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Cystic Fibrosis Related Diabetes

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Abstract

Cystic fibrosis related diabetes (CFRD) is a common co-morbidity of cystic fibrosis. It is associated with diminishing lung function, poorer nutritional state, and a worse prognosis and its early diagnosis and treatment is important. In addition, the adverse pulmonary effects of CFRD may be present for up to 10 years prior to diagnosis.

Prevalence increases with age from 1 to 2% below 10 years of age, 20% of adolescents and 40-50% by adulthood, and up to 90% of adults with CF will have some degree of glucose intolerance by 40 years of age.

Although its pathophysiology is not well understood, the primary cause is thought to be the fatty infiltration of the pancreas leading to fibrosis and destruction of the pancreatic cells resulting in beta cell destruction and progressive insulin deficiency.

Oral glucose tolerance testing (OGTT) remains the method of choice for a diagnosis of type I, type II and gestational diabetes; it is less discriminating in CFRD where early glucose trends are important, and continuous glucose monitoring may prove a more useful diagnostic and management tool.

Diabetic complications occur in CFRD and annual screening for these is necessary. As life expectancy rises, diabetic complications may become more prevalent.

This chapter discusses the diagnosis and treatment of CFRD and touches on developments in research which will enhance the future management of this increasingly common and important manifestation of the CF condition.

Keywords: Cystic fibrosis related diabetes, Screening, Oral glucose tolerance testing, Continuous glucose monitoring, Cystic Fibrosis Related Diabetes

1. Introduction

Cystic Fibrosis Related Diabetes (CFRD) is a form of abnormal glucose handling (dysglycaemia) that is quite different to other forms of diabetes. It is uncommon in childhood, rarely occurring in those under 10 years of age, but its incidence rises inexorably as patients survive longer, affecting up to 50% of CF adults [1, 2].

The development of CFRD is associated with a significantly higher mortality rate [2, 3, 4], and has a deleterious impact on pulmonary function [5] with the degree of glucose intolerance being directly related to the decline in FEV1 [6]. Those with CFRD suffer more frequent infective exacerbations and have a higher burden of colonisation with pathogens such as *Pseudomonas aeruginosa* and *Burkholderia cepacia* as well as a poorer nutritional status – all of which are known to be associated with poorer outcomes [7].

However, dysglycaemia is a progressive phenomenon in many CF patients, and the associated increased morbidity occurs many years prior to a formal diagnosis of CFRD [8, 9, 10]. This has fuelled the debate as to how the diagnosis should be made – the current "gold standard" diagnostic test for diabetes mellitus (the oral glucose tolerance test, OGTT) [11] may not be appropriate in the CF population, since the optimal time to introduce treatment (currently limited exclusively to insulin-based therapies) may be at an earlier stage of dysglycaemia.

We will explore these issues as well as consider future developments in this emerging area of CF care.

2. Epidemiology, prevalence and incidence

Historically, CFRD was typically only seen in paediatric practice as a pre-terminal complication in those with advanced respiratory failure. It remains relatively rare in children under the age of 10 (2), affects less than 5% of individuals during their early teen years, but the incidence rises exponentially with age, occurring in approximately 20% of adolescents and up to 50% of individuals in their fourth decade. The average age of onset for CFRD is 18-21 years (12).

Furthermore, it is estimated that 70-90% of all adult CF patients will have some degree of glucose intolerance and therefore dysglycaemia is the commonest co-morbidity that complicates care in adult CF and its prevalence is likely to increase further as life expectancy continues to rise.

In addition to age, other factors associated with an increased incidence of CFRD are severity of CFTR mutation, poor pulmonary function, low BMI, pancreatic insufficiency, liver dysfunction, and corticosteroid use (5, 7, 13, 14).

3. Pathophysiology

The pathophysiology of CFRD is still poorly understood. CFTR may have a role in the cell signalling that contributes to both the timely release of and response to insulin and restoration of abnormal CFTR function.

However, although Ivacaftor (which corrects the underlying gene product defect in patients with a gating mutation) has reportedly led to normalisation of sugar handling in a single individual [15], it seems likely that the pathways directly involving CFTR are of only minor significance to overall glucose homeostasis.

CFRD involves a complex interplay between a state of relative insulin deficiency, particularly during the first phase response, and variable insulin resistance during infective exacerbations. Some level of dysglycaemia is detectable in most pancreatic-insufficient patients and the hallmark of CFRD is the presence of post-prandial glucose excursions that may be followed by spontaneous hypoglycaemic episodes.

Below we consider mechanisms that contribute to abnormal glucose handling in CF.
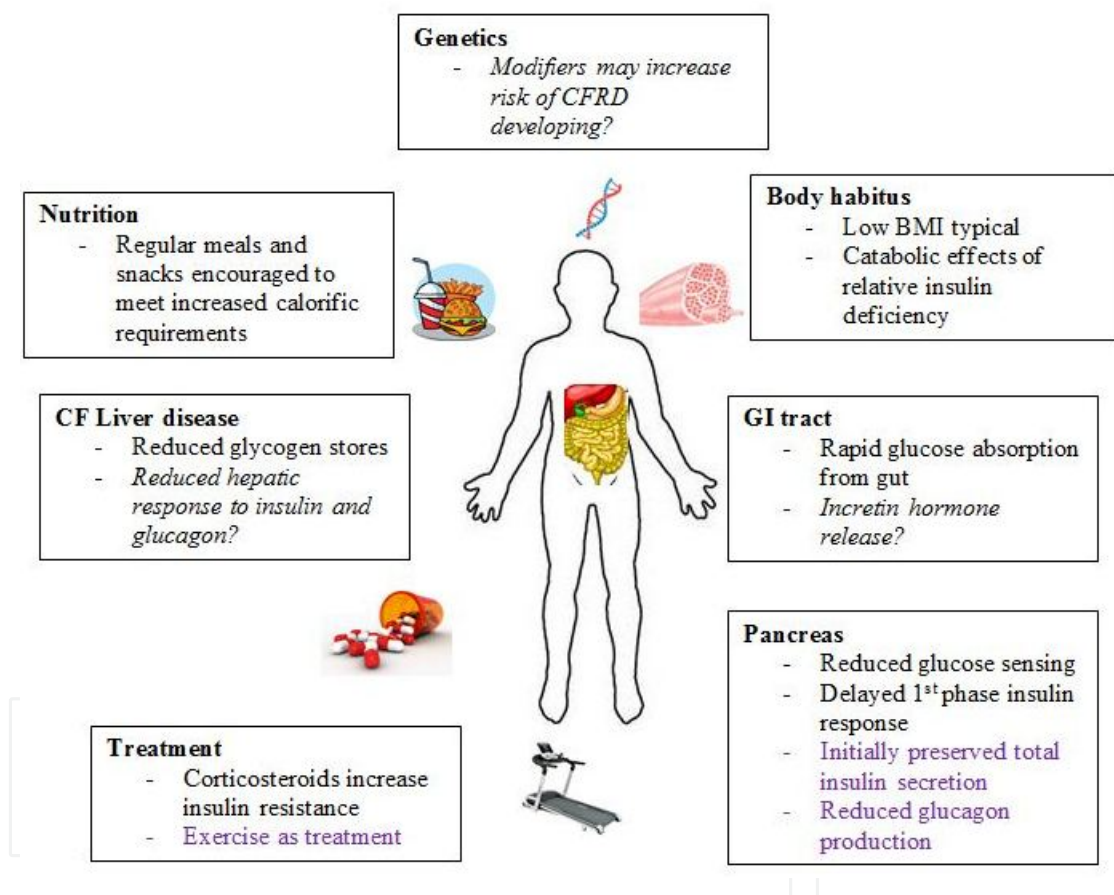
Figure 1. Factors influencing glucose handling in CF. *Italicised* – unclear role. Purple – factors pre-disposing to reactive hypoglycaemic episodes

3.1. Pancreatic responses in CF

The predominant mechanism underpinning dysglycaemia in CF patients is sluggish clearance of proteolytic enzymes from the pancreatic ducts causing progressive β-cell destruction that directly reduces insulin levels, as well as causing ischaemic damage and amyloid deposition [16], further impairing the ability of remaining islet cells to sense and respond to glucose levels

appropriately [17]. It seems likely that the same mechanism might also prevent incretin hormones (e.g. GLP-1 and GIP) from evoking their physiological insulinogenic effect during the post-prandial period, although this is an area still under investigation (see below).

Loss of pancreatic endocrine function is a continuum in patients with CF with impaired release of both insulin and glucagon [18]. Those with significant pancreatic insufficiency (almost 90% of patients with CF use pancreatic enzyme supplements [5]) have deranged glucose handling even if not formally diabetic [17], typically displaying a slow and prolonged insulin response to stimulation [18, 19].

The initial abnormality seen in CF patients is a delayed first-phase insulin response combined with preserved total insulin secretion that occurs in response to various stimuli even in CF subjects with normal glucose tolerance [10, 18, 20, 21, 22, 23]. Even at this early stage, patient outcomes can be affected and the loss of pulmonary function is directly related to the degree of dysglycaemia [6]: this has implications for CFRD screening and diagnosis (see below).

The CFTR mutation also causes rapid absorption of glucose from the small intestine compared to the non-CF gut [23]. This combination of rapid glucose absorption and slow prolonged insulin response helps to explain both the typical high post-prandial glucose excursions seen in this group (Fig. 2) (an independent marker of worsening clinical status prior to a formal CFRD diagnosis [10]), as well as the symptomatic hypoglycaemia (often termed reactive or rebound) that may develop several hours later, as insulin continues to be secreted despite falling glucose levels (see Fig. 2) [24, 25]. A tendency to spontaneous hypoglycaemia may be further exacerbated by intense periods of exercise, something that forms a cornerstone of treatment in CF [11] (see below).
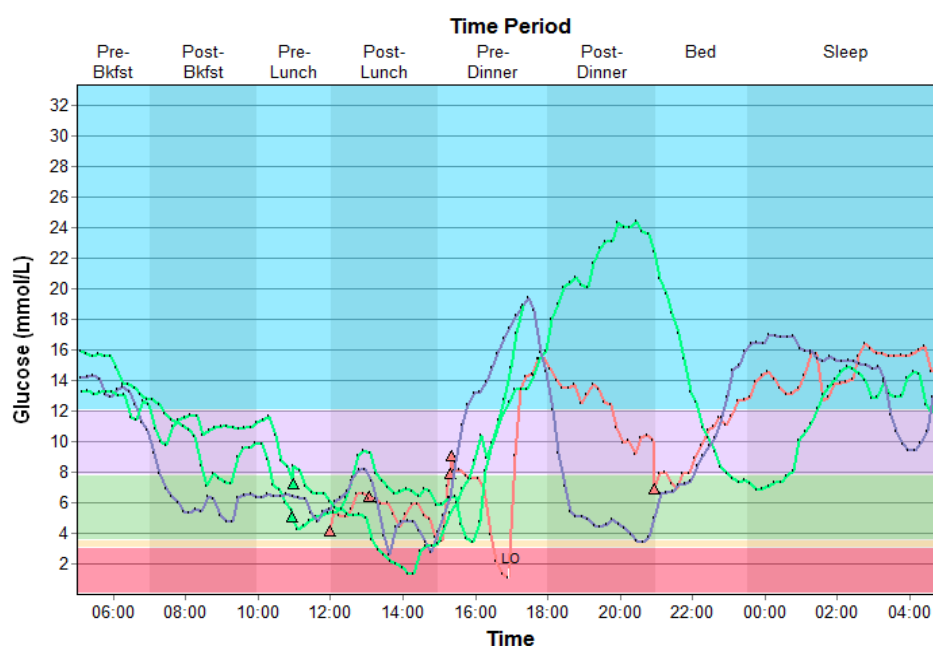
Figure 2. Continuous glucose monitoring showing a typical glucose profile seen in CFRD

As progressive damage to the pancreas accumulates, there is an associated loss of endocrine tissue such that over time patients become relatively insulinopaenic [26]. Although pancreatic β-cell mass may be significantly reduced in patients with CFRD [27, 28], absolute insulino-paenia and ketoacidosis, typical features of Type 1 Diabetes (T1DM) [29], do not occur even in the minority of patients with sufficient pancreatic damage to cause fasting hyperglycaemia. Indeed, the presence of true ketoacidosis is so rare in this population that its occurrence should stimulate investigation for the development of concurrent T1DM [11, 30, 31]. It is possible that the loss of α-cells as part of the indiscriminate pancreatic damage that occurs in CF results in relatively low glucagon levels, protecting against the development of ketosis as well as adding to the propensity for symptomatic hypoglycaemia [32].

3.2. Insulin sensitivity in CF

The role of insulin sensitivity in the development of CFRD is unclear: CFTR may have a theoretical role in cell signalling to increase glucose uptake by peripheral tissues but such responses are predominantly mediated through GLUT receptors. Insulin resistance increases during periods of acute illness [33] including pulmonary exacerbations which may frequently occur in those with an underlying suppurative lung condition. Hardin et al. [34] suggested that insulin sensitivity may be abnormal even in clinically stable CF patients, where on-going indolent infection may up-regulate inflammatory pathways, thereby inducing a degree of chronic insulin resistance.

However, despite these mechanisms, it is relatively rare for pancreatic-sufficient CF individuals, even when colonised with pathogens and suffering regular exacerbations, to develop significant dysglycaemia [35] and overall it has been shown that insulin resistance is not a major determinant of the development of diabetes in CF [36].

It is recognised that at times of high inflammatory stresses or concurrent glucocorticoid use – such as during a pulmonary exacerbation – insulin resistance may contribute to or unmask clinically relevant dysglycaemia in predisposed individuals [17, 30, 34] and extra glucose monitoring is therefore recommended during such periods [37] since initiation or escalation of treatment may be required [30]. As the nutritional aspects of CF care are increasingly well addressed particularly by the early institution of highly effective pancreatic enzyme supplementation, it is becoming increasingly common for patients with CF to have a raised BMI - indeed almost a quarter of patients in one recent series were reported to be overweight or obese [38]. It may be that in future, insulin resistance will play a larger role in the development of dysglycaemia in this population.

3.3. Other factors

Not all CF individuals with pancreatic insufficiency develop CFRD, raising the possibility that other genetic factors might play a part [39].

However, with few exceptions, antibodies associated with the development of T1DM have not been found in CFRD [40-42]. Genetic variation in the CAPN10 gene, which encodes Calpain-10, may be a common risk factor for the development of both CFRD and T2DM [43], explaining

in part why CF individuals with a familial history of T2DM are at increased risk of developing CFRD themselves [35] despite a lack of insulin resistance.

It seems likely that genetic modifiers have a significant role in determining to what extent dysglycaemia complicates the clinical course of an individual with cystic fibrosis. [35].

Glucose handling may also be disturbed in individuals with CF-related liver disease, particularly in severe cases where the hepatic uptake and storage of glucose is diminished, potentially rendering treatment for hypoglycaemia with exogenous glucagon ineffective. Chronic kidney disease, which may develop in CF because of recurrent uroliathiasis/nephrocalcinosis, repeated exposure to nephrotoxic medications or indeed as a complication of CFRD itself, may also effect glucose regulation.

Although it is unclear how important this is for overall blood sugar control, severe renal failure may lead to an accumulation of exogenous insulin therapy causing an apparent improvement in diabetic control (if judged by insulin requirements) as well as predisposing to hypoglycaemic episodes.

Incretin hormones released from the bowel are a major determinant of pancreatic responses in the post-prandial period, causing significantly more insulin to be secreted compared to the presence of glucose alone – this so-called incretin effect is lost in T2DM and a range of treatments that target components of the diffuse endocrine system have revolutionised the treatment of this condition. Whilst it has been shown that enteroendocrine cells are present in the expected amounts in the bowels of both animal models and direct intestinal biopsies from children with CF [44, 45], the incretin effect itself has not been definitively investigated in a CF setting, with various small-scale studies showing conflicting results. Whether or not the incretin system is attenuated in CF, it is unclear whether augmenting its function pharmacologically would in any way improve the responses of a pathologically damaged pancreas.

Considering the mechanisms above, it is clear to see that although CFRD has a number of features in common with both T1DM and T2DM it is clearly significantly different to both – a comparison of CFRD with the more common forms of diabetes is shown in Table 1.

	CFRD	T1DM	T2DM
Insulin resistance	Variable	Minimal	Significant
Insulin deficiency	Relative	Absolute	Variable
Typical BMI	Low	Low	High
Complications	Pulmonary, weight loss, microvascular	Microvascular	Macrovascular
Treatment	Insulin	Insulin	Oral agents +/- insulin
Ketosis	Very rare	Common	Rare

Table 1. Comparison of CFRD with other forms of diabetes

4. Screening and diagnosis

Dysglycaemia is often detectable for several years prior to a formal diagnosis of CFRD, and early detection is important to prevent pulmonary function decline and weight loss developing [6, 8]. Timely intervention with appropriate treatment may have a profound impact on a patient's health and well-being. In the next section, we will discuss the various methods of screening for CFRD.

4.1. Diagnosis

The World Health Organisation, Diabetes UK, American Diabetes Association and UK CF Trust all consider that the formal diagnosis of CFRD should be based on responses to a standard 75 g oral glucose tolerance test (see Table 2) and recommend that it is carried out annually from late childhood. Given the impact of pulmonary decline in early CFRD, tighter thresholds were discussed, but currently the general diagnostic criteria are still applied to CF.

- 2-hr 75g OGTT plasma glucose result ≥11.1 mmol/l

- Fasting plasma glucose ≥7.0 mmol/l

- HBA1C ≥6.5% (A1C <6.5% does not rule out CFRD because this value is often spuriously low in CF.)

- Classical symptoms of diabetes (polyuria and polydipsia) in the presence of a casual glucose level ≥11.1 mmol/l

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Table 2. Diagnostic criteria for CFRD (any of the following)

These criteria were originally established by consensus opinion in 1998 [3]. The previously used sub-categorisation of the diabetic response to recognise whether or not fasting hyperglycaemia was also present (often abbreviated as CFRD FH+ and CFRD FH-, respectively), is now considered to be obsolete since the differentiation adds little to management [46].

The OGTT was originally designed to detect individuals, predominantly with insulin resistance, who were most likely to benefit from intervention aimed at preventing the microvascular sequelae of dysglycaemia. Although these do occur in CFRD, they are relatively late phenomena, where pulmonary decline (leading to increased mortality) occurs much earlier.

Furthermore, OGTT responses are highly variable in the CF population, where insulin resistance waxes and wanes and glucose absorption alters depending on a variety of factors peculiar to this cohort [17]. An opportunistic annual screen for diabetes carried out when an individual with CF is well may poorly reflect their overall glucose handling.

Screening for diabetes based on the 2-hour glucose value alone has been shown to be of less use in the CF population [47]. Furthermore, the dose of glucose used to stress the endocrine function of the pancreas during an OGTT may be inadequate in CF, where individuals have high calorific requirements and may routinely ingest carbohydrate loads much higher than the 75 g bolus typically used in the diagnostic test.

Given these facts, as well as the typical insulin response profile seen in patients with CF, basing the diagnosis of, as well as screening for, CFRD by means of an OGTT, as is currently recom-

mended [11], is clearly imperfect [48], leading to the conclusion that the under-diagnosis of clinically relevant dysglycemia is common.

Patients with CF may experience significant hyperglycaemic excursions shortly after eating, which then rapidly correct to the euglycaemic range as the delayed first-phase insulin response belatedly begins; this not only devalues diagnostic tests such as the OGTT (which uses the 2-hour glucose value to diagnose diabetes) but also means that measures of average glucose control, such as glycosylated haemoglobin levels (the HbA1c test), may be misleadingly normal or even low in this group and therefore of much less clinical relevance in CFRD than in other forms of diabetes [49]. One study from Denmark found only 16% of patients had elevated HbA1c values at the time CFRD was diagnosed [50]; others have found similar results [49]. The utility of HbA1c may be further devalued by the increased red cell turnover commonly seen in CF patients [49, 51]. As progressive decline in pancreatic endocrine function in the CF population is related to increased morbidity years before a formal diagnosis of CFRD is made by OGTT [8, 9, 10] and given that HbA1c is at best an unreliable marker of glucose handling [49], other methods of assessing clinically important dysglycaemia, such as 1-hour OGTT result, serial glucose monitoring or Continuous Glucose Monitoring (CGM), have now been advocated as better markers of clinically relevant dysglycaemia.

Elevation of 1-hour glucose level during an OGTT has been shown to be a better predictor of declining pulmonary function than a standard 2-hour result [9] as well as correlating better with other methods of diabetic screening [53]. Currently, the UK CF Trust advocates the use of both a standard 2-hour OGTT as well as a period of serial glucose monitoring (that entails checking levels before and 2-hours after meals and at bedtime for several days) to establish if clinically relevant hyperglycaemia requiring treatment is present [49].

For effective serial glucose monitoring to take place, patients must be empowered and educated with regards to the technique including timing, hand washing, correct sampling procedures as well as meter and strip management. Misleading results have been documented [54] due to poor technique, therefore patient-recorded measurements should be considered with a degree of caution, particularly one-off abnormal readings. Additionally, there is a risk that patients, fearful of a further increase in their treatment burden associated with being diagnosed with CFRD, will report lower glucose readings, fail to document high levels or simply fabricate results altogether.

However, a CGM system circumvents many of the inherent weaknesses associated with self-reported serial monitoring whilst enabling an accurate glucose profile to be established. Worn for a period of 3-5 days typically on the arm or abdomen, a CGM system consists of a transmitter with a flexible plastic sensor which sits just below the skin allowing regular measurement of interstitial glucose. Readings are sent wirelessly to a receiver automatically every minute without any user input, although an occasional finger-prick reading is required to calibrate readings against blood glucose levels.

The use of CGM has been validated in the CF population [55] whilst others have shown that it may be superior to other modes of screening for dysglycaemia [56]. The visual output obtained from a CGM can be a useful tool in highlighting sugar control issues with patients

Figure 3. CGM in situ with separate base unit

and allow for highly individualised treatment regimens to be decided. A positive CGM result – that is a value of more than 7.87.8mmol/l for over 4.5% of the test – is associated with a worse prognosis in terms of CF-specific endpoints (i.e. pulmonary function and weight) as well as being a better predictor of future risk of development of CFRD than an OGTT [57], which has been shown to give unreliable results when used as a screening tool [58].

5. Clinical features, signs and symptoms

The biochemical and clinical detection and diagnosis of CFRD can be difficult, since symptoms of polyuria, polydipsia and weight loss only occur in one third of cases [8]. An unexplained decline in pulmonary function or difficulty maintaining or gaining weight should alert health care professionals to the possibility of underlying significant dysglycaemia, impaired glucose tolerance or even CFRD. Poor weight gain or weight loss can often be identified in the preceding 12 months prior to a diagnosis of CFRD [57].

6. Consequences of dysglycaemia in CF

Multiple studies and reviews of large registry datasets have demonstrated a clear link between dysglycaemia and poor outcomes in pulmonary health in CF [3, 5, 43], but the mechanism by which hyperglycaemia, often intermittent rather than sustained in this population, causes the

observed decline in lung function is less clear. Plausible theories include direct pulmonary damage or suppression of various components of the immune system in the setting of hyperglycaemia leading to an increased risk of pulmonary infections which might also be more severe in nature [14], as has been demonstrated in other types of diabetes [44]. Insulin therapy has been shown to reduce sputum pathogen levels in CF patients [45]. It has also been hypothesised that the predominant factor in the decline in both respiratory function and nutritional status is a direct consequence of the altered protein metabolism experienced by CF patients who become relatively deficient in insulin therefore losing its important anabolic effects [14]. CFRD has been considered to be a risk factor for the development of distal intestinal obstruction syndrome in cystic fibrosis patients [59]; however, it is unclear how strong the association really is between these two conditions [60] or what causal mechanism might be involved.

6.1. Microvascular complications

Microvascular complications may develop in CFRD leading to the typical associated pathologies (retinopathy, nephropathy and neuropathy), any of which may significantly impact the on-going management of the condition, particularly the development of visual impairment, gastroparesis and renal failure.

Where glucose control has deteriorated to the point that fasting hyperglycaemia is present (a relatively rare occurrence in the CFRD population), a significant proportion will also have developed retinopathy and microalbuminaemia (16% and 14%, respectively) [61]. Almost half of all CFRD patients will display some degree of neuropathy, in most cases where the dysglycaemia has been present for over a decade [43].

Examples of autonomic dysfunction and gastroparesis have been reported [61], although the latter condition may be difficult to differentiate from the delayed gastric emptying that occurs in up to 50% of the CF population regardless of their glucose tolerance [43].

Overall, the prevalence of microvascular complications is less in CFRD than in other forms of diabetes, possibly due to the partially preserved endogenous insulin production and sensitivity leading to relatively short periods of hyperglycaemia.

6.2. Macrovascular complications

Although there is nothing to suggest dysglycaemia is not a significant risk factor for the development of macrovascular complications in individuals with CF, as it is in other populations, at present their occurrence very infrequently complicates the management of CFRD.

Although there are case reports of both coronary artery disease and strokes occurring in diabetic CF patients [62, 63], there is at present no evidence of excess mortality attributable to cardiovascular or cerebrovascular disease despite these patients often having co-existing dyslipidaemia.

Currently, the consequences of significant dysglycaemia are likely to manifest earlier and more profoundly in other ways, e.g. deteriorating lung function, but as the life expectancy of the

general CF population continues to rise there is likely to be both a concurrent increase in the incidence of CFRD and ultimately macrovascular complications.

7. Treatment and management

Treatment of CFRD is currently exclusively limited to insulin therapy, since by the time CFRD is formally diagnosed the predominant issue is one of failure of insulin secretion. Evidence of improved outcomes with insulin therapy is established for those who have a positive OGTT with and without fasting hyperglycaemia [2, 39, 64]. It is also recommended that insulin is initiated in those patients that exhibit diabetic responses whilst suffering an infective exacerbation [11], which presumably reflects a group with poor pancreatic reserve, meaning that they are unable to respond adequately when peripheral insulin resistance increases due to higher levels of inflammation or treatment with corticosteroids. The UK CF Trust (2004) guidelines for the management of CFRD [11] have produced recommendations for instigation of treatment, which are as follows; Treatment should be considered:

• When impaired glucose tolerance on OGTT is associated with weight loss or deteriorating clinical condition

• When there are episodes of transient hyperglycaemia

• When a diabetic glucose tolerance on OGTT, but normal glucose monitoring, is associated with weight loss or deteriorating clinical condition

Definite indications for initiating treatment are:

• CF-related diabetes, that is, diabetic OGTT and/or regular hyperglycaemia

• Pregnancy with impaired glucose tolerance or diabetes

Better awareness and more aggressive management of CFRD have led to a considerable improvement in outcomes over the last 5 years including mortality [2]. As discussed above, the concept of truly normal glucose tolerance in the majority of adult CF patients, especially if pancreatic-insufficient, is a fallacy and all such patients could be reasonably considered in a 'pre-diabetic' state; however, the role of early treatment to prevent CFRD is less clear. Small studies have previously suggested only a trend towards improvement in various outcomes when CF patients with impaired glucose tolerance (IGT) received long-acting insulins [65].

As total insulin secretion is often preserved or only marginally decreased in non-diabetic CF patients, the use of insulin therapy in such a group may not be as efficacious and any benefits must be weighed against the increased treatment burden (which is considerable for the vast majority of CF patients) and the risk of hypoglycaemia.

However, there is now increasing evidence to support initiation of treatment in non-diabetic groups with improvement in pulmonary and other clinical outcomes seen after insulin treatment was started [64, 66, 67], particularly those with positive CGM results [57], although

it is currently too early to know if such benefits are sustained long-term or will impact upon mortality rates.

The treatment of CFRD can prove challenging with treatment strategies having to constantly be changed due to the variability and disease progression of CF. There are many different variables associated with CF that have to be taken into consideration when managing CFRD.

7.1. Pharmacological treatments of CFRD

Whenever treatment for dysglycaemia in CF patients is initiated, the only modality with an established evidence base is insulin therapy. Biguinide therapy potentially offers anti-inflammatory activity as well as anti-diabetic effects and was shown to improve glucose control in 4 patients without significant side effects over a 10-year period [68]. However, given that insulin resistance is not the predominant abnormality in stable CF patients [36], coupled with concerns about an increased risk of hepatitis, lactic acidosis, weight loss and pancreatitis [69], metformin has not been widely used in this cohort.

A small study (n=12) using acarbose in a group of CF patients with IGT receiving inpatient antibiotics for a pulmonary exacerbation showed an improvement in glucose profile compared to placebo but also a very high incidence of GI side effects [70].

Secretagogues, such as the sulphonylureas, have been shown to be of little benefit in a CF setting whilst increasing the risk of symptomatic hypoglycaemia in this group [71].

Dietary modification can play a role in decreasing very high post-prandial glucose excursions in CF patients and Balzer et al. have suggested that adopting a low glycaemic index diet could be advantageous in CFRD [72]. As such, insulin remains the only recommended treatment for CFRD [11]; however, even the use of short-acting insulin in a bolus regime, attempting to control post-prandial glucose excursions, still risks symptomatic hypoglycaemia developing as endogenous hormone levels belatedly rise.

The incretin system is particularly important in the post-prandial handling of carbohydrate; therefore, agents that enhance its effects are of considerable interest in the management of CFRD, particularly as theoretically at least they have a much lower propensity to cause hypoglycaemia. However, the widespread use of these agents has not yet been investigated in a CF-specific setting, although initial small-scale use seems to have been well tolerated [73].

7.2. Insulin regimes for insulin therapy

Different types of insulin are available for use to treat CFRD. Their different modes of action need to be correlated with glucose profiles and individual requirements of the patient in order to manage glucose levels effectively.

The main categories of insulin are:

- Long-acting insulin analogues – Normally administered once daily with a duration of 18-24 hours, achieving a steady state after 2-3 days (e.g. insulin glargine; detemir or degludec).

- Intermediate insulin – Onset of action 2-3 hours with a duration of 16-35 hours (e.g. insulin isophane).

- Short-acting insulin – Onset of action 30-60 minutes and duration of up to 8 hours (e.g. soluble insulin).

- Rapid-acting insulin analogues – Onset of action 15 minutes and duration of action 2-5 hours (e.g. insulin aspart, lispro or glulisine).

- Pre- mix insulin – Onset of action 30-60 minutes duration up to 24 hours (e.g. biphasic isophane insulin).

- Pre-mix insulin analogue – Onset of action 15 minutes duration up to 24 hours (e.g. biphasic insulin aspart, lispro).

Typically, either a basal/bolus or a combination of both is used to treat CFRD [74].

Short acting rapid insulin before meals remains the insulin of choice for those without fasting hyperglycaemia.

Taking into account treatment burden, long lasting basal insulin needs to be considered and is frequently given [74].

Pre-mix insulin is used in some cases although with the variability in eating patterns this may prove detrimental.

7.3. Multidisciplinary approach to management

When diagnosing and managing patients with CFRD, it is of paramount importance that the multidisciplinary team have excellent knowledge relating to this complication. In ideal circumstances an endocrinologist with experience of CF will form part of the regular multi-disciplinary team caring for patients, but in many centres the task of coordinating diabetic care will be delegated to a specialist nurse.

Communication is crucial to ensure patients are fully informed about the condition, particu-larly the differences between CFRD and other types of diabetes as patients may come with pre-conceived notions that could impact their engagement with treatment and on-going management, e.g. undertake wholly inappropriate calorie restriction.

Wherever possible, both the specialist CF dietician and clinical psychologist should be involved at the earliest opportunity to ensure the best possible expert care and management for the patient.

8. Screening for complications in CFRD

An important aspect of managing CFRD is effective screening for the development of com-plications. As such it is recommended that at least annually patients with CFRD have the following assessed:

- Clinical history - number of admissions with reasons

- Height, weight and BMI

- Pulmonary function

- Blood pressure

- Alcohol and smoking

- Hypoglycaemia – identify cause and optimise treatment

- Exercise

- Foot examination - pedal pulses, sensory and vibration check.

- Sexual dysfunction

- Frequency of distal intestinal obstruction syndrome (DIOS)

- Full dietetic review - Meals, snacks, enzymes, supplements, feeds.

- Insulin therapy

- Injection technique.

- Insulin site check

- Home blood glucose monitoring.

- Psychosocial support

- Urine sample for Microalbuminuria

- HbA1c

- Urea and electrolytes, creatinine clearance (selected cases)

- Lipid profile

- Retinopathy screening referral

Additionally, annual screening is an opportunity to identify educational gaps and discuss how the patient is coping with their CFRD.

9. The challenges of CFRD

The distinct glucose profile typically seen in CFRD presents clear challenges not only for establishing the diagnosis in the first place but also for managing the condition in general.

9.1. Dietary considerations

The primary aim of nutritional management in relation to CFRD is the achievement of a normal nutritional status [3]. CFRD has different and conflicting dietary recommendations from that

of type 1 or type 2 diabetes. CFRD patients have up to 150% the calorific requirements of other diabetic patients and require a diet containing both high fat and protein levels.

Patients with CF require regular snacks in between meals in order to meet their increased metabolic requirements and often resort to consuming foodstuff that is high in refined sugars – such as so called 'energy drinks' – in order to maintain their weight, especially as it obviates the need to medicate with enzyme supplements [75].

Ingestion of products that contain even modest quantities of highly refined sugar can not only cause glucose excursions but may also precipitate a reactive hypoglycaemic episode – a phenomenon that can be seen during 7-15% of diagnostic OGTTs [24, 76].

The use of a diet rich in carbohydrates that have a low glycaemic index (GI) is encouraged in type 2 diabetics both to aid blood glucose control and weight reduction, however little robust evidence exists of benefit from a similar approach in a CFRD population and there are concerns that low GI diets might lead to inappropriate weight loss in this group [72].

Recommendations from American researchers have suggested that carbohydrate counting may have a role in CFRD [3] however in other countries this approach is reserved for T1DM alone, with the CF dietetic community in the United Kingdom favouring regular meals and snacks containing a mixture of both complex and refined carbohydrates be taken with or just after eating other foods [75]– an approach that anecdotally can reduce both the post-prandial glucose excursions as well as subsequent reactive hypoglycaemia occurring.

Dietary assessment is therefore an important part of the management of CFRD particularly to assess and modify refined sugar intake whilst ensuring overall calorific requirements and a healthy weight are maintained.

9.2. Exercise

Regular exercise forms an important cornerstone of the general management of CF and is widely advocated [46] although direct evidence that it specifically improves overall blood sugar control in CFRD is lacking [77] although there is an on-going trial exploring this currently [78] CFRD patients need to be aware of the risk of precipitating hypoglycaemia during exercise and should be educated about extra monitoring during times of exertion.

9.3. Liver disease

CF affects all of the major organs in the body including the liver and the prevalence of CFRD is higher in patients who have liver disease [79]. As discussed previously significant liver disease may lead to a reduction in hepatic glycogen stores, exacerbating the risk of sympto-matic hypoglycaemia developing and potentially reducing the response to exogenous glucagon used to treat such episodes. In addition, although it may be difficult to quantify, CF-liver disease could lead to subtle impairments of hepatic insulin secretion and catabolism which may contribute to the overall dysglycaemia suffered by this group [79].

9.4. Hypoglycaemia

As mentioned elsewhere in this chapter hypoglycaemia is not uncommon in CFRD [24]. Furthermore, it has been demonstrated that hypoglycaemia awareness is also impaired as a result of frequent subclinical hypoglycaemic episodes and a diminished glucagon response [32]. Therefore, careful consideration must be given to when blood sugar monitoring is carried out as well as the timing, type and amount of insulin used for treatment.

9.5. Corticosteroids

Oral corticosteroids (e.g. prednisolone) are frequently used during pulmonary exacerbations in CF, and the concomitant elevation in blood glucose may necessitate a change in diabetes management in these patients. Patients may also require increased supervision and treatment during times of infection where blood glucose levels often fluctuate rapidly. There is evidence that CF patients with normoglycaemia exhibit diabetic glucose tolerance during pulmonary exacerbations [80]. This is likely to be due to the stress of infection and inflammation that unmasks the early alterations in glucose homeostasis [81]. Additionally, when infection subsides and patients stop corticosteroids, blood glucose can dramatically drop causing hypoglycaemia and careful support and advice is required during this time.

10. Future developments

There are a number of areas currently at a research stage that may be of benefit in the management of CFRD.

Many centres are moving away from a reliance on the standard 2-hour OGTT to diagnose CFRD, with the use of CGM becoming more widespread to detect clinically significant dysglycemia at an earlier stage.

A number of clinical trials are exploring the use of incretin based therapy in individuals with CF [82, 83] and such therapies theoretically offer an ideal combination of glucose lowering effects with a smaller risk of precipitating hypoglycaemia, especially as concerns about the risk of pancreatitis associated with these type of medications have somewhat lessened recently [84].

Ultimately novel experimental treatments being developed for other forms of diabetes such as stem cell implantation may be applicable to individuals with CFRD.

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