The diagnosis and management of cystic fibrosis-related diabetes

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Article points

1. As advances in treatment and management improve, the life expectancy of people with cystic fibrosis (CF) and consequently, the prevalence of CF-related diabetes (CFRD) is increasing.
2. Its pathophysiology remains unknown, but CFRD shares characteristics with both type 1 and type 2 diabetes, in that it is associated with both insulin insufficiency and insulin resistance, and it can be exacerbated during acute illness.
3. Screening and diagnosis is difficult, as the common symptoms of diabetes occur in only 33% of people with CFRD. Treatment (ideally with insulin injections) needs to be adapted to match the variable course of the condition and the on-going treatment for CF itself.

Key words

- Cystic fibrosis-related diabetes

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Cystic fibrosis (CF) is the most commonly inherited genetic disorder in the UK, affecting over 10 000 people. Improved treatments, therapies and medication have led to an increase in the mean life expectancy of people with CF and, consequently, the incidence of CF-related diabetes (CFRD), the most common comorbidity of CF. While the pathophysiology of CFRD is still not properly 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 the destruction of beta-cells and insulin deficiency. Detection and diagnosis of CFRD can prove difficult, both biochemically and clinically. Although CFRD has similarities with both type 1 and type 2 diabetes, there are fundamental differences that need to be addressed when screening, diagnosing and managing this complex condition.

Cystic fibrosis (CF) is the most commonly inherited genetic disorder in the UK, affecting over 10 000 people. It is caused by a fault in the CF transmembrane conductance regulator (*CFTR*) gene, which is responsible for regulating the amount of chloride that passes through cell membranes. The defect results in thick, sticky secretions that affect the whole body, including the lungs, digestive system and pancreas.

Improved treatments, therapies and medication have led to an increase in the mean life expectantly of people with CF, which currently stands at around age 41 years (CF Trust, 2014). However, as these individuals have begun living well into adulthood, the complications of the disease have become more apparent. One such complication is CF-related diabetes (CFRD).

The importance of the effective diagnosis and treatment of CFRD has been highlighted, as the condition is associated with worse lung function and poorer nutritional status compared with people with CF but without diabetes (Lanng et al, 1992). CFRD has also been linked to an up to six-fold increase in risk of early death (Rodman et al, 1986).

Pathophysiology of CFRD

The pathophysiology of CFRD is still not properly understood, but the primary cause is thought to be the fatty infiltration of the pancreas, leading to fibrosis and destruction of the pancreatic cells, followed by destruction of the beta-cells and insulin deficiency (Couce et al, 1996). Autopsy findings have demonstrated pancreatic fibrosis and atrophy, with a reduction in islet mass of up to 50% (Couce et al 1996). Progressive beta-cell loss is thought to be the cause of CFRD (Dobson et al, 2004).

In addition, people with CF have delayed insulin secretion following a glucose load compared to normal, matched controls, with an impairment in glucagon release (Holl et al, 1995). However, not all people with pancreatic

insufficiency develop CFRD; therefore, a genetic predisposition might exist (Moran et al, 1999).

Epidemiology

It has been reported that few people with CF have normal glucose metabolism and that CFRD is the most common comorbidity of CF (Moran et al, 2009; 2010).

A common and well-recognised complication, CFRD occurs in around 10–15% of all people with CF, and the prevalence increases significantly with age; 50% of people with CF develop CFRD by 30 years of age (Lanng, 2001). The average age of CFRD onset is 18–21 years, and it has been predicted that 70–90% of all adults with CF will have some degree of glucose intolerance by 40 years of age (Lanng et al, 1995).

The prevalence and incidence of impaired glucose intolerance (IGT) in people with CF is much higher than any other controlled group (Lanng et al, 1991). It is also higher in people with CF who have liver disease (Holstein et al, 2002), and oral corticosteroids may increase the tendency to develop CFRD (Adler et al, 2008).

Similarities and differences between type 1 and type 2 diabetes

CFRD has features of both type 1 and type 2 diabetes; however, its pathophysiology and clinical differences mean that it is treated and managed differently. Oral therapy is not advocated in CFRD; rather, insulin injections are deemed to be the most effective way of treating dysglycaemia (Onady and Stolfi, 2013).

Although unique, CFRD shares characteristics with both type 1 and type 2 diabetes (Moran et al, 1999). Like type 1 diabetes, it is associated with insulin insufficiency. People with CFRD can be young and generally do not have the features associated with type 2 diabetes, such as hypertension and hyperlipidaemia (Moran et al, 2010), and insulin injections are the treatment of choice (CF Trust, 2004). Like type 2 diabetes, CFRD is associated with insulin resistance, has an insidious onset and is rarely associated with diabetic ketoacidosis, as endogenous insulin production still occurs. However, thick viscous secretions surrounding the pancreas can lead to obstruction, inflammation and eventually destruction of the ducts, leading to beta-cell dysfunction and depletion. Several studies have demonstrated a delay in first-phase insulin release, which results in reduced total insulin response over time (Lippe et al, 1977; Moran et al, 1991; De Schepper et al, 1992; Lanng et al, 1993).

Intermittent glucose intolerance/CFRD can occur in CF during illness and with oral corticosteroid use. It is, therefore, not uncommon for people to be commenced on treatment during acute illness and to be taken off following discharge.

Page points

1. Detection and diagnosis of cystic fibrosis-related diabetes (CFRD) can prove difficult both biochemically and clinically. If the diagnosis of CFRD was based on symptoms alone, the majority of people developing the condition would not be recognised.
2. The Cystic Fibrosis Trust produced guidelines for the management of cystic fibrosis-related diabetes, which state that all people with cystic fibrosis require an oral glucose tolerance test annually from the age of 10 years.
3. Continuous glucose monitoring is recommend in people with cystic fibrosis as it shows a glucose trend, with readings every minute, rather than single-point measurements. This enables capture of increased blood glucose levels over a 24-hour period, which reflects the variable nature of cystic fibrosis-related diabetes.

Symptoms, screening and diagnosis

Detection and diagnosis of CFRD can prove difficult, both biochemically and clinically. The usual symptoms of polyuria, polydipsia and weight loss have been reported to occur in only 33% of the CFRD population (Lanng et al, 1995). Therefore, if the diagnosis of CFRD was based on symptoms alone, the majority of people developing the condition would not be recognised. Overall health and clinical status need to be taken into consideration; in particular weight and lung function, which can be the first clinical indications of elevated blood glucose.

The CF Trust (2004) produced guidelines for the management of CFRD, which state that all people with CF require an oral glucose tolerance test (OGTT) annually from the age of 12 years. Historically, the OGTT was the gold standard and was usually carried out if the individual was reasonably well. More recently, however, some concerns have been expressed as to whether or not this is the most effective screening tool for CFRD. Additionally, recent research has shown that a 1-hour OGTT measurement may prove more beneficial than a 2-hour measurement, given the delayed first-phase insulin release that occurs in CFRD (Schmid et al, 2014).

Another method of diagnosing CFRD is to measure HbA_{1c} levels. An elevated HbA_{1c} is suggestive of CFRD but is a late occurrence and people with CF often have spuriously low HbA_{1c} levels (Lanng et al, 1995), meaning that the test is not a reliable tool for diagnosis (O'Riordan et al, 2009). It can be prone to false negatives due to the increased red blood cell turnover that occurs in people with CF (Brennen et al, 2006; Godbout et al, 2008).

Serial glucose monitoring to determine a glucose profile is advocated in association with an OGTT, assessment of clinical condition and/or measurement of HbA_{1c} levels. Blood glucose monitoring, before and 2 hours after meals and at bedtime, should be undertaken to explore the extent of any hyperglycaemia in order to determine therapy (Lanng et al, 1995). For effective serial glucose monitoring to take place, people must be empowered and educated with regard to technique, including timing, hand washing, correct sampling procedures, and meter and strip management. In addition to this, there is the added risk that individuals will report lower glucose readings or fabricate results for fear that they may be diagnosed (Tonyushkina and Nichols, 2009).

Continuous glucose monitoring

Continuous glucose monitoring (CGM) has become more popular in recent years and has been validated in CF (O'Riordan et al, 2009). Hameed et al (2011) highlighted the need for early CFRD diagnosis and treatment, and warned of the detrimental clinical effects if CGM showed blood glucose levels over 7.8 mmol/L for just 4.5% of the time.

The benefit of CGM, as opposed to other diabetes screening methods, is that it shows a glucose trend, with readings every minute, rather than single-point measurements. This enables capture of increased blood glucose levels over a 24-hour period, which reflects the variable nature of CFRD. Experiential evidence has shown that CGM, used with a self-report diet and exercise diary, is a useful diagnostic tool and provides vital information regarding management and insulin choices for people who develop CFRD (Dyce et al, 2012).

Treatment and management of CFRD

The CF Trust (2004) produced recommendations for instigation of treatment for CFRD. Treatment should be considered in the following circumstances:

- When IGT on OGTT is associated with weight loss or deteriorating clinical condition.
- When there are episodes of transient hyperglycaemia.
- When, despite normal glucose monitoring results, diabetic glucose tolerance according to OGTT is associated with weight loss or deteriorating clinical condition.

Definite indications for initiating treatment are as follows:

- CFRD (diabetes according to OGTT and/or regular hyperglycaemia).
- IGT or diabetes in pregnancy.

The treatment of CFRD can prove challenging, with treatment strategies having to constantly change owing to the variability and disease

progression of CF. One consideration is the use of corticosteroids (such as prednisolone), which is used to treat pulmonary exacerbations in CF. Individuals also require more intensive management and treatment during times of infection, when blood glucose levels often rise rapidly. There is evidence to suggest that people with CF and normoglycaemia exhibit diabetic glucose tolerance during pulmonary exacerbations (Sc et al, 2010). This is likely to be a result of the stress of infection and inflammation, which unmasks the early alterations in glucose homeostasis (Zeller et al, 2006). Additionally, when infection subsides and an individual stops corticosteroids, blood glucose levels can dramatically drop, causing hypoglycaemia. Careful management support and advice is required during this time.

Hypoglycaemia is not uncommon in CFRD (Battezzati et al, 2007). Due to the complex nature and pathology of CFRD and global islet cell involvement, it is recognised that impaired pancreatic alpha-cell and polypeptide cell function results in a diminished glucagon response when hypoglycaemia occurs (Moran et al, 1991). Furthermore, it has been demonstrated that hypoglycaemia awareness is impaired as a result of frequent hypoglycaemia and a diminished glucagon response (Drummond et al, 2011).

The prevalence of CFRD is higher in individuals with liver disease, and there is an associated risk of hypoglycaemia due to the reduction of hepatic glycogen stores (Holstein et al, 2002). In addition, impaired hepatic insulin secretion and catabolism may be an added cause for concern.

CFRD has different and conflicting dietary recommendations from those for type 1 or type 2 diabetes. People with CFRD require up to 150% of the energy intake of those with type 1 or type 2 diabetes, involving a high-fat, high-protein diet that enables them to consume a large amount of calories, usually high in sugar, in order to maintain their weight (Ashworth et al, 1999; CF Trust, 2004). People who develop CFRD often have poor nutritional status and rely on refined sugars for energy. The UK dietetic community suggests that regular meals and snacks containing complex carbohydrates and refined carbohydrates be taken with or just after eating other foods (Ashworth and Leonard, 1995).

Insulin therapy, by means of basal or bolus injections, or a combination of both, should be adjusted according to meals and determined by postprandial blood glucose measurements or CGM values.

Role of the CFRD clinic

People are seen in the CFRD clinic for a variety of reasons and are usually reviewed every 2 months as part of their routine CF clinic visit. During this time, they will be seen by the advanced nurse practitioner (ANP) and a specialist dietitian, and they also have access to a clinical psychologist. The CFRD clinic provides an annual screening programme, which is linked to the person's general CF annual screen. All the elements of the diabetes screen are carried out except for retinopathy screening, which is undertaken at the individual's nearest screening centre. Results are then disseminated to the individuals and their GPs.

Separate training and education appointments for patients and family members are carried out with either the ANP or the CF nurse specialist. Due to the risk of cross-infection in CF, patients are not allowed to mix; therefore, education needs to be given on a one-to-one basis, with home visits available for those requiring extra training and education. Patients are contacted and invited to a separate clinic appointment to discuss CGM results. The ANP, specialist dietitian and the individual meet and, using a tripartite approach, a written personal management plan is formulated. Separate inter-professional clinic appointments with the clinical psychologist and ANP are also available for compliance, adherence issues or general advice on coping with a secondary illness.

Conclusion

The CF population is getting older, and the prevalence of CFRD is growing as clinical outcomes improve. It is important that the cause of CFRD is properly understood in order to ensure effective management of this complex condition.

Page points

1. The prevalence of cystic fibrosis- related diabetes (CFRD) is higher in individuals with liver disease, and there is an associated risk of hypoglycaemia due to the reduction of hepatic glycogen stores.
2. CFRD has different and conflicting dietary recommendations from those for type 1 or type 2 diabetes. People with CFRD require up to 150% of the energy intake of those with type 1 or type 2 diabetes, involving a high-fat, high-protein diet that enables them to consume a large amount of calories, usually high in sugar, in order to maintain their weight.
3. Patients are seen in the CFRD clinic for a variety of reasons and are usually reviewed every 2 months as part of their routine CF clinic visit.

"The mechanisms that cause CFRD are being explored, with on-going research into the incretin response and the link with the CFTR gene."

The mechanisms that cause CFRD are being explored, with on-going research into the incretin response and the link with the *CFTR* gene. Clinical trials in America have used animal models to attempt to fully understand the pathophysiology involved in CFRD (Boom et al, 2007). Further studies are also required to determine the effectiveness of oral agents that could potentiate insulin action and may prove clinically advantageous in conjunction with anti-inflammatory agents (Kelly and Moran, 2013). ■

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