Cystic fibrosis-related diabetes: Prevalence, screening, and diagnosis

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ABSTRACT

Cystic fibrosis-related diabetes (CFRD) is the most common comorbidity in patients with cystic fibrosis (CF). Prevalence of CFRD increases with age and is greater with severe mutations. Other risk factors associated with CFRD are female sex, pancreatic insufficiency, liver disease, need for gastrostomy tube feedings, history of bronchopulmonary aspergillosis, and poor pulmonary function. CFRD is related to worse clinical outcomes and increased mortality. Early diagnosis and treatment have been shown to improve clinical outcomes. Screening for CFRD is recommended with an annual oral glucose tolerance test (OGTT) starting at age 10 years. Diagnosis of CFRD is made by standard American Diabetes Association (ADA) criteria during baseline health. CFRD can also be diagnosed in individuals with CF during acute illness, while on enteral feeds, and after transplant. In this review we will discuss the epidemiology of CFRD and provide an overview of the advantages and pitfalls of current screening and diagnostic tests for CFRD.

Background

Cystic fibrosis (CF) is a rare genetic disease with multiorgan involvement which ranges in severity and is associated with early death. With medical advancements and better management of the disease process, the mean predicted survival age of children born in 2019 has increased to 48.4 years, compared to 36.6 years for individuals born in 2008 [1,2]. The number of individuals over 18 years living with CF is increasing steadily. The Cystic Fibrosis Foundation (CFF) annual report in 2019 reported that 56% of individuals with CF were over 18 years of age compared to 31.1% in 2004 [1]. With increasing age, patients are facing new challenges and the prevalence of comorbidities have significantly increased. Cystic fibrosis-related diabetes (CFRD) is the most common comorbidity in patients with CF. Microvascular and macrovascular complications of diabetes are well described in individuals with type 1 (T1DM) and type 2 diabetes (T2DM). Although microvascular complications are uncommon, macrovascular complications are seen with CFRD [3]. In addition, CFRD is associated with decline in pulmonary function, worse nutritional status, and increased mortality [4]. CFRD is associated with not only complications related to insulin deficiency and hyperglycemia, but also with significantly increased burden of disease and reduced quality of life [5,6]. Increasing awareness about CFRD, early diagnosis and treatment are key to reducing morbidity, improving pulmonary function and overall survival.

Epidemiology

The reported prevalence of CFRD varies in studies. This is likely related to low and variable screening rates at many CF centers. The University of Minnesota CF center has had one of the highest screening rates in the country for decades. Moran et al published data in 2009 that the prevalence of CFRD increases with age, with 2% children, 19% adolescents, and 40–50% adults affected by CFRD [4]. In a 5 year prospective study by Laang et al in 1995, prevalence of CFRD at a single center increased from 11% to 24% with annual screening [7]. In a large epidemiologic study of the European Cystic Fibrosis foundation patient registry published in 2020 prevalence of CFRD in 2015 was noted to be 0.8% in patients<10 years of age; 9.7% in 10–19 year old; 24.1% in 20–29 year old and 32.7% in individuals ≥ 30 years of age [8]. Prevalence of CFRD is closely associated with screening rates. A recent study by Thompson et al shows that centers with lower screening rates had more rapid pulmonary decline before CFRD diagnosis. Centers with...
better screening can have up to three times higher incidence and prevalence of CFRD and better pulmonary function at the time of diagnosis [9].

In addition to increasing age, patients with more severe CFTR mutations are at increased risk for CFRD and greater mortality[10]. Other risk factors associated with the development of CFRD include female sex, pancreatic insufficiency [8,11], family history of type 2 diabetes, worse lung function, history of allergic bronchopulmonary aspergillosis (ABPA), gastrostomy tube feedings, and liver disease [12].

Table 1, Risk factors associated with CFRD from European and Canadian CF Registries [8,12].

There is an increased incidence of post-transplant diabetes mellitus (PTDM) in patients with CF. Several studies have examined the prevalence of diabetes before and after transplantation in the CF population, especially lung transplantation [13]. Hadjiliadis et al reported that prevalence of CFRD increased from 28.6% before transplant to 50% after transplant. In this study, 20.8% of patients had new-onset diabetes after transplantation. Increased stress from surgery and infections as well as post-transplant medications can lead to hyperglycemia and diabetes [14]. Systemic corticosteroids cause hyperglycemia from impaired glucose uptake in muscle and adipocytes and increased hepatic gluconeogenesis. Calcineurin inhibitors (tacrolimus and cyclosporin) and inhibitors of mammalian target of rapamycin (mTor) (sirolimus) are associated with hyperglycemia resulting from beta-cell dysfunction and insulin resistance, with tacrolimus being the most diabetogenic among these [15].

CFTR modulator therapy has been shown to impact prevalence of CFRD. Observational data from existing US and UK CF registries show a lower prevalence of CFRD after introduction of Ivacaftor in 2012. Increase in prevalence of CFRD was lower in the Ivacaftor group (12.1% in US and 2.4% in UK) than comparator group (18.3% in US and 8.2% in UK) [16]. Further studies are needed to understand the impact newer highly effective modulator therapies may have on the mechanisms and progression of glucose intolerance and future prevalence of CFRD.

Screening and diagnosis

CFRD is an insidious disease and if left untreated can cause decline in lung function and decreased survival. It can be clinically silent for several years before presenting with symptoms including poor pulmonary function and weight loss. Early glucose abnormalities are common, especially in adolescents [1] and have been associated with clinical decline even before the diagnosis of CFRD [17,18]. Because CFRD does not present with classic symptoms of diabetes (such as polyuria and polydipsia), patients with early glucose abnormalities in particular benefit from routine screening [1].

Screening rates are increasing but remain low. The US CFF 2019 Patient Registry Annual Data Report noted that only 66.6% of eligible people <18 years and 36.9% in people over 18 years with CF were screened with an OGTT [1].

The significance of CFRD in the CF population was highlighted in 1988 after a report from the University of Minnesota associated improved CFRD screening rates with decreased pulmonary function and decreased mortality [19]. The American Diabetes Association (ADA) first published its standards for diabetes care in 1997 which included screening and diagnostic criteria for diabetes. Specific clinical care guidelines for CFRD were developed as a combined effort with the CFF, ADA and Pediatric Endocrine Society (PES) and published in 2010.

Annual screening of all individuals with CF not yet diagnosed with CFRD is recommended to start at age 10 years with an oral glucose tolerance test (OGTT) [20], although some centers screen children starting as young as 6 years of age.

During a period of stable baseline health, the diagnosis of CFRD is made with the same diagnostic criteria as other forms of diabetes as outlined in the ADA guidelines (Table 1). Hyperglycemia seen during acute illness can last for several weeks and routine screening should be done 6 weeks after acute illness has resolved [20]. The onset of diabetes is defined when patients first meet diagnostic criteria. Hyperglycemia should be confirmed on laboratory plasma glucose measurement. Results in the diabetes range should be confirmed with a second test on a separate day unless unequivocal symptoms of hyperglycemia or symptoms of hyperglycemia with a random plasma glucose of ≥ 200 mg/dl are present [21].

Table 2, Adapted from diagnostic criteria for CFRD [21].

Cfrd screening and diagnosis in special circumstances

All CF patients with acute illness or pulmonary exacerbation requiring intravenous antibiotics with or without glucocorticoids should be screened for CFRD by monitoring fasting and 2 h postprandial plasma glucose for the first 48 h. A diagnosis of CFRD is confirmed when FPG ≥ 126 mg/dl (≥7 mmol/l) or 2-hour postprandial plasma glucose rises ≥ 200 mg/dl (11.1 mmol/l) and persists for 48 h with 2 or more abnormal readings [20].

CF patients on enteral feeders should be screened with mid and immediate post-feeding plasma glucose levels at the time of initiation and then monthly. CFRD is diagnosed when mid- or post-feeding plasma glucose readings are ≥ 200 mg/dl (11.1 mmol/l) on 2 separate days [20].

CF patients planning pregnancy should be screened for preexisting CFRD with 2 h 75-g OGTT if not done in the previous 6 months. All pregnant patients with CF should be screened for gestational diabetes (GDM) screening with 2 h 75 g OGTT at 12–16 weeks and 24–48 weeks of gestation. Patients diagnosed with GDM are not considered to have CFRD and should have a repeat OGTT at 6–12 weeks after end of delivery to screen for CFRD [20]. Diagnostic criteria for GDM in pregnant CF patients are the same as in the general population. Diagnosis is made with a 75 g OGTT if FPG ≥ 92 mg/dl (≥5.1 mmol/l), 1hG ≥ 180 mg/dl (≥10.0 mmol/l), and 2hG ≥ 153 mg/dl (≥8.5 mmol/l) [20,22].

Table 2

| Diagnostic criteria for CFRD. |
|-----------------------------|
| Diagnostic test | Diagnostic criteria |
|-----------------|---------------------|
| At baseline health | Random plasma glucose | ≥200 mg/dl (≥11.1 mmol/l) + classical symptoms of diabetes (polyuria and polydipsia) |
| 2-hour OGTT glucose | Fasting blood glucose (FPG) | ≥126 mg/dl (≥7 mmol/l) |
| Hemoglobin A1c | ≥6.5% |
| On enteral feeds | Random plasma glucose | ≥200 mg/dl (11.1 mmol/l) during or after feedings on 2 separate days |
| During acute illness | Fasting blood glucose (FPG) | ≥126 mg/dl (≥7 mmol/l) |
| 2-hour postprandial plasma glucose | ≥200 mg/dl (11.1 mmol/l) and persist for 48 h |
| During pregnancy | 75 g OGTT | FPG ≥ 92 mg/dl (≥5.1 mmol/l), 1hG ≥ 180 mg/dl (≥10.0 mmol/l), and 2hG ≥ 153 mg/dl (≥8.5 mmol/l). |

Table 1 Risk Factors Associated with development of CFRD.

| Risk Factor | Odds Ratio (OR) | Confidence Interval (CI) |
|-------------|-----------------|-------------------------|
| Severe genotypes | 3.11 | 95%: 2.77–3.48 |
| Pancreatic insufficiency | 1.46 | 95%: 1.39–1.53 |
| Female gender | 1.28 | 95%: 1.21–1.34 |
| Gastronomy tube | 2.3 | 95%: 1–3.43 |
| ABPA | 3.2 | 95%: 1–1.36 |
| Liver disease | 4.2 | 95%: 2.0–8.8 |
| FEV1% | 0.98 | 95%: 0.97–0.99 |
All CF patients without history of CFRD undergoing transplantation should be screened with a 75 g OGTT if not done in the previous 6 months [20]. Screening and diagnosis guidelines for CFRD after transplantation are similar to those described for the general CF population [20].

**Screening tests**

**OGTT**

The 2-hour OGTT is considered the gold standard for screening of CFRD. Annual screening should start at age 10 years since the incidence and prevalence of CFRD increases significantly after that [20]. An OGTT is done by administering oral dextrose 1.75 mg/kg body weight up to a maximum of 75 g after 8 h fasting [21]. Plasma glucose is measured at baseline and 2 h after oral dextrose. There is increasing evidence that mid-OGTT glucose levels may better predict risk for CFRD and clinical decline than 2hG levels [23,24]. Consideration should be given to measuring intermediate glucose levels, such as a 1hG or every 30 min glucose during the OGTT [25,20,26]. Impaired glucose tolerance (IGT) is defined as plasma glucose at 2 h between ≥140 mg/dL (>7.8 mmol/L) and <200 mg/dL (<11.1 mmol/L). Indeterminate hyperglycemia is defined as plasma glucose at 1 h ≥200 mg/dL (≥11.1 mmol/L) with plasma glucose at 2 h <140 mg/dL (<7.8 mmol/L). The OGTT is a time-consuming test requiring overnight fasting, hence overall screening rates remain low in the US. There are several patient barriers associated with low screening rates including need for prolonged fasting, separate and long appointment times, and insufficient awareness about the importance of screening [27,28].

Furthermore, OGTT thresholds for diagnosing CFRD are adopted from populations at risk for T2DM and are designed to identify adults at risk for microvascular complications of diabetes and may not be the optimal thresholds for identifying individuals with CF who may benefit from CFRD treatment [20,21]. Given the challenges surrounding OGTT screening, alternative methods of screening CFRD have been examined, although with limited success [21].

**Hemoglobin A1c**

ADA accepted Hemoglobin A1c (A1c) as a screening and diagnostic tool for diabetes in 2010 [29]. However in individuals with CF, A1c can be unreliable for diagnosing CFRD given its low sensitivity compared to the OGTT. Although an elevated A1c ≥6.5% can be diagnostic of CFRD (Table 1), most individuals will not present with an elevated A1c in this range and A1c values below this cutoff will miss CFRD diagnosable by OGTT. Lower thresholds for CFRD screening (ex. HbA1c of 5.8% and 5.5%) have been proposed, but different studies have reported varying sensitivities at these thresholds [30,31]. Historically, anemia resulting from iron deficiency and increased red blood cell turnover from chronic illness have been cited as reasons for spuriously low A1c levels in people with CF, however, more recent evidence has indicated that A1c in fact accurately reflects mean glucose levels in individuals with CF [32,33]. However, A1c and OGTT reflect differing components of glucose metabolism and are not interchangeable. Although A1c reflects mean glucose, other components of glucose metabolism including post-prandial glycemic excursions in response to an oral glucose load (ie OGTT) better capture partial insulin insufficiency. Therefore, OGTT is better suited for CFRD screening than A1c or other markers of average glycemia.

**Fasting plasma glucose**

ADA accepted fasting blood glucose (FPG) as one of the diagnostic criteria for diabetes in 1997 [34]. FPG of ≥126 mg/dL (7 mmol/L) is included as one of the diagnostic criteria of CFRD [20]. However, FPG concentrations can remain normal for several years in patients with CFRD [35]. Thus, FPG alone is unreliable for screening of CFRD [36]. There is no need to differentiate between CFRD with or without fasting hyperglycemia for diagnostic purposes as studies have demonstrated that patients with CFRD without fasting hyperglycemia benefit from insulin therapy as well [4,20]. Patients with CFRD without fasting hyperglycemia may require only prandial insulin while patients with CFRD with fasting hyperglycemia often require a basal and bolus insulin regimen.

**Other screening methods**

Fructosamine and glycated albumin are glycated proteins which can be used as an alternate marker to assess glycemic control in individuals with diabetes when hemoglobin A1c is unreliable [37]. Another alternate method that reflects glycemia, is 1,5-anhydroglucitol (1,5-AG), a naturally occurring dietary polyol that competes with glucose for renal tubular reabsorption. 1,5-AG decreases can reflect both mean and post-prandial hyperglycemia and this test can be used to assess short-term glycemic control over 2 weeks [38]. In small studies, neither serum fructosamine, glycated albumin, nor 1,5-AG showed concordance with OGTT categories and similar to A1c, these tests are likely to miss early glucose abnormalities diagnostic of CFRD, and are not recommended for screening or diagnosis of CFRD at this time [21,33,39].

**Continuous glucose monitoring**

Continuous glucose monitors (CGM) have become increasingly accurate in recording blood glucose. Currently, most CGM research has focused on T1DM and T2DM with limited literature in the CFRD population. Increasingly studies are associating glucose abnormalities on CGM with clinical decline in CF prior to an overt diagnosis of CFRD [11,40–43]. There is much interest in use of CGM for detection of early glucose abnormalities in CF patients but as of yet, there have been inadequate studies to support use of CGM as a screening or diagnostic tool for CFRD. CGM has been validated in patients with CF [44] and can help with early detection of glucose abnormalities [45]. Hyperglycemia on CGM also appears to correlate with intermediate glucose elevations on OGTT [46]. CGM has been shown to improve glycemic control, time in range, and improve quality of life in non-CF populations [47–49]. International consensus for CGM data interpretation and time in range (TIR) were published for type 1 and type 2 diabetes and different criteria may be more appropriate for CFRD [50]. Although accepted as a useful tool for management of CFRD, before it can be incorporated as a tool for screening and diagnosis of CFRD, additional research is needed to identify specific CGM variables that predict decline in CF-specific clinical outcomes [42].

**Future directions**

It is desirable to develop alternate screening methods which are highly sensitive and are less cumbersome than the OGTT. Additional research is needed to better understand the role of CGM for screening and diagnosis of CFRD and the impact of early treatment of glucose abnormalities on the clinical course of CF [42]. As we enter an era of widespread use of highly effective modulator therapies, ongoing research to assess the impact of these treatments on CFRD prevalence and complications, including microvascular and potentially macrovascular outcomes, are needed.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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