Evaluating screening for long-term complications of cystic fibrosis-related diabetes

Paula Dyce and Maureen Wallymahmed

Article points

1. As life expectancy has increased for people with cystic fibrosis (CF), cystic-fibrosis-related diabetes (CFRD) and its inevitable complications are becoming more prevalent.
2. Determinants of CFRD complications include HbA_{1c}, cholesterol level, liver function tests, albumin:creatinine ratio, inspection of injection sites, foot screening and retinal screening.
3. Annual screens for CFRD complications are important, and a formal process should be adopted by all adult CF units in an attempt to improve the care of this growing subgroup of individuals.

Key words

- Complications
- Cystic fibrosis-related diabetes
- Screening programme

Paula Dyce is a Cystic Fibrosis Nurse Specialist and Lead for CFRD based at the Amanda Unit, Liverpool Heart and Chest Hospital; Maureen Wallymahmed is a Diabetes Nurse Consultant, Aintree University NHS Foundation Trust, Liverpool.

Cystic fibrosis-related diabetes (CFRD) differs from type 1 and type 2 diabetes, but has similar characteristics (Moran et al, 2010). As life expectancy has increased for people with cystic fibrosis (CF), CFRD and its inevitable complications are becoming more prevalent. The CF Trust (2004) guidelines suggest that all people with CFRD are screened annually for complications. This article reports on a screening programme for CFRD complications performed at a centre for adults with CF, where 38% of individuals have CFRD. The study demonstrates that annual screening for CFRD complications is important. A formal screening process should be adopted by all centres for adults with CF in an attempt to improve the care of this growing subgroup of people with CFRD.

Cystic fibrosis-related diabetes (CFRD) is different from type 1 and type 2 diabetes, but shares some characteristics of both (Moran et al, 2010). The pathophysiology of CFRD is still not properly understood; however, the primary cause is thought to be the fatty infiltration of the pancreas leading to fibrosis and destruction of the pancreatic cells. This results in the destruction of beta-cells and insulin deficiency (Couce et al, 1996). It is important that people who develop CFRD be treated effectively to avoid declining lung function and reduced longevity (Lanng et al, 1992). As life expectancy has increased for people with cystic fibrosis (CF), CFRD and its inevitable complications are becoming more prevalent. This has prompted the CF Trust (2004) to recommend that all people who have been diagnosed with CFRD are screened annually for diabetic complications. Although screening can be performed in primary care or by a non-CF diabetes clinic, the authors sought to deliver specialised holistic care and to avoid potentially conflicting information given by general diabetes healthcare practitioners. Thus during 2009–10 the authors undertook an in-house CFRD complication screening programme at a large regional adult CF unit.

Individuals with CFRD

Individuals with CFRD sometimes only require intermittent insulin at the time of illness or when treated with corticosteroids. This can prove confusing and problematic

"The measurement of HbA_{1c} in cystic fibrosis-related diabetes is viewed with caution, as it is not the most effective way to diagnose individuals and can be prone to false-negative results because of the increased red cell turnover in individuals with cystic fibrosis."

for both individuals and staff at diagnosis and when screening for long-term complications. In some cases, glucose levels will revert to normal following a pulmonary exacerbation and inpatient stay; therefore, close monitoring is required following discharge.

Diagnosis of CFRD can prove a challenge, and reliance on the observation of symptoms such as polyuria, polydipsia and weight loss may prove to be detrimental, as such symptoms only occur in approximately 33% of individuals with CFRD as a result of the production of endogenous insulin in CF (Lanng et al, 1992). This would mean that most individuals who develop CFRD would not be diagnosed.

Both the UK's CF Trust (2004) and the American Diabetes Association (Moran et al, 2010) guidelines recommend oral glucose tolerance testing (OGTT) to diagnose CFRD. However, OGTT is often labour intensive, difficult for the individuals because of repeated sampling and may prove misleading in CF as the results are based on a single day's testing, which can be performed when the individual is in good health (Dobson et al, 2005). Therefore, the CF Trust guidelines suggest that, in addition to OGTT, individuals should undertake serial glucose monitoring before a diagnosis can be made (CF Trust, 2004).

The measurement of HbA_{1c} in CFRD is viewed with caution, as it is not the most effective way to diagnose individuals (O'Riordan et al, 2008) and can be prone to false-negative results because of the increased red cell turnover in individuals with CF (Brennen et al, 2006; Godbout et al, 2008). Instead, individuals should be provided with a blood glucose monitor to test at home without insulin once steroids have been discontinued. Following this, a definitive diagnosis of CFRD can be made.

Current Driver and Vehicle Licensing Agency (DVLA) guidance stipulates that individuals must declare having CFTD if they have required insulin injections for longer than 3 months (DVLA, 2010).

Background to study

Liverpool Heart and Chest Hospital is a regional centre in the North West of England with approximately 260 individuals with CF; ninety-nine of these individuals require insulin, either continuously or intermittently, and have been diagnosed with having CFRD. The CFRD service is led by a CF nurse specialist trained to degree level in the care and management of diabetes (BA [hons] in specialist practice) as well as having completed a training session relating to foot screening. The other CF nurse specialists as well as the specialist dietitians and pharmacists have also been trained to care for individuals with CFRD in an attempt to deliver specialist holistic care.

Methods

CF nurse specialists were trained to screen for complications of CFRD using a set protocol that included HbA_{1c}, cholesterol level, liver function tests (LFTs), albumin:creatinine ratio (ACR), inspection of injection sites, foot screening and blood pressure. In addition, individuals were asked to attend local retinal screening. Participants who were drivers were asked whether the DVLA had been informed about their use of insulin. Individuals' management of hypoglycaemia and hyperglycaemia were discussed, as was how they were coping with a second medical condition in addition to CF.

Results

A total of 68 individuals (69% of the available population) with CFRD were screened during 2009–10. Some of the other individuals had already had screening at their local GP practices or diabetes centres, but as the results were not available they could not be included in this audit. In addition to this, there were two individuals who had not attended the clinic for over a year.

The 68 individuals with CFRD were aged 17–42 years; 36% were male and 64% were female. Each diabetic complication was audited, and the results were as follows.

HbA_{1c}

There are no specific targets for HbA_{1c} in CFRD; therefore, the standard NICE guidance (NICE, 2002) is followed, with a target level of <58 mmol/mol (<7.5%). The audit found that 12 individuals (18%) had HbA_{1c} levels ≥58 mmol/mol (≥7.5%; *Figure 1*).

Cholesterol

According to NICE (2008), the minimum acceptable standard for total cholesterol is ≤5 mmol/L, with the target for people with diabetes being <4 mmol/L (Joint British Society Guidelines, 2005). Three individuals were identified as having a cholesterol level >5 mmol/L (*Figure 1*), which is surprising as most individuals with CF have fat malabsorption. Figueroa et al (2002) reported that individuals with CF have lower cholesterol levels than normal. As individuals with CF are encouraged to have a high-calorie, high-protein diet and require 150% of the calories a person without CF would require, this complication may need to be addressed in the future, especially as individuals with CF have increasing longevity.

LFTs

It is already known that the liver plays an important role in the regulation of carbohydrate homeostasis, which can affect blood glucose control. In individuals with CF, the liver is an organ that can be affected by the condition, which can lead to cirrhosis. It has also been identified that liver disease can be a risk factor for the development of CFRD (Minicucci et al, 2007); therefore, LFTs have been added to the annual complication screening programme in order to identify individuals who may be predisposed to CFRD or who may prove difficult to control post-diagnosis. In our sample we had a total of 17 individuals (25%) with raised LFTs (*Figure 1*).

Microalbuminuria

It has been debated whether microalbuminuria is an appropriate screening marker for CFRD, as assessed by ACR. Considerations in individuals with CF include having a low muscle mass, resulting in reduced urinary creatinine and elevated urinary albumin, increased urine albumin excretion caused by infection or sepsis, and concurrent renal disease as a result of nephrotoxic use of intravenous antibiotics. CF-related factors, such as a low muscle mass, may result in the ACR being a less sensitive tool for the detection of microalbuminuria (Dobson et al, 2005).

Taking all of these factors into consideration for the audit, a spot urine sample was obtained from participants in the morning for ACR. Eleven individuals (16%) had significant microalbuminurea; five were not screened because of continuous intravenous antibiotic use, as the drugs used are often nephrotoxic and could make the results unreliable.

Lipohypertrophy

At screening, individuals' injection sites were examined, and advice was given regarding rotation of sites and size of needle. Some individuals with CFRD use insulin only intermittently, such as when on steroids or unwell; others are managed effectively on once-daily basal insulin. It is surprising that even with a relatively small sample, six individuals (9%) had developed lipohypertrophy. As individuals with CF live longer, many more may develop this complication.

Foot checks

The CF nurse specialists were trained by a podiatrist to check foot pulses, colour, temperature and detection of any problems, including the use of a microfilament test to assess sensation. Microvascular complications, in particular peripheral neuropathy, have been reported in individuals with CFRD with similar prevalence rates to people with other types of diabetes (Swartzenberg et al, 2007). In this audit there was one individual with existing peripheral neuropathy, who had been diagnosed with CFRD 11 years ago (*Figure 1*).

Page points

1. There are no specific targets for HbA_{1c} in CFRD; therefore, the standard NICE guidance (NICE, 2002) is followed, with a target level of <58 mmol/mol (<7.5%).
2. According to NICE (2008), the minimum acceptable standard for total cholesterol is ≤5 mmol/L, with the target for people with diabetes being <4 mmol/L.
3. In individuals with CF, the liver is an organ that can be affected by the condition, which can lead to cirrhosis. It has also been identified that liver disease can be a risk factor for the development of CFRD.

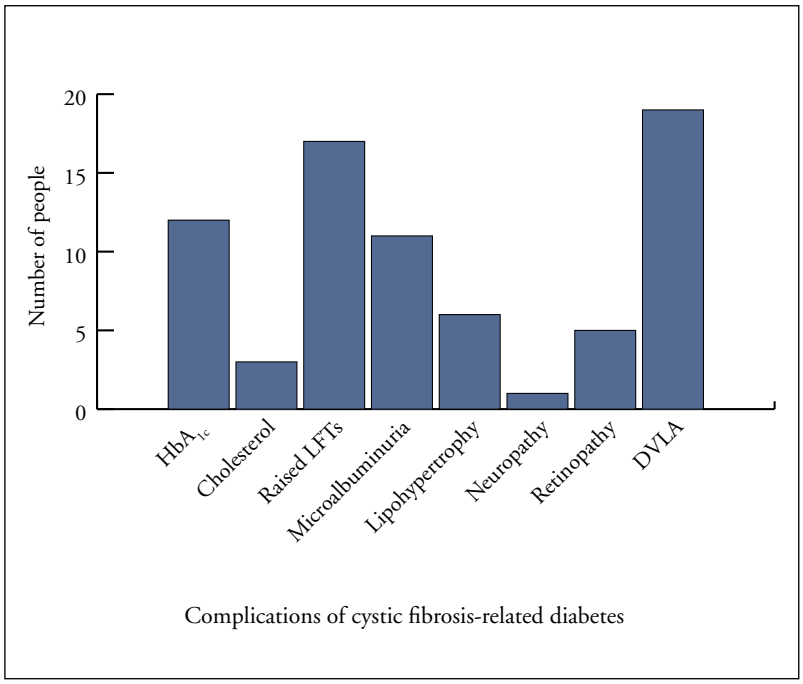

Figure 1. Prevalence of cystic fibrosis-related complications in the audit sample (n=68). DVLA=not declaring insulin requirement to the Driver and Vehicle Licensing Agency; LFTs=liver function tests.

Retinopathy screening

Retinopathy screening could not be carried out during the screening visit as there is no ophthalmology department at the trust. Eye screening was discussed at the annual screen, and a letter was given to the individuals asking them to attend their local retinopathy screening centre. In addition to this, the GPs were sent a copy of the results and asked to check whether the individuals were involved in the retinopathy screening programme.

The results of eye screening were only known for 22 individuals (32%), as results had not been sent to the authors' clinic. Retinopathy was never thought to be a significicant problem for people with CF, because of some protection offered by endogenous insulin production and because these individuals have less hyperlipidemia and hypertension (Moran et al, 2010). Alarmingly, the authors identified five individuals who had developed proliferative retinopathy requiring treatment (*Figure 1*).

Driving

Out of a total of 52 drivers from the sample, 19 (37%) had not informed the DVLA that they required insulin injections (*Figure 1*). On further questioning, individuals who developed CFRD displayed confusion on diagnosis. This was partially because some individuals only require insulin during exacerbation of illness during infection or if prescribed oral steroids.

Psychological issues

CF and its treatment burden can be challenging, and having the extra diagnosis of CFRD can have a huge impact on individuals. Annual screening gives an opportunity to discuss how individuals are coping generally, regardless of the duration of their CFRD. In addition to this, involving a CF clinical psychologist at the diagnosis of CFRD is of paramount importance, providing guidance and support; often individuals have found the extra diagnosis of CFRD overwhelming. At annual screen, individuals are asked how they are coping both physically and mentally with their diabetes and are offered extra support by means of a home visit, psychology input and sometimes a joint appointment with a nurse specialist and psychologist combined. Consideration is given to each individual's lifestyle when determining insulin regimens, thus minimising treatment burden and providing an individualised approach to care.

Conclusion

The prevalence of CFRD is increasing, and this audit has shown a significant number of complications associated with CFRD. These complications are likely to become more prevalent as life expectancy in CF increases. Annual screens for CFRD complications are important, and a formal process should be adopted by all adult CF units in an attempt to improve the care of this growing subgroup of individuals. A structured programme of screening would also give opportunity for individuals to identify difficulties and address issues relating to compliance.

CFRD is sometimes viewed by individuals as unimportant; this could be partly because of the fact that they feel no different whether they administer insulin or not. Some individuals feel that they do not have "proper diabetes", and getting the message across to individuals that they are at risk of diabetes-related complications continues to be challenging. Also, confusion surrounding an absolute diagnosis of CFRD, with some individuals only requiring intermittent use of insulin, can be problematic for both individuals and staff.

A limitation of this audit is that the sample size was small (n=68), and a multi-centred approach may prove more beneficial. However, this audit does demonstrate that CFRD and its related complications are common and may even be more prevalent than first thought. ■

Brennen AL, Gyi KM, Wood DM et al (2006) Relationship between glycosylated haemoglobin and mean plasma glucose concentration in cystic fibrosis. *J Cyst Fibros* **5**: 27–31

Couce M, O'Brian TD, Moran A et al (1996) Diabetes mellitus in cystic fibrosis is characterised by islet amyloidosis. *J Clin Endocrinol Metab* **81**: 1267–72

Cystic Fibrosis Trust (2004) *Guidelines for the Management of Cystic Fibrosis-Related Diabetes.* CF Trust, Bromley, Kent

Dobson L, Stride A, Bingham C et al (2005) Microalbuminuria as a screening tool in cystic fibrosis-related diabetes. *Paediatr Pulmonol* **39**: 103–7

Driver and Vehicle Licensing Agency (2010) *At a Glance Guide to the Current Medical Standards to Drive.* Available at: http://www.dft.gov.uk/dvla/medical/ataglance.aspx (accessed 10.06.12)

Figueroa V, Milla C, Parks EJ et al (2002) Abnormal lipid concentrations in cystic fibrosis. *Am J Clin Nutr* **75**: 1005–11

Godbout A, Hammana I, Potvin S et al (2008) No relationship between mean plasma glucose and glycated haemoglobin in patients with cystic fibrosis-related diabetes. *Diabetes Metab* **34**: 568–73

Joint British Society Guidelines (2005) Guidelines on the prevention of cardiovascular disease in clinical practice. *Heart* **19**: V1–52

Lanng S, Thorsteinsson B, Nerup J, Koch C (1992) Influence of the development of diabetes mellitus on clinical status in patients with cystic fibrosis. *Eur J Paediatr* **151**: 684–7

Minicucci L, Lorini R, Giannattasio A et al (2007) Liver disease as a risk factor for cystic fibrosis-related diabetes development. *Acta Paediatr* **96**: 736–9

Moran A, Becker D, Casella SJ et al (2010) Epidemiology, pathophysiology and prognostic implications of cystic fibrosis-related diabetes. *Diabetes Care* **3**: 2677–83

NICE (2002) *NICE Issues National Guidelines for the Management of Blood Glucose Levels in People with Type 2 Diabetes.* Available at: http://www.nice.org.uk/guidance/index.jsp?action=article&o=29002 (accessed 07.06.12)

NICE (2008) *Lipid Modification: Cardiovascular Risk Assessment and Modification of Blood Lipids for the Primary and Secondary Prevention of Cardiovascular Disease.* Available at: http://www.nice.org.uk/nicemedia/pdf/CG67NICEguideline.pdf (accessed 07.06.12)

O'Riordan SM, Robinson PD, Donaghue KC, Moran A (2008) Management of cystic fibrosis-related diabetes. *Pediatr Diabetes* **9**: 338–44

Swartzenberg SJ, Thomas W, Olsen TW et al (2007) Microvascular complications in cystic fibrosis-related diabetes. *Diabetes Care* **30**: 1056–61