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Review article

Clinical importance of cystic fibrosis-related diabetes

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Abstract

The prevalence of cystic fibrosis-related diabetes (CFRD) and glucose intolerance (IGT) has risen dramatically over the past 20 years as survival has increased for people with cystic fibrosis (CF). Diabetes is primarily caused by pancreatic damage, which reduces insulin secretion, but glucose tolerance is also modified by factors that alter insulin resistance, such as intercurrent illness and infection. CFRD not only causes the symptoms and micro and macrovascular complications seen in type 1 and type 2 diabetes in the general population, but also is associated with accelerated pulmonary decline and increased mortality. Pulmonary effects are seen some years before the diagnosis of CFRD, implying that impaired glucose tolerance may be detrimental.

Current practice is to screen for changes in glucose tolerance by regular measurement of fasting blood glucose, by oral glucose tolerance test or a combination of these approaches with symptom review and measurement of HbA_{1C}. Treatment is clearly indicated for those with CFRD and fasting hyperglycaemia to control symptoms and reduce complications. As nutrition is critical in people with CF to maintain body mass and lung function, blood glucose should be controlled in CFRD by adjusting insulin doses to the requirements of adequate food intake and not by calorie restriction. It is less clear whether blood glucose control will have clinical benefits in the management of patients with CFRD without fasting hyperglycaemia or with impaired glucose tolerance and further studies are required to establish the best treatment for this patient group.

Keywords: Cystic fibrosis; Cystic fibrosis-related diabetes; Diabetes mellitus

Contents

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1. Introduction

Cystic fibrosis (CF) is the commonest lethal autosomal recessive disorder in Caucasian populations, with an incidence of 1 in 2500 live births [1]. Over 1000 unique mutations have been described in the cystic fibrosis transmembrane conductance regulator gene, the commonest of which is a deletion of phenylalanine in the amino acid position 508. These mutations lead to defective production of a protein called CF transmembrane conductance regulator (CFTR) that functions as a cAMP-regulated chloride channel. Impaired function of CFTR affects the transepithelial transport of ions and water mainly in the cells of the respiratory, gastrointestinal, hepatobiliary and reproductive systems. The common pathological finding in these organs is accumulation of thick viscous secretions associated with progressive scarring and destruction.

Improved clinical care has led to a dramatic increase in life expectancy for people with CF. In the 1950s, life expectancy for people with CF was less than 1 year, whereas in 2001 predicted survival for people on the Cystic Fibrosis Foundation Patient Registry was 33.4 years [2]. As people with CF live longer, glucose intolerance and cystic fibrosis-related diabetes (CFRD) are becoming more common [2]. Pre-existing lung disease means the implications of developing diabetes for people with CF are very different from those for people with type 1 and type 2 diabetes mellitus. People with CF who develop diabetes experience accelerated decline in CF clinical status and pulmonary function [3–6], as well as having a higher mortality rate than those without diabetes [3,7]. Understanding the pathogenesis and optimal methods of diagnosis and treatment for CFRD is therefore important, not only to prevent the micro and macrovascular complications associated with all forms of diabetes mellitus, but also to prevent and treat deterioration in pulmonary disease.

2. Prevalence OF CFRD

The average age of onset of CFRD in the 1990s was 19 to 21 years [8,9]. It is therefore only within the last 20 years that a significant proportion of people with CF has survived long enough to develop CFRD. The reported prevalence figures for CFRD over the last 50 years are difficult to compare between decades as the criteria employed for defining CFRD have gradually evolved over this time.

The Cystic Fibrosis Foundation Patient Registry, which collects information from 22,732 people with CF of all ages in the United States and Canada, has shown that the diagnoses of glucose intolerance and diabetes in CF are becoming more prevalent (Fig. 1) [2]. The most recent estimate in 2002 showed that 12% had diagnoses of CFRD and glucose intolerance based on physician reports [2]. In centres where annual oral glucose tolerance testing is routinely performed, CFRD and glucose intolerance are detected more frequently. Of 311 people with CF who underwent an OGTT in Denmark in 1994, 14.7% were diabetic, while a further 13.7% had IGT [9]. 11% of people with CF over the age of 5 years in Minnesota had CFRD, while 17% had CFRD without FH [10]. The prevalence of CFRD increases with age (Fig. 2) [11], with more than 25% of people over the age of 20 receiving a diagnosis of CFRD

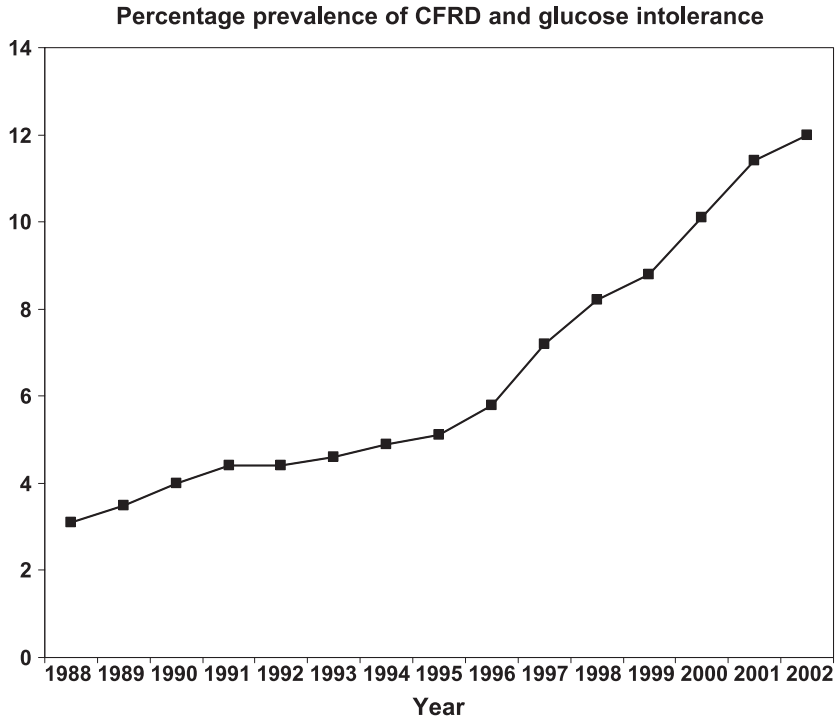

Fig. 1. Graph demonstrating prevalence of CFRD and glucose intolerance over the last 14 years in people registered on the Cystic Fibrosis Foundation Patient Registry.

[9]. Since the predicted survival of people with CF is becoming longer each year, the proportion with abnormal glucose tolerance is likely to continue to increase.

3. Pathophysiology of CFRD

All forms of diabetes are characterised by chronic hyperglycaemia resulting from defects in insulin secretion, action or both. CFRD is distinct from both type 1 and type 2 diabetes in its pathogenesis. Type 1 diabetes is typified by the absence of insulin due to autoimmune destruction of the β-cells within the islets of Langerhan. Type 2 diabetes is a combination of the effects of relative insulin deficiency compared to need, and increased insulin resistance, where the tissues are unable to respond to insulin. The American Diabetes Association places CFRD in the category of "other specific types—diseases of the exocrine pancreas" [12].

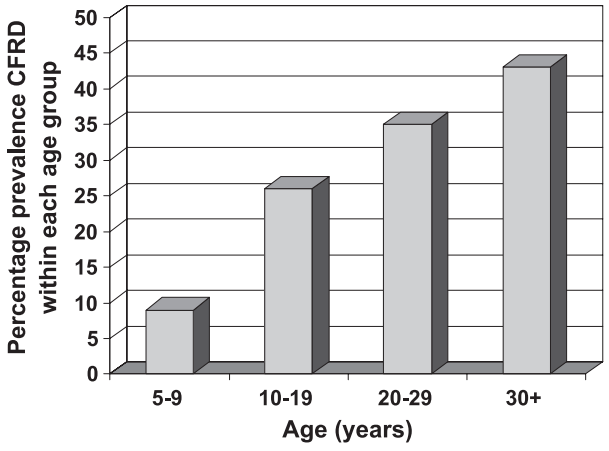

Fig. 2. The percentage prevalence of CFRD within age groups in people with CF attending the clinic at University of Minnesota in 1996. People with CFRD include those who required long-term insulin to prevent FH and those who intermittently required insulin during periods of stress (adapted from Moran et al. [11]).

The aetiology of CFRD is complex and the mechanisms leading to the development of CFRD are not fully understood. A possible sequence of events that could lead to glucose intolerance is proposed in Fig. 3.

3.1. Reduced insulin secretion

3.1.1. Structural abnormalities of the endocrine pancreas

The pancreas is histologically abnormal in almost all people with CF. Many investigators have proposed that pancreatic damage arises from changes in the composition of pancreatic secretions secondary to CFTR mutations. Abnormal expression of CFTR in intralobular duct cells and pancreatic centroacinar cells appears to cause reduced chloride and bicarbonate ion secretion with reduced fluid secretion into the pancreaticobiliary ducts [13,14]. Pancreatic proteins including enzymes become concentrated within the pancreatic ducts, causing protein precipitation and ductal obstruction. A reduced intraluminal pH, resulting from the reduction in bicarbonate secretion, may exacerbate

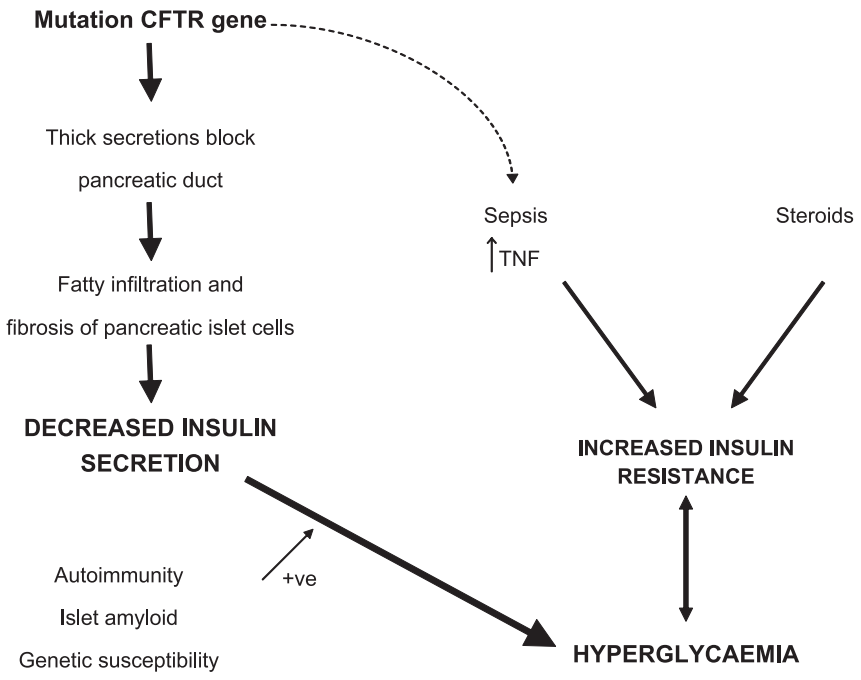

Fig. 3. Possible sequence of pathological events leading to abnormal glucose homeostasis in people with CF.

protein precipitation. Obstruction of the pancreatic ducts causes interstitial oedema in the surrounding acinar tissue, probably impairing blood flow within the pancreatic tissue leading to ischaemic damage. Activated proteases and lipases within the obstructed ducts may lead to autolysis of the pancreas.

Post mortem studies of pancreatic morphology have been performed in people with CF varying in age from preterm infants to 32 years. These have confirmed a spectrum of histological abnormalities, which become more severe with increasing age. Even in infancy, there is a lack of normal pancreatic maturation, with focal accumulation of secretory material within the pancreatic ducts associated with duct dilation [15,16]. In older people with CF there is atrophy and fibrosis of the pancreatic acinar tissue with reduction in the number of acini and replacement of exocrine tissue with fatty infiltration [17,18]. Of importance there is a significant reduction in the proportion of β-cells within the residual islets from people with CFRD as compared to those with normoglycaemia. The loss of endocrine pancreatic tissue may contribute to the development of CFRD [18,19].

Deposition of islet amyloid may contribute to impairment of endocrine pancreatic function in people with CF. It is not clear how islet amyloid is formed, but it appears to be derived from amylin, a 37 amino acid polypeptide which is normally produced by the β cells and co-packaged with insulin. A high proportion of people with type 2 diabetes has islet amyloid deposits, the extent of which increases with the severity of diabetes. It has been proposed that increased redox stress within the islets of people with type 2 diabetes may promote unfolding of the native secondary structure of β-cell derived amylin, which then may refold into the anti-parallel crossed β-pleated sheet structure of islet amyloid [20]. The role of islet amyloid in the development of cellular damage or dysfunction remains unclear. Intracellular amyloid particles have been shown to be cytotoxic to β-cells, inducing apoptosis by membrane disruption [21]. Progressive accumulation of extracellular islet amyloid may increase the severity of diabetes by acting as a diffusion barrier for insulin and glucose within the islet, thus reducing the glucose sensing ability of islet cells and impairing secretion of insulin. Couce et al. identified islet amyloid in pancreases from 11 of 16 (69%) people with CFRD, 2 of 12 (17%) people with CF with borderline diabetes, and 0 of 13 of people with CF without diabetes [22]. Islet amyloid deposition appears to be dependent on intracellular pH. Hence CFTR mutations, which may alter intracellular pH, could predispose to intracellular aggregation of islet amyloid [23,24].

3.1.2. Functional evidence of endocrine pancreatic insufficiency

Approximately 85% of people with CF exhibit signs and symptoms of exocrine pancreatic insufficiency. There is a strong association between exocrine pancreatic disease and the development of CFRD [25]. Insulin secretion and hormone responses are normally intact in people with CF who have exocrine pancreatic sufficiency [26]. However, the normal insulin response to oral glucose challenge is compromised in people with exocrine pancreatic insufficiency, even in those with normal glucose tolerance.

People with CF and exocrine pancreatic insufficiency had a 41% reduction in peak plasma insulin concentration in response to oral glucose and a substantial delay in the time to reach peak insulin concentration compared to healthy controls (Fig. 4) [27]. In a second study, people with pancreatic insufficiency had a delayed first phase C-peptide response to oral glucose, although the total amount of insulin secreted was normal [26]. Insulin secretion is progressively reduced as pancreatic damage worsens and glucose tolerance deteriorates. The time to reach peak insulin concentration following oral glucose load was increasingly delayed from 20–60 min in healthy volunteers, to 30–120 min in people with CF with NGT, 60–120 min in people with CF with IGT and 150 min in people with CFRD (Fig. 4) [26]. In addition, the total quantity of insulin secreted was reduced in people with CFRD [26,27]. Therefore since a rapid postprandial rise in glucose is typically followed by a delayed but prolonged insulin response, people may develop symptoms of both hyper and hypoglycaemia [28].

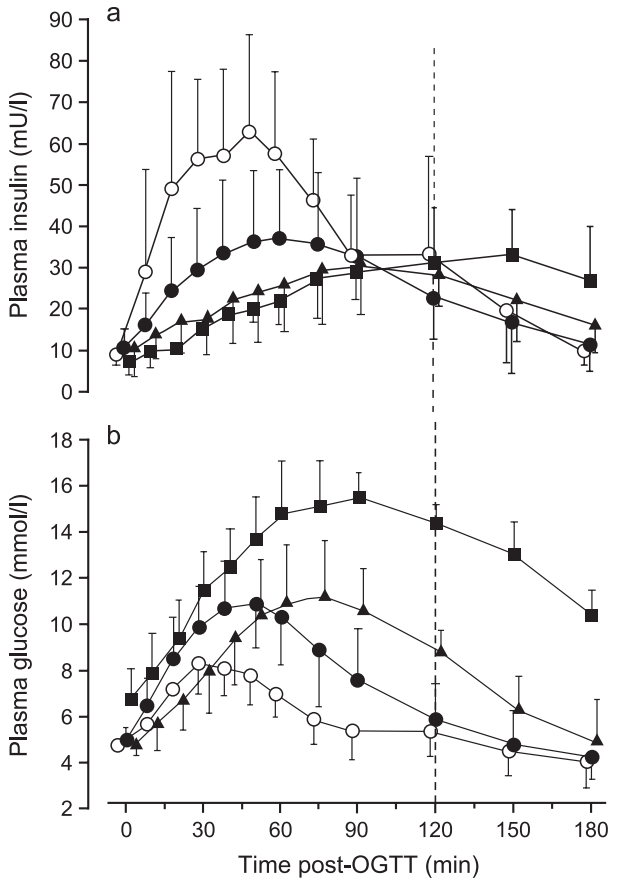

Fig. 4. Mean (a) plasma insulin and (b) glucose profiles following extended oral glucose load in healthy controls (○, n=8) and in people with cystic fibrosis with differing glycaemic status (normal glucose tolerance, ●, n=16; impaired glucose tolerance, ▲, n=6; diabetic glucose tolerance, ■, n=2). The 120-min cut-off time point for determining glycaemic status is also shown (reproduced from Yung et al. [27]).

3.1.3. Factors determining susceptibility to endocrine pancreatic damage

Although the majority of people with CF develop exocrine pancreatic damage, not all develop glucose intolerance. A second aetiological factor may determine individual risk of developing CFRD.

3.1.3.1. Genetic susceptibility. The clinical phenotype of people with cystic fibrosis varies greatly and some studies have linked phenotypic variability and severity of CF with the type of genetic mutation causing the disease [25]. The European Epidemiologic Registry of Cystic Fibrosis study [25] analysed the link between different classes of mutations carried and the severity of major disease manifestations in 8693 patients. It demonstrated that people homozygous for the milder Class IV mutations were less likely to develop diabetes (only 1 of 65 patients) than those homozygous for class II mutations, e.g. ÄF508 (22.1% of 1276 patients). People with Class IV disease are less likely to develop pancreatic damage and exocrine insufficiency, which may account for the low prevalence of CFRD in this group.

No link has been found between the development of CFRD and HLA alleles DR3, DR4, DR3/4 and HLA-DR2, which are associated with type 1 diabetes in the general population [29].

3.1.3.2. Autoimmune processes. In the general population type 1 diabetes is caused by autoantibodies to islet β cells which trigger cell-mediated immune destruction and insulin deficiency. Formation of these antibodies may be triggered by a viral infection, such as mumps, measles and coxsackie. Islet cell antibodies are found in 85–90% of people with type 1 diabetes at the time of diagnosis, but have rarely been detected in the sera of people with CFRD [29–32]. Antibodies to glutamic acid decarboxylase (GAD), an intracellular protein which shares amino acid sequences with a Coxsackie virus protein, also are present in people with type 1 diabetes. GAD autoantibodies were found by a single group in 15 of 30 people with CF [33]. Whether these antibodies cause β-cell damage and diabetes, or are formed in response to the release of antigens during cellular injury is currently unknown.

There is some evidence that serum antibody responses to bacterial antigens are related to the development of diabetes in people with CF. In retrospective longitudinal studies, IgG antibodies to the *Pseudomonas aeruginosa* antigen 60-kDa GroEL were measured in serum from prediabetic and non-diabetic people with CF stored over 5–9 years [34]. 60-kDa GroEL IgG increased in both groups by 5–6% per year during the observation period, but increased by 24.6% in the prediabetic group 3–12 months prior to the onset of diabetes. The 60-kDa GroEL protein is a member of a group of bacterial 60–65 kDa hsps peptides, which induce diabetes in animal models [35,36]. This immunological response to pulmonary infection could

augment pancreatic damage, leading to the development of diabetes.

3.2. Increased insulin resistance

Insulin resistance is the inability of insulin to produce its usual biological actions at circulating concentrations that are effective in normal subjects. It occurs when there is impaired ability of insulin to stimulate glucose uptake by skeletal muscle and/or suppress hepatic glucose production.

The "gold-standard" method for measuring insulin resistance is the hyperinsulinaemic euglycaemic clamp technique, which involves simultaneous infusion of insulin and glucose. If endogenous hepatic glucose production is completely inhibited by an infusion of insulin, then the quantity of exogenous glucose required to maintain euglycaemia is a reflection of the net sensitivity of peripheral tissues to insulin. This technique has been used to study the role of increased peripheral insulin resistance in the development of CFRD [37–42]. There is some evidence that people with CFRD have increased insulin resistance [38,41,42]. The findings are less clear in people with NGT and IGT. Moran et al. [38] found normal insulin resistance in people with NGT, but reduced peripheral insulin resistance in people with IGT. Hardin et al. [41] found increased insulin resistance in all CF people with NGT and IGT. Several factors may explain the differences observed between studies. First, the clinical status of the people studied in these trials varied markedly, particularly in respect to pulmonary function. Second, although the insulin infusion rates used in the experiments were adequate to suppress hepatic glucose production in people without CF, hepatic glucose production was not completely suppressed in people with CF [38] and insulin resistance may therefore have been underestimated.

The molecular and cellular basis for insulin resistance is not fully understood. Aetiological factors include decreased numbers of insulin receptors, impaired post-receptor signaling or impaired translocation of glucose transporters, which mediate glucose uptake, to cell membranes. In CF altered insulin resistance does not appear to be due to a reduction in the number of insulin receptors, in fact the number of insulin receptors are increased [43]. However, insulin binding to the receptor is reduced [43,44]. In addition, translocation of the glucose transporter GLUT4 to the plasma membrane is reduced in people with CF [42].

People with CF are likely to have variable insulin resistance dependent on their clinical status. During times of illness cytokines (e.g. tumour necrosis factor-α, interleukin-6) or corticosteroid administration can precipitate hyperglycaemia by increasing insulin resistance. TNF-α levels increase during periods of acute infection and are also higher in people with worse clinical status [42]. TNF-α affects insulin resistance by altering the phosphorylation cascade of insulin signaling at the receptor level [45]. Glucocortioid therapy reduces glucose uptake by skeletal muscles and impairs insulin-mediated suppression of hepatic glucose production. Insulin resistance may therefore modulate the degree of glucose intolerance in some people with CF.

4. Clinical impact of CFRD

CFRD was initially thought to be mild and uncomplicated. However, it has become increasingly clear that CFRD not only causes micro and macrovascular complications but also has a negative impact on both pulmonary function and mortality.

4.1. Impact of diabetes on survival in CF

People with CFRD have a higher mortality rate than people with CF without diabetes. In a study of 448 people with CF, fewer than 25% of people with diabetes survived to age 30 years, whereas nearly 60% of people without diabetes reached this age [3]. More recently the Cystic Fibrosis Foundation Patient Registry reported that people with CF and diabetes have a 6-fold greater mortality rate than people without diabetes [7].

4.2. Effect of diabetes on pulmonary disease

4.2.1. Pulmonary function and CFRD

The presence of CFRD is tightly linked to poor lung function. Cross-sectional analysis of 7566 people enrolled in the European Epidemiologic Registry of Cystic Fibrosis (ERCF) [46] found that FEV_1% predicted was lower in people with diabetes than in those without diabetes at all ages (Fig. 5). For the whole group the mean FEV_1%

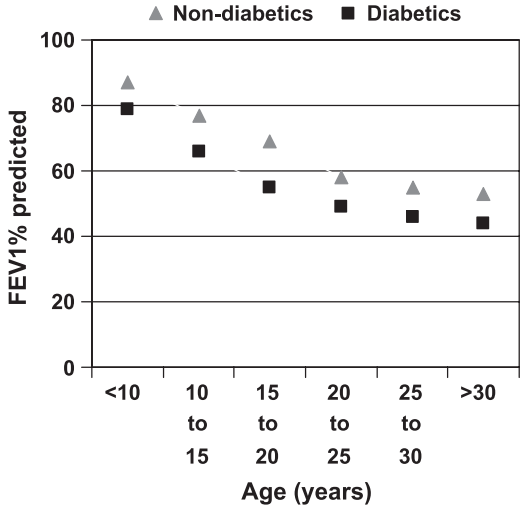

Fig. 5. Mean values of FEV_1, expressed as percent predicted for gender and height (FEV_1%), in people with CF with and without CFRD by age group (adapted from Koch et al. [46]).

predicted value was 72% in people without diabetes, but 52% in people with CFRD. In addition, FVC% predicted value and weight-for-age percentiles were lower in people with CFRD than in people without diabetes in all age groups.

4.2.2. Prediabetic decline in pulmonary function

The effect of the prediabetic state on clinical status of people with CF is a much debated question. Several retrospective studies have clearly demonstrated that the rate of decline of FEV_1 and FVC increases in people with CF over a 2–4-year period prior to the diagnosis of CFRD [3–6]. In one study the rate of decline in pulmonary function was directly proportional to the severity of glucose intolerance and the degree of insulin deficiency [5]. Lanng et al. [4] found that FEV_1 and FVC were already 20% and 10% lower in people with CFRD than in carefully matched people with CF without diabetes 6 years prior to the onset of diabetes. Insulin therapy in people with CFRD restored FEV_1 and FVC to the levels recorded at the start of the 6-year period. However, lung function remained reduced in people with CFRD compared to non-diabetic controls.

4.3. Possible mechanisms of pulmonary decline in CFRD

The mechanisms leading to pulmonary decline in people with CFRD are unclear, but it is most likely that the combined effects of hyperglycaemia and insulin deficiency are responsible.

4.3.1. Pulmonary effects of hyperglycaemia

Hyperglycaemia could cause the decline in pulmonary function seen in people with CFRD directly, through structural changes in lung tissue, or indirectly, by reducing pulmonary defence against infection.

4.3.1.1. Direct pulmonary damage. Chronic abnormalities in lung function have been identified in people with type 1 and type 2 diabetes mellitus without pre-existing lung disease. In the Framingham Heart Study a diagnosis of diabetes and a higher fasting blood glucose concentration were both associated with lower than predicted spirometric measures of pulmonary function [47]. FEV_1 and FVC were also consistently lower in diabetic individuals compared with healthy individuals in the Copenhagen City Heart Study (n=17,506), with a reduction of approximately 8% in predicted values [48]. Hyperglycaemia is associated with structural changes in lung tissue, which may account for the development of abnormal pulmonary function in people with diabetes. In an animal model, pulmonary changes were observed in hamsters with streptozotocin-induced diabetes after only 6 weeks of hyperglycaemia (23–25 mmol/l) [49,50]. The pulmonary capillary endothelium became full of plasmalemmal vesicles, alveoli collapsed and the lung interstitium enlarged. In human subjects autopsy studies have shown lungs from diabetic subjects to be abnormal, with thickened alveolar epithelial and pulmonary capillary basal laminae [51]. Hyperglycaemia may cause pulmonary damage by a number of mechanisms including overproduction of superoxide molecules, increased production of advanced glycation end products and changes in inflammatory mediators. The combined effect of these processes is cellular stress and damage, which could contribute to decline in pulmonary function in people with CFRD.

4.3.1.2. Increased predisposition to infection. Pulmonary infections are more common and have a worse prognosis in people with type 1 and type 2 diabetes than in those without diabetes [52–54]. Hyperglycaemia may have local and systemic effects, which reduce pulmonary defence against infection. Systemic neutrophil phagocytic activity and chemokinesis are impaired by hyperglycaemia but function can be restored by rigorous control of blood glucose [55]. Hyperglycaemia reversibly impairs mitogen stimulated proliferation of lymphocytes [56] and causes non-enzymatic glycosylation of immunoglobulins after only a few hours, sufficient to cause impairment of function [57]. The function of innate immune proteins such as collectins is also reduced by glycosylation. Hyperglycaemic diabetic mice were less able to resist pulmonary replication of collectin-sensitive viruses than their non-diabetic counterparts [58]. There are no direct studies of the effect of hyperglycaemia on pulmonary defence in people with CFRD, however treatment with insulin reduced the percentage of sputum cultures positive for *Streptococcus pneumoniae* and *Haemophilus influenzae* from people with CFRD [59].

4.3.2. Pulmonary effects of insulin deficiency

In type 1 diabetes, insulin deficiency has been associated with significant reduction in inspiratory muscle and diaphragmatic strength compared to healthy controls leading to impaired pulmonary function [60]. Insulin is an anabolic hormone that is critical in the regulation of protein metabolism [61]. Whole body protein balance cycles between periods of protein synthesis and breakdown. Postprandial insulin secretion normally causes a dose-dependent suppression of protein breakdown. People with CF, who are not acutely ill, have both increased protein synthesis and breakdown, resulting in balanced whole body turnover [62]. However, when insulin secretion is decreased or insulin resistance is increased the suppressive effect of insulin on protein breakdown is reduced, resulting in net protein catabolism [63]; therefore negative protein balance may contribute to increased morbidity and mortality. Improved nutritional status [64] and reversal of protein catabolism stabilises pulmonary function [65,66].

4.4. Vascular complications of CFRD

4.4.1. Microvascular complications

In the general population, microvascular complications of diabetes are determined by the duration of diabetes, the

level of glycaemic control, smoking, hypertension and other undetermined factors. Background retinopathy is unusual before diabetes has been present for 5 years and the incidence of nephropathy peaks 15–16 years after the onset of diabetes. People with CF develop diabetes in the second and third decade of life, and have only recently survived long enough to develop diabetic complications. However, reports of microvascular disease in CFRD are increasing.

In three separate small cross-sectional studies the prevalence of diabetic retinopathy in people with CFRD was found to be 15.8%, 5% and 16% [9,67,68]. In case reports and cross-sectional studies of people with CFRD who had retinopathy, all were adults (age 27 (18–35) years (median (interquartile range)) and had developed CFRD for 12 (3–23) years prior to the diagnosis of retinopathy [9,69–72]. The severity of retinal defects ranged from mild background retinopathy to proliferative retinopathy, vitreous haemorrhages and cataract formation. In almost all these cases either raised HbA_{1C} values or high random glucose levels suggested poor long-term glycaemic control.

Diabetic nephropathy has been reported in 11 people with CF [9,69–73]. In the majority of people, nephropathy developed over 10 years after the diagnosis of CFRD was made (12 (1–24) years). In four people renal biopsies demonstrated typical features of diabetic nephropathy, which included capillary basement membrane thickening, diffuse diabetic glomerulosclerosis and nodular glomerular sclerosis.

4.4.2. Macrovascular complications

The processes leading to atherosclerosis are complex but a current concept called "the response to injury hypothesis" considers it to be a chronic inflammatory response to some sort of injury to the vascular endothelium. Risk factors that predispose to atherosclerosis in the general population include hyperlipidaemia, hypertension, cigarette smoking, diabetes and genetic factors.

At the current time there is no documented risk of accelerated atherosclerotic macrovascular disease associated with CFRD. Hypertension is uncommon in the CF population as is hypercholesterolaemia. In a study of 192 people with CF (age 21±11 years (mean±S.D.)), 4% had elevated cholesterol and 16% had elevated triglycerides, however, there was no relationship between abnormal lipid concentrations and glucose tolerance [74]. Whether hyperlipidaemia increases the risk of cardiovascular disease in people with CF is unknown, but may become more important as people with CF live longer.

5. Diagnosis and screening

5.1. Diagnostic criteria

The oral glucose tolerance test (OGTT) is regarded as the "gold standard" for the diagnosis of diabetes. In 1998, the Cystic Fibrosis Foundation consensus conference defined four glucose tolerance categories for people with CF based on the results of the 1.75 g/kg (max 75 g) OGTT; normal glucose tolerance (NGT), impaired glucose tolerance (IGT), cystic fibrosis-related diabetes without fasting hyperglycaemia (CFRD without FH) and cystic fibrosis-related diabetes with fasting hyperglycaemia (CFRD with FH) (Table 1) [7,75]. These are based on the American Diabetes Association (ADA) classification [75], but the consensus committee also recognised CFRD without fasting hyperglycaemia (FH) as a separate category. The ADA categories define blood glucose concentrations above which intervention has been shown to prevent diabetic complications [75], however, the level of glycaemic control required to prevent pulmonary deterioration or reduce mortality in people with CF has not been fully established.

5.2. Screening

As glucose tolerance in CF is defined by the oral glucose tolerance test, this is the gold standard method for identifying people with CFRD or IGT. However, the consensus committee felt that it was not practical to screen the whole CF population by this method as OGTTs are time and resource consuming for both patients and staff [7]. The consensus committee therefore suggested that if the random blood glucose concentration is <7.0 mmol/l, there is no need for further work-up unless symptoms of hyperglycaemia are present (Table 2). However, this method may fail to detect all people with CFRD or IGT, as the prevalence of people identified with CFRD or IGT is greater in centres where OGTT is routine than in those where other screening methods are used. A compromise between approaches which screen either all or no patients with an OGTT is to perform OGTTs only in those identified as likely to have glucose tolerance abnormalities through possession of one or more of the following criteria: abnormal random blood glucose, abnormal HbA_{1C}, symptoms of hyperglycaemia (Table 2) or weight loss [76]. These criteria have 92% sensitivity and 79% selectivity in the diagnosis of CFRD [76].

Even though the OGTT is considered the gold standard for the diagnosis of diabetes, the OGTT result may vary

Table 1
Categories of glucose tolerance in people with CF defined by an oral glucose tolerance test [7]

Glucose tolerance categories	FPG, mmol/l	2-h PG, mmol/l
Normal glucose tolerance (NGT)	<7.0	<7.8
Impaired glucose tolerance (IGT)	<7.0	7.8–11.1
CFRD without fasting hyperglycaemia	<7.0	≥11.1
CFRD with fasting hyperglycaemia	≥7.0	OGTT not necessary

FBG—fasting plasma glucose before test, 2-h PG—plasma glucose 2 h after ingestion of 1.75 g/kg glucose.

Table 2
Criteria for the diagnosis of CFRD [7]

- 2-h Fasting plasma glucose at ≥11.0 mmol/l during a 75g OGTT
- FPG ≥7.0 mmol/l on two or more occasions
- FPG ≥7.0 mmol/l plus casual glucose level ≥11.0 mmol/l
- Casual glucose levels ≥11.0 mmol/l on two or more occasions with symptoms of diabetes (Table 3)

over time in people with CF. In a 4-year prospective study where glucose tolerance and clinical status were monitored in 84 people with CF, OGTT categories deteriorated in 22% of people, but improved in 18% of people during the study period [5]. Alteration in insulin resistance, due to change in clinical status or drug therapies, may be responsible for variability in OGTT category over time. A single abnormal OGTT therefore reflects abnormal glucose handling and a need for close monitoring, but may not alone determine need for treatment.

6. Treatment of CFRD

The treatment of diabetes in the general population is based on two general principles: first, the immediate need to control symptoms such as polydipsia and polyuria; and second, a long-term requirement to reduce the risk of microvascular and macrovascular complications. In people with CFRD there are additional unique factors to be considered when deciding the optimal therapeutic approach and the time to initiate treatment (Fig. 6).

6.1. When should blood glucose control be initiated in people with CF?

People with CFRD with FH often have symptoms of hyperglycaemia at the time of diagnosis [77], although the diagnosis is frequently made at the time of an intercurrent infection. In this situation the decision to treat, both to relieve symptoms and to prevent complications is relatively straightforward. For people with CFRD without FH or with IGT, it is less clear whether the benefits of glycaemic control outweigh the disadvantages of intervention.

There is some evidence that treatment may benefit people with CF, even before CFRD has developed. Clinical status and pulmonary function decline 2–4 years prior to the diagnosis of CFRD with FH, perhaps due to progressive glucose intolerance. Pre-diabetic pulmonary and clinical decline can be reversed with insulin, suggesting a role for early initiation of therapy as glucose intolerance develops [54,78]. Insulin therapy also reversed decline in lung function and weight loss in four people with long standing CF who had normal glucose tolerance on OGTT, but intermittent abnormal random blood glucose concentrations [79]. Early treatment of diabetes, however, has huge resource implications as treatment would become indicated in around 17% of people with CF who have CFRD without FH and around 11% of people with CF who have IGT [10]. This highlights the need for controlled trials to define the degree of glucose intolerance at which treatment becomes beneficial. In the United States a 1-year randomised, placebo-controlled trial is underway to compare the benefits of insulin, an oral hypoglycaemic agent (repaglinide) and placebo on muscle mass, body weight and lung function in people with CFRD with FH and CFRD without FH. If treatment is found to improve clinical status and lung function in people with CFRD without FH, then similar studies of people with IGT may also be indicated. Until results of such studies are available, treatment is indicated for all people with CFRD with FH but should be determined for people with CFRD without FH and IGT on an individual basis dependent on nutrition, pulmonary function and symptoms (Table 3).

6.2. Type of treatment

6.2.1. Nutrition

The dietary management of CFRD is very different from that of type 1 and type 2 diabetes (Table 4). In type 1 and 2 diabetes calorie control is important to prevent weight gain which may worsen insulin resistance. In CFRD caloric restriction is never appropriate, since malnutrition is associated with stunted growth, pubertal delay, deterioration of lung function and early death. Some, but not all, current dietary recommendations for diabetes mellitus advise the use of low glycaemic index foods [80,81]. However, as many people with CF rely on refined sugary foods as a source of energy, restriction of the use of these foods may impact nutritional status. Therefore in CFRD normalisation of blood glucose should be achieved by balancing insulin requirements with sufficient calorie intake [7]. Dietary recommendations for people with diabetes mellitus encourage a reduction in saturated and polyunsaturated fat and a promotion of monounsaturated fat to reduce atherosclerosis [81]. People with CFRD require a high fat intake to maintain body weight because of malabsorption secondary to exocrine pancreatic insufficiency. No specific recommendations have been made for the type of fat to be eaten by people with CFRD, although a mix would be prudent. To date there have been no reports of people with CFRD developing macrovascular complications of diabetes on this potentially atherogenic diet. However, in time, the recommendations on fat intake may need to be adjusted as a small proportion of people with CF have recently been shown to have hypertriglyceridemia and

Table 3
Symptoms of hyperglycaemia in CF

- Unexplained polyuria or polydipsia
- Failure to gain weight despite nutritional intervention
- Poor growth velocity
- Delayed progression of puberty
- Unexplained chronic decline in pulmonary function

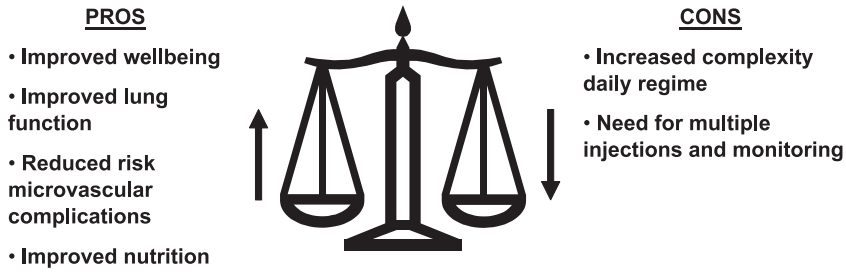

Fig. 6. The advantages and disadvantages of blood glucose control in people with CF.

hypercholesterolemia, suggesting that macrovascular disease could develop as people live longer [75].

6.2.2. Insulin therapy

Insulin deficiency is the primary defect in people with CFRD, therefore insulin therapy is currently the only recommended treatment for this condition [7]. People with CFRD characteristically require very little basal insulin therapy, but need supplemental insulin for meal coverage. The CF Foundation recommends multiple daily injections of short-acting insulin before each meal with a small dose of long-acting insulin at night [7]. Food intake in people with CF is often more uneven than in people with type 1 or type 2 diabetes, with higher proportions of food being eaten later in the day. In addition, people with CF are encouraged to eat snacks, which are often high in kilocalories and may receive overnight supplemental feeding. The use of short-acting insulin provides flexibility required by this diet, allowing the insulin dose to be adjusted to the carbohydrate content of each meal and additional boluses to be given for snacks or night feeds. People with CF and NGT or IGT who develop hyperglycaemia during infective exacerbations may require insulin therapy temporarily to restore glycemic control, which can be withdrawn when the exacerbation is controlled.

Table 4
Comparison between the recommended dietary management type 1/type 2 diabetes and CFRD (adapted from Moran et al. [97])

	Type 1/type 2 diabetes	CFRD
Calories	• Calculated for maintenance, growth or reduction diets	• 120–150% RDA • Calories never restricted
Carbohydrate	• Individualised	• Total intake unrestricted
Fat	• Individualised • <10% calorie intake from saturated fats • Dietary cholesterol intake <300 mg/day	• High fat intake (35–40% of total calories)
Protein	• Protein reduction in presence of diabetic nephropathy (0.8 g/kg)	• Protein reduction may not be appropriate
Sodium	• Salt restriction to reduce macrovascular complications (<2400 mg/day)	• High sodium diet essential (>4000 mg/day)

6.2.3. Oral hypoglycaemic agents

6.2.3.1. Agents that augment insulin release. Sulphonylureas enhance insulin secretion by acting on the sulphonylurea receptor in pancreatic β cells, stimulating insulin release, and therefore may be useful in people with CFRD who have residual β-cell function. A retrospective study compared the clinical outcomes of people with CFRD treated either with a sulphonylurea (glibenclamide) or with insulin [82]. Diabetic treatment was initiated with glibenclamide and the decision to switch to insulin was based on clinical criteria suggesting poor control, e.g. random blood glucose above the recommended range and HbA_{1c} in the diabetic range. At the point of analysis HbA_{1c} and blood glucose concentrations were lower in the sulphonylurea-treated group than in the insulin-treated group and there was no difference in FEV_1, FVC and weight-for-height index between the two groups. This study implies that a subgroup of people with CFRD have residual β-cell function and can benefit from glycaemic control with a sulphonylurea, at least in the short-term, delaying the need for insulin therapy. However, there are theoretical concerns about the use of sulphonylureas, which are able to bind to and inhibit CFTR and could potentially interfere with new therapies designed to improve CFTR function [83,84].

Repaglinide stimulates insulin secretion and has been shown to increase insulin release and reduce glucose concentrations in people with CFRD without FH [85]. In addition, repaglinide has a plasma half-life of 1 h, which reduces the risk of between-meal or nocturnal hypoglycaemia.

6.2.3.2. Agents that reduce insulin resistance. As insulin resistance is not the major aetiological factor in the development of CFRD, drugs which reduce insulin resistance are unlikely to control blood glucose in CFRD when used as a single agent. Metformin, which reduces insulin resistance and may reduce weight gain in type 2 diabetes, is contraindicated in CFRD due to the risk of fatal lactic acidosis in people with hypoxia and the occurrence of gastrointestinal side effects such as abdominal pain, nausea and diarrhea which are unacceptable for most people with CF. Thiazolidinediones reduce peripheral insulin resistance [86] and improve glycaemic control in people with type 2 diabetes [87,88]. However, no studies have been performed

in people with CF to test efficacy and their use is likely to be limited in CFRD.

6.3. Monitoring

All people with CFRD should monitor blood glucose levels at home. Ideally people treated with insulin should measure blood glucose levels at least 3–4 times per day and should be taught to adjust insulin doses accordingly. In people with type 2 diabetes guidelines suggest that plasma glucose should be maintained at 5.0–7.2 mmol L^{-1} fasting and <10 mmol L^{-1} 2 h post prandially to reduce the long-term risk of complications [89]. However, in people with CFRD the goals may vary dependent on clinical status. In some people, such as individuals expected to survive more than 5–10 years from diagnosis, even tighter control may be desirable to minimise the risk of complications, i.e. fasting glucose 4–6 mmol L^{-1} and 2 h post meal glucose 4–7 mmol L^{-1}.

Glycosylated haemoglobin (HbA_{1c}) is the standard method for assessing long-term glycaemic control in diabetes mellitus. Glycosylated haemoglobin levels (HbA_{1C}) reflect blood glucose concentrations over the preceding 2–3 months. In type 1 DM a 1.98 mM increase in mean 24 h plasma glucose is associated with an increase of 1% in HbA_{1c} [90]. This relationship allows clinicians to set day to day plasma glucose goals. In healthy subjects with normal glucose tolerance HbA_{1C} is <6% and in people with diabetes every 1% increase in HbA_{1C} above this level is associated with a 30% increase in the risk of microvascular complications [91]. However, as red cell turnover may be increased in people with CF [7,92], it is not known whether HbA_{1c} is as accurate a measure of glycaemic control in CFRD.

In the outpatient clinic people with CFRD also need to be screened annually for microvascular complications of diabetes. Assessment should include fundoscopy, measurement of urinary albumin concentration and blood pressure and foot examination for peripheral sensory neuropathy.

6.4. Adherence to treatment

People with CF have complex and time consuming daily treatment regimes to manage problems including chronic lung disease, infection, exocrine pancreatic insufficiency and malnutrition. They spend a considerable part of each day taking medications such as oral and/or nebulised antibiotics, pancreatic supplements, nebulised mucolytics agents, and vitamin supplements as well as performing daily physiotherapy treatments [93,94]. A new diagnosis of CFRD adds significantly to the complexity of the daily treatment regimen, as people are required both to monitor and to control blood glucose concentrations.

Poor adherence to therapy is a common problem in people with chronic illness and cystic fibrosis is no exception to this. Adherence of people with CF to physiotherapy, pancreatic supplements and exercise is reported to be 53%, 83% and 46%, respectively [95]. When people were asked their reasons for poor adherence the most consistent answers included busy time schedule, apathy and forgetfulness as well as the commonly expressed beliefs “I am not as serious as others with the disease” and “I feel well without treatment” [95]. People tend to decide which treatments to perform based on their understanding of the effects and priority of each therapy within their own regime [93]. As the duration and complexity of treatments increases, adherence generally decreases [96]. Although no data exists on adherence to diabetic therapy and monitoring in people with CF, it would surprise few clinicians if this were less than ideal.

6.5. Summary

The prevalence of CFRD and glucose intolerance has risen dramatically over the past 20 years as survival has increased for people with cystic fibrosis. However, although understanding of these conditions has increased, there are still difficult areas in the diagnosis and management of CFRD that require further research and development.

Current guidelines are clear that people with CFRD and fasting hyperglycaemia should be identified by random blood glucose levels or oral glucose tolerance testing and treated with insulin to relieve symptoms and prevent complications. It is less clear what should happen for those with CFRD without fasting hyperglycaemia or impaired glucose tolerance. Oral glucose tolerance tests are currently used to look for CFRD without FH and IGT, but these are not performed in all centres and may not reliably predict chronic hyperglycaemia. Where CFRD without FH or IGT are identified, it is not known when benefits of treatment outweigh the burden of management of a second chronic disease and at which point treatment should be initiated. Further studies are required to establish optimum screening methods to identify people with CFRD without FH and IGT and to determine whether early management of hyperglycaemia in these people can prevent pulmonary decline and prolong survival.

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