Screening for cystic fibrosis-related diabetes: a systematic review

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Executive summary

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Background

Cystic fibrosis (CF) is caused by a genetic defect. The defective gene has to be inherited from both parents. CF occurs in about 1 in every 2500 births in the UK. The effect is to make some normal bodily fluids much thicker and more viscous than usual, and this affects particularly the lungs and the digestive system. The lungs become prone to infection and subsequent damage, and the main cause of death in cystic fibrosis is respiratory failure.

The pancreas is also affected, particularly the β-cells that produce insulin. Over time, many people with CF develop cystic fibrosis-related diabetes (CFRD) due to insulin deficiency.

Treatment of CF has improved and survival has greatly improved. Over decades, CF has changed from a disease that was normally fatal in childhood, to one in which most patients survive into adulthood. Because survival is now much better, more people with CF live long enough to develop diabetes. About half of people with CF now live to about 40 years of age. It has been estimated that children born in 2000 with CF will, on average, live to reach the age of 50 years.

Patients with CFRD do not live as long as those with CF who do not develop CFRD. The onset of CFRD is insidious, and there may be none of the classical symptoms of diabetes. However, the diabetes may be causing harm, such as promoting colonisation of the lungs with harmful bacteria.

Objectives

The primary objective of this review was to identify the most clinically effective and cost-effective way of screening for CFRD. As the aim of screening would be earlier diagnosis and treatment of CFRD, a secondary objective was to review the evidence on treatment at different stages. However, it became clear that there were problems with the definition of CFRD, and so we examined how CFRD was currently defined and considered alternatives.

We started from the position that insulin treatment was beneficial in CFRD (compared with no treatment) and so the review of treatment focused on two main questions:

1. Are oral glucose-lowering agents useful?
2. Are any treatments beneficial at lesser stages of hyperglycaemia, such as impaired glucose tolerance (IGT), i.e. when should treatment start?

Methods

We carried out systematic reviews of studies of treatment of, and screening tests for, CFRD. We used a highly sensitive search strategy in order to capture all relevant studies, with no restriction on study type or language. We searched MEDLINE, EMBASE, Web of Science, ISI Proceedings, and the Cochrane Central Register of Controlled Trials. Auto-alerts were run in MEDLINE and EMBASE from May 2008 to December 2010. Reference lists of included studies and relevant review articles were scanned. The internet was searched for grey literature, including websites of the Cystic Fibrosis Trust (UK) and similar organisations in other countries. We searched
meeting abstracts of Diabetes UK, American Diabetes Association, European Association for the Study of Diabetes, European Cystic Fibrosis Society, Annual North American Cystic Fibrosis meetings, and International Society for Pediatric and Adolescent Diabetes up to 2010. For research in progress, we searched ClinicalTrials.gov, Controlled-trials.com and the UK Clinical Research Network.

We also searched for studies of the economics of CFRD, including quality-of-life (QoL) studies, with a view to populating a decision tree economic model. We used the software package Simul8 (Simul8 Corporation, Boston, MA, USA) to create a model.

Screening studies were included in the systematic review if they provided sufficient detail for the construction of 2 × 2 tables for calculating sensitivity and specificity. Other studies were included in a narrative section. We looked for results for both CFRD and for the IGT stage.

Results

Diagnosis of cystic fibrosis-related diabetes

The commonest forms of diabetes are type 1 (T1DM, formerly called insulin-dependent diabetes) and type 2 (T2DM, formerly called non-insulin-dependent diabetes). These are defined in terms of the level of blood glucose (BG) above which diabetic eye disease – retinopathy – occurs.

Cystic fibrosis-related diabetes is a distinct type of diabetes, due to a slowly progressive loss of the insulin-producing β-cells in the pancreas.

The organ most at risk in CF is the lung, and as hyperglycaemia has several adverse effects on the lung, our conclusion from review of the literature is that CFRD should be defined according to the level at which lung damage (‘pulmonopathy’) occurs, an early manifestation of which may be weight loss. The lung secretions are usually very low in glucose, but if BG is high there may be more glucose in the lung secretions than usual, and this may promote microbial colonisation at levels well below the diabetes level, perhaps starting around 8 mmol/l. This has implications for choice of screening test, as it suggests that we should be screening for, and intervening at, the IGT stage. It may be that intervention should start earlier, at the stage of postprandial hyperglycaemia (PPH) [i.e. plasma glucose (PG) high at 1 hour but normal by 2 hours after meals or the oral glucose tolerance test (OGTT)].

Treatment

The evidence base on treatment was poor, with few trials. Most evidence came from small case series, usually of short duration.

There were seven studies of oral agents. There was some evidence that sulfonylureas had some effect. One trial used acarbose, but only for 2 weeks, and adverse effects were a problem.

One good-quality (although possibly underpowered) trial compared insulin and the short-acting insulin secretagogue repaglinide. Insulin was more effective in improving body mass index (BMI), with an increase of 0.39 kg/m², compared with a non-significant rise of 0.15 kg/m² in the repaglinide group. There was no difference in the level of glycated haemoglobin (HbA₁).)

There were no trials of the newer agents: the glucagon-like peptide 1 (GLP-1) analogues (exenatide, liraglutide) or the dipeptidyl peptidase 4 (DPP-4) inhibitors (e.g. sitagliptin, vildagliptin). In the case of the GLP-1 analogues, the initial nausea they cause would be undesirable in a group characterised by low BMI.
In summary, oral agents did not appear useful and international guidelines do not support their use. Insulin is the treatment of choice.

The insulin studies were also disappointing, with only one trial comparing different insulins. This trial compared glargine and neutral protamine Hagedorn (NPH) insulins, and found little difference. There were no differences in HbA1c or postprandial BG levels, but fasting PG was slightly lower with glargine (2 mg/dl lower, statistically but not clinically significant), and the glargine group gained 1 kg more in weight than the NPH group (not statistically significant, although with only 19 patients in the study, statistical power was low). The study was not blinded and was funded by the manufacturer of glargine.

Two studies used continuous subcutaneous insulin infusion (CSII), which might be beneficial by providing greater flexibility, but they were uncontrolled case series with small numbers (three and nine subjects).

Most studies of insulin treatment measured outcomes before and after starting insulin.

Five studies examined insulin treatment at the IGT stage, but some had very small numbers (3, 6 and 9 subjects). Two studies (with 54 and 6 subjects) reported that the decline in forced expiratory volume (FEV) was halted or reversed by insulin treatment. One study with 13 patients reported a reduction in pulmonary exacerbations. Two were inconclusive. Only one study was a randomised controlled trial. Most were available only as abstracts, with little detail.

One before-and-after study with only four patients suggested that treatment at the PPH stage might be useful, with improvements in weight ranging from 0.7 kg to 5.7 kg on doses of insulin ranging from 6 to 12 units daily, and also improvements in FEV.

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We used the 75-g OGTT as the reference standard. Most studies reported only the fasting and 2-hour glucose levels. The full OGTT (FOGTT) includes measurements at baseline and at 30, 60, 90 and 120 minutes after an oral glucose load.

Most studies used HbA1c or fasting plasma glucose (FPG). These tests did not appear satisfactory for detecting either CFRD or IGT, because their sensitivity was poor. However, this depended on cut-off levels chosen, and, as expected, higher sensitivity tended to be achieved at the cost of poorer specificity. Sensitivities ranged from 23% to 100% with HbA1c, and from 25% to 70% with FPG. Sensitivity was better when the aim was to detect CFRD rather than both CFRD and IGT.

There were few studies of newer methods, such as continuous glucose monitoring systems (CGMSs) and profiles (a series of BG measurements over the course of the day) but they appeared to be more useful, especially for detecting hyperglycaemia, which occurs more often at certain times of day, such as during the evenings. CGMSs may become the method of choice.

The most sensitive test may be the 1-hour postprandial glucose, but evidence is lacking on the benefits of treatment if that is the only abnormality. This could be measured by two tests: the 50-g glucose challenge test (GCT) or the FOGTT.

There is some evidence that treatment is beneficial at the IGT stage, and we conclude that screening should be for both CFRD and IGT.
Quality of life in cystic fibrosis-related diabetes

There was very little evidence on QoL in CFRD, but more on QoL in CF. The effect of CFRD appeared to be less than the effect of T1DM, but the one study that reported this had a low response rate.

Modelling

We constructed a model with arms for no screening, and for different screening tests, but there were insufficient data to populate it. We have listed the data required. In the no-screening arm, there would be three groups: (1) those who never develop diabetes; (2) those who develop symptomatic diabetes and are treated; and (3) those who develop diabetes but are never diagnosed, who die earlier than they would have done had they been treated.

The most important gap in the evidence concerns the level at which hyperglycaemia in CF should be treated. Other gaps include expected survival in those in the age group that would be screened (probably 10–30 years), and the number of life-years lost owing to CFRD, which could be as much as 11 years.

Conclusions

The evidence base in CFRD is disappointing. There is some evidence that harm to pulmonary function occurs at BG levels below those used for defining other types of diabetes, and perhaps around the 8-mmol/l level, with episodic PPH being harmful to the lung by promoting colonisation and infection.

As diseases should be defined based on the harm they do, CFRD should be defined according to the level at which pulmonary harm occurs, and not by the same thresholds of PG as are used for T1DM and T2DM.

Screening for CFRD is justified, but the case for screening for lesser degrees of hyperglycaemia is less strong.

The highest research priority is for a trial of starting insulin treatment at different stages of hyperglycaemia, starting with PPH, diagnosed by 1-hour glucose challenge, or by CGMSs or serial profiles. Outcomes should include weight and lung function, not just glycaemic control. If our hypothesis is correct, i.e. that transient hyperglycaemia exceeding 8 mmol/l is harmful to the lung, then treatment at the stage of isolated PPH would be beneficial for lung function. Trials should be of adequate duration, of at least several years.

Trials of different insulin regimens are required. These could include a basal insulin, compared with short-acting meal-time insulins alone (especially as in the early stages hyperglycaemia is mainly postprandial) and (perhaps at later stages) CSII. More data are required on the relative merits of NPH, glargine and detemir, particularly in view of the cost differences.

Given the considerable treatment burden associated with CF and CFRD, the impact of different regimens and screening methods needs to be assessed.

More evidence on the relative merits of the 1-hour GCT, CGMSs and serial profiles is required, with the aim being to detect any hyperglycaemia > 8 mmol/l.

In the longer term, we need to find out if pancreatic damage can be prevented and diabetes avoided or delayed.
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**Publication**

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 07/45/05. The contractual start date was in July 2008. The draft report began editorial review in October 2011 and was accepted for publication in February 2012. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors’ report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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