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Cystic fibrosis related diabetes—a new perspective on the optimal management of postprandial glycemia

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ABSTRACT

As the average life expectancy of patients with cystic fibrosis (CF) improves, the long term co-morbidities assume increasing importance. CF related diabetes (CFRD) has adverse effects on both nutrition and pulmonary function, and is associated with increased mortality. Abnormalities of glucose metabolism in CF represent a continuum; however the predominant abnormality is postprandial, not pre-prandial, glycemia. Insulin is currently recommended as the treatment of choice for CFRD, but its use is associated with a number of limitations, including hypoglycemia. Both the rate of gastric emptying and the consequent release of the 'incretin' hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like-peptide-1 (GLP-1), from the gut are important determinants of overall glycemic control, particularly postprandial glycemia. Both are abnormal in conditions associated with exocrine pancreatic insufficiency. Incretin based therapies that have the capacity to slow gastric emptying and/or modulate the release of 'incretin' hormones, are now used widely in type 2 diabetes (T2D). This paper explores the determinants of glycemic control in CF, with a particular focus on the roles of gastric emptying and 'incretin' hormones, providing a rationale for the use of therapies that delay gastric emptying, including incretin mimetics, to minimize postprandial glycemia and improve nutritional status.

1. Introduction

The establishment of specialized CF centers, and substantial nutritional and pharmaceutical advances during the last 60 years, have improved mean life expectancy for CF by more than 38 years, with the consequent clinical challenge of prevention and management of long-term co-morbidities, of which CFRD has increasing prominence (Bethesda). The abnormalities of glucose metabolism in CF represent a continuum from normal, through pre-diabetes, to overt diabetes with the pathogenesis characterized by postprandial, rather than pre-prandial, hyperglycemia. Insulin is currently the treatment of choice for CFRD although the acceptance and compliance with this therapy are challenging due to the already high burden of care in the CF population. Newer therapies are available that specifically modify postprandial glycemia, such as those based on the incretin system, which are widely utilized in the management of T2D. These therapies may represent a logical treatment for CFRD, as monotherapy or in combination with basal insulin, as they specifically address postprandial hyperglycemia.

1.1. CFRD prevalence and significance

The prevalence of CFRD increases with age, such that more than 50% of patients over 40 years are affected (Moran, Dunitz, et al., 2009). The mortality rate for CFRD has been estimated at 3.5 per 100 person years, from a peak 20 years ago of 6.2 per 100 person years, but remains substantially higher than in CF patients without diabetes (Moran, Dunitz, et al., 2009). This improvement is largely due to increased awareness and detection in the pre-diabetic state, which is imperative in light of persuasive evidence that the optimal management and long-term prognosis of CF, are affected greatly by the presence of carbohydrate intolerance. The long term implications of CFRD for pulmonary health and body mass index (BMI) are considered

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of greater relevance than the microvascular and macrovascular complications classically associated with type 1 diabetes (T1D) and T2D, although with increased survival microvascular complications have now become apparent, as will be discussed. CFRD with fasting hyperglycemia is associated with a decline in pulmonary function and nutrition, an increase in the incidence of *Pseudomonas aeruginosa* and *Burkholdaria cepacia* infection, doubling of hospitalization rates, and an increase in the prevalence of liver disease (Marshall et al., 2005). CFRD also adversely affects prognosis after lung transplantation (Belle-van Meerkerk et al., 2012).

Whether these associations are a direct effect of CFRD, or reflect more severe disease is uncertain; however the degree of clinical decline, particularly in respiratory function, correlates directly with glycemic control. Moreover, there is now persuasive evidence that the decline in nutritional and pulmonary status occurs 2–6 years before the diagnosis of CFRD, when postprandial hyperglycemia is less marked (Bizzarri, Lucidi, Ciampalini, Bella, & Cappa, 2006; Moran, Pekow, et al., 2009). This suggests that even 'early' carbohydrate intolerance, with relatively modest postprandial glycemic excursions, is metabolically detrimental to pulmonary function. Upper airway glucose concentrations are higher in CF when compared with healthy subjects, and those with T1D or T2D, with the potential to facilitate bacterial growth and subsequent lung damage (Brennan, Gyi, & Wood, 2007). Direct toxic effects of hyperglycemia on airway function remain to be established.

Microvascular complications occur in CFRD, albeit with a lower prevalence than in T1D or T2D, and are related both to the duration of diabetes and glycemic control. Ten years from the diagnosis of CFRD, 50% of patients are reported to have peripheral neuropathy, 16% retinopathy and 14% microalbuminuria (Schwarzenberg et al., 2007). Macrovascular complications in CFRD have not featured in the literature, possibly reflecting both the shorter life expectancy and beneficial effect conferred by the genetic mutation and fat malabsorption.

1.2. CFRD pathogenesis

The pathogenesis of CFRD is multifactorial, with both the CF genotype and innate and adaptive immunity contributing to β cell destruction (Rana, Munns, Selvadurai, Donaghue, & Craig, 2010; Rana et al., 2011). CFRD is characterized by predominantly postprandial, rather than pre-prandial, hyperglycemia. This contrasts with T1D, and the proportional elevation of postprandial glucose in CF, relative to fasting glucose, is greater than in T2D. The primary defect has been regarded as insulin deficiency, with a variable contribution from insulin resistance, dependent on clinical state, infection, inflammation and concurrent steroid medication. There is, however, a poor correlation between clinical diabetes and the degree of islet cell damage, suggesting that other factors, such as autoimmunity, may be involved. However, the prevalence of islet antibodies and T1D susceptibility alleles in CFRD appears to be comparable to the general population, although CFRD and T1D co-exist in a minority (Lanng et al., 1993). It has been suggested that CFRD may be more closely related to T2D, with islet amyloid deposits, as seen in T2D, being evident in 69% at autopsy (Couce, O'Brien, Moran, Roche, & Butler, 1996). It is not clear whether amyloid deposits play a direct role in the pathogenesis of β cell death or are simply a marker of increasing β cell stress (Huang, Haataja, et al., 2007; Huang, Lin, et al., 2007). Susceptibility genes that increase the risk of T2D in the general population have been found in CFRD, strongly suggesting these genes may increase the propensity to diabetes in CF, and a family history of T2D increases the risk of CFRD substantially (Lanng, Thorsteinsson, Pociot, et al., 1993).

The cystic fibrosis transmembrane conductance regulator (CFTR) protein may play a direct role in insulin secretion. Ivacaftor, a CFTR potentiator, is a new therapy that improves chloride transport through the dysfunctional CFTR protein in individuals with the G551D mutation. The implications for glycemic control are uncertain; however in a pilot study of 5 CF patients Ivancafor improved insulin secretion, albeit without affecting glycemic control (Bellin et al., 2013).

1.3. CFRD diagnosis

Carbohydrate intolerance in CF represents a continuum on which patients fluctuate, depending on clinical variables including infection, energy requirement, nutritional state, gastrointestinal absorption and steroid therapy. The diagnosis of CFRD is challenging, not just because of this intra-individual variability, but also because of the lack of a 'gold standard' diagnostic test. In practice, carbohydrate intolerance in CF is commonly classified into categories of normal glucose tolerance, indeterminate glucose tolerance, impaired glucose tolerance, CFRD without fasting hyperglycemia, and CFRD with fasting hyperglycemia (Table 1) based on an oral glucose tolerance test (OGTT, 1.75 g/kg body weight, maximum 75 g) using fasting and 120 minute glucose levels (Moran, Dunitz, et al., 2009).

Previously, the OGTT was regarded as the diagnostic gold standard with high sensitivity (Moran et al., 1999); however more recent evidence indicates that many patients experience large glycemic excursions at 30, 60 and 90 minutes after oral glucose, which may be clinically significant, but have normal blood glucose levels at baseline and 2 hours (Hameed et al., 2010). While there is a relationship between the 2 hour OGTT blood glucose value and glycemic excursions following a mixed meal in healthy subjects, and those with impaired glucose tolerance or overt diabetes (Meier et al., 2009), the absolute blood glucose concentrations vary substantially between the two tests. The OGTT tends to elicit greater glycemic excursions, while a mixed meal more accurately represents the glycemic variations occurring in everyday life. In CF, this is particularly important, since exocrine pancreatic insufficiency may influence the response to a mixed meal, but not to oral glucose. Moreover, unless blood glucose is measured more frequently than at 2 hours (e.g. every 30 min), the OGTT may miss an early glycemic peak. The OGTT also has poor specificity, with up to 58% of patients with impaired glucose tolerance being shown to revert to normal glucose tolerance and only 14% progressing to CFRD over the following 5 years (Lanng, Hansen, Thorsteinsson, Nerup, & Koch, 1995). Measurement of insulin and C-peptide responses to an OGTT may aid in detecting abnormalities in carbohydrate metabolism and progression. A delayed and reduced insulin peak and first phase insulin response to oral and intravenous glucose tolerance tests are evident in CF subjects with impaired, compared with those with normal glucose tolerance (Tofe et al., 2005). This information may facilitate identification of those at high risk of progressing to CFRD however more studies are required. HbA1c cannot be used to screen for CFRD, as levels are often falsely normal in CF and do not reliably correlate with glycemic control.

1.4. CFRD current management

The 2009 International Society for Pediatric and Adolescent Diabetes (ISPAD) clinical practice guidelines for the management of CFRD recommend a combination of basal (long-acting) and bolus

Table 1
Categories of carbohydrate intolerance in CF by OGTT.

Categories	Fasting plasma glucose (mmol/L)	2 h plasma glucose (mmol/L)
Normal glucose tolerance	<7.0	<7.8
Indeterminate glucose tolerance	<7.0	<7.8 with levels during 2 hours ≥11.1
Impaired glucose tolerance	<7.0	7.8–11.1
CFRD without fasting hyperglycemia	<7.0	≥11.1
CFRD with fasting hyperglycemia	≥7.0	OGTT not necessary