The unique challenges of cystic fibrosis related diabetes

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# Running Title: Cystic fibrosis related diabetes

# Novelty points

# Cystic fibrosis related diabetes (CFRD) is distinct from type 1 and type 2 diabetes

* CFRD and impaired glucose tolerance have an adverse effect on clinical status in CF and treatment of CFRD is primarily aimed at reducing this impact.
* Treatment may be required at an earlier stage than for other types of diabetes to prevent deterioration of lung function and weight loss.
* The treatment of choice is insulin but should take account of other medical issues in CF.

# Abstract

Individuals with cystic fibrosis and pancreatic insufficiency have a gradual decline in insulin secretion over time, which results in an increase in the prevalence of diabetes with age; up to 50% of adults with cystic fibrosis aged over 35-40 years have diabetes.

Cystic fibrosis related diabetes (CFRD) differs from type 1 and type 2 diabetes in several ways; there is a pattern of insulin deficiency with reduced and delayed insulin response to carbohydrates but sparing of basal insulin that results in glucose abnormalities, frequently characterized by normal fasting glucose and post-prandial hyperglycaemia.

Insulin deficiency and hyperglycaemia, even at levels which do not reach the cut off for a diagnosis of diabetes, have an adverse impact on lung function and clinical status in people with cystic fibrosis. Although the risk of microvascular complications occur as in other forms of diabetes, the main reason for treatment is to prevent deterioration in lung function and weight loss and so treatment may be required at an earlier stage than for other types of diabetes. Treatment is usually with insulin, but management needs to take into account all the other medical issues in cystic fibrosis.

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## Introduction

Cystic fibrosis (CF) is an autosomal recessive disorder caused by a mutation of the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Progress in treatment for CF has increased life expectancy; in the 1960s, survival beyond childhood was rare, but now median life expectancy is over 45 years. CF has multisystem effects, and clinical features include pulmonary infections with deteriorating lung function, exocrine pancreatic failure, liver disease, and osteoporosis. Cystic fibrosis related diabetes (CFRD) is a common complication of CF, with an increasing prevalence with age; up to 50% of adults develop CFRD by the age of 35-40 years [1]. Increased life expectancy in CF has resulted in a steady increase in the number of adults with CF and prevalence of CFRD. 1,982 (18.3%) of the 10,810 people recorded in the CF Trust registry for 2015 were receiving diabetes treatment [2].

The pathophysiology of CFRD differs from type 1 and type 2 diabetes (table 1). In CRFD, there is a reduced and delayed insulin response to carbohydrates while basal insulin is often spared; this leads to glucose abnormalities, which are frequently characterized by normal fasting glucose and post-prandial hyperglycaemia. CFRD and hyperglycaemia, at levels below the diagnostic threshold for diabetes, have an adverse impact on clinical status and lung function in CF. These differences mandate a unique clinical approach to CFRD, with regards to screening, diagnosis and management.

This review will describe the glucose and insulin abnormalities in CF and the adverse impact of CFRD on clinical status before discussing the approach to diagnosis and treatment compared to type 1 and type 2 diabetes.

## Methods

This review is based on a symposium held on 9 March 2017 at the Diabetes UK Professional Conference. The authors undertook a literature review in preparation for the meeting and synthesized their findings into this review.

## Pathophysiology of CFRD

CFRD occurs almost exclusively in individuals with pancreatic insufficiency, which occurs in most people with CF. There is a progressive decrease in insulin secretion with increasing age, and a decrease in the number of pancreatic insulin secreting β cells. Limited data from postmortem studies suggest a reduction in β-cell numbers, with fibrosis and amyloidosis of the pancreas [3, 4]. Studies of the ferret model of CF show loss of β cells at birth with further β-cell loss associated with inflammation and fibrosis of exocrine pancreatic tissue [5]. There may also be a direct effect of the CF mutation on insulin secretion as the CFTR has a role in β-cell function and insulin secretion [6]. As discussed below, ivacaftor, a drug, which reverses the effect of CFTR mutations in some genetic forms of CF, improves insulin secretion and diabetes control [7].

## Insulin and glucose abnormalities in CFRD

The main defect in CFRD is insulin deficiency. Insulin secretion in people with CF declines from childhood [1, 8], even in individuals with normal glucose levels [9, 10]. Insulin sensitivity is usually normal in CF [11] but reduced insulin sensitivity contributes to hyperglycaemia in situations where there is another cause of insulin resistance, such as infection or systemic corticosteroid treatment. Basal insulin secretion is relatively preserved, but the insulin response to a glucose load is reduced and delayed. Consequently, the fasting glucose is often normal at the start of CFRD and can remain so for years. There is a characteristic pattern of abnormal glucose levels; glucose is lowest before breakfast and rises after meals, with the highest levels after the evening meal (figure 1).

The delay in insulin secretion commonly results in hypoglycaemia, even in individuals who do not have CFRD. 13% of children and adolescents with CF experience hypoglycaemia during routine OGTT and this represents a mismatch between the prompt absorption of an oral glucose solution and delayed first phase insulin secretion in CF [12]. Those with hypoglycaemia during OGTT do not appear to have an increased risk of developing diabetes [1]. Reactive hypoglycaemia may also occur, typically 1-2 hours after a meal or drink that is high in refined carbohydrate and low in fat, most likely after breakfast. Individuals with hypoglycaemia after meals can be symptomatic and need advice on the avoidance of hypoglycaemia by dietary modification. Ketosis and diabetic ketoacidosis are unusual in CFRD.

## The impact of diabetes on CF

The impact of CFRD on mortality has been recognized for a long time, with registry studies from the 1980s and 1990s showing significant increases in mortality in CFRD [13, 14], even after adjustment for other risk factors. In 2005, Milla *et al* published retrospective data showing that compared to those with no diabetes, CFRD resulted in a 17 year decrease in median survival rates in females, with no significant difference in males [15] (although other studies have shown an impact in males as well [16]). The same group published data for more recent cohorts in the same clinic, showing reductions in mortality with time. These improvements are likely to be related to earlier recognition of CFRD, screening and treatment. Comparing cohorts for 1992-97 and 2008-12, age adjusted mortality for individuals with CFRD fell from 4.9 to 1.8 per 100 person years [17].

Differences for adults with CFRD, however, still persist; overall mortality in the latest cohort was doubled compared with those with CF without diabetes. Genotype impacted both mortality and diabetes risk: adults with severe *CFTR* genotypes experienced greater mortality at every age older than 32 years than those with milder genotypes, and the risk of CFRD was also increased in those with severe genotypes [17].

There is evidence of deteriorating health status for 2-6 years prior to a diagnosis of CFRD. Finkelstein et al reported clinical deterioration in National Institute of Health scores (which look at clinical markers of disease severity in CF) in 448 people with CF up to 2 years prior to the diagnosis of CFRD [18]. Furthermore Lanng and colleagues reported decreases in weight, BMI, and markers of lung function up to 6 years prior to the diagnosis of CFRD [19]. Females may decline more quickly than males. Trials assessing the impact of insulin therapy have also reported clinical decline prior to insulin initiation [20].

The reasons why worsening glycaemia adversely affects clinical status are not fully understood but are likely to be multifactorial. There is a gradual loss of the anabolic effect of insulin, leading to weight and lean body mass loss, which is an independent predictor of survival. Increasing airway glucose levels may be an additional factor, promoting bacterial growth. Although elevated airway glucose concentrations are seen in people with diabetes without CF, airway glucose levels appear to be higher in people with CFRD [21]. In people with CFRD undergoing continuous glucose monitoring, glucose was detected in airway secretions when blood glucose levels rose above 8 mmol/L. This level was exceeded for 45% of the day in those with CFRD, compared with 6% of in people with CF and normal glucose tolerance. The same study showed that *S. aureus* growth increased when airway glucose levels reached 0.5 mmol/L while *P. aeruginosa* growth rates increased at 1-4 mmol/L, levels demonstrated in the lungs of people with CFRD. Unsurprisingly infection rates are increased and lung function declines more quickly in people with CFRD.

There is emerging evidence that hyperglycaemia affects lung function in people with diabetes unrelated to CF; there is loss of lung elasticity and recoil with the stiffened lungs reflected by reductions in FEV1 and FVC. Diffusion capacity is reduced through thickening in the alveolar epithelium, rather akin to the changes seen in the diabetic kidney. For the most part in people with diabetes, these changes do not cause a clinical problem but in the setting of CFRD, the additional burden reduces life expectancy and increases the need for lung transplantation [13].

*The effect of subtle glucose changes on clinical status*

The magnitude of hyperglycaemia in CF appears to be linked to clinical status. A UK registry study reported that among people treated for CFRD, over a 2 year period, the mean glycated haemoglobin (HbA1c) was 56 mmol/mol (7.3%) in those who died compared with 49 mmol/mol (6.6%) in the survivors, with a 3-fold increased mortality in those with HbA1c over 48 mmol/mol (6.5%) [22]. The effect of glucose abnormalities on clinical status extends to prediabetes and situations where the diagnostic criteria for diabetes are not met. Clinical status is worse in those impaired glucose tolerance following an oral glucose tolerance test (OGTT), compared with those with normal glucose tolerance [23, 24]. There are a few studies in CF demonstrating an association between clinical status and markers of lung function and relatively minor changes in glucose levels in those who do not meet the criteria for diabetes [25, 26]. Continuous glucose monitoring (CGM) frequently demonstrates glucose abnormalities in individuals with CF who have normal glucose tolerance by OGTT and HbA1c in the non-diabetic range [27]. Leclercq et al showed that in people with normal OGTT, abnormalities on CGM predicted worse lung function [28]. Hameed et al examined OGTT (with 30 minute sampling) and CGMS glucose results in a group of 33 children and adolescents [29]. After excluding two individuals who had diabetes on OGTT, they found that a blood glucose measured on CGMS >7.8 mmol/L for over 4.5% of the time, or a glucose over 8.2 mmol/L at any time during OGTT, correlated with declining weight SD score and lung function in the previous 12 months. The evidence that glucose abnormalities, which do not fulfil the diagnostic criteria for diabetes, can significantly impact clinical status influences the decision to treat CFRD.

# Reasons to treat and when to treat

The rationale for treating hyperglycaemia in other type of diabetes is the alleviation of osmotic symptoms and the prevention of the long-term complications. The risk of microvascular and macrovascular complications is related to glycaemia, as measured by HbA1c, and the need to lower HbA1c is balanced with the need to avoid iatrogenic side effects, such as hypoglycaemia. While it was previously thought that people with CFRD did not develop microvascular complications, recent studies have suggested that the prevalence of retinopathy is 15% in people whose duration of diabetes is greater than 10 years with rates of neuropathy and nephropathy of 50% and 16% respectively [30]. This study found no cases of macrovascular disease. Although treatment of CFRD should prevent microvascular complications, the main challenges in the management of CF are the prevention of lung infection and decline of lung function and weight loss.

Lung function declines more rapidly in people with CFRD or impaired glucose tolerance than those with normoglycaemia, and there are increased mortality and lung transplantation rates [13]. In people with CF, hyperglycaemia affects the lung at levels well below the current diagnostic limits for diabetes. The diagnostic criteria for type and type 2 diabetes (based on OGTT, fasting glucose or HbA1c) do not define the stage of hyperglycaemia at which there is a clinical impact in CF. Cut off levels for treatment have not been defined but there is evidence of benefit from treatment in individuals who do not reach the criteria for a diagnosis of diabetes. Individuals who meet the criteria for a diagnosis of diabetes should be treated, and treatment should be considered in individuals with abnormal glucose levels who do not meet the criteria for diabetes (for example impaired glucose tolerance on OGTT or post prandial glucose levels >8mmol/l), if there is evidence of declining lung function or weight loss.

# Screening for CFRD

The clinical impact of CFRD has resulted in an increased awareness of the importance of monitoring glucose levels and prompted the introduction of systematic screening as part of the routine annual CF review. OGTT remains the commonest screening test and yearly OGTT is the suggested in CF Trust and ADA guidelines, commencing from 10 years of age [31, 32]. The pattern of glucose abnormalities in CFRD means that fasting glucose is usually unhelpful.

While OGTT is widely used as a screening tool in CF, it may not be the best way of assessing glucose status. The insulin abnormalities in CF mean that glucose levels can be high during an OGTT but “normal” at 120 minutes [9, 24]. Some centres measure glucose at 30 minute intervals during the test to obtain more information, and a classification of glucose status based on this has been suggested [33]. There has been interest assessing glucose status using CGM and more recently intermittently scanned CGM (flash glucose monitoring). Caution is needed when screening during acute illness because temporary hyperglycaemia may occur at this time.

HbA1c is measured at annual review in CF and used to monitor treatment of CFRD. There is no evidence for the use of HbA1c to diagnose CFRD, although one study examined the use of HbA1c as a screening test before an OGTT [34]. HbA1c is affected by the lifespan of red blood cells; under normal circumstances, it provides a retrospective measure of the average glucose concentration over the previous 6–8 weeks. In CFRD, however, there are a number of conditions that affect red blood cell turnover. Iron deficiency occurs commonly in CF and may be associated with higher HbA1c in people with diabetes. Conversely, increased red cell turnover, which is associated with reduced HbA1c, has also been observed in CF.

## How should we treat CFRD?

Dietary advice in CF

Cystic fibrosis creates a catabolic state through increased energy expenditure, partly due to increased work of breathing and frequent infection. Cystic fibrosis is also associated with malabsorption, with exocrine pancreatic enzyme deficiency and abnormal intestinal transit times. The goal of nutritional management in CF is to provide a high calorie diet through increased macronutrient provision. Often supplements or enteral tube feeding are needed. Routine supplementation with multivitamins and additional fat-soluble vitamins A, D, E, and K is needed together with liberal sodium intake.

Many adults with CF have unusual eating patterns. Diet and calorie intake has been a focus for them since childhood, concentrating on snacks, sweet and high calorie foods, and they often omit breakfast because they have their physiotherapy in the morning and do not feel like eating.

The need to consume an above normal calorie intake to maintain weight must continue when diabetes is diagnosed and dietary restrictions should not be imposed. If necessary, insulin treatment should be tailored to cover the food intake (including supplements and feeds). Standard dietary advice for type 2 diabetes which promotes weight loss and high fibre intake is not suitable in CF. In CFRD management it is reasonable to advise avoidance of heavily refined sugars, such as sugary carbonated beverages, but largely the CF dietary needs outweigh those of diabetes. Physical activity should be encouraged because this is beneficial for both lung function and glycaemic control.

Many people with CF take pancreatic enzyme supplementation to improve food absorption and prevent steatorrhoea. This is also important for optimal glucose control. People with CF have rapid gastric emptying and impaired incretin hormone secretion, which can be improved at least in part by pancreatic enzyme supplementation [35].

Insulin and other anti-diabetes drugs

The mainstay of treatment in CFRD is insulin, although some studies have reported the use of sulfonylureas, and there are on-going trials of DPP-4 inhibitors. Sulfonylureas have a limited duration of response with most people ultimately needing insulin, most likely as a result of on-going β-cell damage. Treatment with insulin has been associated with up to 22 mmol/mol (2%) improvement in HbA1c after 1 year’s treatment, and 11 mmol/mol (1%) after 5 years, although other studies have shown less benefit. Improved glycaemic control is associated with improvements in body weight (1-3 Kg/m2 BMI) and lung function (6-35% increased FEV1) [36]. Insulin therapy may also lead to a reduction in the frequency of chest infection [37], although this has not been demonstrated in all studies.

There is no convincing evidence to support the use of one regimen or type of insulin over another as different insulin regimens have demonstrated improved nutritional markers and lung function with insulin treatment [36, 38, 39]. The insulin regimen should be individualised to the patient’s needs; for example, for someone with postprandial hyperglycaemia, meal-time rapid acting insulin may suffice, while someone receiving steroids may require an intermediate insulin dose. The management of hyperglycaemia around overnight feeds can be challenging, often requiring a combination of short and long acting insulin.

Hypoglycaemia related to treatment with insulin or oral hypoglycaemic agents can occur in CFRD as in anyone receiving these therapies. While people with CF do not have a good glucagon response to hypoglycaemia, the catecholamine response is usually retained. Education on prevention and treatment of hypoglycaemia is important. The effect of hypoglycaemia on driving and the importance of monitoring glucose before driving should be explained. Severe hypoglycaemia, however, appears to be less common in CFRD than in Type 1 diabetes because of the residual endogenous insulin secretion. The risk factors for severe hypoglycaemia (hypoglycaemia requiring the assistance of a third party) and hypoglycaemia unawareness are the same as in type 1 diabetes.

## The effect of medications and illness

The pharmacokinetics of many medications are altered in cystic fibrosis and this can affect glycaemic control in those with CFRD. Prednisolone clearance is increased by 60%, with a 46% increase in volume of distribution and a 35% lower peak concentration [40]. Absorption of medications is also affected, for example, enteric coated prednisolone is very poorly absorbed in CF, and the tablet form of itraconazole is also poorly absorbed unless taken with an acidic substance. If medications are absorbed poorly this can have a significant effect on glycaemia, altering the impact of prednisolone on glucose levels during the day. On withdrawal of these medications, insulin resistance related to prednisolone disappears rapidly but effects from itraconazole may last months following withdrawal, due to its very prolonged elution from tissues.

Marked alterations in glucose tolerance can occur at the time of infection even in those without a previous diagnosis of CFRD, because of the impact of the infection and nutrition. On the one hand, calorie requirement may be increased due to infection and increased work of breathing while on the other, calorie intake may limited through poor appetite due to nausea, vomiting related to swallowed sputum and uncontrolled coughing particularly in the morning. Many people with CF rely on nutritional supplements to maintain their body weight, with high calorie high GI foods causing further glucose excursions.

## The effect of CFTR modulators on CFRD

CFTR modulators, such as ivacaftor, are relatively new agents in managing CF, which partially reverse the effects of the mildest mutations in CF (gating mutations); there are newer agents in development with effects on the more severe mutations. There are case reports of the resolution of CFRD with treatment with ivacaftor [41]. A study of 5 people with CF (3 with normal glucose tolerance, one with recent diagnosis of CFRD and one with CFRD for 16 years) showed that after 1 month’s treatment with ivacaftor, the insulin response to oral glucose improved by 66–178%, except for the individual with long standing diabetes who showed no improvement [7]. The mechanism for this improvement is not wholly understood but points to the role of the CFTR in the regulations of insulin secretion.

# Monitoring and glycaemic targets in CFRD

Tight glycaemic control will reduce the adverse impact of CFRD on clinical status [22] as well as reducing the risk of microvascular complications. The burden of all the other therapies for CF must be taken into account when supervising diabetes management in CF; however, improved diabetes control can have a positive impact on clinical status and patient wellbeing and so intensive treatment can be justified even in individuals with complex problems and poor lung function. Those with frequent infective episodes or receiving intermittent high dose steroids may need to make frequent dose adjustments.

To support tight glycaemic control, people with CFRD are advised to self-monitor their capillary glucose or undertake continuous glucose monitoring if this is available. This needs to be individualized, with those taking insulin needing more testing than those on diet and lifestyle modification alone. Increased testing may be needed at times when insulin requirements change, such as during a period of infection.

Glucose levels should be checked in any individual with CF commenced on enteral tube feeding. The CF Trust recommends glucose testing pre feed, two hours into the feed and immediately post feed to ascertain whether additional insulin is required [31]. The type and dose of insulin prescribed depends on the profile of glucose levels during the feed and the duration of the feed. It is important to repeat these measurements if changes are made to the feed type, volume or duration, and also if the patient’s clinical status changes, for example during illness or following changes in weight. There is a risk of hypoglycaemia if the feed is interrupted after insulin has been given or if the feed is not completed or regurgitated. Overnight PEG feeding pumps should have an appropriate alarm, which sounds if the feed stops so that hypoglycaemia does not ensue.

Despite the caveats relating to the use of HbA1c, this should be monitored regularly in people with CFRD. Furthermore, microvascular screening for retinopathy, neuropathy, foot problems and nephropathy should be performed as for the wider population of people with diabete.

**CFRD and lung transplantation**

In 2015 in the UK, 46 adults with CF received transplants, 42 bilateral lung transplant and the others liver or kidney. As the median survival after lung transplantation is currently 5 years, this procedure is only offered for end stage lung disease; nevertheless, it increases life expectancy with ~20% surviving longer than 10 years after transplant [42]. The prevalence of diabetes is high prior to transplantation and many individuals develop diabetes shortly afterwards. In a study from the Netherlands, 63% of individuals with CF had diabetes before lung transplant and 80% after. CFRD diagnosed before transplant increased mortality [43].

Long term steroid treatment taken after transplant has an adverse impact on glycaemic control, and the need to carry on with some aspects of CF treatment (such as enzyme replacement) and anti-rejection drugs, as well as diabetes management, means these individuals may have a very complex drug regimen that can be challenging to maintain. There are no data about the impact of glycaemic control on long-term survival after transplant.

# Burden of disease

There have been few studies of the burden of CFRD but one study reported that CFRD has less effect on quality of life than Type 1 diabetes [44]. People with CFRD take multiple medications and adherence to diabetes self-management plans can be challenging. To date there have been no studies examining the effect of insulin therapy on quality of life.

# Diabetes services in CF

One of the major challenges in the organisation of CF services is the prevention of cross-infection. Dedicated clinic areas without communal waiting areas are needed with clinicians moving to the patient rather than vice versa. As a result, structured group diabetes education is not feasible and one-to-one training is needed.

Most large CF centres now have dedicated CFRD clinics, which allow for CFRD management to be considered alongside the wider management of CF, as well as meeting the standards for reducing cross infection.

Management of diabetes must take into account the practical and psychological effects of adding insulin treatment to the other treatments for CF. For some individuals with CF, diabetes care is shared between their CF centre, primary care and sometimes another diabetes service. This can help with the practical management of diabetes and routine screening, but it is important people are not incorrectly labelled as having type 1 or type 2 diabetes, given incorrect dietary advice or put on inappropriate oral agents. Diabetes self-management education, including information about the unique nature of CFRD, can help support people with CFRD in their interactions with health professionals.

# Conclusion

CFRD is a unique form of diabetes that is becoming more common as individuals with CF live longer. It is characterized by insulin deficiency and periods of reduced insulin sensitivity. Postprandial hyperglycaemia with normal fasting glucose levels are the most frequently seen abnormalities. Diabetes and hyperglycaemia, even at levels which do not reach the cut off for a diagnosis of diabetes, have an adverse effect on lung function and clinical status and this is the primary reason for starting treatment.

Therefore, individuals who do not meet the criteria for a diagnosis of diabetes may benefit from treatment, although the criteria to start treatment and the best way to screen remain uncertain. Insulin deficiency is present in early childhood and gradually worsens with age, but it is not clear at which point starting treatment leads to clinical benefit.

The mainstay of treatment is insulin but new therapies are being investigated. In particular, the novel CFTR modulators, such as ivacaftor, appear to improve glucose tolerance.

**References**

1. Moran A, Doherty L, Wang X, Thomas W. Abnormal glucose metabolism in cystic fibrosis. *J Pediatr* 1998; **133**:10-17.

2. Carr S, Cosgriff R, Rajabzadeh-Heshejin V, Committee TUCRS. UK Cystic Fibrosis registry 2015. *CF Trust* 2015; **27**.

3. Couce M, O'Brien TD, Moran A, Roche PC, Butler PC. Diabetes mellitus in cystic fibrosis is characterized by islet amyloidosis. *J Clin Endocrinol Metab* 1996; **81**:1267-1272.

4. Iannucci A, Mukai K, Johnson D, Burke B. Endocrine pancreas in cystic fibrosis: an immunohistochemical study. *Hum Pathol* 1984; **15**:278-284.

5. Olivier AK, Yi Y, Sun X, Sui H, Liang B, Hu S*, et al.* Abnormal endocrine pancreas function at birth in cystic fibrosis ferrets. *J Clin Invest* 2012; **122**:3755-3768.

6. Osorio J. Diabetes: A role for CFTR in beta-cell function. *Nat Rev Endocrinol* 2014; **10**:577.

7. Bellin MD, Laguna T, Leschyshyn J, Regelmann W, Dunitz J, Billings J*, et al.* Insulin secretion improves in cystic fibrosis following ivacaftor correction of CFTR: a small pilot study. *Pediatr Diabetes* 2013; **14**:417-421.

8. Yi Y, Norris AW, Wang K, Sun X, Uc A, Moran A*, et al.* Abnormal Glucose Tolerance in Infants and Young Children with Cystic Fibrosis. *Am J Respir Crit Care Med* 2016; **194**:974-980.

9. Yung B, Noormohamed FH, Kemp M, Hooper J, Lant AF, Hodson ME. Cystic fibrosis-related diabetes: the role of peripheral insulin resistance and beta-cell dysfunction. *Diabet Med* 2002; **19**:221-226.

10. Alicandro G, Battezzati PM, Battezzati A, Speziali C, Claut L, Motta V*, et al.* Insulin secretion, nutritional status and respiratory function in cystic fibrosis patients with normal glucose tolerance. *Clin Nutr* 2012; **31**:118-123.

11. Moran A, Pyzdrowski KL, Weinreb J, Kahn BB, Smith SA, Adams KS*, et al.* Insulin sensitivity in cystic fibrosis. *Diabetes* 1994; **43**:1020-1026.

12. Haliloglu B, Gokdemir Y, Atay Z, Abali S, Guran T, Karakoc F*, et al.* Hypoglycemia is common in children with cystic fibrosis and seen predominantly in females. *Pediatr Diabetes* 2016.

13. Bismuth E, Laborde K, Taupin P, Velho G, Ribault V, Jennane F*, et al.* Glucose tolerance and insulin secretion, morbidity, and death in patients with cystic fibrosis. *J Pediatr* 2008; **152**:540-545, 545 e541.

14. Navarro J, Rainisio M, Harms HK, Hodson ME, Koch C, Mastella G*, et al.* Factors associated with poor pulmonary function: cross-sectional analysis of data from the ERCF. European Epidemiologic Registry of Cystic Fibrosis. *Eur Respir J* 2001; **18**:298-305.

15. Milla CE, Billings J, Moran A. Diabetes is associated with dramatically decreased survival in female but not male subjects with cystic fibrosis. *Diabetes Care* 2005; **28**:2141-2144.

16. Chamnan P, Shine BS, Haworth CS, Bilton D, Adler AI. Diabetes as a determinant of mortality in cystic fibrosis. *Diabetes Care* 2010; **33**:311-316.

17. Lewis C, Blackman SM, Nelson A, Oberdorfer E, Wells D, Dunitz J*, et al.* Diabetes-related mortality in adults with cystic fibrosis. Role of genotype and sex. *Am J Respir Crit Care Med* 2015; **191**:194-200.

18. Finkelstein SM, Wielinski CL, Elliott GR, Warwick WJ, Barbosa J, Wu SC*, et al.* Diabetes mellitus associated with cystic fibrosis. *J Pediatr* 1988; **112**:373-377.

19. Lanng S, Thorsteinsson B, Nerup J, Koch C. Influence of the development of diabetes mellitus on clinical status in patients with cystic fibrosis. *Eur J Pediatr* 1992; **151**:684-687.

20. Rosenecker J, Hofler R, Steinkamp G, Eichler I, Smaczny C, Ballmann M*, et al.* Diabetes mellitus in patients with cystic fibrosis: the impact of diabetes mellitus on pulmonary function and clinical outcome. *Eur J Med Res* 2001; **6**:345-350.

21. Brennan AL, Gyi KM, Wood DM, Johnson J, Holliman R, Baines DL*, et al.* Airway glucose concentrations and effect on growth of respiratory pathogens in cystic fibrosis. *J Cyst Fibros* 2007; **6**:101-109.

22. Adler AI, Shine B, Haworth C, Leelarathna L, Bilton D. Hyperglycemia and death in cystic fibrosis-related diabetes. *Diabetes Care* 2011; **34**:1577-1578.

23. Lavie M, Fisher D, Vilozni D, Forschmidt R, Sarouk I, Kanety H*, et al.* Glucose intolerance in cystic fibrosis as a determinant of pulmonary function and clinical status. *Diabetes Res Clin Pract* 2015; **110**:276-284.

24. Coriati A, Ziai S, Lavoie A, Berthiaume Y, Rabasa-Lhoret R. The 1-h oral glucose tolerance test glucose and insulin values are associated with markers of clinical deterioration in cystic fibrosis. *Acta Diabetol* 2016; **53**:359-366.

25. Brodsky J, Dougherty S, Makani R, Rubenstein RC, Kelly A. Elevation of 1-hour plasma glucose during oral glucose tolerance testing is associated with worse pulmonary function in cystic fibrosis. *Diabetes Care* 2011; **34**:292-295.

26. Suratwala D, Chan JS, Kelly A, Meltzer LJ, Gallagher PR, Traylor J*, et al.* Nocturnal saturation and glucose tolerance in children with cystic fibrosis. *Thorax* 2011; **66**:574-578.

27. Schiaffini R, Brufani C, Russo B, Fintini D, Migliaccio A, Pecorelli L*, et al.* Abnormal glucose tolerance in children with cystic fibrosis: the predictive role of continuous glucose monitoring system. *Eur J Endocrinol* 2010; **162**:705-710.

28. Leclercq A, Gauthier B, Rosner V, Weiss L, Moreau F, Constantinescu AA*, et al.* Early assessment of glucose abnormalities during continuous glucose monitoring associated with lung function impairment in cystic fibrosis patients. *J Cyst Fibros* 2014; **13**:478-484.

29. Hameed S, Morton JR, Jaffe A, Field PI, Belessis Y, Yoong T*, et al.* Early glucose abnormalities in cystic fibrosis are preceded by poor weight gain. *Diabetes Care* 2010; **33**:221-226.

30. Schwarzenberg SJ, Thomas W, Olsen TW, Grover T, Walk D, Milla C*, et al.* Microvascular complications in cystic fibrosis-related diabetes. *Diabetes Care* 2007; **30**:1056-1061.

31. CF Trust. Standards for the Clinical Care of Children and Adults with cystic fibrosis in the UK. CF Trust 2011.

32. Moran A, Brunzell C, Cohen RC, Katz M, Marshall BC, Onady G*, et al.* Clinical care guidelines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. *Diabetes Care* 2010; **33**:2697-2708.

33. Hameed S, Jaffe A, Verge CF. Cystic fibrosis related diabetes (CFRD)--the end stage of progressive insulin deficiency. *Pediatr Pulmonol* 2011; **46**:747-760.

34. Burgess JC, Bridges N, Banya W, Gyi KM, Hodson ME, Bilton D*, et al.* HbA1c as a screening tool for cystic fibrosis related diabetes. *J Cyst Fibros* 2016; **15**:251-257.

35. Perano SJ, Couper JJ, Horowitz M, Martin AJ, Kritas S, Sullivan T*, et al.* Pancreatic enzyme supplementation improves the incretin hormone response and attenuates postprandial glycemia in adolescents with cystic fibrosis: a randomized crossover trial. *J Clin Endocrinol Metab* 2014; **99**:2486-2493.

36. Moran A, Pekow P, Grover P, Zorn M, Slovis B, Pilewski J*, et al.* Insulin therapy to improve BMI in cystic fibrosis-related diabetes without fasting hyperglycemia: results of the cystic fibrosis related diabetes therapy trial. *Diabetes Care* 2009; **32**:1783-1788.

37. Franzese A, Spagnuolo MI, Sepe A, Valerio G, Mozzillo E, Raia V. Can glargine reduce the number of lung infections in patients with cystic fibrosis-related diabetes? *Diabetes Care* 2005; **28**:2333.

38. Hameed S, Morton JR, Field PI, Belessis Y, Yoong T, Katz T*, et al.* Once daily insulin detemir in cystic fibrosis with insulin deficiency. *Arch Dis Child* 2012; **97**:464-467.

39. Bizzarri C, Lucidi V, Ciampalini P, Bella S, Russo B, Cappa M. Clinical effects of early treatment with insulin glargine in patients with cystic fibrosis and impaired glucose tolerance. *J Endocrinol Invest* 2006; **29**:RC1-4.

40. Dove AM, Szefler SJ, Hill MR, Jusko WJ, Larsen GL, Accurso FJ. Altered prednisolone pharmacokinetics in patients with cystic fibrosis. *J Pediatr* 1992; **120**:789-794.

41. Hayes D, Jr., McCoy KS, Sheikh SI. Resolution of cystic fibrosis-related diabetes with ivacaftor therapy. *Am J Respir Crit Care Med* 2014; **190**:590-591.

42. Weiss ES, Allen JG, Merlo CA, Conte JV, Shah AS. Factors indicative of long-term survival after lung transplantation: a review of 836 10-year survivors. *J Heart Lung Transplant* 2010; **29**:240-246.

43. Belle-van Meerkerk G, van de Graaf EA, Kwakkel-van Erp JM, van Kessel DA, Lammers JW, Biesma DH*, et al.* Diabetes before and after lung transplantation in patients with cystic fibrosis and other lung diseases. *Diabet Med* 2012; **29**:e159-162.

44. Tierney S, Deaton C, Webb K, Jones A, Dodd M, McKenna D*, et al.* Isolation, motivation and balance: living with type 1 or cystic fibrosis-related diabetes. *J Clin Nurs* 2008; **17**:235-243.