**Diabetic retinopathy in patients who do not meet the diagnostic criteria for cystic fibrosis related diabetes**

**Abstract**

The UK Cystic Fibrosis (CF) Trust guidelines state that the diagnosis of CF related diabetes (CFRD) should only be made after an oral glucose tolerance test in the diabetic range and hyperglycaemia on serial monitoring. We report three patients with CF who were known to have abnormal glucose tolerance but did not meet the diagnostic criteria for CFRD. As the patients were commenced on insulin they were referred for annual diabetic complication screening and all were diagnosed with diabetic retinopathy.

As these patients developed complications without being diagnosed with the causative disease, it questions the current diagnostic criteria for CFRD. This patient group also disproves the hypothesis that CFRD patients without fasting hyperglycaemia do not develop microvascular complications and suggests that, in some patients, such complications may develop earlier than previously thought. Copyright © 2015 John Wiley & Sons.

**Key words**
cystic fibrosis; cystic fibrosis related diabetes; diabetic retinopathy

**Introduction**

The UK Cystic Fibrosis (CF) Trust guidelines (2004) state that the diagnosis of cystic fibrosis related diabetes (CFRD) should only be made after an oral glucose tolerance test (OGTT) in the diabetic range (glucose ≥11.1mmol/L at 2 hours) and hyperglycaemia on serial monitoring. It suggests that a single diabetic OGTT may only indicate a period of abnormal glucose handling and therefore, unless accompanied by unequivocal symptoms of hyperglycaemia, should not be used for CFRD diagnosis in isolation. This is reflected in some patients having an OGTT in the diabetic range that subsequently normalises when repeated. In contrast to the UK guidelines, the United States (US) CF Foundation guidelines (2010) state that during a period of stable baseline health, the diagnosis of CFRD can be made with two positive tests carried out on separate days. These can be a diabetic OGTT, fasting hyperglycaemia (glucose ≥7mmol/L), an HbA1c ≥6.5% or in the presence of classical symptoms of diabetes a random glucose ≥11.1mmol/L. In recognition of the fact that in CF glucose tolerance may fluctuate, the US guidelines define the date of onset of CFRD as the first time a patient meets the diagnostic criteria for CFRD even if their glucose tolerance later returns to normal; this is again different from the UK guidelines.

Patients with CF should be commenced on subcutaneous insulin if they are diagnosed with CFRD or if they have an impaired OGTT (glucose ≥7.8 to <11.1mmol/L at 2 hours) associated with weight loss, clinical deterioration or hyperglycaemia. The UK CF Trust recommends that annual screening for microvascular complications should occur in all patients with CFRD older than 12 years, whereas the US CF Foundation guidelines state that, as microvascular disease does not typically become clinically apparent in CFRD until patients have had the disease for at least five years and have developed fasting hyperglycaemia, screening should only start five years after the diagnosis is made. We report three adult patients with CF (all homozygous Phe508del and pancreatic insufficient) who did not meet the diagnostic criteria for CFRD but required insulin and have...
Case report

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Figure 1. Patient 1. Retinal photograph showing background diabetic retinopathy in the right eye

subsequently been diagnosed with diabetic retinopathy.

Case 1

Before transition to the adult CF unit at 18 years of age, this male had two impaired OGTTs. The first occurred aged 11 (glucose: 4.8mmol/L at 0 hours and 8.8mmol/L at 2 hours) and he was commenced on 6 units of insulin glargine at night due to hyperglycaemia on home monitoring. Insulin was discontinued after 10 months as repeat OGTTs and glucose monitoring returned to normal. While on treatment he started annual screening for diabetic complications; this continued after treatment stopped. Aged 16 years he had a second impaired OGTT (glucose: 5.4mmol/L at 0 hours and 10.4mmol/L at 2 hours) but as home glucose monitoring was normal he was not restarted on insulin. Within 18 months of transitioning to the adult CF unit he had three OGTTs; all of these were normal (glucose: 4.2, 4.7 and 5.9mmol/L at 0 hours and 5.8, 4.0 and 5.7mmol/L at 2 hours). In view of the upward trend for initial fasting glucose, at age 19 years he was monitored with a continuous glucose monitoring system (CGMS). This showed stable but relatively elevated glucose levels overnight (5.0–6.0mmol/L) and between meal-times (5.6–7.0mmol/L); glucose excursions were also seen after some meals. Around the time of the CGMS, his annual eye review revealed microaneurysms in the right eye and background diabetic retinopathy was therefore diagnosed (see Figure 1). In view of the CGMS result and the retinopathy, he was restarted on 6 units of insulin glargine; this was subsequently reduced to 3 units due to recurrent episodes of hypoglycaemia.

Case 2

This female had a CGMS at age 37 years, as her HbA1c results had been steadily increasing (4.9% seven years previously and 6.1% the year of the CGMS). The patient had one previous diabetic OGTT (glucose: 6.8mmol/L at 0 hours and 16.6mmol/L at 2 hours), but this had been performed when the patient was unwell and receiving oral prednisolone. A repeat OGTT undertaken during a period of clinical stability was normal (glucose: 3.1mmol/L at 0 hours and 4.4 at 2 hours). The CGMS showed high glucose excursions (11 to 17mmol/L) immediately post meals (see Figure 2).

In view of the CGMS and HbA1c results, the patient was commenced on 2 units of insulin lispro with meals and booked into an annual screening programme for diabetic complications. On her first eye screening appointment, microaneurysms were seen in both eyes and background diabetic retinopathy was therefore diagnosed. The patient only used the insulin lispro intermittently as it was not successful in controlling the postprandial hyperglycaemia and also caused hypoglycaemic episodes. Due to subsequent concerns regarding weight loss she was changed to 2 units twice daily of biphasic insulin lispro which has given her good diabetic control.

Case 3

At age 28 years, this female had a diabetic OGTT (glucose: 4.9 at 0 hours and 12.1 at 2 hours). A subsequent period of home glucose monitoring was normal but the patient was commenced on 2 units of insulin lispro with large meals due to concerns regarding weight loss. At this time she was booked into an annual screening programme for diabetic complications. She discontinued the insulin therapy after nine months due to multiple hypoglycaemic episodes. A repeat OGTT off insulin showed impaired glucose tolerance (glucose: 5.0mmol/L at 0 hours and 9.2mmol/L at 2 hours). When the patient was 34, a repeat OGTT again showed impaired glucose tolerance (glucose: 5.6mmol/L at 0 hours and 8.6mmol/L at 2 hours) but she was recommenced on insulin as she required a long-term course of oral prednisolone as part of her respiratory CF regimen. During this course of prednisolone, 8 units of isophane insulin was required to control her blood glucose concentrations. She had continued to attend her annual eye screening and during this second period of insulin treatment, preproliferative diabetic retinopathy was diagnosed in her right eye after an area of intraretinal microvascular abnormality was seen (see Figure 3a) and background diabetic retinopathy was diagnosed in her left eye after an area of intraretinal microvascular abnormality was seen (see Figure 3a) and background diabetic retinopathy was diagnosed in her right eye after an area of intraretinal microvascular abnormality was seen (see Figure 3a) and background diabetic retinopathy was diagnosed in her left eye after an area of intraretinal microvascular abnormality was seen (see Figure 3a).

None of the patients have been diagnosed with microalbuminuria or peripheral neuropathy.
Patients can develop diabetic retinopathy despite not fulfilling the UK Cystic Fibrosis Trust diagnostic criteria for cystic fibrosis related diabetes (CFRD). This disproves the hypothesis that CFRD patients without fasting hyperglycaemia do not develop microvascular complications. Microvascular complications of CFRD may develop earlier than previously thought.

Figure 3. Patient 3. Retinal photographs showing: (A) right eye preproliferative diabetic retinopathy with an area of intraretinal microvascular abnormality (white arrow); and (B) left eye background diabetic retinopathy with microaneurysms (white arrow).

Discussion
The diagnosis of diabetes is based on the glycaemic thresholds at which the risk for diabetic retinopathy occurs as determined from population-based studies of people not known to have diabetes. These thresholds have been assumed to be the same in the CF population although no population-based study of retinopathy has been carried out in non-diabetic patients with CF. We report the cases of three patients with CF who have been diagnosed with diabetic retinopathy despite not meeting the UK CF Trust diagnostic criteria for CFRD. Although they did not have a formal diagnosis of CFRD, all three were commenced on insulin (two for an abnormal CGMS result and one for impaired OGTT and treatment with prednisolone). None of the patients had fasting hyperglycaemia. The treatment with insulin led to referral for annual diabetic complication screening and the subsequent diagnosis of diabetic retinopathy. These cases highlight the difference in the CFRD diagnostic criteria between the UK and US and suggest that the current diagnostic criteria for CFRD may not identify all patients with the disease who are at risk of developing complications. It also disproves the hypothesis that CFRD without fasting hyperglycaemia is not associated with microvascular complications and questions the US practice of only referring patients for annual diabetic complication screening five years after a diagnosis of CFRD is made.

We suspect that across the UK there are many patients with abnormal glycaemic control who do not meet the UK CF Trust diagnostic criteria for CFRD. Clinicians may be falsely reassured by the patient not fulfilling the CFRD diagnostic criteria and refrain from prescribing insulin from which the patient is likely to benefit. This paper suggests that a percentage of these patients are at risk of microvascular complications and so annually screening for diabetic complications should be considered. If the UK diagnostic criteria for CFRD were brought into line with the US guidance then a significant proportion of these patients would achieve a diagnosis of CFRD and therefore receive screening for its complications.

CFRD is characterised by qualitative and quantitative deficits in insulin secretion, but not insulin resistance. The explanation for these patients having developed diabetic retinopathy without meeting the criteria for the diagnosis of CFRD is not clear. It is possible that they are caused by postprandial glucose excursions secondary to first-phase insulin loss that is not picked up by GGT. Another possible hypothesis is that the retinas of patients with CF are more sensitive to glucose toxicity than in patients with type 1 diabetes exposed to a matched hyperglycaemic load. More research is needed in this interesting area. The incidence of developing microvascular complications of CFRD increases with poor glycaemia control and increased time since diagnosis, especially when this is more than five years. It is this evidence that supports the US guidance that annual diabetic complication screening should not commence until five years post CFRD diagnosis. These cases question this guidance as diabetic retinopathy has developed in a much shorter time frame. The statement that patients with CFRD without fasting hyperglycaemia do not get microvascular complications is based on a study of 285 patients with CFRD in which none of the 103 patients without fasting hyperglycaemia had retinopathy or microalbuminuria. Again, these cases show that there are exceptions to this statement.

The UK CF Trust guidance on screening and diagnosis is now 11 years old and therefore does not reflect the current best available evidence. This has resulted in a wide variety in practice across the UK with increasing numbers of CF centres using CGMS as a screening tool. Further studies are required to clarify whether this practice is justified. In the meantime, it is reasonable to suggest a low threshold for undertaking a CGMS in patients with CF with any evidence of dysglycaemia.

In summary, we have reported the cases of three patients who have been diagnosed with diabetic retinopathy despite not fulfilling the UK CF Trust diagnostic criteria for CFRD and not having evidence of fasting hyperglycaemia. These diagnostic criteria may need to be reviewed as may the guidance on referring patients for annual screening for diabetic complications.

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References
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References