cell function, and insulin therapy is the standard of care. Management includes individualized insulin regimens and use of diabetes technology (e.g. insulin pumps and continuous glucose monitoring). Increasingly, dietary management, and, in select cases, non-insulin therapies can be beneficial, although long-term studies of non-insulin therapies in CFRD are few and monitoring for side effects are needed. Individuals with CFRD should be monitored for traditional microvascular and macrovascular complications of diabetes mellitus and a multidisciplinary team approach is essential. Additional long-term studies are needed to understand how CFTR modulator therapies may influence the natural history of CFRD.

Key words: Cystic Fibrosis, Cystic Fibrosis-related diabetes, diabetes mellitus, atypical diabetes.

Outline:

1. Introduction

Cystic fibrosis (CF) is a multisystem disease caused by recessive mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Functional loss of CFTR results in dysregulation of chloride, bicarbonate, and water transport across epithelial membranes. This increases fluid viscosity, and in the exocrine pancreas, leads to ductal plugging and acinar loss. In the endocrine pancreas, CF leads to islet aggregation and remodeling, fibrofatty infiltration, inflammation, and resultant decreases in islet mass and beta cell function.[1] The risk of cystic fibrosis-related diabetes (CFRD) increases with age.[2] Additional risk factors include pancreatic exocrine insufficiency, severe CFTR mutations, reduced pulmonary function, CF liver disease, use of enteral feeds, and corticosteroids. CFRD prevalence is as high as 40% to 50% in adults, and in individuals with severe CFTR mutations, lifetime risk for development of CFRD exceeds 80%.[3,4] As life expectancy improves, the prevalence of CFRD is expected to rise.[5] CFRD has been linked to poorer clinical status[6], worse lung function[7], and decreased survival.[8] Figure 1 provides an overview of our current understanding of CFRD pathophysiology, screening, and management.

Abbreviations used in this paper: CFRD, cystic fibrosis-related diabetes; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; T1D, type 1 diabetes; T2D, type 2 diabetes; GWAS, genome-wide association studies; PRS, polygenic risk scores; ADA, American Diabetes Association; OGTT, oral glucose tolerance test; GLP1RA, GLP-1 receptor agonists; DPP4i, dipeptidyl peptidase-4 inhibitors.

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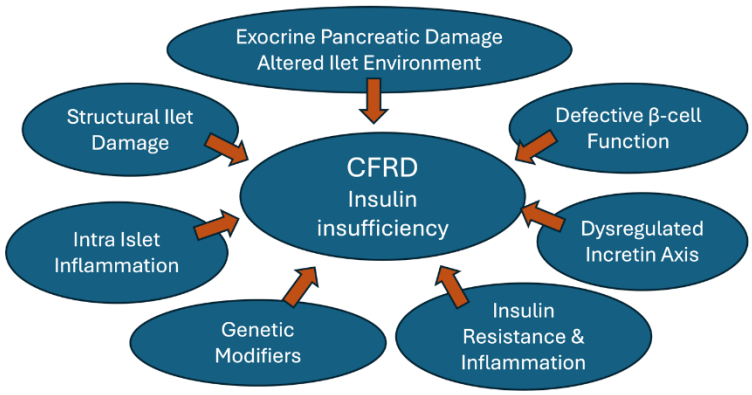
Figure 1. Schematic illustration of our current understanding of the pathophysiology of cystic fibrosis related diabetes (CFRD) adapted from a figure in review by Moheet et al.[9]



2. Pathophysiology of CFRD

CFRD is a common comorbidity in individuals with CF and pancreatic exocrine insufficiency.[10] CFRD has a distinct pathophysiology, sharing features of both type 1 (T1D) and type 2 diabetes (T2D), and is characterized by a relative insulin deficiency that manifests early in life as impairments in early phase insulin secretion.[11] Unlike type 1 diabetes, CFRD is not caused by autoimmunity, and diabetic ketoacidosis is uncommon due to residual endogenous insulin production; however, CFRD is characterized by a deficient first phase insulin secretory response.[12] Insulin sensitivity is typically normal in CFRD, unlike T2D[12], although it can be impaired during periods of acute illness.[13] Structural islet abnormalities alone do not fully explain the high CFRD prevalence among those with pancreatic exocrine insufficiency. Evidence from young children with CF demonstrates pancreatic beta cell dysfunction even before exocrine damage leads to fatty replacement and fibrosis of the pancreas. Defective paracrine signaling, oxidative stress, inflammation, and abnormalities of the islet microenvironment have also been implicated.[14,15] Other factors involved in the pathophysiology of CFRD, include incretin axis dysfunction and increased genetic susceptibility conferred by T2D associated genes[9], are schematically represented in Figure 1.

There is substantial genetic overlap between T2D and CFRD, evident both at gene-level and polygenic risk. Variants in the TCF7L2 gene are a well-established shared risk factor for both T2D and CFRD. In addition, genome-wide association studies (GWAS) have identified overlapping risk variants in genes such as CDKAL1, CDKN2A/B, and IGF2BP2. Polygenic risk scores (PRS), while not yet used in clinical practice, may support future screening strategies. These findings highlight the potential for incorporating polygenic risk into precision medicine approaches for early identification and risk stratification in CFRD.[16]

Risk factors for CFRD.[17,18]

- Increasing age
- Female sex
- Family history of type 2 diabetes
- Pancreatic exocrine insufficiency
- CFTR mutation severity
- Cystic fibrosis related liver disease
- Lower lung function
- Chronic lung infections
- Corticosteroid therapy
- Enteral or parenteral nutrition
- Lung transplantation

3. Screening and Diagnosis of CFRD

Table 1 summarizes CFRD screening and diagnostic criteria as recommended in the American Diabetes Association (ADA) position statement endorsed by the Cystic Fibrosis Foundation.[19] A 2-hour oral glucose tolerance test (OGTT) is currently the standard of care for diagnosing CFRD. A 2-h 75-g OGTT is performed during a period of stable health (> 6 weeks after acute exacerbation) using the World Health Organization protocol: Consume a minimum of 150 g (600 kcal) of carbohydrate per day for 3 days prior to test, followed by an 8-hour fast. On the morning of the test, a standard beverage containing 1.75 g/kg glucose (maximum 75 g) dissolved in water is consumed followed by sitting quietly for the next 2 hours. In people with CF, in addition to the 2-hour glucose, a 1-hour glucose is also recommended. Of note, individuals with CF are at increased risk for hypoglycemia[11] and it is recommended that patients consume a carbohydrate-containing meal following the OGTT. Incidence of hypoglycemia during or after the OGTT has been reported to be as high as 65%.[20]

A diagnosis of CFRD is made with a fasting plasma glucose ≥126 mg/dL and/or a 2-hour value ≥ 200 mg/dL, with at least one confirmatory test on a separate day. A 2-hour glucose of 140–199 mg/dL (impaired glucose tolerance, IGT) or a 1-hour glucose ≥ 200 mg/dL with a normal fasting and 2-hour glucose ("indeterminate glycemia", INDET) are abnormal and are associated with an increased risk for development of CFRD. Like CFRD, indeterminate glycemia has been associated with poorer lung function.[21-24] An A1C ≥ 6.5% also meets diabetes criteria, although a normal A1C does not exclude CFRD, due to low sensitivity. Notably, given the challenges of adhering to annual OGTTs in this population, a 2024 Canadian CFRD working group recommended a two-step screening approach recommending

OGTT only for individuals with A1c >5.5% would be offered a routine screening OGTT that year.[25] A1c would not be recommended as first-line screening due to unreliable and falsely low A1C values in individuals with hemoglobinopathies, splenomegaly, renal disease, recent blood transfusions, and organ transplantation.

Considerations for Diagnosis

Currently, there are no formal recommendations for routine islet autoantibody testing to screen for T1D in children or adults diagnosed with CFRD. However, in cases where the clinical presentation is atypical for CFRD (e.g., acute presentation severe hyperglycemia, diabetic ketoacidosis, or onset before the age of 10), or in adults experiencing a sudden change in glycemic control, testing for T1D-associated autoantibodies is warranted to evaluate for autoimmune diabetes. C-peptide testing is not routinely recommended in CFRD, though it can be valuable in specific clinical situations, such as when assessing the degree of insulin insufficiency in these patients.

4. Treatment of CFRD

Goals of Management

Goals of CFRD management include optimizing glycemic control to maintain or improve BMI and pulmonary function, as well as preventing development of diabetes-related microvascular complications. Although macrovascular disease has not historically been described in people with CF, with increasing longevity and increased rates overweight and obesity, macrovascular complications may emerge in this population over time.[26] Data on long-term complications in modulator-treated individuals are still emerging.

Management Strategies

Approach to management of CFRD is very individualized and changing with the burgeoning use of CFTR modulator therapies. Existing studies support the benefits of insulin therapy for improving weight and pulmonary function in people with CF. However, most supporting data precedes CFTR modulator therapies which increase longevity but also associated with an increased prevalence of overweight and obesity. At least two case series have now been published citing improvements in A1c and weight loss with GLP-1 receptor agonist therapies in people with CF.[34,35] Caution is advised with these medications as gastrointestinal side effects appear more common in individuals with CF than in the general population. Individuals

Table 1. Screening and Diagnostic Criteria for CFRD

Gold Standard Recommendations for CFRD Screening and Diagnosis	Details
Screening for CFRD	Oral glucose tolerance test (OGTT) - Annual testing starting at age 10 years with a 2-h 75-g OGTT (obtain plasma glucose fasting, 1 hour and 2 hours post glucose load)
Diagnosis of CFRD by OGTT: Must meet at least one criterion and confirm on a separate day	Fasting plasma glucose ≥ 126 mg/dL and/or 2-hour plasma glucose ≥ 200 mg/dL
Special circumstances allowing for diagnosis of CFRD	
Diagnosis of CFRD by A1C or elevated random glucose	- A1C ≥6.5% *confirmed on a separate day - Elevations in random glucose ≥200 mg/dL x2 with classic symptoms of diabetes (polyuria and polydipsia)
Persistent hyperglycemia during illness treated with IV antibiotics and/or systemic glucocorticoid therapy	Monitor fasting and 2-postprandial finger stick blood glucose values in the first 48 hours of therapy. If glucose concentrations are ≥200 mg/dL, confirm with a plasma glucose when able, and initiate insulin. *Due to underlying decreased beta-cell reserve, people with CF are particularly prone to stress-induced and steroid-induced hyperglycemia requiring insulin with illness/hospitalization. If blood sugars normalize upon discharge, insulin may not be required between episodes. Intermittent CGM can be helpful to guide insulin needs during periods of baseline health.
Persistent hyperglycemia during enteral feedings	Measure mid- and immediate post-feeding plasma glucose levels at initiation of feeding and monthly thereafter. If glucose during or after feeding ≥200 mg/dL on two consecutive days, confirm with a plasma glucose and initiate insulin for hyperglycemia. *CGM can be helpful for identifying overnight excursions with enteral feedings

with CFRD should receive nutritional counseling as well as insulin therapy, with recommendations to avoid sugar-sweetened beverages and limit simple carbohydrates, while maintaining overall caloric goals as recommended for people with CF to achieve target BMI.

Individuals with cystic fibrosis typically follow a high-calorie, high-salt, high-fat diet, a recommendation which may be evolving with increasing rates of overweight and obesity.[36,37] Carbohydrate counting is generally recommended, especially with use of a pre-meal short acting insulin regimen.[38] Ongoing consultation with a registered dietician and diabetes educator knowledgeable about CF and diabetes is recommended.

Principles of Outpatient Insulin Therapy (ISPAD)

Insulin is the mainstay of treatment and the only officially recommended treatment for CFRD. Before a diagnosis of CFRD, insulin for abnormal glucose tolerance may be helpful in individuals who have low BMI or have low lung function, although data to support this practice are limited to small, typically retrospective reports. More recent studies have not consistently shown the benefit of insulin for people with CF prior to development of CFRD[39], and other data show insulin use in abnormal glucose tolerance may not mitigate weight loss or protein catabolism.[40,41] In the context of unexplained declines in pulmonary function or weight, insulin therapy could be considered, although evidence-based data to support benefits of this practice remain limited. For people with CFRD without fasting hyperglycemia, carbohydrate coverage or pre-prandial insulin may be all that is required. Regular and intermediate-acting insulin can be helpful for hyperglycemia related to overnight enteral tube feedings.[42] For individuals with fasting hyperglycemia, total daily doses of 0.5-0.8 u/kg/d or more are often required. In the setting of acute illness, particularly with systemic corticosteroids, higher doses of 2-4 times the usual total daily dose are often necessary.[42]

Advanced diabetes technology is now integral to management of CFRD. Continuous glucose monitors reduce the burden of outpatient glycemic monitoring, and insulin pumps facilitate insulin delivery, especially those with automated insulin delivery (AID) or hybrid closed loop algorithms that improve time in range, decrease glycemic variability and reduce hypoglycemia.[43-45]

Principles of Inpatient CFRD management with insulin:

When individuals with CFRD are admitted for inpatient care, management of hyperglycemia should be individualized, based on factors such as baseline insulin regimen, current glucocorticoid use (oral or IV), and enteral feeding status.[42]

Non-insulin therapy:

While there are no formal guidelines recommending use of non-insulin therapies in the management of CFRD, there is limited and early evidence supporting the off-label use of non-insulin oral or injectable therapies including repaglinide, GLP1 receptor agonists, DPP4 inhibitors and metformin, summarized in Table 3. Repaglinide, a short-acting insulin secretagogue in the meglitinide class, has shown variable effects on glycemic control in CFRD. A Cochrane review and a 2018 expert review concluded available studies were inconclusive regarding whether repaglinide is equivalent to insulin therapy in terms of glycemic control.[46,47] Incretin mimetics, including GLP-1 receptor agonists (GLP1RA) and dipeptidyl peptidase-4 inhibitors (DPP4i), are increasingly used off-label to manage CFRD, CF-related abnormal glucose tolerance or coexisting metabolic syndrome. Sitagliptin, a DPP4i, has been shown to reduce glycemic excursions and improve overall glycemia when monitored with CGM[48], and improve incretin responses.[49] Case series involving GLP1Ra such as exenatide have reported beneficial effects on glycemic control and weight, though gastrointestinal side effects were more frequent in individuals with CF compared to the general population.[34,35,50] Metformin, a biguanide medication commonly used in T2D for its insulin sensitizing effect, has limited evidence supporting its use in CFRD. A 2020 Cochrane review concluded that data were insufficient to support routine use.[46] However, two recent abstracts (2023, 2019) of single-center observational data reported modest improvements in glycemia and good tolerability among individuals with CFRD receiving metformin.[51,52] Finally, CFRD is part of a broader category of "diabetes of the exocrine pancreas" which includes diabetes due to chronic pancreatitis, cystic fibrosis, pancreatic surgery, hemochromatosis, and other forms of pancreatic injury. These conditions may be associated with a more labile form of diabetes and an increased risk of pancreatic cancer. Metformin has been proposed to have anti-cancer effects, potentially lowering pancreatic cancer risk based on animal. dels and observational studies.

Table 2. Complications of CF-related diabetes

CF-related clinical complications
Weight loss, BMI decline[6-8]
Lung function decline[6-8] *The acute clinical impact of CFRD in the CFTR modulator era is not well defined.
Infection risk including Staph aureus, Pseudomonas aeruginosa, Burkholderia cepacia[27-29]
Acute kidney injury, Dehydration
Diabetes-related clinical complications
Microvascular complications[30]
Macrovascular complications (historically rare)[31,32]
Hypertension[33]

Table 3. Summary of Non-Insulin Therapies for Cystic Fibrosis–Related Diabetes (CFRD): Mechanisms, Considerations, and Evidence

Therapy	Mechanism of action	When to consider?	Is there any evidence?
Biguanides (Metformin)	Inhibits hepatic gluconeogenesis.	Consider for CFRD patients with insulin resistance and elevated HbA1c levels.	Cochrane Review and published abstracts for observational studies assessing Metformin use in CFRD indicating tolerability and improvement in glycemic control.[46,51,52]
Sodium-glucose co-transporter-2 inhibitors (SGLT2i)	Inhibits renal glucose reabsorption.	Not recommended for CFRD due to lack of evidence supporting efficacy and safety.	No evidence in the current literature for CFRD.
Dipeptidyl peptidase-4 inhibitors (DPP4i)	Inhibits the enzymatic inactivation of incretin hormones.	Consider in cases of abnormal OGTT, as Sitagliptin has shown improvement in glycemic control.	Observational study of 25 patients with pancreatic insufficiency reporting Sitagliptin use was associated with short term glycemic improvements in early CFRD (2023).[48] Retrospective case series of 23 patients with 100% tolerability and improvement in glycemia (2024).[50] RCT of 12 adults with AGT and pancreatic insufficient CF showing 6 months of sitagliptin therapy was well tolerated and improved incretin response but not postprandial glycemia as compared to placebo (2021).[49]
Glucagon-like peptide-1 receptor agonists (GLP-1RAs)	Augments glucose-dependent insulin secretion and suppresses glucagon release.	Consider for CF patients with impaired glucose tolerance and postprandial hyperglycemia. Use with caution if pancreatitis is a risk.	Crossover RCT in 6 patients with CF and IGT showing significant improvements in postprandial hyperglycemia after exenatide (2018).[56] A case series of 11 patients reporting glycemic, pulmonary and weight benefits of semaglutide and tirzepatide and 20% reporting GI intolerability (2025).[35]
Sulfonylureas	Stimulates insulin secretion from pancreatic β-cells.	Not recommended for CFRD due to lack of evidence supporting efficacy and safety.	No supportive evidence in CFRD.[57]
Thiazolidinediones (TZDs)	Improves insulin sensitivity by enhancing peripheral glucose uptake.	Not recommended for CFRD due to lack of evidence supporting efficacy and safety.	No supportive evidence in CFRD.[57]
Meglitinides (Repaglinide)	Stimulates glucose-dependent insulin release from pancreatic β-cells.	Consider in CFRD patients with postprandial hyperglycemia. Potential risk of hypoglycemia.	A Cochrane Review (2020), reviews by Moheet & Moran (2018) and Ode et al (2019) reporting limited evidence comparing repaglinide to insulin, with no clear superiority over insulin.[46,47,58]
Acarbose	Inhibits enzymes in the small intestine that break down complex carbohydrates into glucose.	Not recommended for CFRD due to limited evidence of efficacy and safety.	No supportive evidence in CFRD.[57]

However, definitive evidence from randomized controlled trials in CFRD or related conditions is currently lacking.[53,54] As the life expectancy of individuals with cystic fibrosis increases, the relative risk of pancreatic cancer compared to the general population is expected to rise, although the absolute risk of pancreatic cancer in the CF population is likely to remain low.[55]

Long-term Monitoring and Complications

CFRD should be managed by an endocrinologist, in conjunction with the CF care team, and long-term monitoring for complications should include screening as follows, in accordance with ADA guidelines:

- Blood pressure should be assessed at each visit due to the elevated risk for hypertension.
- Annual monitoring for microvascular complications of diabetes starting 5 years after diagnosis, including retinopathy, nephropathy and peripheral neuropathy.
- If microvascular disease or hypertension are present, patients with CFRD should receive treatment per the standard of care for the applicable condition. Patients with CF should avoid sodium or protein restriction as part of their management.

Patients with exocrine pancreatic sufficiency, obesity, organ transplantation, or a family history of coronary artery disease require an annual lipid profile.

5. Future Directions in CFRD and Precision Medicine

Despite significant advances in CF treatment, particularly widespread use of CFTR modulator therapies, CFRD remains a challenging condition to screen for and manage. CFTR modulators can partially restore CFTR function, dramatically improving pulmonary function, nutritional status, and overall clinical outcomes for individuals with CF. However, data from the PROMISE study, a real-world longitudinal observational study of the effects of clinically prescribed elexacaftor/tezacaftor/ivacaftor in individuals aged ≥12 years, demonstrate persistent glucose tolerance abnormalities and CFRD in the CFTR modulator era.[59] Earlier introduction of CFTR modulators at younger ages has the potential to alter CFRD trajectory, though long-term outcomes remain uncertain.

Individuals with severe CFTR mutations (e.g., homozygous DeltaF508) face an extremely high lifetime risk of CFRD. GWAS have identified genetic modifiers of CFRD risk that overlap with genetic risk for type 2 diabetes, and may support stratified screening protocols in the future.[16,18,60] Greater availability of testing for these genetic modifiers will help to personalize CFRD management and guide future research targeted at delaying or preventing CFRD.

Historically, CF nutritional care was aimed at preventing malnutrition but CFTR modulators have improved nutritional outcomes for many and also introduced new challenges related to overweight and obesity.[37,61,62] These changes necessitate individualized approaches to optimize insulin sensitivity, exercise tolerance, and cardiometabolic risk profiles. Although insulin is the cornerstone of CFRD therapy, use of adjunctive, off-label pharmacotherapies—such as GLP1RA[35]—is increasing.

Early detection and treatment of CFRD remains a priority, because delayed diagnosis can contribute to pulmonary decline and worsened health outcomes. Given the challenges of annual OGTTs, targeted screening strategies are needed as well as additional research into the utility of alternative approaches, such as CGM. Further studies are needed to define clinically meaningful CGM thresholds in the CF population.

Insulin remains the standard treatment for CFRD, however, active research into CFRD specific dietary and exercise recommendations and pharmacotherapies is underway.[63] Future advances in CFRD screening, monitoring and insulin delivery technology will support more individualized and effective CFRD care.

6. Conclusion

The future of CFRD care is evolving with advances in CF treatment, including widespread CFTR modulator use, earlier initiation, and novel gene therapies. A multidisciplinary team—including endocrinologists, diabetes educators, and pharmacologists—will be essential. These ongoing studies will play a central role in guiding future strategies for screening, prevention and treatment: (BEGIN [NCT0450905], PROMISE [NCT04613128], MAYFLOWERS [NCT04828382], STRONG-CF [NCT05639556], Bionic Pancreas CFRD [NCT06449677], SPECTRUM [NCT06837181].

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