Management of cystic fibrosis-related diabetes in children and adolescents

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Introduction

Cystic fibrosis (CF) is the most common lethal genetic autosomal recessive disease in Caucasians, with a worldwide prevalence of 1 in 2500 live births. Cystic fibrosis related diabetes (CFRD) has emerged as the most common co-morbidity in CF (1, 2). There are important differences between CFRD and both type I and type 2 diabetes, which necessitate a unique approach to diagnosis and management (Table 1).

Definitions

Modified OGTT categories have been developed by the 1998 North American CFRD Consensus Committee in reporting CFRD with and without fasting hyperglycemia (fasting plasma glucose ≥ 7.0 mmol/l (126 mg/dl) or < 7 mmol/l; and 2 hour plasma glucose ≥ 11.1 mmol/l (200 mg/dl)) based on the suggestion that the prognosis may differ between these two groups in CF (2) (E). CFRD falls at one end of a spectrum of progressive glucose tolerance abnormalities. Few CF patients have completely normal blood glucose levels at all times. The earliest change is variable, intermittent post-prandial hyperglycemia followed by impaired glucose tolerance (IGT), then diabetes without fasting hyperglycemia, and diabetes with fasting hyperglycemia. A diagnosis of “normal” glucose tolerance on oral glucose tolerance testing does not exclude abnormal post-prandial glucose levels at home (when far more than 75 grams of carbohydrate may be consumed) (2) (B).

Assigning a specific diagnostic category to CF patients is complicated by the fact that glucose tolerance and insulin resistance are often variable in an individual subject. Factors specific to CF that cause fluctuations in glucose metabolism include: respiratory infection and inflammation, increased energy expenditure, malnutrition, glucagon deficiency, and gastrointestinal abnormalities (malabsorption, altered gastric emptying and intestinal motility and liver disease).

Table 1. A comparison of type 1 diabetes, type 2 diabetes and CFRD

<table>
<thead>
<tr>
<th></th>
<th>Type 1 diabetes</th>
<th>Type 2 diabetes</th>
<th>CFRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Acute</td>
<td>Insidious</td>
<td>Insidious</td>
</tr>
<tr>
<td>Peak Age of Onset</td>
<td>Children and adolescents</td>
<td>Adults</td>
<td>18-24 yrs</td>
</tr>
<tr>
<td>Antibody (+)</td>
<td>YES</td>
<td>NO</td>
<td>Probably NO</td>
</tr>
<tr>
<td>Insulin Secretion</td>
<td>Eventually absent</td>
<td>Decreased</td>
<td>Severely decreased but not absent</td>
</tr>
<tr>
<td>Insulin Sensitivity</td>
<td>Somewhat decreased</td>
<td>Severely decreased</td>
<td>Somewhat decreased*</td>
</tr>
<tr>
<td>Treatment</td>
<td>Insulin</td>
<td>Diet, oral meds Insulin</td>
<td>Insulin</td>
</tr>
<tr>
<td>Microvascular Complications</td>
<td>YES</td>
<td>YES</td>
<td>YES but less</td>
</tr>
<tr>
<td>Macrovascular Complications</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Cause of Death</td>
<td>Cardiovascular disease</td>
<td>Cardiovascular disease</td>
<td>Pulmonary disease</td>
</tr>
</tbody>
</table>

*Insulin sensitivity becomes severely decreased during acute illness.

Fig. 1. Glucose tolerance categories in CF patients at the University of Minnesota, expressed as percent prevalence within age groups. n=total number of patients studied within that age group (from reference 3).

Prevalence

The reported prevalence of CFRD varies depending on the screening and diagnostic criteria utilised. The prevalence may be underestimated at centers where universal screening is not undertaken. While it can occur at any age, CFRD prevalence increases with age: 9% of 5–9 year olds, 26% of 10–20 year olds (Minnesota (3)), (Figure 1) and 50% by 30 years (Denmark (8)). Repeated OGTTs have shown that glucose tolerance status can vary from year to year in CF patients (4) (B).

Pathophysiology of cf-related diabetes

Genetics of CFRD and relation to the CF mutation

CFRD mainly occurs in people with the most severe CF mutations, all of which are associated with exocrine pancreatic insufficiency (5–7) (C). There is no correlation with known T1D susceptibility genes such as HLA class II (8) (B) or insulin VNTR (5) (C), but a possible link has been described between CFRD and T1D susceptibility genes associated with inflammation such as tumor necrosis factor (8) (B) heat shock protein (8, 9) (B,C) and T2D susceptibility genes such as calpain10 (10) (C).

Pancreatic pathology

Abnormal chloride channel function in CF results in thick viscous secretions causing obstructive damage to the exocrine pancreas with progressive fibrosis and fatty infiltration. This results in disruption and destruction of islet architecture leading to loss of endocrine beta, alpha and pancreatic polypeptide cells (11–13) (B). Beta-cell dysfunction is not related to autoimmune disease in CF, outside of isolated case reports of autoantibody positive individuals with CFRD (14).

The role of insulin deficiency

The primary defect in CFRD is severe but not absolute insulin deficiency. Virtually all exocrine insufficient patients with CF, with and without diabetes, show evidence of beta-cell dysfunction (4, 15–17) (A). Fasting insulin and C-peptide concentrations are normal, but there is delay and blunting of peak insulin secretion during a standard OGTT (18) (B). This effect is more pronounced with worsening glycaemic status (18–21) (B, C). Delayed insulin secretion during the OGTT is related to loss of first phase insulin secretion, which is found even in CF patients with normal glucose tolerance (22) (B). Secretion of other islet hormones is also impaired in CF, in particular loss of glucagon responses (18) (22) (B).

The role of insulin resistance

In CF patients without diabetes, insulin sensitivity is variable (21, 23–26) (B) (17, 27) (B). While most
of these patients are sensitive to insulin in their baseline state of health, infection and inflammation increase insulin resistance (28) (B). CF patients with diabetes are insulin resistant, due to both decreased peripheral glucose uptake and poor insulin suppression of hepatic glucose production (26, 27) (B). Insulin resistance can become acutely severe during infectious exacerbations (E).

Clinical features of CFRD

CFRD develops insidiously and patients may be asymptomatic for years. Symptoms of CFRD are listed in Table 2. Diabetic ketoacidosis (DKA) is rare, most likely because of the persistence of endogenous insulin secretion or because glucagon secretion is also impaired (22, 29, 30) (B). CFRD often first presents during situations where insulin resistance is increased, such as acute pulmonary infection, chronic severe lung disease, glucocorticoid therapy, high-carbohydrate food supplementation (oral, intravenous, nasogastric or percutaneous gastrostomy tubes), and in association with immunosuppressive regimens following transplantation. The incidence of CFRD is higher in those with CF liver disease (31) (C). Hypoglycaemia is more common and more concerning in CF patients with liver disease. In the absence of liver disease, fasting hypoglycaemia is generally only seen in malnourished patients and the very young. Reactive hypoglycaemia may occur in CF patients with impaired glucose tolerance and may be helped by spreading carbohydrate intake more evenly during the day (E).

Survival and prognosis

Increased mortality in CFRD

The presence of CFRD is associated with worse lung function, poorer nutritional status, and decreased survival compared to non-diabetic CF patients (31–38) (A–C). One retrospective analysis of 448 CF patients followed for 10 years, demonstrated 25% survival with CFRD at 30 years compared to 60% of those without CFRD (32) (C). Recently a marked gender difference in survival in CFRD has been documented with median survival of 47–49 years for males in comparison to only 31 years for female subjects (39) (B). This survival gender difference was not seen however in a recent 17 year prospective cohort of 237 French children with CF (29) (B).

Increased morbidity in the pre-diabetes state

An insidious decline in clinical status can occur 2–6 years before the diagnosis of CFRD (34–37) (32) (B). Pulmonary deterioration correlated with the degree of insulin deficiency at baseline (41). There is a known association between protein catabolism, malnutrition and death in CF. The potent anabolic role of insulin (ie the nutritional impact and metabolic effects relating to insulin deficiency) may be of greater consequence in CF than the metabolic impact of hyperglycaemia (E).

Microvascular complications

Microvascular complications have been described in CFRD patients, sometimes with significant morbidity (40–42) (C). A Danish study has reported a 36% incidence of retinopathy in patients with CFRD for more than 10 years duration (43) (B). Another larger series of CFRD patients with fasting hyperglycaemia found, microalbuminuria in 14%, retinopathy in 16%, neuropathy in 55% and gastropathy in 50% after 10 years duration. Microvascular complications were rare before 10 years duration of CFRD with fasting hyperglycaemia. No microvascular complications were found in CFRD patients without fasting hyperglycaemia for up to 14 years duration (44). Macrovascular Complications have not been reported in CFRD to date.

Testing for CFRD

It is important to identify patients before the onset of symptoms as CFRD often has an insidious onset. The following methods of testing for CFRD have been considered: hemoglobin A1c (HbA1c), Oral Glucose Tolerance Test (OGTT), random or fasting glucose levels, and Continuous glucose monitoring (CGM).

HbA1c as a diagnostic tool

HbA1c has been shown to be unreliable in the diagnosis of CFRD (4, 19, 32, 45) (B). HbA1c is often normal, regardless of the degree of hyperglycaemia, with only 16% of CF patients having elevated HbA1c values at the time of diabetes diagnosis (4) (B).

Oral glucose tolerance testing (OGTT)

The OGTT is the standard test for CFRD in many centres (4) (A) (46) (E). Diabetes without fasting hyperglycaemia can only be detected by OGTT. Measuring insulin concentrations every half hour during the OGTT may be clinically useful to assess the degree of insulin deficiency (E).
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Random and fasting glucose levels for CFRD diagnosis

While hyperglycemia is diagnostic for diabetes, normal fasting or random glucose levels do not exclude a diagnosis of diabetes in CF (A).

Continuous glucose monitoring (CGM)

In the research setting, CGM can detect abnormal glucose tolerance earlier than the OGTT, but the clinical significance is still under investigation. CGM has been validated for use in children and adolescents with CF (47–50, 51). CGM may aid the diagnosis of CFRD when considered in conjunction with the OGTT result and the clinical scenario (16, 48, 49) (C).

Clinical Suspicion of CFRD

If the OGTT result is normal or borderline abnormal and diabetes is suspected based on clinical symptoms, a period of home glucose monitoring (pre & 2h post-prandial and in the middle of an overnight tube-feeding) or CGM may provide additional useful information (E).

Treatment of CFRD

Medical nutritional therapy

A high calorie, high fat diet is important in CF (52) (A). Caloric restriction is thus contraindicated. Table 3 compares the CFRD to the standard diabetes diets.

Insulin therapy

Insulin is the only recommended medical therapy for CFRD (2) (E). Insulin therapy may help to stabilize lung function and improves nutritional status in patients with CFRD (34, 36, 37, 53) (C). There are no definitive data to date on the benefits of insulin therapy for CF children and adolescents with milder forms of abnormal glucose tolerance, although a small case series has demonstrated similar benefit (16, 54) (C).

Choice of the insulin regimen depends on individual needs and characteristics of the patient. The standard basal bolus regimen provides background insulin and a continuous anabolic effect. The short acting insulin controls postprandial hyperglycaemic episodes and provides flexibility for variable eating patterns (55) (B). Alternatively, effective basal-bolus therapy can be accomplished with insulin pump therapy (56, 57) (E).

Twice daily isophane with or without short acting insulin can be used, but may not be optimum therapy to allow for meal flexibility due to nausea or anorexia or other treatment requirements especially in the morning.

The current medical treatment program of the patient, and compliance history, should be evaluated when deciding on an insulin regimen.

For patients on enteral night-time feeds, more insulin will be required at night. Monitoring of blood glucose during the feed is recommended so the dosage can be appropriately adjusted (Table 4).

Oral diabetes agents

Oral diabetes agents are currently not recommended in CFRD (2) (E). A recent Cochrane review has highlighted the lack of randomized controlled trials (58) (A). The insulin secretagogue repaglinide increased endogenous insulin levels but was less effective than rapid-acting insulin in regulating post-prandial hyperglycaemia in an experimental setting (59) (B). There are concerns about hypoglycaemia with sulphonylureas in patients with CF (60, 61) (B). Agents that reduce insulin resistance are unlikely to be effective as a single therapy in CFRD, because insulin resistance is not the major aetiological factor. The gastrointestinal side effects of metformin such as nausea, diarrhoea and abdominal discomfort are unacceptable to most people with CF (61) (C). Thiazolidinediones have recently been associated with osteoporosis. The decreased gastric emptying due to incretins limits their utility in CF.

CFRD without fasting hyperglycemia and CF with impaired glucose tolerance

While insulin treatment of CFRD with fasting hyperglycemia has been the accepted standard-of-care for several years, treatment of less severe glucose tolerance abnormalities has been more controversial. Results from a recent multi-center, randomized, placebo-controlled clinical trial demonstrate that pre-meal insulin therapy reversed chronic weight loss in adults with CFRD without fasting hyperglycemia and this effect was sustained over 1 year of treatment (62). Thus, insulin therapy is now recommended for all patients with CFRD with or without fasting hyperglycemia (B). There are insufficient data at present to make recommendations for patients with IGT or those who have NGT by OGTT testing but intermittent asymptomatic hyperglycemia when tested at home.

Inpatient management of CFRD

During an acute illness, CF children and adolescents are at increased risk of developing hyperglycaemia (2) (E) Whilst data from other populations suggest that intensive insulin therapy may be beneficial in this setting, no studies have examined the benefits of maintaining euglycemia in hospitalized CF patients. Insulin requirements may be large during acute illness:

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up to four times the usual baseline insulin dosage needed in some CFRD patients (E). The insulin dose must be aggressively reduced as the patient improves, to avoid hypoglycaemia, and in many CF patients blood glucose levels return to normal after the illness resolves (2) (E).

Recommendations

I. Diagnostic criteria for CFRD
– CF with and without hyperglycaemia have different prognoses (A)
– It is important to recognize that glucose tolerance diagnostic categories are relative rather than absolute markers of risk in CF. Glucose tolerance fluctuates with overall health status in CF.

II. TESTING FOR CFRD
– Routine annual testing for diabetes should be performed in CF patients aged 10 years and older during a time when they are clinically well (in their baseline state of health) (E).
– The 2 hour OGTT is the preferred test for routine screening (E).
– Circumstances when extra glucose monitoring is recommended include:
  – Development of diabetes symptoms as listed in Table 2
  – During infective exacerbations
  – During systemic corticosteroid treatment
  – After commencing supplemental enteral tube feeding
  – Before and after major surgery
  – Symptoms of hypoglycaemia
  – Pregnancy requires special consideration (63) (C).

III. Treatment of CFRD

The decision to treat should be based on consideration of blood glucose levels and the impact of treatment on the individual’s overall condition.

CFRD with Fasting Hyperglycaemia
– Insulin is recommended therapy (B). The insulin regimen should be tailored to the patient’s individual needs, but in general must be flexible enough to

Table 3. Differences in the dietary management of type 1 and type 2 diabetes versus CF related diabetes (CFRD)

<table>
<thead>
<tr>
<th></th>
<th>Type 1 and Type 2 diabetes</th>
<th>CFRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calories</td>
<td>≤ 100% of normal for age and gender — often have to watch or restrict calories to prevent overweight</td>
<td>Usually require 120-150% (or more) of normal caloric intake for age and gender to prevent underweight</td>
</tr>
<tr>
<td>Fat</td>
<td>30-35% of total energy</td>
<td>40% of total energy</td>
</tr>
<tr>
<td>Refined Sugars</td>
<td>Up to 10% of total energy</td>
<td>No Restriction</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>50-55% total energy</td>
<td>45-50% of total energy</td>
</tr>
<tr>
<td>Dietary Fibre</td>
<td>Encouraged due to beneficial effects (Age in years + 5g per day)</td>
<td>Encouraged in the well nourished, but in poorly nourished patients, it may compromise energy intake</td>
</tr>
<tr>
<td>Protein</td>
<td>10-15% of total energy; not &gt;1g per kg body weight</td>
<td>200% of reference nutrient intake</td>
</tr>
<tr>
<td>Salt</td>
<td>Low intake ≤ 6g /day</td>
<td>Increased requirement — unrestricted intake</td>
</tr>
</tbody>
</table>

Table 4. General principles of insulin therapy in CFRD

<table>
<thead>
<tr>
<th>Meal Coverage</th>
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<tbody>
<tr>
<td>● A common starting dose is 0.5-1 iu rapid-acting insulin for every 15 grams</td>
</tr>
<tr>
<td>of carbohydrate consumed. Insulin pens or syringes that deliver half units</td>
</tr>
<tr>
<td>may be needed.</td>
</tr>
<tr>
<td>● The dose is adjusted by increments of 0.5 iu per 15 grams carbohydrate to</td>
</tr>
<tr>
<td>achieve 2-hr post-prandial blood glucose goals.</td>
</tr>
<tr>
<td>● For very young patients or those who are unsure of what they will eat due to</td>
</tr>
<tr>
<td>nausea or gastroparesis, the dose can be given right after the meal.</td>
</tr>
<tr>
<td>● Pre-meal correction can be started at 1 iu rapid-acting insulin for every</td>
</tr>
<tr>
<td>2.8 mmol/L (50 mg/dl) above 8.3 mmol/L (150 mg/dl) and adjusted as needed.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Correction Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Basal insulin can be started at 0.25 iu per kg body weight per 24 hours,</td>
</tr>
<tr>
<td>and adjusted based on the fasting glucose level.</td>
</tr>
<tr>
<td>● Frequently a single dose of isophane plus regular insulin will cover an</td>
</tr>
<tr>
<td>overnight drip feeding. The regular insulin covers the first 4 hours and the</td>
</tr>
<tr>
<td>isophane the second 4 hours. Glucose levels 4 hours into the feeding and at</td>
</tr>
<tr>
<td>the end of the feeding are used to adjust the insulin dose.</td>
</tr>
</tbody>
</table>

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accommodate wide daily variation in carbohydrate timing and quantity, and must take into account changing insulin requirements such as during acute illness, glucocorticoid therapy, pregnancy, or intensive enteral or parenteral nutrition (A).

- Oral agents are not recommended due to lack of efficacy data as well as concerns about potential side-effects.

- The high-calorie, high-fat diet used to maintain nutritional status should contain (A). The insulin dose needs to be adjusted to match carbohydrate intake (E).

- Treatment aims are to eradicate symptoms of hyperglycaemia/hypoglycaemia and maintain adequate nutrition, growth and respiratory function (A).

- Good communication between the CF pulmonary and endocrinology teams is essential. Clear roles, responsibilities and treatment aims are important, particularly at times of intermittent illness and during admissions to the hospital (E).

- Management requires significant input from the patient or caregiver. The health care team plays a critical role in educating, supporting, advising, and motivating the patient and family (A).

- CGM has been validated and provides additional useful information in children in CF (C).

- Patients should be screened annually for microvascular complications (B).

CFRD without Fasting Hyperglycemia: Insulin is now recommended therapy (B)

CF with Impaired Glucose Tolerance.

- Currently, insulin therapy is not universally recommended unless the individual patient demonstrates persisting signs of poor growth, inability to maintain weight, unexpected decline in pulmonary function, despite optimisation of other medical management, or develops overt signs of diabetes (E) Some patients may require insulin during times of increased insulin resistance (B).

- Patients with IGT and patients with CFRD without fasting hyperglycemia are at significant risk of progression to CFRD with fasting hyperglycemia, and should be monitored with annual OGTTs (B).

- More intensive monitoring of blood glucose (pre and 2hr post prandially or CGM) should be performed during periods of increased stress, such as acute pulmonary exacerbations. (E)

References

1. CFF 2001 Cystic Fibrosis Foundation Patient Registry Annual Data Report In: CF Foundation Bethesda, Maryland.


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