Cystic fibrosis related diabetes: Medical management

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ABSTRACT

Cystic Fibrosis Related Diabetes Mellitus (CFRD) drives excess pulmonary morbidity and mortality in patients with cystic fibrosis (CF). The recommended treatment is insulin therapy. Insulin therapy in CF should be customized to the specific patient. CF patients typically require intensive insulin regimens such as multiple daily injections or insulin pump therapy, but frequently require lower doses than in type 1 diabetes mellitus. Patients with CF may also need insulin to cover intravenous or enteral feedings. Pre-diabetic glycaemic abnormalities are also associated with clinical decline in cystic fibrosis prior to the diagnosis of CFRD; however, whether and how this should be treated is not fully determined. There is also interest, but inadequate data regarding other treatments besides insulin (i.e., oral medications) for treatment of pre-diabetes or CFRD. CFRD potentiatior and corrector therapy has yet to demonstrate an effect on the rate of CFRD, but may improve insulin secretion. There is great opportunity for further research to better understand when and how best to treat glycaemic abnormalities in cystic fibrosis.

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ARTICLE INFO

Article History:
Received 3 July 2019
Revised 7 August 2019
Accepted 9 August 2019

Keywords:
Cystic fibrosis
cystic fibrosis related diabetes mellitus
Insulin
Treatement
Oral hypoglycaemic agents
Insulin pump

1. Background

Although Dorothy Anderson described glycaemic abnormalities in her seminal paper that first described the disease we now know as cystic fibrosis (CF) [1], it was not until the 1990s that systematic efforts to screen for, diagnose, and treat cystic fibrosis related diabetes mellitus (CFRD) were put in place [2].

It is now well established that CFRD increases the rate of pulmonary decline in cystic fibrosis and contributes to pulmonary morbidity and mortality [3-4]. People who have CF and CFRD are at significantly increased risk for earlier mortality than those with CF without diabetes, even when adjusted for underlying disease severity [4].

Therefore, there is a clear imperative to treat CFRD and to attempt to prevent the excess morbidity and mortality arising from glycaemic abnormalities in CF. We have made progress towards this goal. The introduction of rigorous screening and aggressive treatment has begun to close the survival gap between those with CF who do and do not have diabetes [5], but there remains significant work to be done in order to better understand which patients are at greatest risk for harm and what the optimal treatment strategy will be.

1.1. Definition of CFRD and abnormal glucose tolerance

Cystic fibrosis related diabetes mellitus (CFRD) is a unique form of diabetes mellitus, separate from type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). CFRD is extremely common in people with CF, occurring in approximately 19% of adolescents and 40–50% of adults with cystic fibrosis [5]. However, pre-diabetic states (also termed abnormal glucose tolerance (AGT) or dysglycemia) are also very common in cystic fibrosis [6]. In CF, diabetes and pre-diabetes are defined by the result of oral glucose tolerance testing (see Table 1) [2]. CFRD is defined as a fasting blood glucose level > 7.0 mmol/L (126 mg/dL), or a 2-hour glucose level greater than or equal to 11.1 mmol/L (200 mg/dL) or both. Impaired glucose tolerance (IGT) is defined as a fasting blood glucose > 7.0 mmol/L (126 mg/dL) and a 2-hour glucose level > 11.1 mmol/L (200 mg/dL) but greater than or equal to 7.8 mmol/L (140 mg/dL). Indeterminate glycemia (INDT) is defined as a fasting blood glucose > 7.0 mmol/L (126 mg/dL) and a 2-hour glucose level greater than or equal to 11.1 mmol/L (200 mg/dL) but greater than or equal to 7.8 mmol/L (140 mg/dL).
Fasting hyperglycaemia is a late In or clinical decline [7]. Associated with subsequent increased risk of progression to CFRD. States (IGT and INDET), impaired fasting glucose in CF has not been associated with subsequent increased risk of progression to CFRD or clinical decline [7].

2. Management

2.1. Dietary management of CFRD

Medical nutrition therapy is essential to management of all forms of diabetes, including CFRD. Importantly, medical nutrition therapy for CFRD differs from that recommended for T1DM and T2DM [2], differing from type 2 in that carbohydrate restriction is not recommended, and from type 1 in that there is need for continuation of the recommended CF diet with increased total calories, salt and fat consumption. Due to the fact that the primary underlying pathophysiology of CFRD is insulin deficiency [8–12], weight loss and dietary restriction will not typically stop or slow the progression of disease. It is important that patients should be counselled not to attempt such dietary restrictions based on the recommendations of other health care providers or relatives or in an attempt to prevent the need for insulin injections. The appropriate approach to medical nutrition therapy, in a patient with CFRD, is to continue the appropriate CF diet prescription (high calorie, high salt, high fat, not carbohydrate restricted) with the addition of meticulous carbohydrate counting. Instruction on adjusting insulin to carbohydrate intake is recommended instead of a fixed carbohydrate meal plan, as appetite can vary from day to day in patients with CF. (please see Kaminiski et al. [13] in this issue for a full discussion of diet and CFRD.)

Of note, if a patient with CFRD needs oral high calorie supplements or enteral feeds, it is recommended to use CF appropriate supplements and enteral feedings, not “diabetic” supplements or formulas. The carbohydrate content of CF-appropriate supplements should be covered with appropriate insulin therapy if needed. (please see Kaminiski et al. [13] in this issue for further details.)

2.2. Exercise

Exercise is essential to the care of all CF patients. It also has significant positive benefits in all forms of diabetes. In CFRD exercise has been shown to reduce postprandial glycaemic excursions and total glucose excursions [14]. Therefore, appropriate exercise should be encouraged after the diagnosis of CFRD or dysglycaemia.

2.3. Insulin therapy

Despite our incomplete understanding of the pathophysiology of CFRD, it is clear that the end result is insulin deficiency [8–11,15]. Insulin is an anabolic hormone, therefore, deficiency of insulin results not only in hyperglycaemia, which has been shown to increase the glycaemic content of airway surface liquid and susceptibility to lung infection [16,17], but also loss of muscle mass and protein stores and induction of a catabolic state [18]. Therefore, insulin is the recommended therapy for CFRD [2].

Unfortunately, at this time, there are no large randomized controlled trials directly comparing different insulin regimens. However, clinically effective insulin regimens do exist [19,20]. The insulin regimens utilized should always be personalized to the degree and timing of glycaemic excursions in each patient as well as what forms of insulin are available (Table 2).

Table 1
Glucose tolerance categories based on OGT.

<table>
<thead>
<tr>
<th>Category</th>
<th>Fasting glucose mmol/L (mg/dL)</th>
<th>Intermediate time points mmol/L (mg/dL)</th>
<th>120 min time point mmol/L (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal glucose tolerance (NGT)</td>
<td>&lt;5.6 (100)</td>
<td>&gt;11.1 (200)</td>
<td>&gt;7.8 (140)</td>
</tr>
<tr>
<td>Impaired fasting glucose (IFG)</td>
<td>&gt;5.6 (100)</td>
<td>&gt;11.1 (200)</td>
<td>&gt;7.8 (140)</td>
</tr>
<tr>
<td>Impaired glucose tolerance (IGT)</td>
<td>&lt;7.0 (126)</td>
<td>&gt;11.1 (200)</td>
<td>&gt;7.8 (140)</td>
</tr>
<tr>
<td>Indeterminate glycemia (INDET)</td>
<td>&gt;7.0 (126)</td>
<td>&lt;11.1 (200)</td>
<td>&gt;7.8 (140)</td>
</tr>
<tr>
<td>Cystic Fibrosis Related Diabetes Mellitus (CFRD)</td>
<td>&gt;7.0 (126)</td>
<td>N/A</td>
<td>&gt;11.1 (200)</td>
</tr>
</tbody>
</table>

N/A = not applicable.

* The diagnosis of CFRD can be made with either a fasting blood glucose level ≥ 7.0 mmol/L or a 120 min blood glucose level ≥ 11.1 mmol/L.

Table 2
Insulin action.

<table>
<thead>
<tr>
<th>Insulina</th>
<th>Onset of actionb</th>
<th>Duration of actionb</th>
<th>Peakb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspart</td>
<td>10–20 min</td>
<td>3–5 h</td>
<td>1–2 h</td>
</tr>
<tr>
<td>Lispro</td>
<td>10–20 min</td>
<td>3–5 h</td>
<td>1–2 h</td>
</tr>
<tr>
<td>Glulisine</td>
<td>10–20 min</td>
<td>3–5 h</td>
<td>1–2 h</td>
</tr>
<tr>
<td>Short acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>30 min</td>
<td>4–6 (up to 8) h</td>
<td>2–4 h</td>
</tr>
<tr>
<td>Intermediate acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isophane insulinc</td>
<td>1–3 h</td>
<td>8–22 h</td>
<td>1–8 h</td>
</tr>
<tr>
<td>Long acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glarginec</td>
<td>1–2 h</td>
<td>18–26 h</td>
<td>None</td>
</tr>
<tr>
<td>Detemirc</td>
<td>1–3 h</td>
<td>12–20 h</td>
<td>None (8 h)</td>
</tr>
<tr>
<td>Ultra long acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degludec</td>
<td>Reaches steady-state at 3–4 days</td>
<td>At least 42 h</td>
<td>None (12h)</td>
</tr>
</tbody>
</table>

a All times vary depending on dose given, location of dose, physical activity of the individual in question and insulin resistance. Insulin kinetics above are in subjects with type 1 diabetes, not subjects with CF.

b Isophane insulin is also known as NPH (Neutral Protamine Hagedorn) insulin.

c Glargine, Detemir and Degludec insulins cannot be mixed with other insulins.
bolus insulin with meals (0.52 units/kg/day vs 0.47 units/kg/day) but less basal insulin (0.27 units/kg/day vs 0.38 units/kg/day) [20]. Although there is increasing literature that insulin sensitivity declines as the CF population ages [24], it is still recommended to initiate insulin at lower doses and then adjust based on the patient’s response. Insulin dosing needs in CFRD typically average <0.5–0.8 units/kg/day, and typically do not differ between adolescents and adults [25].

All appropriate insulin regimens in CFRD require accurate carbohydrate counting on the part of the patient and family and all regimens will need to be adjusted based on patient activity and disease status. Exercise will decrease insulin needs, whereas growth, pulmonary exacerbation or other illness will increase them [26]. The expectation is that insulin regimens will be flexible, and that ongoing adjustment will be required.

Given that CF patients can be very thin, it is also important to carefully rotate insulin injection sites in order to avoid lipohypertrophy. Lipohypertrophy is caused by overgrowth of adipose tissue at the site of insulin injection when an injection site is used too frequently. This results in a palpable firm but mobile lump in the subcutaneous tissue. Insulin that is injected into an area of lipohypertrophy absorbs poorly, resulting in hyperglycaemia. Given that CF patients may be thin with less subcutaneous fat, they may already have limited ability to rotate insulin injection sites, and so it is especially important for care to be given to adequate rotation. Also, lipohypertrophy requires strict avoidance of the areas until completely resolved, which can worsen functional sites further. (Please see Fig. 1 for a picture of what lipohypertrophy may look like.)

2.3.1.3. Insulin regimens- multiple daily injection. Multiple daily injection (MDI) is a common type of insulin regimen used in CFRD. In a person with CFRD and fasting hyperglycaemia, this would include a longacting basal insulin such as insulin glargine, insulin degludec, or insulin detemir in combination with meal coverage. In CFRD without fasting hyperglycaemia, meal coverage alone, basal insulin alone, or both may be used [22,23].

In an MDI regimen, meals are covered with an insulin to carbohydrate ratio using rapid acting insulin (insulin aspart, insulin lispro, insulin glulisine). Meal insulin should always be given before meals, ideally 15–30 min prior to a meal. Most people with CF have meal plans that include substantial snacks. To optimize nutritional status and best control glycaemic excursions, we recommend that insulin be given for all meals and all snacks. (Meaning that a typical patient with CFRD would give prandial insulin 3–6 times per day). All insulin dosing must be personalized, but a potential starting dose for carbohydrate coverage would be 1 unit for every 30 g of carbohydrate (0.5 units for every carbohydrate exchange (15 g of carbohydrate).

Insulin syringes or pens with half-unit markings support more careful titration of insulin dosing to match carbohydrate intake (see Fig. 2). An MDI regimen typically also includes a correction factor (sensitivity factor) for treating hyperglycaemia utilizing rapid acting insulin given with meals in addition to carbohydrate coverage. The correction dose depends on patient size and insulin sensitivity; however, a typical starting correction could be 1 unit of rapid acting insulin to lower blood glucose by 5 mmol/L (or one-half unit to lower blood glucose by 50 mg/dL); these doses are not exactly equivalent due to goals for ease of use (5 mmol/L – 90 mg/dL). The correction dose is adjusted as needed to achieve the patient’s target range for blood glucose.

For CFRD without fasting hyperglycaemia, premeal rapid acting insulin alone was shown to reverse chronic weight loss and is the standard of care [2,22,23], although the newest ISPAD guidelines note that some CFRD patients without fasting hyperglycaemia who eat multiple small meals throughout the day may be managed successfully with basal insulin alone, given in the morning [23]. If this is done, a small dose of basal insulin is started and titrated upward as long as the patient is not experiencing hypoglycaemia.

For a patient on an MDI regimen, blood glucose monitoring should be performed before breakfast, 2 h after breakfast, before lunch, 2 h after lunch, before supper, and prior to bedtime. If the patient requires basal insulin, overnight glucose monitoring should be performed as needed and when changes are made to basal insulin doses. Overnight monitoring is typically performed at 3 am or at midnight and 3 am. With the newer types of continuous glucose monitors (CGM), CGM readings may be utilized in place of self-monitoring of blood glucose levels. Please see Chan et al. in this issue for additional details [27].

2.3.1.4. Insulin regimens- insulin pump. Insulin pump therapy (or continuous subcutaneous insulin infusion (CSII)) therapy has been associated with improved glycaemic control in CFRD in small studies, mostly secondary to better coverage of meals and snacks [28]. An insulin pump device consists of a plastic body housing the insulin reservoir and electronics to allow control of the rate of insulin infusion. There are two main types of insulin pumps, patch pumps and pumps with tubing. With a patch pump, such as the OmniPod (see Fig. 3), the pump itself is held directly to the skin with adhesive tape and a small catheter from the underside of the pump inserts into the subcutaneous tissue. This pump is then controlled by a separate device (or the patient’s smartphone) via Bluetooth or radio frequency. Pumps with tubing (examples are the Medtronic MiniMed pumps or the T-slim pumps (see Fig. 4)) consist of a device which contains the insulin reservoir with buttons and information screen allowing direct control of the insulin infusion. Plastic tubing then extends from this device (normally worn on the belt with a clip) to the skin where an infusion site extends tubing under the skin into the subcutaneous tissue (see Fig. 4 for Medtronic and t-slim pumps and Fig. 5 for an example of an infusion site). The patch pump or the infusion site (for a pump with tubing) should be changed every 48–72 h to prevent stoppage of insulin flow from site occlusion.

Determination of insulin dosing when using the pump is very similar to MDI. However, for pump therapy, only rapid acting insulin is used. The appropriate units of basal insulin are divided over 24 h to calculate the basal rate. The pump is programmed with a basal rate to infuse the required basal insulin in units/h, which the pump administers as a continuous subcutaneous infusion. In addition to more convenient meal and snack coverage, the pump utilizes a setting called “active insulin time” which accounts for insulin that has previously been taken, reducing risk for hypoglycaemia secondary to overlapping dosing, which can otherwise occur in CF patients who require frequent insulin dosing to cover snack. Another advantage of insulin pump therapy is that the basal rate can be varied during the day and overnight, to account for of decreased and/or increased insulin sensitivity, such as regular exercise. Additionally, some pumps can utilize very low insulin infusion rates. The insulin to carbohydrate ratio and

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**Fig. 1. Lipohypertrophy.**

This picture shows lipohypertrophy of the abdomen. There is thickening and slight darkening of the skin just inferior and lateral to the umbilicus. [http://aditidiabetes.com/diabetes-guide/](http://aditidiabetes.com/diabetes-guide/)
hyperglycaemia correction factor are determined in a similar fashion as for MDI. The appropriate insulin to carbohydrate ratio and correction or sensitivity factor are then programmed into the pump. When the patient is ready to eat or needs a correction bolus, the patient will enter the amount of carbohydrate and their current blood sugar into the pump. The pump will perform mathematical calculations based on the pre-programmed carbohydrate ratio and sensitivity factor and suggest a dose to the patient, who will then accept or adjust that dose. Once the dose is confirmed by the patient, the pump will then administer the bolus.

Blood glucose monitoring for an insulin pump patient, similar to MDI, would be recommended to be done before breakfast, 2 h after breakfast, before lunch, 2 h after lunch, before supper and prior to bedtime. Overnight glucose monitoring should be performed as needed and when changes are made to basal rates. Continuous glucose monitoring (CGM) may also be useful in conjunction with insulin pump therapy (please see Chan et al. in this issue for detailed information on CGM use [27]).

2.3.1.5. Insulin regimens-isophane/regular insulins. Isophane (also known as Neutral protamine Hagedorn (NPH)) insulin is an intermediate acting insulin with a long history of effective use in type 1 diabetes mellitus. NPH/regular insulin regimens have been used with success in CFRD, but are currently rarely used in MDI regimens, except in cases where the newer analogue insulins cannot be obtained, as they are markedly less expensive. They have the major disadvantage of being inflexible, which is problematic for those with CF who have variable appetites. When using and NPH/regular insulin for MDI 2/3 of the total daily dose (TDD) is given in the morning, with 2/3 of that being NPH and 1/3 regular insulin. The other 1/3 of the TDD is administered in the evening, half as NPH and half as regular. NPH lasts for 8 h and has a marked peak at 4 h. Therefore, a patient who is treated with NPH must eat lunch and must eat an appropriate bedtime snack, or they are at significant risk for severe hypoglycaemia.

There has been one small study done in patients with CFRD and fasting hyperglycaemia comparing a single dose of NPH insulin at bedtime to a single dose of glargine insulin at bedtime in a crossover study in 19 subjects. This study found greater weight gain on glargine and greater reduction in fasting blood glucose levels [29]. Also, not statistically significant, but clinically telling, is that all of the subjects elected to remain on glargine once the study was complete [29].

2.3.1.6. Insulin regimens- nutritional support. Because nutritional failure is tightly linked to outcomes in CF [30,31], and insulin insufficiency is a driver of catabolism and weight loss [18], patients with CFRD will often benefit from supplemental oral, enteral, or intravenous feedings [32]. However, in many cases, they will require insulin coverage for the carbohydrate in these feedings.

2.3.1.6.1. Overnight tube feedings. Enteral tube feedings may be necessary to maintaining weight and BMI in CF [32]. Insulin regimens for overnight enteral feeds are relatively simple and very effective in reversing weight loss. In the experience of the authors, insulin with overnight enteral feeds only (without basal insulin and/or insulin for daytime carbohydrate intake) may be adequate to reverse weight loss. For a typical overnight feed of eight hours, the carbohydrates...
are well covered with a combination of NPH (isophane) and regular insulin. To determine the dose, one determines the total carbohydrate content of the feed and the insulin to carbohydrate ratio. To start the dose is often given as 70% NPH and 30% regular insulin mixed and administered at the beginning of the overnight tube feed. Pre-mixed NPH/regular or NPH/rapid acting (such as NPH/lispro or NPH/aspart) can also be used. However, with premixed insulins the amount of NPH and regular/rapid acting insulin cannot be titrated separately. For patients using insulin pumps, tube feedings may be covered by an extended bolus in which the pump delivers insulin at an increased rate for the duration of the tube feeding.

For overnight feedings, the blood glucose level is monitored at the start of the feed, in the middle of the feed, and at the end of the feed. If the blood sugar is elevated at the 4-h point, the amount of regular insulin is increased. If the blood sugar is elevated at the end of the feeding, the amount of NPH insulin given is increased.

2.3.1.6.2. Bolus enteral feeds/supplements. Daytime supplemental feeds, either given via tube feed or orally, are common and useful for weight maintenance in CF. Daytime bolus tube feeds and oral supplements are covered with insulin as if they were meals. The total carbohydrate content of the bolus feed/supplement is calculated and an insulin to carbohydrate ratio is determined (or a previously established insulin to carbohydrate ratio is used). This ratio is then used to determine the insulin needed to cover the carbohydrate content of the feed. This insulin dose is given prior to the time the feed is drunk or administered via tube feed. If it is an oral supplement, or a tube feeding given as a bolus or in 4 h or less, short or rapid acting insulin should be used to cover the oral supplement or feeding. Blood glucose monitoring would be performed at the beginning of the feed/prior to drinking the supplement, 2 h later and prior to the next meal or bolus feeding.

Longer feedings can still be covered with appropriate insulin regimens. (See Table 2 for different types of available insulins and their duration of action). Regardless of the duration of the feeding, the insulin dose is still calculated by determining the total carbohydrate content of the feed and the appropriate insulin to carbohydrate ratio. However, the type of insulin given is varied based on the duration of the feeding. Care must be taken if continuous feedings need to be interrupted or discontinued given that the patient is at risk for hypoglycaemia. Many centres have a policy to run fluids with 10% dextrose if a continuous feeding is interrupted [33,44]. With continuous feedings, in the absence of significant oral intake/regular meals, blood glucose levels are typically monitored every 4 h while awake, at bedtime, at the midpoint of the sleep period, and at awakening. Also, it is important to remember with continuous feedings that the patient is constantly in a post prandial state, so the goal glucose range chosen should reflect that (often 140–180).

2.3.1.6.3. TPN. People with CF can require parenteral nutrition or total parenteral nutrition (TPN). TPN typically has significant glucose as a nutrition source and patients may require insulin therapy with the TPN to maintain blood glucose levels in goal range. TPN can be covered in a similar fashion to a continuous enteral feed, utilizing a subcutaneous insulin injection of appropriate duration, dosed using the patients known or calculated insulin to carbohydrate ratio to appropriately cover the carbohydrate content of the TPN. This is given when the TPN bag is hung, in the same manner as one would cover an enteral feeding of the same duration as the planned TPN infusion. However, it is extremely important that if the care team has to suspend the infusion of TPN, they either replace the carbohydrate content of the TPN with a dextrose infusion, or check the patient’s blood glucose levels frequently until the TPN can be restarted. Another method to administer insulin with TPN is to add regular (human) insulin to the TPN bag itself. This method may not be allowed by institutional policy. However, if it is allowed it has one
The use of oral or high dose glucocorticoid therapy is not as common as it once was in the treatment of cystic fibrosis. However, in some cases, such as allergic bronchopulmonary aspergillosis (ABPA) or severe co-occurring asthma, or autoimmune or neoplastic disease, such treatment may be necessary. Glucocorticoid therapy causes marked insulin resistance. In those with CF, glucocorticoids can cause diabetic-range blood glucose levels even in patients without previous diagnosis of CFRD. In those with pre-existing CFRD, glucocorticoids typically cause need for increasing insulin dosing to keep blood glucose levels in goal range [19]. Glucocorticoids can also increase hunger, thereby driving carbohydrate intake.

Prednisone is the commonly used glucocorticoid in clinical practice. The blood glucose effect of prednisone usually lags the onset of prednisone therapy by about 24 h, with increased blood glucose levels sometimes persisting for 24–48 h after the prednisone therapy is discontinued. Typically, patients with CFRD on prednisone will require marked increases in insulin dosing (usually 30–40% increase in insulin doses [19], but could need much more, especially with meals). Some patients without history of pre-existing CFRD will require new insulin therapy for the duration of prednisone therapy. Steroid induced hyperglycaemia is typically most marked after meals [33], so adequate treatment will often require initiation of or increase in carbohydrate coverage, which will require teaching of carbohydrate counting if the patient is not already counting carbohydrates. Alternatively, NPH (isophane) insulin can be used to cover prednisolone or prednisone therapy. This can be utilized in patients both with and without pre-existing CFRD. If NPH is used, it is given at the same time as the prednisone dose and the underlying insulin regimen is left otherwise unchanged. The NPH is then adjusted as the prednisone/prednisolone dosing is adjusted [33].

Intravenous methylprednisolone can be the glucocorticoid of choice for APBA and serious autoimmune diseases. Short term administration of methylprednisolone causes postprandial hyperglycaemia lasting 6–12 h. Similarly to above, some authors have recommended the administration of NPH (isophane) insulin at the same time as the methylprednisolone infusion at a dose of 0.1–0.15 Units of NPH per 1 mg of methylprednisolone for insulin naïve patients and 0.25 units per mg of methylprednisolone in patients on pre-existing insulin therapy [19].

**2.3.1.6.5. Pulmonary exacerbations.** Illness, including acute pulmonary exacerbation, may increase insulin resistance markedly. Due to this, pulmonary exacerbation can be a time when CFRD first manifests [26]. If diabetic range blood glucose levels persist past the first 48 h of illness in a patient with CF with or without pre-existing CFRD, treatment may be required [2]. People with CF who have hyperglycaemia only during pulmonary exacerbation have been documented to be at risk for complications of diabetes mellitus, which indicates that these glycaemic excursions during illness are not benign [34]. Recommendations for initiation of insulin therapy for new onset hyperglycaemia during illness are the same as CFRD diagnosed at baseline health. Patients with CF may have diabetic range blood sugars during illness that require treatment, but then subsequently normalize after the illness is over [26] and be able to discontinue insulin therapy.

Because of the increase in insulin resistance, patients with known CFRD who are on insulin therapy may require increases in insulin dosing during pulmonary exacerbation, potentially even two to four times their usual doses to maintain blood glucose levels at goal. Once the pulmonary exacerbation resolves, insulin resistance typically returns to baseline. During this time, to reduce the risk of hypoglycaemia, it is recommended that the patient should self-monitor blood glucose closely and be in regular communication with the health care team.

### 2.4. Other therapies

Inulin is the only treatment for CFRD recommended by guidelines, as there is inadequate systematic data available for other therapies at this time [22,23,35].

#### 2.4.1.1. Repaglinide

Repaglinide is an oral antidiabetic. It is a meglitinide analog which works by blocking ATP-dependent potassium channels and increasing glucose dependent insulin release from the beta cell. Other than insulin, repaglinide has the most data on use in CFRD, although there are only two available systematic trials. The most recent multi-centre trial randomized 75 patients with CFRD 10 years of age or older to either repaglinide or insulin therapy. The starting dose of repaglinide was 1.5 mg/day divided TID, which could be increased to as much as 12 mg TID based on blood glucose values. The insulin group injected regular insulin three times daily before meals begun at a total daily dose of 0.15 IU/kg and titrated based on 2 h postprandial blood glucose levels. There was no difference in HbA1c or lung function between groups. The insulin group had greater improvement in BMI at 12 months of therapy but that did not persist at 24 months [36]. The previous randomized controlled trial of repaglinide and insulin in 81 CF patients with CFRD or “severe” IGT found sustained improvement in BMI at 12 months in the insulin-treated CFRD group only. The repaglinide group had transient improvement in BMI at 6 months, but none at 12 months, with no change in A1C in any group [22]. The studies, did, however, use different insulin therapy (regular insulin vs rapid acting), with different dosing schedules for both insulin and repaglinide, making direct comparison somewhat challenging. At this point, further research is needed to determine best use of non-insulin therapies in CFRD.

#### 2.4.1.2. GLP-1 agonists

Post-prandial hyperglycaemia and lack of first phase insulin secretion are the primary defects found in patients with CF. This pattern is temporally consistent with lack of incretin effect, suggesting that incretin-based therapies could be beneficial. GLP-1 (glucagon-like peptide 1) is often considered the most clinically relevant incretin. It stimulates insulin release and delays gastric emptying as well as inhibiting glucagon. GLP-1 therapy is an effective treatment for Type 2 diabetes mellitus (T2DM). GLP-1 may be reduced in cystic fibrosis, although the literature is not consistent [37,38]. Interest in the use of incretin-based treatment for CF has been present for many years, but there is only one small systematic trial of the use of GLP-1 agonist therapy in cystic fibrosis (in patients with IGT). This showed improvement in glycaemic excursions with therapy, but interestingly this effect seemed to be secondary not to improvements in insulin secretion, but via delays in gastric emptying [39].

The use of GLP-1 agonists in CF has raised concerns secondary to the increased risks for pancreatitis seen with some of these medications. This is particularly concerning as people with CF, especially those with some preservation of exocrine function, have increased risk of pancreatitis. GLP-1 agonists can also drive weight loss, which can also be a concern in CF.

#### 2.4.1.3. DPP-4 inhibitors

Due to the potential risks of GLP-1 agonist in patients with cystic fibrosis, it seems reasonable to consider DPP-4 inhibitors instead, which increase levels of endogenous GLP-1 and are not associated with weight loss or risk for pancreatitis. However, despite multiple trials being developed, no data has yet been published and several trials have been closed due to lack of enrolment (see [https://clinicaltrials.gov](https://clinicaltrials.gov)).
2.4.1.4. Metformin. Due to the potential risks of weight loss and lack of adequate data, metformin has not previously been recommended for the treatment of CFRD, however, there is emerging evidence that metformin therapy may be well tolerated in patients with CF [40].

3. Complications of CFRD and their management

The major complication of CFRD is increased rate of pulmonary function decline and increased morbidity and mortality from respiratory failure[4], even when adjusted for the severity of the underlying CF disease [4]. Increased glucose is present in the lung fluid once the serum glucose level exceeds 7.8 mmol/l (140 mg/dL) [17]. This increases the viscosity of airway surface liquid and increases bacterial colonization and pulmonary exacerbation [41]. However, in a cohort with strict glycaemic control, there was no difference found in the rate of pulmonary exacerbation in CF patients with and without CFRD [42], implying that insulin treatment of CFRD reduces complication rates.

The microvascular complications of diabetes (retinopathy, nephropathy, neuropathy) are also described in CFRD, typically only in cystic fibrosis patients who have had at least some degree of fast- ing hyperglycaemia. As in type 1 diabetes, these tend to occur with diabetes durations of 10 years or longer, although by that point, 30–50% of patients may have complications [34,43].

There is no CF specific data in regard to the management of microvascular complications of diabetes in CF. Currently, these conditions are managed utilizing standard recommendations for patients with type 1 diabetes mellitus.

Death from macrovascular complications have not yet been reported in patients with cystic fibrosis, although ischemic heart disease has been described [44].

4. Complications of treatment

The only significant complication of insulin treatment for CFRD is hypoglycaemia. However, hypoglycaemia in CF appears to be somewhat unique when compared to other forms of diabetes. Please refer to Moheet et al. in this issue for further details [45].

5. Potential impact of CFTR modulation

The development of potentiators and correctors has revolutionized care for cystic fibrosis, providing, for the first time, a treatment that directly changes the underlying pathophysiology of the disease.

5.1. Role of potentiators/correctors in treatment

The effectiveness of potentiators/corrector treatments for cystic fibrosis related lung disease raises very interesting questions regarding their effect on the other complications of cystic fibrosis, including CFRD. The pathophysiology of CFRD is still controversial with some groups finding CFTR in the beta or alpha cells in the islet and other groups finding no proof that CFTR is present in human islets [46]. However, what is clear is that CFTR dysfunction effects beta cell function, whether directly or indirectly [46]. Given this, it can be extrapolated that effectively correcting CFTR function might be able to prevent or delay the development of CFRD if done early enough or if pathologic changes are reversible. To date, CFTR modulators have not been shown to alter the incidence or prevalence of CFRD. However, Kelly et al. found signs of improvement in insulin secretion parameters in young CF patients with gating mutations receiving ivacaftor [47], and this finding is supported by other small studies [48]. Whether these changes are of clinical significance is unknown, but these studies raise the possibility that highly effective CFTR correction may have the potential to prevent, delay, or even reverse CFRD.

6. Potential clinical trials and endpoints

At this point, the treatment of CFRD is hampered by the lack of systematic data. There are no large, systematic trials conclusively comparing any two treatments for CFRD. Given this, it is not surprising that the data is sometimes conflicting (e.g. for repaglinide) or tainting but inadequate (e.g. GLP-1 agonists, DPP-4 agonists).

6.1. Proposed future research

What is truly needed is a large, multi-centre, multi-national, systematic treatment trial much like the diabetes control and complication trial (DCCT trial) that revolutionized our understanding of type 1 diabetes mellitus. Ideally, given the nature of glycaemic abnormalities in Cystic Fibrosis, such a trial would evaluate screening and diagnosis of CFRD, alongside treatment, given that our current measures likely underestimate glycaemic pathology in CFRD.

7. Future directions

7.1. Pre-diabetic states

7.1.1. Appropriate diagnostic cut-offs for treatment of dysglycaemia in CF are lacking

Currently the recommended screening test for CFRD is the oral glucose tolerance test (OGTT) [2]. Although abnormalities on this test predict long term outcomes in CF, the diagnostic endpoints we currently use are based on data from adults with type 2 diabetes and are not specific to CF. There is evidence that CF patients who do not meet formal criteria for glucose abnormalities by OGTT are still experiencing clinical decline [21,49]. However, at this point, there have been no large systematic trials to determine what cut points would be best for determining risk for adverse clinical outcomes in cystic fibrosis.

7.1.2. Evidence for the detrimental effects of pre-diabetic states

Decline in BMI and lung function begins several years before the diagnosis of CFRD [21]. It has become increasingly clear that prediabetes/abnormal glucose tolerance in patients with CF is problematic. Blood glucose levels over 11.1 at the 60 min time point on OGTT (what has been termed INDET) (see Table 1) is associated with increased decline in lung function [50]. Impaired glucose tolerance has been associated with BMI decline [22].

7.1.3. Evidence for the treatment of pre-diabetes in CF

Many authors have advocated the need to treat pre-diabetic states based on the clear association between these states and clinical decline in people with CF. Most data that has been published to this point uniformly shows benefit from insulin therapy, however, they are typically very small studies and not randomized or truly controlled [51–53]. The only randomized or controlled trial of treatment for pre-diabetes in CF is Moran et al. comparing repaglinide and insulin therapy. The authors included a subgroup of patients with “severe” IGT in their intervention. However, the IGT group did not show benefit from either premeal insulin or repaglinide therapy [22]. The question of whether to treat CF patients who do not yet meet criteria for CFRD is a high-priority research question from the CF community (see: Areas of Encouragement- https://www.cff.org/Research/Researcher-Resources/Awards-and-Grants/Research-Awards/Clinicai-Research-Award-Policies-and-Guidelines.pdf/) and two large studies are underway in the US and Australia (see clinicaltrials.gov “Cystic Fibrosis, Insulin Deficiency – Early Action, CF-IDEA Trial” clinicaltrials.gov: CT01100892 and “The Impact of Insulin Therapy on Protein Turnover in Pre-Diabetic Cystic Fibrosis Patients” clinicaltrials.gov: NCT02496780).
8. Clinical practice points

8.1. Medical management goals (adapted from Moran et al 2010)

- Patients with CFRD should ideally be seen quarterly by a specialized multidisciplinary team with expertise in diabetes and CF.
- Patients with CFRD should receive ongoing diabetes self-management education from diabetes education programs that meet national standards for Diabetes Self Management Education.
- Patients with CFRD should be treated with insulin.
- Oral diabetes agents are not as effective as insulin in improving nutritional and metabolic outcomes in CFRD and are not recommended outside the context of clinical research trials.
- Patients with CFRD who are treated with rapid-acting insulin should monitor blood glucose at least three times a day.
- Blood glucose goals for patients with CFRD are consistent with glucose goals per the American Diabetes Association (ADA) recommendations for all people with diabetes. Higher or lower goals may be indicated for some patients and that individualization is important.
- A1C measurement is recommended quarterly for patients with CFRD.
- A1C treatment goal is <7%. Higher or lower goals may be indicated for some patients and that individualization is important.
- Diabetes education about the symptoms, prevention, and treatment of hypoglycaemia, including the use of glucagon, is recommended for patients with CFRD and their care partners.
- Blood pressure should be measured at every routine diabetes visit per ADA guidelines. Systolic blood pressure >130 mmHg or diastolic blood pressure >80 mmHg or >90th percentile for age and sex for pediatric patients should have repeat measurement on a separate day to confirm a diagnosis of hypertension.
- Annual monitoring for microvascular complications of diabetes is recommended using ADA guidelines, beginning 5 years after the diagnosis of CFRD or, if the exact time of diagnosis is not known, at the time that fasting hyperglycaemia is first diagnosed.
- Patients with CFRD who have hypertension or microvascular complications should receive treatment as recommended by ADA for all people with diabetes, except that there is no restriction of sodium and, in general, no protein restriction.
- An annual lipid profile is recommended for patients with CFRD and pancreatic exocrine sufficiency or if any of the following risk factors are present: obesity, family history of coronary artery disease, or immunosuppressive therapy following transplantation.
- Patients are advised to do moderate aerobic exercise for at least 150 min per week.

9. Summary

Cystic fibrosis related diabetes mellitus and pre-diabetic or dysglycaemic states in cystic fibrosis have significant impact on morbidity and mortality in people who have cystic fibrosis. Therefore, it is essential to adequately treat these disorders. Medical nutrition therapy is essential to the treatment of all forms of diabetes, but in CF, it is important to maintain weight and BMI status. Therefore, carbohydrate restriction is not recommended. CF patients may also need nutritional supplements or feedings. In those cases, CF specific formulae should be used and not “diabetic” formulae. Insulin therapy is the only diabetes treatment that has been shown to reduce morbidity and mortality in CFRD. Although there are no randomized controlled trials at this time comparing specific insulin regimens or medical nutrition therapies in cystic fibrosis, intensive insulin management is recommended. For CF patients with fasting hyperglycaemia, multiple daily injection regimens with basal/bolus therapy or insulin pump therapy are effective, but insulin dosing tends to be lower than what is used in type 1 diabetes, especially basal insulin doses. For CF patients without fasting hyperglycaemia, meal coverage, basal only, or combined basal bolus regimens may be used. There is increasing evidence that CF patients experience clinical decline prior to the diagnosis of CFRD and small studies have shown improvement in clinical outcomes in CF patients with pre-diabetes treated with insulin therapy. However, there is insufficient evidence to recommend this routinely at this time. CFTR correctors and potentiators are transforming lung disease in CF and may likewise be able to treat or improve glycaemic abnormalities in CF, but the evidence is still emerging. At this time, there is inadequate data to recommend the use of non-insulin therapies for CFRD. However, there are great opportunities for research- understanding the potential of non-insulin therapies for CFRD, understanding the level of dysglycaemia at which it is best to intervene/ the best treatment for pre-diabetic states in CF, and the understanding of how potentiators and correctors with change the pathophysiology of CFRD. Large systematic trials are needed to study the diagnosis and treatment of CFRD and pre-diabetic states in CF.

Declaration of Competing Interest

Authors declare no conflict of interest.

Funding

This paper is part of a Supplement supported by the Cystic Fibrosis Foundation.

Acknowledgments

KLO, CLC, AG and AM received grant support through the Cystic Fibrosis Foundation, Emerging Leaders in CF Endocrinology (Envision) Program. The authors would like to thank the Cystic Fibrosis Foundation and all the faculty members of the EnVision: Emerging Leaders in CF Endocrinology program for support and mentorship, especially Dr. Moran.

The authors would also like to thank Carol Brunzell, RD, CDE for teaching KLO and AM about nutrition therapy for CFRD.

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