Official Journal of the Asian Pacific Society of Respirology
Respirology

CLINICAL PRACTICE GUIDELINE

Australian standards of care for cystic fibrosis-related diabetes

PETER G. MIDDLETON,[1] MONICA WAGENAAR,[2] ANGELA G. MATSON,[2] MARIA E. CRAIG,[3] DEBORAH JANE HOLMES-WALKER,[4] TAMARAH KATZ[5] AND SHIHAB HAMEED[5,6]

[1]*CF Centre,* [4]*Department of Endocrinology, Westmead Hospital,* [3]*Sydney Children's Hospital Network (Westmead) ,* [5]*Sydney Children's Hospital Network,* [6]*School of Women's and Children's Health, Faculty of Medicine, University of New South Wales, Sydney, New South Wales, and* [2]*Prince Charles Hospital, Brisbane, Queensland, Australia*

ABSTRACT

Multiple guidelines have been published over the last few years for the diagnosis and management of cystic fibrosis (CF) and cystic fibrosis related diabetes (CFRD), although some of the recommendations are based on extrapolation from other forms of diabetes and/or expert opinions. This document seeks to combine the guidelines to provide an Australian approach to the management of CFRD and establish the guidelines within the Australian CF Standards of Care.

It is intended that this document will provide assistance to doctors, nurses, dietitians, physiotherapists, diabetes educators and CF patients concerning the issues surrounding CFRD, and will be reviewed and updated in 2016.

Key words: cystic fibrosis, diabetes, guidelines, standards of care.

Abbreviations: ADA, American Diabetes Association; BGL, blood glucose level; CF, cystic fibrosis; CFRD, CF-related diabetes; GI, glycaemic index; OGTT, oral glucose tolerance test.

INTRODUCTION

One of the major complications of cystic fibrosis (CF) is CF-related diabetes (CFRD), which increases in incidence with age, from 1–2% below the age of 10 years up to 25% in early adult life and over 50% in those above the age of 40.[1,2] Over the last 40 years, with the ageing of the CF population, the prevalence of recognised CFRD has more than tripled, from <5% in the 1960s to recent reports of >20% in Australia,[3] >10% in Europe (European CF Society Registry data, 2007) and >40% in some other clinics.[4]

Multiple guidelines have been published concerning the diagnosis and management of CFRD, including the American Diabetes Association (ADA)/US Cystic Fibrosis Foundation,[4,5] International Society for Paediatric and Adolescent Diabetes (ISPAD)[6] and the Australasian Diabetes in Pregnancy Society.[7]

In this document, recommendations are referenced to the above guidelines where appropriate, with the level of recommendation as listed in Table 1.

PATHOPHYSIOLOGY

The primary abnormality predisposing to CF-related diabetes (CFRD) appears to be slowly progressive insulin deficiency.[8] Multiple studies have demonstrated impaired first-phase insulin secretion in response to various agents.[9] However, patients with CFRD do not have the same HLA DR3/4 associations that are seen in type 1 diabetes,[10] and rarely develop antibodies to the pancreatic β cell, suggesting that autoimmunity is not a significant pathogenic factor. Furthermore, recent genetic association studies demonstrated that a family history of type 2 diabetes was associated with an increased risk of CFRD.[11] Insulin clearance may also be increased in cystic fibrosis (CF) subjects, whether diabetic or not.[12]

In addition to insulin deficiency, insulin resistance can also be demonstrated in many patients with CFRD. While euglycaemic clamp studies demonstrate normal peripheral muscle insulin sensitivity in non-diabetic CF patients,[12] glycaemic status may be worsened in CF patients by factors, which reduce insulin sensitivity, including growth hormone (especially during adolescence), catecholamines, cortisol and other inflammatory cytokines present during respiratory exacerbations. Malabsorption, liver dysfunction and glucocorticoid therapy may also be involved in the development of CFRD. While most patients with CFRD have had exocrine pancreatic insufficiency for many years, CFRD is found in 5% of pancreatic sufficient patients,[13] so CFRD still needs to be considered in patients with CF who are pancreatic sufficient.

OUTCOMES

The progressive evolution of CFRD may impair pulmonary function and nutritional status for several years before clinical diagnosis. Longitudinal studies

Correspondence: Peter G. Middleton, Ludwig Engel Centre for Respiratory Research, Westmead Millennium Institute, University of Sydney, Westmead, NSW 2145, Australia. Email: peter.middleton@sydney.edu.au

Received 13 September 2013; invited to revise 8 October 2013; revised 28 October 2013; accepted 12 November 2013 (Associate Editor: Claire Wainwright).

Table 1 ADA classification system for level of evidence[5]

	Description
A	Clear evidence from well-conducted, generalizable, randomized, controlled trials that are adequately powered, including • Evidence from a well-conducted multicenter trial • Evidence from a meta-analysis that incorporated quality ratings in the analysis Compelling non-experimental evidence, that is 'all-or-none' rule developed by the Centre for Evidence-Based Medicine at Oxford Supportive evidence from well-conducted, randomized, controlled trials that are adequately powered, including • Evidence from a well-conducted trial at more than one institution • Evidence from a meta-analysis that incorporated quality ratings in the analysis
B	Supportive evidence from well-conducted cohort studies, including • Evidence from a well-conducted prospective cohort study or registry • Evidence from a well-conducted meta-analysis of cohort studies Supportive evidence from a well-conducted case-control study
C	Supportive evidence from poorly controlled or uncontrolled studies, including • Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results • Evidence from observational studies with high potential for bias (such as case series with comparison with historical controls) Conflicting evidence with the weight of evidence supporting the recommendation
E	Expert consensus or clinical experience

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have shown that loss of lung function is more rapid in those with CFRD compared with CF patients who have impaired glucose tolerance or normoglycaemia.[14] Higher blood glucose levels (BGL) may directly affect airway surface liquid glucose, which then promotes the growth of respiratory pathogens such as *Staphylococcus* and *Pseudomonas*.[15]

At a clinical level, uncontrolled CFRD is known to worsen pulmonary function, increase the frequency and severity of chest infections, and result in nutritional decline.[13] Many studies have demonstrated increased morbidity and mortality in CF patients with CFRD,[16] especially in females,[17] although more recently, this gender difference has resolved.[18] Poorer outcomes have also been demonstrated after lung transplant in the presence of CFRD.[19]

SCREENING

As CFRD is often clinically silent until fasting hyperglycaemia develops, routine screening should be performed using the oral glucose tolerance test (OGTT).

• Standard 75 g (1.75 g/kg) 2 h OGTT appears to be the most specific and sensitive tool presently available for screening for CFRD (American Diabetes Association (ADA)-E[5]). At least 150 g of carbohydrate should be ingested daily for 3 days before testing, but this is rarely an issue in the high calorie diet of most CF patients. At present, the current diagnostic criteria are based on 0- and 120-min values only, but the use of intermediate time points (e.g. 30, 60, 90 min) increases the recognition of the peak glucose value.[20]

• As glucose tolerance can be affected by intercurrent illness or corticosteroids, OGTT should be performed, if possible, while the patient is clinically stable, and not taking systemic corticosteroids. However, in patients with recurrent chest infections, it may be difficult to have sufficient time after an 'exacerbation' to perform the OGTT. In those patients requiring long-term corticosteroids, it would be advisable to check an OGTT during a period of stability at the lowest reasonable maintenance dose of oral corticosteroid.

• Elevated fasting BGL (≥ 7.0 mmol/L) may be used to diagnose CFRD, but this is often a late event in the evolution of CFRD and indicates the need for insulin therapy including a basal insulin.

• Following an abnormal OGTT (elevated 2 h values), home blood glucose monitoring should be performed for 2 weeks, including both fasting and 2-h post-prandial responses to higher carbohydrate meals. For lesser degrees of glucose intolerance (e.g. elevated 1 h recording with normal 2 h recording) there is currently neither evidence for, nor against performing home blood glucose monitoring.

• During a pulmonary exacerbation requiring hospitalization or following commencement of systemic corticosteroids, patients with CF should be screened for CFRD by monitoring fasting and 2-h post-prandial BGL using a home blood glucose monitor (ADA-E[5]).

• With commencement of enteral feeds, BGL monitoring is recommended mid-feed and immediately after the feed, during initiation while in hospital and repeated every month while feeds continue (ADA-E[5]). Elevated self-measured BGL should be confirmed in an accredited laboratory. If blood glucose is elevated then the patient should be instructed in home blood glucose monitoring. Continuous glucose monitoring for 72 h appears to offer greater sensitivity than an OGTT,[21] but criteria for diagnosis of CFRD using

continuous glucose monitoring have not been established. Standard OGTT criteria should continue to be used to diagnose CFRD.
• Random BGL may miss post-prandial elevations, so they should not be used to exclude CFRD.
• HbA_{1c} is insensitive for CFRD so is not recommended for screening (ADA-B[5]) but does offer some use in the management of CFRD (see below).

INDICATIONS FOR OGTT TESTING[5]

• OGTT should be performed annually from 10 years of age in all patients who do not have CFRD, or earlier/more frequently if indicated by abnormal test results or unsatisfactory clinical progress (ADA-B[5]). The annual screen may be considered prior to commencing enteral tube feeding.
• Women with CF who are planning a pregnancy or are confirmed pregnant should be screened for pre-existing CFRD using an OGTT if they have not already had a normal OGTT within the last 6 months (ADA-E[5]).
• Testing for gestational diabetes should be performed using an OGTT at both 12–16 and 24–28 weeks gestation with measures at 0, 1 and 2 h (ADA-E[5,7]) using the specific Gestational Diabetes criteria listed below.
• In those with gestational diabetes, repeat OGTT is recommended when clinically stable, approximately 6–12 weeks after the end of the pregnancy (ADA-E[5,7]), although this may need to be deferred on clinical grounds, for example if unwell.
• The annual OGTT may be performed earlier if a patient with CF develops recurrent chest infections or poor nutritional status. However, as glycaemic control worsens during a pulmonary exacerbation,[5] an OGTT should still be performed on resolution of the exacerbation. Clinical expertise is required to determine optimal timing of an OGTT.
• If a patient with CF develops symptoms of hyperglycaemia (polyuria, polydipsia, weight loss), a blood glucose should be performed. If >11.0 mmol/L, then a diagnosis of CFRD is established without need for an OGTT.

CRITERIA FOR DIAGNOSIS OF CFRD

Test results are separated into three groups according to the consensus guideline criteria.[5]
1 CFRD—a 2-h BGL > 11.0 mmol/L. Previously, this was further separated into those with and without fasting hyperglycaemia (CFRD+FH, CFRD-FH respectively). However, as recent data suggest that both CFRD+FH and CFRD-FH benefit from insulin therapy, this distinction is not necessarily helpful.[5] CFRD+FH may indicate longer periods of glucose elevation than CFRD-FH diagnosed on OGTT screening, which may then indicate a greater risk of microvascular complications.
2 Impaired glucose tolerance—a 2-h BGL of 7.8–11.0 mmol/L.
3 Normal glucose tolerance—a fasting BGL ≤ 5.5 mmol/L and 2 h BGL of ≤7.0 mmol/L.
• The majority of patients are diagnosed using the OGTT with BGL before (fasting) and 2 h following a standard oral glucose dose of 1.75 g/kg body weight, maximum 75 g.
• Annual screening OGTT should be performed during a period of stability, generally is the first indicator of CFRD, before clinical symptoms and lung function worsen.
• Elevated BGL may be seen earlier than 2 h,[22] suggesting loss of early phase insulin secretion, a precursor to established diabetes. This is sometimes termed 'indeterminate' glucose tolerance, although the clinical significance of these abnormalities is at present uncertain.
• Both impaired glucose tolerance and CFRD, as diagnosed by OGTT, can be transient findings—many with CFRD at initial testing may have impaired glucose tolerance or even a normal OGTT in subsequent tests, even without pharmacological treatment.[23]

CRITERIA FOR DIAGNOSIS OF GESTATIONAL DIABETES[5,24]

Specific criteria for diagnosis of gestational diabetes should be used.

Currently, the reference values for a positive OGTT in pregnancy are either of the following:
• Fasting glucose ≥5.5 mmol/L, or
• 2-h glucose ≥8.0 mmol/L.

However, it is likely that these criteria, still based on the 75 g OGTT, may be adjusted in the future, with cutoff values for a positive test of: fasting ≥ 5.1 mmol/L, 1 h ≥10.0 mmol/L, 2 h ≥8.5 mmol/L. The impact of these potential new criteria for diagnosis of gestational diabetes in patients with CF has not been studied.

MANAGEMENT

• Patients with CFRD should be seen regularly by a specialized multidisciplinary team with expertise in both diabetes and CF, including ongoing diabetes self-management education from diabetes education programmes that meet national standards (ADA-E,[5] ISPAD guidelines[6]). The team should include an endocrinologist, diabetes educator and dietitian with experience in CF and CFRD.
• Knowledge specific to CFRD is paramount to the education of CF patients who have high energy requirements due to respiratory disease, recurrent infections and the need for exercise regimens.
• Associated factors such as delayed gastric emptying and need for pancreatic enzyme supplements further complicates oral intake and the time course of any glucose elevations.
• Exercise and physiotherapy routines may also need adjustment given their impact on blood glucose absorption and metabolism.

• Patients with CFRD and clinical symptoms or fasting hyperglycaemia should be treated with insulin therapy (ADA-A,[5] ISPAD guidelines[6]). Commencement of insulin is associated with improved lung function, weight gain and reduced frequency of pulmonary exacerbations.[5] Those with asymptomatic elevation of OGTT values who have clinically stable nutrition and lung function may attempt to reduce BGL excursions with exercise and dietary measures (e.g. spreading carbohydrates through the day—see Nutrional Treatment below). However, in the non-obese CFRD patient, calorie restriction is not recommended.
• Oral agents are not as effective as insulin in improving nutritional and metabolic outcomes in CFRD and are not recommended outside the context of clinical research trials (ADA-A[5]).
• During initiation of insulin, BGL monitoring both pre- and post-prandially as well as at bedtime and overnight may help determine dosage requirements.
• Special care should be given to BGL before and after exercise and physiotherapy sessions.
• Patients with CFRD who are on insulin should perform self-monitored blood glucose testing at least three times a day (ADA-E[5]).
• More frequent glucose monitoring is recommended in pregnancy, especially in those with pre-gestational CFRD. Consideration should be given to involvement of a multidisciplinary specialist diabetes—pregnancy service if available.
• Continuous glucose monitoring is under investigation as a potential new measure of prandial glucose control,[21] especially in the more difficult cases of CFRD.
• Once a patient has established CFRD, follow up should be tailored to the severity of the glycaemic abnormalities and the difficulty of treatment.
• Patients should be seen every 2–3 months over the first year, with frequent contact between clinic appointments to discuss glycaemic control.
• Where possible, participation of an endocrinologist in the CF clinic facilitates a coordinated approach from the two teams.

BGL GOALS

• Patients with CFRD should strive to attain plasma glucose goals as per the ADA recommendations for all people with diabetes. However, glycaemic goals may need to be modified for some CF patients, taking into consideration respiratory, nutritional and psychosocial factors (ADA-E[5]).
• Generally BGL goals are
  ◦ 4–7 mmol/L before meals
  ◦ <10 mmol/L 2 h after meals.
• During pregnancy targets are more rigid, aiming for tighter control[7]
  ◦ 4.0–5.5 mmol/L fasting and before meals
  ◦ <8.0 mmol/L at 1 h after meals
  ◦ <7 mmol/L at 2 h after meals.
• Measurement of blood glucose before, during and after enteral feeds should be used to determine insulin requirements for the feed.

Table 2 Outline of different scales for HbA_{1c} values

HbA_{1c} % (old units)	mmol HbA_1c / mol haemoglobin (new units)
5.0	31
5.5	37
6.0	42
6.5	48
7.0	53
8.0	64
9.0	75
10.0	86
11.0	97
12.0	108

• Consideration should be given to using an insulin or combination of insulins with similar profile to that of the meal or the feed, which may involve a rapid or short acting insulin and/or intermediate acting insulin.
• Rapid acting insulin has an onset of action 1–20 min post-injection, peak effect at 1 h and duration of 3–5 h—recommended to inject immediately before eating. Short-acting insulin lowers BGL within half an hour, has peak effect at 2–4 h, and duration 6–8 h—recommended injection half an hour before eating.

HbA_1c—GOALS

• As HbA_{1c} is insensitive for the presence of CFRD, it is not recommended for screening (ADA-B[5]).
• HbA_{1c} measurement is recommended quarterly for patients with established CFRD (ADA-E[5]).
• As HbA_{1c} is often spuriously low in CF patients, the treatment goal for HbA_{1c} in CFRD will often be <7% (53 mmol/mol). Higher or lower goals may be indicated for some patients.
• HbA_{1c} values may not accurately reflect average home blood glucose monitoring in CF patients.[25]

As the units for HbA_{1c} have changed recently from % to mmol HbA_1c/mol haemoglobin, Table 2 outlines the old and new scales.

INSULIN TREATMENT OF CFRD

• Insulin is the only recommended treatment for CFRD (ADA-A[5]). In addition to its role in controlling glycaemia, insulin is a potent anabolic hormone.
• There is little evidence for superiority of any specific insulin regimen, thus clinical judgement should be used to choose the most suited regimen for each individual patient.

Insulin must be given by subcutaneous injection, generally in the abdomen. Pen devices are available with increments in half units (non-disposable) or one unit (disposable and non-disposable types). CFRD patients are often quite insulin sensitive when well, so devices with half unit increments can sometimes be

helpful. Patients need to be reminded to rotate their injection sites to avoid scarring or lipohypertrophy.
• CF patients with minimal subcutaneous fat should use shorter needles (4/6 mm instead of 8/12 mm) to help avoid inadvertent intramuscular injection.
• The doses required for good glycaemic control (maintaining BGL in the 4–8 mmol/L range) depend on individual insulin sensitivity, so stabilization can take many weeks.

With chest infections, diabetic control may worsen considerably, so insulin doses may need to be titrated upward, especially if systemic corticosteroids are required. These doses should be titrated down as the chest infection improves.

HYPOGLYCAEMIA

Hypoglycaemia is a side effect of insulin treatment that occurs with varying frequency in CFRD but can be an issue, especially in relation to exercise and driving. Post-prandial hypoglycaemia is also observed in patients with liver disease.
• Prior to commencing insulin, the CF patient should be educated about hypoglycaemia detection, prevention and treatment. Hypoglycaemia is generally preceded by warning symptoms that allow the patient/carer to intervene early and prevent a severe episode, but warning symptoms can wane over time especially in patients with concurrent liver disease.
• The patient and their carers may benefit from instruction on the use of glucagon for the emergency treatment of severe hypoglycaemia particularly if they reside a long distance from medical centres, require large doses of insulin or have frequent hypoglycaemia.
• Patients with CFRD should be advised to wear a medical alert for diabetes.

A severe hypoglycaemic episode is defined as an episode where the patient required assistance from another person or there was loss of consciousness or a seizure.
• Following a severe hypoglycaemic episode, the cause/precipitant should be considered, and if no clear cause is identified, then review by the endocrinologist is recommended and consideration should be given to reducing insulin dosages for 3–4 days.
• At each CFRD review, careful questioning about the presence and frequency of hypoglycaemic episodes ('hypos') should be undertaken. One to two mild episodes per week is generally acceptable for those with very good control (defined above), but this needs to be determined on an individual basis.
• Modified control goals should be considered for those with
  ◦ Loss of warning symptoms for hypoglycaemic episodes
  ◦ Living alone
  ◦ Physical/cognitive impairment

Less severe hypoglycaemia (i.e. not requiring assistance from another individual) may occur in CF patients with or without CFRD. It can occur in the fasting state (which may reflect malnutrition, liver disease and/or increased energy needs due to inflammation and infection). Post-prandial reactive hypoglycaemia is common and likely relates to delayed and disordered insulin secretion.[5]

NUTRITIONAL TREATMENT

There are currently no randomized controlled trials of dietary intervention in CFRD, so recommendations for nutritional management of CFRD are based on cohort studies and current clinical practice reported in clinical consensus guidelines.

These consensus guidelines tend to reflect national practice that varies from country to country.[1] Any conflicts between dietary therapy of CF (e.g. high calorie) and diabetes mellitus should generally be resolved in favour of the high calorie, carbohydrate-rich diet. The two however are not mutually exclusive, and it is possible to maintain calories with carbohydrate intake by increasing intake of low glycaemic index (GI) carbohydrate and reducing high GI foods (e.g. soft drinks). If glycaemic control is suboptimal despite appropriate insulin dose adjustment, distributing carbohydrate evenly throughout the day may help optimize blood glucose control without any compromise to total caloric intake. In a mixed meal, high GI foods paired with lower GI foods give a 'medium' GI response.
• It is advisable to teach patients the composition and portion size of different carbohydrates. Carbohydrates should be included in most snacks and all meals to avoid severe hypoglycaemia in those patients requiring insulin.
• Consumption of refined sugars needs to be individualized and depends on the individual's energy requirements, dietary preferences, knowledge of insulin to carbohydrate ratio and adjustment for other factors such as exercise.
• Where it is necessary to include sweet foods and beverages in order to meet energy requirements, it is advisable to consume these as part of a meal or substantial snack to minimize any rapid rise in blood glucose. The inclusion of these high GI foods (e.g. lollies and soft drinks) needs to be individualized.
• The use of an individually determined insulin to carbohydrate ratio together with carbohydrate counting or estimations to guide insulin therapy can help to optimize glycaemic control, even when the diet includes refined sugars (ADA-E[5]).

Different dietary recommendations may be necessary for those patients using only short-acting insulin compared with those using long-acting insulins or other combinations. The emphasis on low GI foods with a low energy density and greater bulk needs to be balanced with the need for overall caloric intake.

SPECIFIC ISSUES RELATED TO CFRD

Exercise and Physiotherapy

Prolonged, moderate intensity exercise tends to lower BGL, and this effect can continue for several hours after the exercise is completed. Usual measures to help prevent exercise-induced hypoglycaemia

include taking extra carbohydrate before or during exercise, and should be guided by BGL measured at appropriate times. High intensity exercise (e.g. sprints) can increase adrenaline and cortisol sufficiently to increase BGL during/after exercise, but may be complicated by delayed hypoglycaemia, so care is required.
• Patients with CFRD should be advised to do moderate aerobic exercise for at least 150 min per week (ADA-E[5]).
• Physiotherapy (without concomitant exercise) has not been assessed for its overall effect on blood glucose control.

Pulmonary Exacerbations

During pulmonary exacerbations hyperglycaemia may occur because of the increased counter-regulatory hormones. However, reduced oral intake during illness may result in reduced BGL. A reduction in exercise when feeling unwell at the start of an exacerbation may also influence glycaemic control. For these reasons, BGL monitoring should be increased during exacerbations.
• It is recommended that during hospital admission for pulmonary exacerbations, BGL are measured fasting and 2 h post-prandially for the first 48 h (ADA-E[5]).

Corticosteroid Effects

Corticosteroid (or glucocorticoid) treatment is generally given in the morning and will typically cause a rise in BGL during the afternoon and evening. Insulin regimens that will assist in managing this effect include intermediate insulin given at the same time as the corticosteroid, or a short-acting insulin given at lunchtime and/or dinner. Individualization is necessary for optimal patient management. The glycaemic effect of corticosteroids will vary between individual patients.
• Following commencement of systemic corticosteroids, patients with CF should be screened for CFRD by monitoring fasting and 2 h post-prandial BGL (ADA-E[5]).

Transplantation

Almost all CF patients undergoing transplantation will require insulin postoperatively as the immunosuppressive regimen often contains glucocorticoids. Overall, the treatment goals and interventions are similar to patients who have not undergone transplantation.
• CF patients not known to have diabetes who are being reviewed for transplantation should be screened preoperatively by OGTT if they have not had CFRD screening in the last 6 months.
• Plasma glucose levels should be monitored closely in the perioperative critical care period and until hospital discharge. Screening guidelines for patients who do not meet diagnostic criteria for CFRD at the time of hospital discharge are the same as for other CF patients (ADA-E[5]).

Driving

• CFRD patients taking insulin should be educated about the need to test BGL before driving, aiming to ensure that their BGL is >5 mmol/L before the start of their drive.
• Fast-acting carbohydrates should be carried at all times to treat any hypoglycaemia.

In Australia, insulin-treated diabetes patients (whether CFRD or not) must seek medical review with their endocrinologist every 1–2 years, especially for education concerning driving and review of driving licence status. Patients need to be informed of their requirement to notify the driving licence issuing board in their state about their diagnosis of diabetes treated with insulin.

Travel

Advice for patients with CFRD wishing to travel overseas should include information concerning safe handling of insulin on airplanes, carriage and storage of insulin and adjustment of insulin doses when crossing time zones. Appropriate travel letters should cover the insulin type/device/dosage as well as the need to carry blood glucose testing kits.

Pregnancy

Many CF patients will require insulin during the pregnancy to maintain the tight BGL goals listed above.
• Women with pre-existing CFRD should have pre-pregnancy counselling and planning to aim for optimal glycaemic control before and throughout pregnancy to minimize adverse pregnancy outcomes.
• Women with normal glucose tolerance pre-pregnancy should still be advised that they may develop glucose intolerance later in the pregnancy, and that repeat OGTT should be performed at both 12–16 and 24–28 weeks gestation with measures at 0, 1 and 2 h (ADA-E[5,7]) using the specific gestational diabetes criteria listed above.
• Plasma glucose levels should be monitored closely in the peri-partum period and until hospital discharge.
• Patients should be reminded to repeat the OGTT 6–12 weeks after the end of the pregnancy (ADA-E[5,7]), provided they have returned to previous baseline level of health.

Psychological Effects

The onset and diagnosis of diabetes in patients with CF represents the development of a second chronic disease with its own burden of monitoring and treatment. This often has significant physical and psychological implications for the patient and their family/carer.
• Appropriate psychosocial support should be available to assist with the psychological aspects of the diagnosis of CFRD and the requirement for treatment.

COMPLICATIONS OF CFRD

Microvascular complications are now being recognized in patients with CFRD. The prevalence increases with time, reaching more than 10% in those

with CFRD and fasting hyperglycaemia for more than 10 years.[26] Although some authors have found the incidence to be less than that of the non-CF diabetic population,[5] others have found it to be similar.[27] Gastroparesis is common in CF patients and may further complicate diabetic control.

- Annual screening for microvascular complications is recommended, commencing 5 years after the diagnosis of CFRD or when fasting hyperglycaemia is first diagnosed (ADA-E[5]).
- Screening for nephropathy usually involves a spot or random urine albumin to creatinine ratio; a positive result should be confirmed by three morning urine albumin to creatinine ratio measurements or a timed (overnight) urine (for measurement of albumin excretion rate) during a period of relative stability.
- Management of nephropathy generally includes consideration of angiotensin-converting-enzyme inhibitors or angiotensin-II antagonists, although these have not been proven to be beneficial in CFRD with nephropathy at present. Referral to a nephrologist may be indicated.

Annual screening for the following complications should be performed:

- Screening for retinopathy with dilated fundoscopy by an ophthalmologist or optometrist.
- Screening for peripheral neuropathy, for example vibration, proprioception.
- Hypertension, although uncommon in CF, should be screened as blood pressure control is critical to the prevention of diabetes-related complications.
- An annual fasting lipid profile is recommended for those CFRD patients with pancreatic sufficiency or if other risk factors are present, for example obesity, family history of coronary artery disease or immunosuppressive therapy following transplantations (ADA-E[5]).

CONCLUSIONS

CFRD represents an important and increasingly common complication of CF, especially with increasing age.

As epidemiological studies show increased morbidity and mortality in patients with CFRD, it is important that the whole CF team always considers CFRD in arranging annual review testing in those over the age of 10 years. Any patient with a deteriorating clinical condition, recurrent chest infections or poor nutritional status, should have CFRD considered, even if the OGTT was normal within the last 12 months. Treatment with insulin and dietary interventions can improve lung function and weight and lessen pulmonary exacerbations. Long-term diabetes-related complications, especially microvascular changes, are now increasingly being recognized, emphasizing the need for early recognition and appropriate management of CFRD.

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