Cystic Fibrosis Trust

Management of cystic fibrosis diabetes

Second edition

November 2022

Uniting for a life unlimited

The UK Cystic Fibrosis Trust Diabetes Working Group

Chair

Paula Dyce, Advanced Nurse Practitioner for CF and Related Diabetes, Liverpool Heart and Chest Hospital

Members

Claire Berry, Specialist Paediatric CF Dietitian, Alder Hey Children's Hospital, Liverpool

Dr Jennifer Beynon, Consultant, Wythenshawe Hospital Manchester NHS Foundation Trust

Dr Nicola Bridges, Paediatric Endocrinologist, Chelsea & Westminster Hospital, London

Dr Thomas Clarke, Principal Clinical Psychologist and Clinical Psychology lead for Blackpool Teaching Hospitals Adult Cystic Fibrosis Service

Dr Sarah Collins, CF Specialist Dietitian, Royal Brompton and Harefield NHS Foundation Trust

Katie Dick, Clinical Nurse Specialist in Children's Cystic Fibrosis, Royal Brompton and Harefield NHS Foundation Trust

Orla Holmes, CF Specialist Nurse, Belfast City Hospital

Professor Daniel Peckham, Professor of Respiratory Medicine, University of Leeds and Honorary Consultant, St James's University Hospital, Leeds

Alison Murray, Paediatric Diabetes Specialist Nurse, South Tees Hospitals NHS Foundation Trust

Sejal Pandya, Specialist CF Dietitian, Liverpool Heart and Chest Hospital

Jennifer Still, Adult CF Specialist Dietitian, NHS Grampian

Harbinder Sunsoa, Cystic Fibrosis Diabetes Nurse Specialist, University Hospitals Birmingham (UHB), NHS Foundation Trust

Cystic Fibrosis Trust

Management of cystic fibrosis diabetes

Report of the UK Cystic Fibrosis Diabetes Working Group

Contents

Glossary

AGP	Ambulatory glucose profiling. Algorithms are used to smooth continuous glucose sensor data. The result shows lines and shaded areas that represent median glucose values and percentiles. The shaded area between highest and lowest percentiles represents 90% of glucose readings at any given time in the day. This is used to pick up patterns.
BGM	Blood glucose monitoring
BMI	Body mass index
CBG	Capillary blood glucose
CFD	Cystic fibrosis diabetes
CGM	Continuous glucose monitoring
CSII	Continuous subcutaneous insulin infusion
DPP-4	Dipeptidyl peptidase-4. An enzyme that can degrade incretins such as GLP-1. DPP-4 inhibitors work by blocking the action of DPP-4.
GI	Glycaemic index
GLP-1	Glucagon-like peptide-1 is a peptide hormone that enhances the secretion of insulin. GLP-1 analogues or receptor agonists work by increasing the levels of hormones called incretins. They are also known as 'incretin mimetics'.
Glucose exposure	The cumulative amount of glucose that the body has been exposed to at a given time since midnight. Often calculated at different thresholds (e.g., below 4mmol/L or above 10mmol/L) and presented as Area Under the Curve (AUC).
Glucose ranges	The percentage of blood glucose data within, above, or below the target range.
Glucose variability	Describing the swings (the highs and lows) in blood glucose levels over a specified time period.
HbA1c	Glycosylated haemoglobin
IGT	Impaired glucose tolerance
MDT	Multidisciplinary team
NGT	Normal glucose tolerance
NICE	National Institute for Health and Care Excellence
OGTT	Oral glucose tolerance test
PERT	Pancreatic enzyme replacement therapy
Postprandial	Occurring after a meal
WHO	World Health Organization

Grading scheme for recommendations

GRADE is a system developed by an international working group for rating the quality of evidence across outcomes in systematic reviews and guidelines; it can also be used to grade the strength of recommendations in guidelines. The system is designed for reviews and guidelines that examine alternative management strategies or interventions, and these may include no intervention or current best management. The key difference from other assessment systems is that GRADE rates the quality of evidence for a particular outcome across studies and does not rate the quality of individual studies.

In order to apply GRADE, the evidence must clearly specify the relevant setting, population, intervention, comparator(s) and outcomes.

Before starting an evidence review, the guidelines development group should apply an initial rating to the importance of outcomes, in order to identify which outcomes of interest are both 'critical' to decision-making and 'important' to patients. This rating should be confirmed or, if absolutely necessary, revised after completing the evidence review. Box 1 summarises the GRADE approach to rating the quality of evidence.

Box 1

The GRADE approach to assessing the quality of evidence for intervention studies

In the GRADE system, the following features are assessed for the evidence found for each 'critical' and each 'important' outcome from a systematic review:

- study limitations (risk of bias): assessing the 'internal validity' of the evidence
- inconsistency: assessing heterogeneity or variability in the estimates of treatment effect across studies
- indirectness: assessing the degree of differences between the population, intervention, comparator for the intervention and outcome of interest
- imprecision (random error): assessing the extent to which confidence in the effect estimate is adequate to support a particular decision
- publication bias: assessing the degree of selective publication of studies.

Other considerations (for observational studies only):

- effect size
- effect of all plausible confounding
- evidence of a dose–response relationship.

The quality of evidence is classified as high, moderate, low or very low (see next page for definitions).

Quality of Evidence Grades	
Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

The working group would like to thank the Cystic Fibrosis Trust and cystic fibrosis (CF) Centres around the UK for their feedback and support for this document.

Although consensus has been challenging in certain areas, our aim is to provide a comprehensive guideline for clinicians to use effectively and acknowledge the differences and similarities amongst centres.

The aim of this document is to facilitate individualised care including screening, diagnosis, and management and to address the management of long-term complications as they become more prevalent as the CF population ages.

Foreword

In these guidelines we present a consensus about the screening and management of diabetes in cystic fibrosis (CF). **There have been significant changes since the previous Cystic Fibrosis Trust guidelines were produced in 2004:**

- Increased awareness and the introduction of regular screening have resulted in increased prevalence of diabetes in individuals with CF.
- There are more data to confirm the adverse effect of abnormal glucose on clinical status in CF and to confirm that treatment can improve this.
- Better continuous glucose monitoring (CGM) technology is available and there has been a move to use this in screening and management.
- Developments in CF care and treatment have resulted in improved life expectancy and better quality of life so reducing the risk of long-term microvascular complications of diabetes has become more important.

These guidelines summarise the current clinical approach to CF diabetes (CFD). The group recognises that there is a limited evidence base to support some areas of practice.

The description and definition of cystic fibrosis diabetes

Since the late 1990s the term cystic fibrosis-related diabetes (CFRD) has been used to describe diabetes in people with CF. Prior to this it was referred to as 'diabetes of cystic fibrosis' or 'cystic fibrosis diabetes mellitus'. As a guideline committee we propose that a new name is warranted. We feel that the term 'related' does not indicate a direct causal relationship between CF and diabetes and this removes emphasis from the significant impact of diabetes on the lives of people with CF. We have therefore adopted the term cystic fibrosis diabetes (CFD) to stress the direct causal relationship between CF and diabetes. This term is also in line with names given to other types of diabetes e.g., type 1 diabetes, type 2 diabetes, gestational diabetes.

In current clinical practice, individuals who do not fulfil the World Health Organization (WHO) criteria for diabetes are being treated. Most CF centres would label them as having CFD and many publications on the subject do the same. It seems reasonable that anyone who is on established medical treatment for abnormal glucose levels is identified as having CFD, since trying to create different classifications would cause confusion.

1. Introduction

Cystic fibrosis diabetes (CFD) is a common complication of CF. The condition is associated with increased morbidity, mortality and a faster decline in lung function.[1–4] Earlier detection and greater awareness of CFD combined with improved life expectancy has resulted in an increased prevalence of CFD across all ages.[5] Glycaemic abnormalities are common in CF and can be present very early in life.[6, 7] Glucose tolerance and insulin resistance can often vary, being influenced by factors such as nutritional status, infection, corticosteroid therapy and liver dysfunction.[6, 7] Pro-active and effective screening of CFD have played a major role in improving survival in people with CF.[5]

CF diabetes is a distinct type of diabetes but shares certain clinical features of both type 1 and type 2 diabetes. Onset is often insidious with many individuals being asymptomatic at diagnosis. In others the first sign may be a decline in weight and lung function, with reactive hypoglycaemia not unusual.[8, 9]

Difficulties may arise in the diagnosis of CFD when the clinical status or treatment of an individual alters their glycaemic status, so that an individual who has overt diabetes during an infective pulmonary exacerbation may return to normal glucose tolerance (NGT) weeks or months later.[10] Screening for postprandial hyperglycaemia and CFD is particularly important with corticosteroid therapy and commencement of enteral tube feeding.

People with CFD very rarely develop ketoacidosis although some may coincidentally have type 1 diabetes also.[11–13] With improved nutrition and modulator therapies, obesity in CF is becoming increasingly recognised and type 2 diabetes may need to be considered in some individuals.

1.1 Epidemiology

CF diabetes is a common and well recognised complication of CF.[14–18] The incidence and prevalence of glucose intolerance and diabetes in CF is much higher than age matched control groups and increases with age and severity of genotype. Median age of diagnosis is presently around 21 years, but this may change with improved health outcomes and the introduction of cystic fibrosis transmembrane conductance regulator (CFTR) modulators.[19, 20] It is usually associated with pancreatic exocrine dysfunction but may occur in people with CF who are pancreatic sufficient, especially after pancreatitis.[5, 21, 22] Around 32% of adults with CF develop CFD, with prevalence increasing to as high as 50% in those over 30.[5, 21, 23] According to the UK CF Registry Annual Data Report 2021, 29.8% of people with CF are receiving treatment for CFD; 8.3% in children aged 10 to 15 years and 35.2% in adults.[24] The European Epidemiologic Registry of Cystic Fibrosis previously reported diabetes in 1.5%, 5%, 12.6% and 23.6% of people with CF aged less than 10, 10–14, 15–19 and over 30, respectively.[25] More recent data since the advent of screening suggests a higher prevalence, with CFD being reported in 2% of children, 19% of adolescents, 40% of adults in their 20s, and around 50% of those 30 and above.[5, 26] CF diabetes appears to present at a younger age in females[27] which is probably a reflection of their earlier onset of puberty and the associated increase in insulin resistance at this time. CF diabetes is very rare in young children but has been reported.[7, 28]

1.2 Pathophysiology

CF diabetes develops as a consequence of pancreatic pathology and occurs infrequently in people with CF who are pancreatic sufficient. In the pancreas there is progressive fibrosis and fatty infiltration, resulting in exocrine pancreas damage, reduced islet density and altered cellular composition. Structural abnormalities in islets are also present in young children.[6] CF diabetes is characterised by insulin and glucagon deficiency, fluctuating insulin resistance and immune infiltration with increased islet IL-1ß immunoreactivity.[29–31] In the newborn ferret model of CF, there is a loss of ß-cells, but the pancreatic structure is relatively normal. Within the first month of life, there is progressive exocrine and endocrine pancreatic loss with local inflammation and glucose intolerance.[31] Despite the relative absence of pancreatic disease, early abnormalities in the regulation of insulin secretion have been identified. There is diminished first phase and accentuated peak insulin secretion in response to glucose, elevated peak glucose levels following glucose challenge, and variably elevated insulin and C-peptide levels.[31] Impaired ß-cell secretory capacity and defective early-phase insulin secretion is seen in people with CF who are pancreatic insufficient with elevated 1-hour oral glucose tolerance test (OGTT) glucose.[32]

In vitro studies have demonstrated a direct link between impaired insulin secretion and loss of CFTR function in human and animal models. In mice, the addition of the CFTR corrector lumacaftor (VX-809) successfully rescues the

defects in F508del ß-cells.[33] This link between CFTR function and ß-cell insulin secretion provides a novel target for CFTR modulator therapy. The recent introductions of CFTR modulators which target CFTR dysfunction in CF have anecdotally resulted in reduced insulin requirement and reversal of CFD in some people. Large long-term studies are needed to characterise the true benefits of such therapy.[19, 34, 35]

1.3 Impact of CF diabetes on clinical status

A diagnosis of CFD is associated with increased mortality compared to individuals without CFD.[4, 22, 36] Studies have demonstrated a relationship between the development of CFD and poor nutritional status, and lung function with a more rapid decline occurring in individuals with impaired insulin secretion prior to diagnosis.[37–40]

Glucose tolerance declines gradually over the years before a diagnosis of CFD and this can be accompanied by deteriorating clinical status with a fall in lung function and weight for up to five years before diagnosis.[2, 37, 38, 41–43] Individuals with impaired glucose tolerance (IGT) on OGTT have worse clinical status compared to those with NGT.[44, 45] Studies have demonstrated that relatively subtle changes in glucose levels on CGM or during OGTT have correlated with markers of clinical status.[46–48]

This historical data is unlikely to reflect the future natural history of CFD in an era of CFTR modulators.[49–51] These medications can dramatically improve clinical stability, increase nutrition status, reduce pulmonary exacerbations and downregulate both local and systemic inflammation.[49–51] Our understanding of CFD in this post-CFTR modulator era will continue to evolve and future diagnostic and treatment regimens will need to reflect these changes.

2. Screening for CF diabetes

2.1 Why screen for CF diabetes?

There is clear evidence that early identification and treatment of CFD has a positive impact on health status. Delaying diagnosis and treatment of CFD can result in an unnecessary deterioration in lung function, weight and clinical status. Screening should start from age 10 years and be repeated annually, or sooner if clinically indicated. Several studies have also shown that in unscreened CF populations, long-standing deterioration in glucose tolerance and an insidious decline in clinical status frequently occur prior to the diagnosis of CFD.[2, 37, 38, 41, 42] People with CF who develop overt symptoms of hyperglycaemia on presentation have been found to have a relatively greater decline in lung function and weight loss as compared to those identified on screening.[38]

Early and effective treatment of CFD is essential to avoid microvascular complications. Identification of glucose intolerance is important to identify those individuals at high risk of developing a decline in lung function, a fall in nutritional status or a new diagnosis of CFD. Retinopathy (16–36%), nephropathy (14–21%) and neuropathy (42–55%) are being reported more frequently in people with CFD.[52–55] To date macrovascular complications have not been reported.[18, 56, 57]

2.2 Evidence of benefit from treatment of CF diabetes

Clinical improvement and reversal of decline in lung function tests have been documented when CFD is treated with insulin.[14, 58–60] Screening and early treatment of CFD has been shown to reduce (but not abolish) the relative increased mortality risk for individuals with CFD compared to those without.[22]

A few small studies of insulin treatment show benefit for individuals with IGT and abnormalities of glucose handling which do not meet the criteria for CFD. Larger studies are needed and currently there are limited data to guide when to start treatment.[58, 59, 61–63]

2.3 Difficulties in diagnosing CF diabetes

Glucose handling can change with clinical status of someone with CF, and blood glucose levels can fluctuate. Some people with CF only need intermittent CFD treatment. CF diabetes has a characteristic pattern of glucose abnormality unlike type 1 or type 2 diabetes. In CFD, insulin secretion following carbohydrate intake is reduced and delayed, resulting in postprandial hyperglycaemia, while basal insulin secretion is retained. This means that in CFD, fasting glucose levels can be normal while glucose levels later in the day are elevated. In CFD there is a gradual loss of insulin secretion with time and eventually fasting glucose levels rise.

The WHO has specified criteria for the diagnosis of diabetes based on symptomatic hyperglycaemia accompanied by measurement of fasting glucose, random glucose levels, and glucose levels 120 minutes after an OGTT or HbA1c measurement. These criteria provide a cut-off level for starting treatment in order to prevent long-term microvascular complications of diabetes such as retinopathy, and apply mainly to type 2 diabetes.

While these definitions apply to CFD, both screening and treatment are approached differently in CF.

- The aims of treatment of CFD are to improve nutritional status and lung function, as well as to prevent secondary complications.
- There is likely to be a different cut-off for treatment for CFD compared to type 2 diabetes.
- The introduction of CFTR modulators is likely to change the natural history of CFD, alter glucose tolerance and potentially increase the prevalence of type 2 diabetes as the proportion of people with CF who are overweight increases.
- Where 120-minute glucose levels are normal or impaired after OGTT, glucose levels can be over 11.1mmol/L if glucose is measured at 30, 60 or 90 minutes during the test.
- In OGTT screening, a 1-hour plasma glucose level above 11.1mmol/L can make a person up to 10 times more likely to develop CFD.[18, 64]

2.4 Methods for screening

The OGTT or CGM are suitable methods for routine screening for CFD, and as discussed below some other methods (such as HbA1c and fasting glucose) are not suitable as screening methods, although they may provide information to guide management.[65]

Screening	Pros	Cons
OGTT	• Standardised protocol • Not influenced by diet or activity • Results linked to historical long-term clinical outcome data	• Eight hours fasting is required • Time-consuming • Fluctuation between normal, impaired and diabetic OGTT with clinical status • Requires serial capillary blood glucose (CBG) or CGM to confirm elevations in glucose levels and support diagnosis
CGM	• Detects subtle glucose abnormalities • Detects postprandial hyperglycaemia • Correlates well with glucose measured at OGTT • Does not require fasting • Measures glucose levels throughout the whole day during normal activity and food intake	• Measures interstitial fluid and not CBG • Time-consuming; need for return of sensors / readers • Can fluctuate with clinical status • High cost of sensors and equipment • Absence of clinically validated cut-off levels for commencing treatment • Requires concurrent food diary
Fasting glucose	• Single blood sample	• Fasting hyperglycaemia absent in many adults with CFD
HbA1c	• Single blood sample • Abnormal HbA1c should trigger screening for CFD	• No data about cut-off levels • Normal HbA1c is often present at the time of diagnosis of CFD

2.4.1 Oral glucose tolerance test

The OGTT with a 75g glucose dose is established as the gold standard for screening for type 2 diabetes and is used to screen for CFD.[18, 66, 67] The results of the OGTT have been linked to long-term clinical outcome data.[18]

The OGTT should be undertaken after eight hours fasting; plasma glucose level should be measured at one and two hours. Blood glucose testing at intermediate times (30, 60, 90 minutes) may provide more information and show elevated glucose levels even if the level at 120 minutes is within normal limits.

The OGTT has the advantage of being a test with a standardised protocol, and unlike CGM is not influenced by diet or activity at the time of the test. However, fasting for the test can be difficult if individuals live a long distance from their CF centre and the test becomes more invasive if intermediate samples are taken.

2.4.2 Continuous glucose monitoring

CGM is now used widely in the screening and monitoring of CFD. CGM measures the glucose in interstitial fluid and not CBG, but there is good correlation between the two and CGM has been demonstrated to correlate well with glucose measured at OGTT in CF.[68]

CGM is a tool to detect abnormal glucose levels and can demonstrate relatively subtle glucose abnormalities and postprandial hyperglycaemia before the development of an abnormal OGTT.[8, 69, 70]

CGM does not require fasting and has the potential of measuring glucose levels through the whole day while the individual is at home with normal diet and activity. As with OGTT, measurements can fluctuate with clinical status and CGM measurements made on an individual day can be influenced by diet and activity. Practical disadvantages include the problem of returning the equipment for downloading and the high cost of the sensors and supportive equipment.

CGM does provide the opportunity to look at glucose trends rather than individual blood glucose levels. There is ongoing research in both the general diabetes and CFD populations to try and establish how to analyse and interpret the CGM data (e.g., time above glucose of 7.8mmol/L, interquartile range, single episodes above glucose of 11.0mmol/L).

However, as yet there are no clinically validated cut-off levels for commencing treatment after CGM and CF centres using CGM should look at clinical markers as well as glucose levels on CGM before commencing treatment.

2.4.3 Fasting plasma glucose

Fasting glucose measurements will not reliably identify CFD. In CFD there is a typical pattern of postprandial hyperglycaemia, and fasting glucose can remain normal while glucose levels after meals or later in the day are significantly over 11.1mmol/L. Only 16 to 25% of people with CFD would be identified according to the WHO definition using this method, as many adults with CFD do not have fasting hyperglycaemia.[27, 71]

2.4.4 HbA1c and fructosamine

HbA1c should not be used to screen for CFD as there are no data about cut-off levels for diagnosis and the measurement can be influenced by clinical factors (including red cell half-life). HbA1c can be of value in monitoring treatment and should be checked regularly for everyone on treatment for CFD. HbA1c should not be recommended as a screening test.[47, 72–75] However, an abnormal HbA1c should immediately trigger additional monitoring of glucose levels. A recent small study by Lam et al reported a significant correlation between fructosamine and 2-hour OGTT in people undergoing CFD screening.[67]

2.5 Assessment after screening test

Further investigations may be needed after a screening test to determine whether treatment is needed.

The following issues need to be considered when assessing the results of screening:

- Screening results can fluctuate with clinical status e.g., infection and steroids.
- OGTT done with only baseline and 120-minute measurements can confirm a diagnosis of diabetes by standard criteria but may miss significant hyperglycaemia. Intermediate samples at 30, 60 and 90 minutes may be helpful.
- An OGTT which meets the criteria for diabetes needs to be followed up with glucose monitoring (with serial CBG measurements or CGM) to identify hyperglycaemia before insulin is started.
- CGM or serial CBG levels should be considered if there are concerns about clinical status and:
  - glucose at 120 minutes on OGTT which fits with a diagnosis of IGT
  - glucose during OGTT at 30, 60 or 90 minutes over 11.1mmol/L.
- CGM needs to be used for a sufficient time and people with CF are encouraged to continue with their usual food intake and activity for the duration of the test.
- If a CGM shows significantly abnormal glucose levels, consideration should be given to whether food intake, activity or clinical status could have influenced the result and a repeat considered.

Glucose handling can fluctuate, so an OGTT result which meets the clinical criteria for diabetes may revert to normal or IGT with changes in clinical status. The finding of IGT is common and may progress to a diabetic OGTT or, in 58% of cases, revert to normal; but an impaired OGTT implies a higher risk for developing CFD than an individual with NGT. The risk is related to an increased glucose area under the curve during OGTT and deterioration in glucose tolerance over time.[74]

2.6 Summary

- Everyone with CF should have yearly screening for CFD from the age of 10 years.
- A variety of tools exist to identify abnormal glucose including OGTT (ideally with intermediate sampling), CGM and serial blood glucose monitoring (BGM).
- Children under 10 years should be screened for CFD if there is concern about weight or height gain, decline in lung function or any symptoms of hyperglycaemia.
- CFTR modulator therapy is likely to influence glucose tolerance and future screening will need to reflect these changes.
- Individual CF centres should decide on the most appropriate screening tools to ensure effective early diagnosis of CFD.

3. Criteria to start treatment in CF diabetes and abnormal glucose levels

The aim is to treat people with CF to prevent elevated glucose levels which may be detrimental to clinical status. This group may include individuals who do not fulfil the WHO clinical criteria for a diagnosis of diabetes. Separate criteria are used for the diagnosis of gestational diabetes — see section 6.

The decision to treat should be made with an assessment of glucose levels together with clinical status. After an abnormal screening test further assessment is needed before deciding to treat. This should include assessment of diet and clinical status as well as additional assessment of glucose status such as CGM or CBG monitoring. Treatment should be considered if there are concerns about clinical status in individuals with IGT or significant abnormalities on additional monitoring. This is current clinical practice in most CF centres. Treating individuals with IGT remains a controversial area because of limited data to support management, and studies are ongoing which may add information.

The decision to treat must be made by a clinician experienced in managing CFD in conjunction with the CF team and the person with CF.

Classification of OGTT and CGM results are helpful in recording the outcome of screening tests but are not evidence-based and do not provide a defined cut-off for treatment.[8, 76, 77]

Good practice points

- All treatment should be individualised taking into account clinical and nutritional status.
- Any individual who fits diagnostic criteria for CFD after investigation should be treated unless there are overwhelming clinical reasons not to.
- Early treatment can be considered in individuals where there are concerns about clinical status (e.g., weight loss, decline in lung function, increased infective episodes, poor growth in children) if CGM or serial CBG levels confirm subtle glucose abnormalities, although this is not enough to justify a diagnosis of CFD.
- Individuals with optimal nutritional status and good lung function may not need treatment for minor abnormalities of glucose handling and dietary interventions may be appropriate.
- Glucose levels and the results of screening tests can change with clinical status and in some clinical situations repeat testing at an interval is needed to confirm if treatment is needed.
- Treatment can be influenced by corticosteroid use, enteral feeding, transplant, pulmonary exacerbations, CFTR modulators and changing clinical status.

3.1 Treatment strategies for CF diabetes

The aims of treatment are to:

- prevent of long-term microvascular and macrovascular complications. Individuals with CFD are at risk of diabetes complications and it is likely that improved control of CFD will reduce this risk as in other forms of diabetes. This is becoming more important as individuals with CF have increasing life expectancy with improved care and the use of CFTR modulators
- reduce the impact of hyperglycaemia on lung function and clinical status. This aim is unique to CFD
- avoid symptoms of hyperglycaemia and acute metabolic complications
- minimise risk of hypoglycaemia. Individuals with CF have the same risks of hypoglycaemia, and/or loss of hypoglycaemia awareness as other forms of diabetes
- optimise nutritional status.

3.2 Treatment agents

Insulin is currently the primary treatment in CFD. With the development of newer diabetes therapies and advancement in our knowledge of the pathophysiology underlying CFD we may be able to make better use of non-insulin therapies in future. This may involve taking a more complex approach to diabetes management with a combination of dietary interventions, insulin and oral medication to better target the numerous parts of the glucose-insulin pathway.

3.2.1 Diet

See section 5.

3.2.2 Insulin

Published data includes a range of different insulin treatment strategies including different types of long- and short-acting insulin, and the use of continuous subcutaneous insulin infusion (CSII). There are no studies comparing these and the choice of treatment regimen depends on the stage of the disease, risks and specific treatment goals for each individual. It should also be remembered that the anabolic effect of insulin can prove advantageous beyond the glycaemic effects.

Insulin regimens

a. Once-daily long-acting insulin given before breakfast may be an appropriate strategy for glucose abnormalities without a significant postprandial rise. Mozzillo et al demonstrated improved FEV_1 and BMI, and a decrease in the number of infective exacerbations following one year of daily insulin glargine.[60] Hameed et al demonstrated improved FEV_1 and BMI following treatment with once-daily insulin detemir.[76]

b. Pre-meal short-acting insulin is often used because it addresses the most common glucose abnormality in CFD, postprandial hyperglycaemia.

c. Multiple dose regimens should be used for individuals with fasting hyperglycaemia as they are likely to need both long- and short-acting insulin.

CSII and insulin pumps should be considered for people with CFD who have suboptimal blood glucose control (see **NICE guidance TA151**). They are being used increasingly in regional CF centres, are well tolerated and can result in significant improvement in diabetic control.[77] To be used effectively and improve glycaemic control, the user needs to be familiar with counting carbohydrates and have an understanding of how different types of carbohydrates are absorbed, particularly with the gastrointestinal issues that can affect people with CF. Keeping a detailed food diary may help with tailoring insulin to food intake. This needs to be done with the support of a multidisciplinary team (MDT) who are experts in the use of insulin pumps and can provide the intensive education and monitoring that is required at the start of such treatment.

3.2.3 Other diabetes agents

Clinical practice guidelines continue to support insulin as the first line therapy for CFD, however there is increasing interest in the use of oral antidiabetic agents.[78] The Cochrane Database review in 2016 analysed 22 trials which compared long-acting insulin, short-acting insulin and repaglinide.[79] This review did not find any evidence that insulin or repaglinide have an advantage over each other in controlling hyperglycaemia or clinical outcomes.

Previously, older oral antidiabetic agents, such as metformin and sulphonylureas, have been trialled, but we now understand far more about the mechanisms underlying the pathophysiology of CFD and this is opening up the possibility of many more treatment options in this area. The recently published trial for GLP-1 has shown an improvement in glycaemic control by delaying gastric emptying rather than directly influencing insulin release.[80] We do understand that the pathways involved in glucose control are complex and involve more than just the pancreas and it is this knowledge that enables us to now look at drugs other than insulin to manage this metabolic dysregulation.

The current CFTR modulator therapies have yet to be proven to improve diabetes management but there is the possibility that when used early in the disease they may prevent the development of CFD. We await further research in this field.[81–83]

There is also evidence that sufficient pancreatic enzyme replacement therapy (PERT) supplementation can aid in the management of postprandial hyperglycaemia.[84, 85] See section 5.

Moreover, clinicians are beginning to see a group of people with CFD who are maintaining a healthy weight, or in fact becoming overweight or obese. It is therefore worthwhile considering whether some individuals are in fact insulin resistant and developing more of a type 2 diabetes condition, thereby requiring treatment with agents such as metformin to manage their systemic insulin resistance as well as or instead of their possible insulin deficiency.[86]

Real-world data has demonstrated the safety of the newer antidiabetic agents over a few years, but large randomised controlled trials are needed to evaluate their impact on long-term outcomes in CF.[87, 88] DPP4, GLP1, biguanides, and alpha glucose inhibitors are all options for treatment either instead of or alongside insulin and should be managed by an experienced diabetes team. They may have an important role in the future treatment of CFD.

4. Management of CF diabetes

All people with CFD should receive appropriate assessment, education, advice, treatment, and psychosocial support. Explanation of the diagnosis should be given. People with CFD should be informed of relevant issues with regards to self-management and screening for complications.

The onset and diagnosis of diabetes in people with CF represents the development of a second chronic disease with its own burden of monitoring and treatment. This often has significant physical and important psychological implications for many individuals. Following the diagnosis of CFD appropriate psychosocial support should be available. The medical team needs to allow the individual a period of adjustment where CFD control may be erratic whilst they adjust and adapt to the new treatment challenges. This highlights the need for individualised assessment of the person with CFD (and their family) and the need for personalised treatment plans which progress at an appropriate rate.

Good practice points

- Insulin is currently the primary treatment for CFD, and the role of other antidiabetic agents is under review.
- Individuals starting on insulin should have education aimed at supporting self-management of their diabetes including BGM and insulin injection techniques.
- Anyone starting on insulin should have an individualised treatment plan which takes into account other aspects of their CF care.
- In all individuals with CFD, treatment must aim to eradicate symptoms of hyperglycaemia and maintain adequate nutrition, growth and respiratory function.
- All people with CFD should aim for optimal control of diabetes to reduce the chances of long-term complications.
- Treatment adjustments may be required during pulmonary exacerbations, corticosteroid therapy or enteral tube feeding.

4.1 Treatment targets in CF diabetes

There are no defined glycaemic targets for CFD, however tighter diabetes control has been shown to correlate with reduced pulmonary exacerbations and decreased mortality risk.[89, 90] The aim is to maintain blood glucose within the most normal range possible to keep HbA1c as normal as possible unless it causes problematic hypoglycaemia.

NICE guidance recommends glucose testing in type 1 diabetes at least four times a day for adults and at least five times a day for children. **They give targets for tight control of type 1 diabetes (these are the same for adults [NG17 2015] and children [NG18 2018]):**

- To aim for a target HbA1c level of 48mmol/mol (6.5%) or lower, to minimise the risk of long-term vascular complications.
- To have:
  - a fasting plasma glucose level of 5–7mmol/L on waking and
  - a plasma glucose level of 4–7mmol/L before meals at other times of the day.
- To have a plasma glucose of 5–9mmol/L after meals.
- NICE guidance suggests tighter criteria for glucose management during pregnancy. See section 6.

People with CFD commonly have postprandial hyperglycaemia accompanied by normal pre-meal glucose levels; consequently, they should be encouraged to regularly check two hours after meals.

Targets for glucose levels and glycaemic control should be assessed on an individual basis. CF is a multisystem disorder, and some individuals are on complex treatment regimens addressing different complications of their CF. Diabetes management must be assessed together with other medical treatments and clinical status, and for some individuals more relaxed targets are needed.

4.2 Management of reactive hypoglycaemia

Reactive hypoglycaemia is relatively common in individuals with CF who are not treated for CFD, typically occurring after intake of sources of high refined carbohydrates.[9, 91] Glucose levels can fall below 4.0mmol/L and result in symptomatic hypoglycaemia. It is not clear whether reactive hypoglycaemia indicates an increased risk of developing CFD.[92, 93] Individuals with reactive symptomatic hypoglycaemia after meals may benefit from dietary adjustment. A reduction in refined carbohydrates taken in isolation and regular meals containing complex carbohydrates may help. If the hypoglycaemia is frequent or troublesome consideration should be given to treatment with insulin which will usually resolve the hypoglycaemia.

4.3 Capillary blood glucose monitoring

NICE guidance suggests that children and young people with type 1 diabetes should be supported to undertake CBG monitoring at least five times a day. Recommendations for adults suggest a minimum of four times a day and up to 10 times a day under circumstances where increased monitoring is required, which includes if HbA1c targets are not met or if there is a legal requirement to do so (such as before driving, in line with the Driver and Vehicle Licensing Agency [DVLA.]).
The same guidelines should apply in CFD, but:

- everyone with CF on insulin should be testing regularly as a routine
- the frequency and timing (fasting, postprandial) of CBG testing should be discussed with clinical teams
- individuals on basal insulin regimens (such as once-daily injections) and low doses may not need to monitor CBG as often.

Poor diabetes control can have a significant impact on clinical status in CF and increased CBG testing and adjustment to try and achieve optimum diabetes control may be needed.

In the following situations people with CF and CFD should monitor their blood glucose status more frequently [high]:

- Before and at the time of solid organ transplantation.
- When there are concerns about deterioration in nutritional status.
- If there are pulmonary exacerbations.
- Starting or adjusting a dose of corticosteroid treatment.
- Commencing enteral tube feeding.
- During pre-conception planning and during pregnancy.
- After starting CFTR modulator therapy.

All hospitals admitting people with CFD should have a local policy covering glucose monitoring, diabetes and insulin self-management.

- Blood glucose should be measured on admission for all people with CF [high].
- Glucose should be monitored for 48 hours if inpatients with CF are commenced on corticosteroid treatment [high].

Ward staff should have regular training in diabetes and insulin management.

4.4 Alternative methods of glucose measurement

Flash glucose monitoring has been approved for funding via NHS England for people being treated for CFD with insulin. Specific issues such as disabling hypoglycaemia may necessitate the use of alarmed continuous monitoring systems, but this should be dealt with by a specialist diabetes team. It is likely that an increasing range of new technologies will become available over the next few years.

These continuous methods of glucose measurement are now leading to standardised ambulatory glucose profiling or AGP. These present a two-week period of data in an easily understood format that clinicians managing people with CFD will need to become familiar with. See glossary.

4.5 Management of children and adolescents with CF diabetes

While CFD increases in prevalence with age it has been reported in young children and infants.[7] Children under 10 years should be screened for CFD if there is concern about weight or height gain, decline in lung function or any symptom of hyperglycaemia. Studies have shown that diabetes has an impact on lung function and nutrition in adolescents and in addition there are studies demonstrating an impact on growth.[42, 94, 95]

Glycaemic targets in children are the same as for adults; the following should be considered:

- Developmental stage has an impact on understanding diabetes and ability to self-care.
- Realistic plans for care in school should be drawn up and added to the healthcare plan for the child.
- Diabetes care is an essential part of transition to adult CF and diabetic services.

4.6 Adjustment of treatment during infection or corticosteroid treatment

Glucose levels can rise during infection and some individuals with NGT can have glucose levels in the range for diabetes during infectious pulmonary exacerbations. Insulin doses should be adjusted if already on insulin treatment. For those not on insulin already, treatment during the episode should be considered if high glucose levels are symptomatic or likely to be having an impact on clinical status. Corticosteroid treatment increases insulin resistance and insulin doses may need to be increased during treatment and reviewed once steroid doses are decreased.

5. Dietary/nutritional treatment

Nutritional status and weight are important in predicting mortality; good nutritional status is associated with positive outcomes.[96] The importance of diet in CF is well established and guidance on dietary management is available.[97] The primary aim in the nutritional management of CFD is to achieve optimal blood glucose control whilst ensuring nutritional requirements are met. At present there are no randomised intervention studies looking at nutritional management of CFD or impaired OGTT, therefore current guidelines tend to be based on consensus reviews and clinical experience.

The main treatments of CFD are insulin therapy and dietary modification. Insulin regimens should be tailored to individual requirements taking into account nutritional and clinical status, dietary intake and psychosocial factors. With the increasing prevalence of overweight and obesity and the use of CFTR modulators in the CF population, dietary modification is a key component of CFD treatment. The quantity and timing of high-refined carbohydrates will need to be modified to optimise blood glucose control. Nutritional status will need to be closely monitored and individualised dietary advice provided to prevent nutritional decline or overnutrition. Close liaison between the specialist CF dietitian, the CF team and the diabetes team is important in the management of CFD to ensure coordination of care.

Dietary modifications and the use of oral antidiabetic agents may be preferential in people with CF at risk of developing type 2 diabetes.

Good practice points

- An experienced specialist CF dietitian should advise the individual on an individualised dietary plan.
- CFD treatment should be individualised, taking into account nutritional and clinical status, dietary intake and psychosocial factors.
- Dietary modification is an essential part of CFD management to prevent nutritional decline and overnutrition.

5.1 Fat

A high-fat diet in the nutritional management of CF is well established.[97] However, with improvements in nutritional status not all people with CF require a high-fat diet to meet their nutritional requirements. Dietary fats are the most concentrated source of energy; people with CFD who are overweight or obese will therefore be advised on reducing their dietary fat intake. Concerns have emerged regarding the potential risks of a high-fat diet impacting cardiovascular health and of long-chain polyunsaturated fatty acids on inflammation.[98–100] Polyunsaturated and monounsaturated fat sources are considered to be healthier and of better quality than saturated fat.[101] These types of fats are preferential as they are likely to be beneficial in CF.[102]

Fat does not directly impact blood glucose levels but can change the rate of glucose absorption.[103] As most people with CF are pancreatic insufficient, they require PERT to help absorb nutrients. There is increasing evidence that optimising PERT treatment is potentially beneficial in management of CFD. Partially digested fats have an important role in reducing gastric emptying. Optimisation of PERT dosing will improve fat lipolysis and therefore slow down the absorption of carbohydrate from a meal.[85] Digestion of fats also restores proper gastric emptying and increases incretin production.[104] It is important to continue to review an individual's PERT use with all meals, blood glucose excursions, CFD treatment and overall diet.

Good practice points

- Quality and quantity of fat should be tailored depending on age, nutritional and clinical status.
- Encourage appropriate use of PERT and regularly review dosing.

5.2 Protein

With the increasing use of CGM in the monitoring of glucose abnormalities there is more evidence of the effect of protein intake on glycaemic control, particularly in type 1 diabetes.[105] Guidelines advise that people with CF should get 20% of their total energy from protein.[106] People with CFD are currently not advised to restrict protein intake and extra insulin is not routinely recommended to cover large protein intakes. However, there is very little evidence supporting advice for protein intake in CF or CFD. Given factors such as the inflammatory disease state and impaired digestibility of protein in CF there is a need for evidence-based recommendations for optimal protein intake.[96]

A systematic review of macronutrient intake and glycaemic index (GI) on postprandial control in type 1 diabetes showed variable results in the

effect of protein on postprandial glycaemia. All studies showed postprandial glycaemia was modified by the addition of protein with an additive effect of fat and glucose.[103] Larger amounts of protein in a meal (>75g) showed an effect on blood glucose concentration late (>3 hours) in the postprandial period. Meals containing at least 30g of carbohydrate and at least 40g of protein were found to require an increase of insulin dose by 15–20%.[105] There are no similar studies in people with CFD but, with increasing evidence for need to manipulate insulin doses depending on protein content of meals alongside carbohydrate and fat in type 1 diabetes, it should be considered in individuals with CFD requiring large doses of insulin.

Good practice points

- If an individual with CFD has a large protein intake (>75g) as part of a meal, insulin dosing adjustment may be required as there may be a delay in postprandial peak in blood glucose levels.

5.3 Carbohydrates

Carbohydrates are the macronutrients that provide the body with its main source of energy. They are divided into two groups: sugars and starches. Sugars, also known as simple carbohydrates, are digested and broken down into glucose quickly and therefore cause a rapid rise in blood glucose levels. Whereas starches, also known as complex carbohydrates, are digested and broken down into glucose much more slowly and therefore cause a slow rise in blood glucose levels.

When managing CFD, it is important to consider both the type and quantity of carbohydrates eaten. Regular meals containing complex carbohydrates are recommended. Close attention should be paid to the quantity and timing of simple carbohydrates. Foods and drinks high in refined carbohydrates have very little nutritional values, and their intake should be restricted in overweight and obese individuals with CFD. In individuals who are underweight or normal weight sources of high refined carbohydrates such as drinks and sweets should be avoided between meals; if they are required then they should be only consumed at mealtimes.[107]

The use of carbohydrate counting in people with CFD is becoming more common, particularly in those on insulin pumps, although it is not currently part of routine CFD management within the UK. Carbohydrate counting and insulin dose adjustment has been shown to result in more dietary freedom in people with type 1 diabetes;[108] such work does not currently exist in the management of CFD with only a few conference abstracts exploring carbohydrate counting.[109–111] Individuals who do not wish to or are unable to carbohydrate count should be encouraged to become more carbohydrate aware.

5.4 Glycaemic index

Glycaemic index (GI) is the term used to describe the effects of different foods upon blood glucose levels. It indicates if a food will raise blood glucose slowly, moderately or quickly. Carbohydrates are digested and broken down at different rates; GI ranks how quickly each carbohydrate containing food or drink raises blood glucose levels after consumption.[112] Foods with high GI e.g., boiled sweets, fizzy drinks (not diet), glucose tablets, and fruit juice will cause blood glucose levels to rise quickly; these are therefore useful to treat hypoglycaemia. Cooking methods, processing and the content of protein and fat in foods will affect their GI. There is a lack of evidence to the effects of low GI diets in CF.[113] Whilst GI is an important consideration, the quantity of carbohydrates (glycaemic load) eaten will have a larger effect on blood glucose levels than GI alone.[112]

Good practice points

- Attention should be paid to the timing and quantity of carbohydrates eaten.
- Sources of high refined carbohydrates such as sugary drinks and sweets should be avoided between meals.
- Detailed food diaries can be very helpful when assessing the impact of different types of carbohydrates on an individual's glycaemic control.
- People with CFD should be educated about carbohydrates; this should be tailored to individual needs.

5.5 Meeting nutritional requirements

People with CFD have been shown to have lower body weight compared to people with CF who do not have diabetes.[25, 38] Therefore, attention to nutritional status is paramount. All people with CF should have access to a specialist CF dietitian who will conduct appropriate nutritional assessments.[114] Nutritional requirements for those with CFD are very individualised.[115] Therefore, the nutritional assessment should include: a review of blood

glucose levels, current dietary intake including meal patterns, carbohydrate content of meals, snacks, the use of oral nutritional supplements and enteral tube feeding.[97, 116]

5.6 Underweight individuals (BMI <20kg/m²)

Energy restrictions are not appropriate in individuals with CFD who are struggling to meet their nutritional requirements.[63] Nutritional deficits in people with CF should be managed as per national guidelines.[97]

Underweight individuals are likely to be taking extra high-energy snacks, oral nutritional supplements, or enteral tube feeds to improve their nutritional status. It is difficult to manage blood glucose levels when diets are high in refined carbohydrates such as sugary drinks, jelly-type sweets and juice-based oral nutritional supplements. Therefore, consideration should be given to the quantity and timing of these and alternative sources of energy. The use of snacks which are high in protein and/or fat or contain slow-release carbohydrate and oral nutritional supplements which are milk-based and/or fat emulsions are more appropriate.

5.7 Enteral tube feeding

Enteral tube feeding is often used for people with CF who are unable to meet their nutritional requirements using diet and oral nutritional supplements. When planning enteral tube feeding, CF teams should liaise closely with their local diabetes specialist.

Adequate glucose control is important during enteral feeding to get the nutritional benefits of the treatment. Enteral tube feeds can cause hyperglycaemia due to the increased carbohydrate load. It can often be difficult to manage insulin with enteral feeds, and it is therefore important to work with local diabetes specialist teams. There is no consensus on insulin regimens with enteral tube feeds. A number of different insulin regimens can be used depending on individualised needs. In people with pre-existing CFD, insulin treatment should be adjusted to optimise glycaemic control.[117] This may mean increasing the dose of current insulin or the addition of another insulin. Insulin will often be chosen to match the duration of feeding for example a bolus enteral feed of less than three-hour duration may be matched with a rapid-acting insulin; an overnight feed of 8–12 hours may be matched with an intermediate-acting insulin. Serial CBG measurements during and after the feed, or CGM, should be used to tailor treatment. People with CF without CFD should have serial CBG measurements or CGM performed once the feed is fully established, and treatment commenced if required.[118]

It is important to ensure people with CFD are made aware of the risk of hypoglycaemia if insulin therapy is given but the feed has been interrupted or not completed.[117]

Good practice points

- The effects of snacking in between meals, oral nutritional supplements and enteral tube feeds on blood glucose levels should be considered.
- People with CF without CFD who start enteral tube feeding should have their glycaemic control assessed.
- People with CFD who receive enteral tube feeding may need modifications in their insulin dose or type.

5.8 Normal weight individuals (BMI 20–24.9kg/m²)

Many factors need to be taken into account when considering treatment options for dysglycaemia in normal weight individuals, including BMI, lung function, pregnancy plans, corticosteroid use, and nutritional requirements. Some normal weight individuals with impaired glucose metabolism may be able to control their blood glucose levels via dietary modifications alone. The decision to start the use of insulin, or other diabetes medications, should therefore be made by the CF and CFD teams in conjunction with the individual.

Good practice points

- Normal weight individuals should be fully assessed prior to commencing treatment.

5.9 Overweight and obese individuals (BMI >25kg/m²)

In 2021, 28.1% of UK adults with CF were overweight and 8.0% were obese, according to figures from the 2021 UK CF Registry Annual Data Report.[24]

There are very few studies looking at the effects of obesity in people with CF and particularly in those with CFD. Recent studies have found no evidence that being overweight or obese has a positive effect on lung function.[119–121] Due to the

increased health risks of obesity and the anabolic effect of insulin, dietary manipulation is an essential part of management for those who are overweight or obese with CFD and may reduce the need for treatment with insulin, or, if deemed appropriate, oral antidiabetic agents.

Local weight management pathways may exist for people with CF with BMI >30 kg/m^2.

Good practice points

- Overweight and obese individuals should be given healthy eating advice and support to lose weight prior to commencing treatment if clinically appropriate.

5.10 CFTR modulator therapy

The introduction of CFTR modulator therapy has brought a number of new challenges in the dietary management of people CF, most notably the control of weight gain. For a significant number of people with CF (including those with CFD) on CFTR modulators, dietary modification has become an essential part of their routine treatment. Clinical experience has even seen some people on CFTR modulators considering stopping this therapy due to obesity or weight concerns. Many people with CF who have followed a liberal diet high in fat and sugar for most of their life, may find it both physically and psychologically challenging to adapt their diet as required when started on CFTR modulator therapies. It is essential that CF teams provide appropriate support for these individuals to help them make informed health choices.

In clinical practice changes in blood glucose levels have been observed in people with CFD on CFTR modulators. This includes lower blood glucose levels which have resulted in a reduction in insulin requirements. Also, higher blood glucose levels and increased insulin requirement have been observed, particularly in those individuals with CFD who have increased their dietary intake. Close monitoring of blood glucose levels is therefore essential in people with CFD on CFTR modulator therapy.

6. Management issues

6.1 Exercise and CF diabetes

Exercise helps improve muscle strength, fitness, lung function and well-being. Exercise can affect blood glucose levels in different ways depending on the type of exercise and its duration. Aerobic exercise, such as running, swimming or cycling, is usually of low to moderate intensity and takes place over a longer duration. Aerobic exercise tends to lower blood glucose levels. Anaerobic exercise, such as weight training or sprinting, is usually of high intensity for a short duration. Aerobic exercise tends to increase glucose levels. Mixed exercise such as rugby, football or hockey can be a combination of both aerobic and anaerobic activity. It is important to monitor glucose levels closely before, during and after exercise. Many people with CFD will need to make changes to their food intake and/or insulin doses to adjust for exercise. CF diabetes teams can provide appropriate advice and support to help people with CFD effectively manage exercise. Additional information on diabetes and exercise can be found at the Diabetes UK page on **Diabetes and exercise**.

6.2 Pregnancy

Pre-existing CFD or gestational diabetes increases the risks for women with CF and their unborn baby. Early identification and optimal control of blood glucose levels is therefore essential.[122, 123]

6.2.1 Pre-existing CF diabetes

The successful outcomes of pregnancy in women with CFD have been attributed to multidisciplinary care; maternal and perinatal outcomes reported are similar to those found in women in the general population.[124] CFD in women has been associated with a higher rate of caesarean sections. However, CFD does not have clinically significant influence on foetal growth or pre-term delivery.[125] In women with CF, changes in nutritional and respiratory status are not influenced by pre-existing CFD.[125]

As no specific guidelines for the management of pregnant women with CFD exist, the NICE guidelines for diabetes in pregnancy should be followed.[126] **This recommends the following blood glucose targets:**

1. Women with diabetes who are planning pregnancy should aim to keep their HbA1c less than 48mmol/mol (6.5%), unless this causes problematic hypoglycaemia.
2. Pregnant women should check their fasting, pre-meal, 1-hour post-meal and before bed blood glucose levels daily using CBG monitoring during pregnancy.
3. Pregnant women should keep blood glucose levels within the following, unless it causes problematic hypoglycaemia:
   - Fasting – <5.3mmol/L
   - 1-hour post-meals – <7.8mmol/L
   - 2-hour post-meal – <6.4mmol/L

To ensure close monitoring, it is recommended that people with CFD or gestational diabetes are referred to specialist antenatal diabetes services during pregnancy.[126]

6.2.2 Gestational diabetes

The following are recommendations for screening in women with CF without CFD:

- In women planning a pregnancy an OGTT should be performed if they have not had a normal CFD screen in the previous six months.[63] (moderate)
- An OGTT should take place at both 12–16 weeks and 24–28 weeks gestation, with venous BGM measured at zero, one and two hours.[63] Table 1 shows the diagnostic ranges for gestational diabetes. (moderate)
- Blood glucose levels should be measured by CBG at every hospital visit and especially during infective exacerbations.[97] (moderate)
- In those diagnosed with gestational diabetes a repeat OGTT should take place 6–12 weeks after delivery.[63] (moderate)

Table 1 Screening for gestational diabetes

Time (hours)	NICE guidelines[126]
0	>5.6mmol/L
2	>7.8mmol/L

6.3 Transplant

Current literature on the impact of CFD on survival after transplant is inconsistent.[127] In a recent systematic review and meta-analysis CFD was not found to be a predictor of mortality after lung transplant.[128] However, the presence of CFD has been shown to significantly increase the risk of death of people with CF on the lung transplant waiting list.[129] This is linked to the negative effects of hyperglycaemia and insulin deficiency upon morbidity and mortality. Optimising glycaemic control in this patient group is therefore vital. However, there are many challenges including: poor nutritional status, recurrent infective exacerbations, corticosteroid use, enteral tube feeding and high treatment burden.

Insulin doses may need adjustment at the time of surgery, and status can change after transplant. Diabetes may resolve in some individuals, presumably related to reduction in pulmonary inflammation. However, for some, diabetes can become much more problematic, potentially due to the anti-rejection medications and changes in diet and lifestyle. Unfortunately, the quality of post-transplant diabetes care is very variable across the UK.

Good practice points

- People with CFD should have access to CFD specialist care following transplantation.

The following are recommendations for people without CFD that have undergone any transplant:[63]

- Blood glucose should be closely monitored in the perioperative intensive care period until discharge. (moderate)
- Screening via an OGTT should take place if the individual has not had screening within the past six months. (moderate)
- Routine screening guidelines for people with CF should then be followed. (moderate)

6.4 Patient education

The provision of diabetes education is considered on three levels:[130]

1. One-to-one advice and information.
2. Informal ongoing learning, such as peer groups.
3. Structured diabetes education programmes meeting specific criteria.[131]

NICE suggests that structured education is an integral part of diabetes care and should be offered to people with type 1 and type 2 diabetes.[131, 132] **NICE has established criteria for what diabetes self-management programmes should consist of; they should:**[131, 132]

- be evidence-based
- have specified aims and objectives
- follow a structured written curriculum with theoretical underpinning
- support the development of self-management of diabetes
- be delivered by trained facilitators
- be quality assured and audited regularly.

There are currently no established diabetes self-management education programmes for people with CFD that meet NICE criteria. Education for people with CFD is usually provided by the CFD team and tailored on an individual basis; this may be face-to-face, or virtually via phone/video. Further research is needed to identify the requirements of structured educational programmes for people with CFD.

6.5 Driving and diabetes

People with CFD have a legal requirement to inform the Driver and Vehicle Licensing Agency (DVLA) and their insurance company if they are on insulin or oral agents. People with CFD should be counselled about the risks of hypoglycaemia and driving. Please refer to the gov.uk webpage on **diabetes and driving**[133] and the **Diabetes UK website**[134] for up to date legal guidance.

7. Annual review and screening for complications

7.1 The need for a CF diabetes annual review

A CFD annual review should be carried out by a specialist MDT. The aims of the CFD annual review are:

- to screen for and, if necessary, treat early complications
- to review management plans
- to assess nutritional management
- to address adherence issues, education and psychosocial issues.

7.2 Microvascular / macrovascular complications

CF diabetes can go undetected for several years as endogenous insulin production can mask elevated glucose levels. Microvascular complications may develop during this time. For this reason, screening for micro and macrovascular complications should take place within the first year of diagnosis of CFD.

Macrovascular complications are rare, but as incidence may increase as new treatments become available, this needs to be incorporated into the annual screening process.

NICE guidance suggests retinopathy and foot screening in children and adults with type 1 and 2 diabetes annually from 12 years of age[135] and this guidance should be followed in CFD.

7.3 Hypoglycaemia

Hypoglycaemia can be troublesome for people with CF with or without diabetes. Previous studies have found fasting hypoglycaemia in 14% of a cohort of children and adults with CF and related this to worsening clinical status.[136] In the same cohort 15% demonstrated reactive hypoglycaemia. This is thought to be related to delayed insulin secretion and diminished glucagon secretion.

Experiential evidence suggests people with CF have had problems with hypoglycaemia after commencing CFTR modulator therapy. More research is required to determine causation, but it is thought to be related to changes in insulin resistance.

Hypoglycaemic episodes should be explored with the aim of identifying the cause. Education should be provided, and medication should be started or adjusted to avoid further repeated episodes and to optimise treatment.

Hypoglycaemia can have a profound effect on a person's confidence and ability to manage their CFD. The emergence of CGM and flash glucose monitoring to alert the individual to rapidly decreasing glucose levels may help them to maintain glucose levels. It is not uncommon for people with CFD to experience rebound lows 3–4 hours after large meals because endogenous insulin works with insulin injections used to reduce postprandial levels. Further guidelines on the management and treatment of hypoglycaemia for adults can be found on at the **Joint British Diabetes Society website**. Information for the treatment of children and young adults is also available.[135]

7.4 Recommendations for annual review of people with CF diabetes

The following should be undertaken at annual review:

- clinical and social history (including pre-pregnancy counselling)
- history of hospital admissions and any escalation of treatment
- weight
- pulmonary function
- history of episodes of distal intestinal obstruction syndrome (DIOS) and variability in gastric motility
- blood pressure
- history of hypoglycaemia – identify cause, educate and optimise treatment
- check awareness of legal requirements for driving
- review of insulin therapy
- check injection technique and injection site
- review of medications
- glucose monitoring
- dietetic review

- lipid profile
- retinopathy screening referral
- urine sample for albumin-to-creatinine ratio (ACR)
- foot examination
- review of psychological adjustment and management.

8. Treatment of long-term complications

8.1 Microvascular disease

The prevalence of microvascular complications increases with time, and it is now clear that all people with CFD are at risk.

8.2 Macrovascular disease

Although death from macrovascular disease is not thought to occur, there has been a case report of ischaemic heart disease in a person with CFD.[99] With an ageing population these types of complications should be considered.

8.3 Renal disease

A cross-sectional study demonstrated moderate chronic kidney disease in 2.7% of the CFD population.[137] This rose to 11% post-transplant. Other studies have produced similar results.[138, 139]

Persistent microalbuminuria is a sign of diabetic nephropathy and is found in 14–21% of people with CFD.[137, 140]

Consideration should be given to the use of nephrotoxic drugs and other CF-related factors that may heighten the prevalence of microalbuminuria.[53]

Procedure for screening for microalbuminuria and diabetic nephropathy:

- A microalbumin sample should be sent annually to measure urinary albumin-to-creatinine ratio during a period of stability (off intravenous antibiotics) and avoiding periods of menstruation and strenuous activity.
- Two abnormal samples are needed to give a diagnosis of diabetic nephropathy (assuming there are no other potential causes for renal dysfunction such as sepsis or concurrent antibiotics).
- Any value >3.0mg/mmol is considered abnormal.
- If three out of four samples remain elevated, referral to the local diabetes or nephrology team should be considered.[141]
- Consideration should be given to commencing antihypertensive therapy to maintain blood pressure below 130/80mm/Hg, with the use of angiotensin II receptor antagonists and other antihypertensives as appropriate.[131]

8.4 Retinopathy

On diagnosis, people with CFD should be referred to their local retinopathy screening programme and reviewed annually. Retinopathy is a growing problem in CFD, and people with CFD should be informed of the importance of screening to support compliance.

It has been suggested that prevalence is approximately 15% in people with CF who have had a diagnosis of CFD for >10 years.[52]

8.5 Gastroparesis

Gastroparesis is common in people with CF and may contribute to dysglycaemia in CFD; it should be treated according to local guidelines when necessary. Careful insulin titration and management with use of CGM has been suggested as best practice.[142]

8.6 Neuropathy

Autonomic neuropathy is present in 52% of people with CFD.[143] The **Diabetes UK Foot Care Pathway** should be followed to triage the severity of any foot care problems.

8.7 Hyperlipidaemia

Although cholesterol levels have been reported to be lower in people with CF, a fasting lipid profile should be carried out at least annually. This is of particular relevance for those who are immunosuppressed post-transplant or have a family history or coronary artery disease.

If total cholesterol is >5mmol/L, repeat the sample. If this remains high, consider treatment as per NICE guidelines.[144]

8.8 Hypertension

Blood pressure should be measured at each clinic visit. If blood pressure is elevated, check again during the consultation. Take the lowest measurement and if >140/90mm/Hg, refer to local diabetes team or GP for ambulatory blood pressure monitoring or further investigation as per NICE guidelines.[145]

9. Psychosocial aspects of CF diabetes

Due to the complexity of secondary psychological issues associated with the diagnosis and management of CFD, it is vital that people with CFD have access to a clinical psychologist with specialist knowledge of CF. The clinical psychologist will be able to offer psychological assessment, formulation and inform MDT working. They will also be able to provide psychologically informed care planning, intervention, or signposting to additional specialist services should this be required.

The difficulties listed below are commonly encountered; clinicians should be vigilant due to their potential impact on management of CFD and impact on overall quality of life. Clinicians should consult with the MDT's clinical psychologist where concerns arise. Furthermore, all issues detailed below have the potential to impact adherence; both specific to CFD treatments, and wider CF-related care plans. These guidelines should be considered in tandem with the more comprehensive psychosocial guidelines for CF care.

A period of elevated anxiety or low mood in response to a diagnosis or changes to the management or prognosis of a health condition could be considered an expected psychological response. Psychological intervention may not be initially needed; however, this should be monitored to ascertain if clinically significant distress remains consistent over a number of weeks and support sought where necessary.

9.1 Anxiety

- This may present as health-related anxiety, focusing on the implications and management of CFD, e.g., insulin use, weight change or longer-term prognosis.
- Phobic or acute adverse stress responses may also become apparent, e.g., using needles.
- The GAD7 is a psychometric tool that can be used to ascertain clinically significant levels of anxiety.[146]
- Additional complexities around historically identified trauma-related responses should be considered as they may impact on aspects of treatment. Where such difficulties are identified consultation should be sought from the service's clinical psychologist.

9.2 Low mood

- Low mood commonly occurs comorbid with anxiety, particularly in the context of lifelong complex health conditions, and is typically associated with increased clinical complexity and risk.[147]
- Low mood is typically associated with feelings of hopelessness and helplessness, which can contribute to challenges regarding treatment adherence.[148]
- Impact of functioning needs to be considered at an individual level with consideration to presentations commonly associated with anxiety or low mood and how they may impact management of CFD, for example changes to motivation, appetite, and sleep.[149]
- The PHQ9 is a psychometric tool that can be used to ascertain clinically significant levels of low mood.[146]
- Where concerns regarding low mood are present, risk should be assessed (e.g., presence of suicidal ideation).

9.3 Adjustment difficulties

Adjustment difficulties are a result of the challenges of adapting to notable life stressors.[150] For example, within the context of CFD this could be the result of diagnosis, changes of insulin regimes and diet, or wider lifestyle adaptions that are required.

Adjustment difficulties can and often do occur alongside low mood and anxiety. Due to the average onset of CFD occurring in early adulthood,[24] it is important to take into consideration that this diagnosis and consequent change of treatment planning and treatment burden occurs at a major life transitional stage. Consequently, this should inform a clinician's expectations of an individual's adaption to new treatments (e.g., adherence and accommodation of the new treatment regimens). Many other psychosocial adjustments occurring and competing priorities will impact the adjustment and adaptation to the new CFD diagnosis. This should also be considered should diagnosis occur parallel to any other major life events or transitional stages.

Good practice points

- The anxiety often associated with adjustment difficulties may present in different ways within the context of CFD, for example the individual reporting continued worry around the diagnosis, reassurance seeking of prognosis, or hypervigilance of blood glucose or insulin use.
- The complexity of the individual's circumstances and resources available should be taken into consideration to avoid pathologising an expected psychological response.
- Due to the complexities in the adaption to the complex psychosocial stressors and changeable nature of CFD, adjustment is rarely linear nor consistent in its trajectory.

9.4 Communication and information processing difficulties

In addition to learning difficulties, the prevalence of attention deficit hyperactivity disorder (ADHD) and Autistic Spectrum Condition (ASC) is being increasingly recognised within CF populations. Where any such difficulties are identified, adaption of the communication of information and structuring of treatment plans is required.

Good practice points

- It is important that any identified learning or communication difficulties be considered in the development of CFD treatment planning, recognising the individual's strengths and where appropriate supporting independence.
- Information being present in several formats e.g., diagrammatic, written and verbal, with numerous opportunities for rehearsal will aid understanding and retention.

9.5 Body image

Due to dietary adaptions and use of insulin, body image issues may become apparent with the diagnosis and subsequent management of CFD if unwanted changes occur (or are anticipated) to body weight. Any clinically significant changes in weight, particularly if alongside the onset of any psychological difficulties, should be explored with the individual.

Good practice points

- With the development of modulator therapies people with CF are learning to adapt their calorie intakes, and clinicians should be aware of this adjustment period, being mindful not to pathologise initial weight gain or loss.
- Fixation on body fat, muscle mass, or body shape or appearance to the detriment of health and/or quality of life should be explored and referral to psychological services considered.
- Where body image concerns or unhealthy eating patterns are historically known, advice should be sought from the MDT clinical psychologist as to how to design and implement care plans recognising these issues and associated risks involved. Similarly, clinicians should be mindful of the potential manipulation of insulin as a method of managing weight when reviewing an individual's CFD treatment where weight gain or loss is a known source of distress.

10. Financial considerations

10.1 Prescription charges

There are no prescription charges for people living in Scotland, Northern Ireland, and Wales. In England, prescription charges do apply to adults with CF, however people receiving medical treatment for CFD (and some other medical conditions) are exempt from paying prescription charges. **Medical exemption certificates** are available from GPs or pharmacies. See also the Cystic Fibrosis Trust webpage on **Prescription charges for cystic fibrosis**.

10.2 Other benefits

Free NHS eyesight tests and chiropody may also be available to people with diabetes.

Further advice and information on these and other benefits available to people with CF and CFD is available from the following:

- Local CF social work team.
- Cystic Fibrosis Trust Welfare and Rights Adviser via the helpline at **helpline@cysticfibrosis.org.uk** or 0300 373 1000.

10.3 Useful sites

- Cystic Fibrosis Trust **Help with health care costs**
- Gov.uk
  - **Benefits, money and tax**
  - **Personal Independence Payment (PIP)**
- Citizen's Advice **Benefits for people affected by sickness or disability**
- NHS Help with Health Costs **Medical exemption certificates**
- NHS **Free eyesight tests**
- **Motability scheme**

11. References

1 Kerem E, Viviani L, Zolin A, MacNeill S, Hatziagorou E, Ellemunter H et al. Factors associated with FEV1 decline in cystic fibrosis: analysis of the ECFS Patient Registry. European Respiratory Journal 2014; 43: 125–133.

2 Milla CE, Warwick WJ, Moran A. Trends in pulmonary function in patients with cystic fibrosis correlate with the degree of glucose intolerance at baseline. Am J Respir Crit Care Med 2000; 162: 891–5.

3 Sims EJ, Green MW, Mehta A. Decreased Lung Function in Female but not Male Subjects With Established Cystic Fibrosis–Related Diabetes. Diabetes Care 2005; 28: 1581–1587.

4 Milla CE, Billings J, Moran A. Diabetes is associated with dramatically decreased survival in female but not male subjects with cystic fibrosis. Diabetes Care 2005; 28: 2141–4.

5 Moran A, Dunitz J, Nathan B, Saeed A, Holme B, Thomas W. Cystic fibrosis-related diabetes: current trends in prevalence, incidence, and mortality. Diabetes Care 2009; 32: 1626–31.

6 Bogdani M, Blackman SM, Ridaura C, Bellocq J-P, Powers AC, Aguilar-Bryan L. Structural abnormalities in islets from very young children with cystic fibrosis may contribute to cystic fibrosis-related diabetes. Sci Rep 2017; 7: 17231.

7 Yi Y, Norris AW, Wang K, Sun X, Uc A, Moran A et al. Abnormal Glucose Tolerance in Infants and Young Children with Cystic Fibrosis. Am J Respir Crit Care Med 2016; 194: 974–980.

8 Hameed S, Morton JR, Jaffé A, Field PI, Belessis Y, Yoong T et al. Early glucose abnormalities in cystic fibrosis are preceded by poor weight gain. Diabetes Care 2010; 33: 221–6.

9 Battezzati A, Battezzati PM, Costantini D, Seia M, Zazzeron L, Russo MC et al. Spontaneous hypoglycemia in patients with cystic fibrosis. European Journal of Endocrinology 2007; 156: 369–376.

10 Sc NNM, Shoseyov D, Kerem E, Zangen DH. Patients with cystic fibrosis and normoglycemia exhibit diabetic glucose tolerance during pulmonary exacerbation. Journal of Cystic Fibrosis 2010; 9: 199–204.

11 Eenkhoorn V, van den Driessche A, van Gaal L, Desager K, de Block C. Diabetic keto-acidosis as a presentation of cystic fibrosis-related diabetes: a case report. J Diabetes Complications; 25: 137–41.

12 Swartz LM, Laffel LM. A teenage girl with cystic fibrosis-related diabetes, diabetic ketoacidosis, and cerebral edema. Pediatr Diabetes 2008; 9: 426–30.

13 Atlas AB, Finegold DN, Becker D, Trucco M, Kurland G. Diabetic ketoacidosis in cystic fibrosis. Am J Dis Child 1992; 146: 1457–8.

14 Lanng S, Thorsteinsson B, Nerup J, Koch C. Diabetes mellitus in cystic fibrosis: effect of insulin therapy on lung function and infections. Acta Paediatr 1994; 83: 849–53.

15 Finkelstein SM, Wielinski CL, Elliott GR, Warwick WJ, Barbosa J, Wu SC et al. Diabetes mellitus associated with cystic fibrosis. J Pediatr 1988; 112: 373–7.

16 Hodson ME. Diabetes mellitus and cystic fibrosis. Bailliere's clinical endocrinology and metabolism 1992; 6: 797–805.

17 Hayes FJ, O'Brien A, O'Brien C, Fitzgerald MX, McKenna MJ. Diabetes mellitus in an adult cystic fibrosis population. Ir Med J; 88: 102–4.

18 Moran A, Pillay K, Becker D, Granados A, Hameed S, Acerini CL. ISPAD Clinical Practice Consensus Guidelines 2018: Management of cystic fibrosis-related diabetes in children and adolescents. Pediatr Diabetes 2018; 19 Suppl 27: 64–74.

19 Hayes D, McCoy KS, Sheikh SI. Resolution of cystic fibrosis-related diabetes with ivacaftor therapy. Am J Respir Crit Care Med 2014; 190: 590–1.

20 Kelly A, de Leon DD, Sheikh S, Camburn D, Kubrak C, Peleckis AJ et al. Islet Hormone and Incretin Secretion in Cystic Fibrosis after Four Months of Ivacaftor Therapy. Am J Respir Crit Care Med 2019; 199: 342–351.

21 Knudsen KB, Mathiesen ER, Eriksen V, Skov M, Nielsen KG, Johannesen J et al. The development of diabetes among Danish cystic fibrosis patients over the last two decades. Pediatr Diabetes 2015; 16: 219–26.

22 Lewis C, Blackman SM, Nelson A, Oberdorfer E, Wells D, Dunitz J et al. Diabetes-related mortality in adults with cystic fibrosis. Role of genotype and sex. Am J Respir Crit Care Med 2015; 191: 194–200.

23 Rana M, Munns CF, Selvadurai HC, Simonds S, Cooper PJ, Woodhead HJ et al. Increased detection of cystic-fibrosis-related diabetes in Australia. Arch Dis Child 2011; 96: 823–6.

24 Cystic Fibrosis Trust. UK Cystic Fibrosis Registry Annual Data Report 2021. London, 2021.

25 Koch C, Rainisio M, Madessani U, Harms HK, Hodson ME, Mastella G et al. Presence of cystic fibrosis–related diabetes mellitus is tightly linked to poor lung function in patients with cystic fibrosis: Data from the European Epidemiologic Registry of Cystic Fibrosis. Pediatric Pulmonology 2001; 32: 343–350.

26 Moheet A, Moran A. CF-related diabetes: Containing the metabolic miscreant of cystic fibrosis. Pediatr Pulmonol 2017; 52: S37–S43.

27 Lanng S, Hansen A, Thorsteinsson B, Nerup J, Koch C. Glucose tolerance in patients with cystic fibrosis: five year prospective study. BMJ 1995; 311: 655–9.

28 Siahanidou T, Mandyla H, Doudounakis S, Anagnostakis D. Hyperglycaemia and insulinopenia in a neonate with cystic fibrosis. Acta Paediatr 2005; 94: 1837–40.

29 Hull RL, Gibson RL, McNamara S, Deutsch GH, Fligner CL, Frevert CW et al. Islet Interleukin-1ß Immunoreactivity Is an Early Feature of Cystic Fibrosis That May Contribute to ß-Cell Failure. Diabetes Care 2018; 41: 823–830.

30 Hart NJ, Aramandla R, Poffenberger G, Fayolle C, Thames AH, Bautista A et al. Cystic fibrosis-related diabetes is caused by islet loss and inflammation. JCI Insight 2018; 3. doi:10.1172/jci.insight.98240.

31 Olivier AK, Yi Y, Sun X, Sui H, Liang B, Hu S et al. Abnormal endocrine pancreas function at birth in cystic fibrosis ferrets. J Clin Invest 2012; 122: 3755–68.

32 Nyirjesy SC, Sheikh S, Hadjiliadis D, de Leon DD, Peleckis AJ, Eiel JN et al. ß-Cell secretory defects are present in pancreatic insufficient cystic fibrosis with 1-hour oral glucose tolerance test glucose ≥155mg/dL. Pediatr Diabetes 2018; 19: 1173–1182.

33 Guo JH, Chen H, Ruan YC, Zhang XL, Zhang XH, Fok KL et al. Glucose-induced electrical activities and insulin secretion in pancreatic islet ß-cells are modulated by CFTR. Nature Communications 2014; 5: 4420.

34 Norris AW. Is Cystic Fibrosis–related Diabetes Reversible? New Data on CFTR Potentiation and Insulin Secretion. American Journal of Respiratory and Critical Care Medicine 2019; 199: 261–263.

35 Bellin MD, Laguna T, Leschyshyn J, Regelmann W, Dunitz J, Billings J et al. Insulin secretion improves in cystic fibrosis following ivacaftor correction of CFTR: a small pilot study. Pediatr Diabetes 2013; 14: 417–21.

36 Chamnan P, Shine BSF, Haworth CS, Bilton D, Adler AI. Diabetes as a determinant of mortality in cystic fibrosis. Diabetes Care 2010; 33: 311–6.

37 Rolon MA, Benali K, Munck A, Navarro J, Clement A, Tubiana-Rufi N et al. Cystic fibrosis-related diabetes mellitus: clinical impact of prediabetes and effects of insulin therapy. Acta Paediatr 2001; 90: 860–7.

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

39 Rosenecker J, Höfler R, Steinkamp G, Eichler I, Smaczny C, Ballmann M et al. Diabetes mellitus in patients with cystic fibrosis: the impact of diabetes mellitus on pulmonary function and clinical outcome. Eur J Med Res 2001; 6: 345–50.

40 Peraldo M, Fasulo A, Chiappini E, Milio C, Marianelli L. Evaluation of glucose tolerance and insulin secretion in cystic fibrosis patients. Horm Res 1998; 49: 65–71.

41 Nousia-Arvanitakis S, Galli-Tsinopoulou A, Karamouzis M. Insulin improves clinical status of patients with cystic-fibrosis-related diabetes mellitus. Acta Paediatrica 2007; 90: 515–519.

42 Terliesner N, Vogel M, Steighardt A, Gausche R, Henn C, Hentschel J et al. Cystic-fibrosis related-diabetes (CFRD) is preceded by and associated with growth failure and deteriorating lung function. J Pediatr Endocrinol Metab 2017; 30: 815–821.

43 Hunt WR, Helfman BR, McCarty NA, Hansen JM. Advanced glycation end products are elevated in cystic fibrosis-related diabetes and correlate with worse lung function. J Cyst Fibros 2016; 15: 681–8.

44 Lavie M, Fisher D, Vilozni D, Forschmidt R, Sarouk I, Kanety H et al. Glucose intolerance in cystic fibrosis as a determinant of pulmonary function and clinical status. Diabetes Res Clin Pract 2015; 110: 276–84.

45 Coriati A, Ziai S, Lavoie A, Berthiaume Y, Rabasa-Lhoret R. The 1-h oral glucose tolerance test glucose and insulin values are associated with markers of clinical deterioration in cystic fibrosis. Acta Diabetol 2016; 53: 359–66.

46 de Schepper J, Dab I, Derde MP, Loeb H. Oral glucose tolerance testing in cystic fibrosis: Correlations with clinical parameters and glycosylated haemoglobin determinations. European Journal of Pediatrics 1991; 150: 403–406.

47 Hameed S, Jaffé A, Verge CF. Cystic Fibrosis Related Diabetes (CFRD)-The End Stage of Progressive Insulin Deficiency. Pediatric Pulmonology 2011; 46: 747–760.

48 Suratwala D, Chan JSH, Kelly A, Meltzer LJ, Gallagher PR, Traylor J et al. Nocturnal saturation and glucose tolerance in children with cystic fibrosis. Thorax 2011; 66: 574–8.

49 Merjaneh L, Hasan S, Kasim N, Ode KL. The role of modulators in cystic fibrosis related diabetes. Journal of Clinical & Translational Endocrinology 2022; 27: 100286.

50 Kaminski BA, Goldsweig BK, Sidhaye A, Blackman SM, Schindler T, Moran A. Cystic fibrosis related diabetes: Nutrition and growth considerations. Journal of Cystic Fibrosis 2019; 18: S32–S37.

51 Balfour-Lynn IM, King JA. CFTR modulator therapies – Effect on life expectancy in people with cystic fibrosis. Paediatric Respiratory Reviews 2022; 42: 3–8.

52 Schwarzenberg SJ, Thomas W, Olsen TW, Grover T, Walk D, Milla C et al. Microvascular Complications in Cystic Fibrosis–Related Diabetes. Diabetes Care 2007; 30: 1056–1061.

53 Andersen HU, Lanng S, Pressler T, Laugesen CS, Mathiesen ER. Cystic fibrosis–related diabetes: the presence of microvascular diabetes complications. Diabetes Care 2006; 29: 2660–2663.

54 Moran A, Pekow P, Grover P, Zorn M, Slovis B, Pilewski J et al. Insulin Therapy to Improve BMI in Cystic Fibrosis–Related Diabetes Without Fasting Hyperglycemia. Diabetes Care 2009; 32: 1783–1788.

55 Mohan K, Israel KL, Miller H, Grainger R, Ledson MJ, Walshaw MJ. Long-Term Effect of Insulin Treatment in Cystic Fibrosis-Related Diabetes. Respiration 2008; 76: 181–186.

56 Rafii M, Chapman K, Stewart C, Kelly E, Hanna A, Wilson DC et al. Changes in response to insulin and the effects of varying glucose tolerance on whole-body protein metabolism in patients with cystic fibrosis. The American Journal of Clinical Nutrition 2005; 81: 421–426.

57 Pu MZMH, Christensen-Adad FC, Gonçalves AC, Minicucci WJ, Ribeiro JD, Ribeiro AF. Insulin therapy in patients with cystic fibrosis in the pre-diabetes stage: a systematic review. Revista Paulista de Pediatria 2016; 34: 367–373.

58 Frost F, Dyce P, Nazareth D, Malone V, Walshaw MJ. Continuous glucose monitoring guided insulin therapy is associated with improved clinical outcomes in cystic fibrosis-related diabetes. J Cyst Fibros 2018; 17: 798–803.

59 Dobson L. Clinical improvement in cystic fibrosis with early insulin treatment. Archives of Disease in Childhood 2002; 87: 430–431.

60 Mozzillo E, Franzese A, Valerio G, Sepe A, de Simone I, Mazzarella G et al. One-year glargine treatment can improve the course of lung disease in children and adolescents with cystic fibrosis and early glucose derangements. Pediatric Diabetes 2009; 10: 162–167.

61 Prentice B, Hameed S, Verge CF, Ooi CY, Jaffe A, Widger J. Diagnosing cystic fibrosis-related diabetes: current methods and challenges. Expert Review of Respiratory Medicine 2016; 10: 799–811.

62 Lanng S, Thorsteinsson B, Erichsen G, Nerup J, Koch C. Glucose tolerance in cystic fibrosis. Archives of Disease in Childhood 1991; 66: 612–616.

63 Moran A, Brunzell C, Cohen RC, Katz M, Marshall BC, Onady G et al. Clinical Care Guidelines for Cystic Fibrosis-Related Diabetes: A position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. Diabetes Care 2010; 33: 2697–2708.

64 Sheikh S, Putt ME, Forde KA, Rubenstein RC, Kelly A. Elevation of one hour plasma glucose during oral glucose tolerance testing. Pediatric Pulmonology 2015; 50: 963–969.

65 Zorrón Mei Hsia Pu M, Gonçalves AC, Minnicucci WJ, Morcillo AM, Ribeiro JD, Ribeiro AF. Continuous glucose monitoring to evaluate glycaemic abnormalities in cystic fibrosis. Archives of Disease in Childhood 2018; 103: 592–596.

66 Hardin DS, Moran A. DIABETES MELLITUS IN CYSTIC FIBROSIS. Endocrinology and Metabolism Clinics of North America 1999; 28: 787–800.

67 Lam GY, Doll-Shankaruk M, Dayton J, Rodriguez-Capote K, Higgins TN, Thomas D et al. The use of fructosamine in cystic fibrosis-related diabetes (CFRD) screening. Journal of Cystic Fibrosis 2018; 17: 121–124.

68 O'Riordan SMP, Hindmarsh P, Hill NR, Matthews DR, George S, Greally P et al. Validation of Continuous Glucose Monitoring in Children and Adolescents With Cystic Fibrosis. Diabetes Care 2009; 32: 1020–1022.

69 Chan CL, Vigers T, Pyle L, Zeitler PS, Sagel SD, Nadeau KJ. Continuous glucose monitoring abnormalities in cystic fibrosis youth correlate with pulmonary function decline. Journal of Cystic Fibrosis 2018; 17: 783–790.

70 Leclercq A, Gauthier B, Rosner V, Weiss L, Moreau F, Constantinescu AA et al. Early assessment of glucose abnormalities during continuous glucose monitoring associated with lung function impairment in cystic fibrosis patients. J Cyst Fibros 2014; 13: 478–84.

71 Yung B, Kemp M, Hooper J, Hodson ME. Diagnosis of cystic fibrosis related diabetes: a selective approach in performing the oral glucose tolerance test based on a combination of clinical and biochemical criteria. Thorax 1999; 54: 40–43.

72 Gilmour JA, Sykes J, Etchells E, Tullis E. Cystic Fibrosis-Related Diabetes Screening in Adults: A Gap Analysis and Evaluation of Accuracy of Glycated Hemoglobin Levels. Canadian Journal of Diabetes 2019; 43: 13–18.

73 Cucinotta D, de Luca F, Scoglio R, Lombardo F, Sferlazzas C, Benedetto A di et al. Factors affecting diabetes mellitus onset in cystic fibrosis: evidence from a 10-year follow-up study. Acta Paediatrica 1999; 88: 389–393.

74 Wright MFA, Gregory J, Nolan S, Bridges N, Carr SB. 290 The utility of serial continuous glucose monitoring for diagnosis of CF-related diabetes in children. Journal of Cystic Fibrosis 2017; 16: S136.

75 Burgess JC, Bridges N, Banya W, Gyi KM, Hodson ME, Bilton D et al. HbA1c as a screening tool for cystic fibrosis related diabetes. Journal of Cystic Fibrosis 2016; 15: 251–257.

76 Hameed S, Morton JR, Field PI, Belessis Y, Yoong T, Katz T et al. Once daily insulin detemir in cystic fibrosis with insulin deficiency. Archives of Disease in Childhood 2012; 97: 464–467.

77 Hardin DS, Rice J, Rice M, Rosenblatt R. Use of the insulin pump in treat cystic fibrosis related diabetes. Journal of Cystic Fibrosis 2009; 8: 174–178.

78 Ballmann M, Hubert D, Assael BM, Staab D, Hebestreit A, Naehrlich L et al. Repaglinide versus insulin for newly diagnosed diabetes in patients with cystic fibrosis: a multicentre, open-label, randomised trial. The Lancet Diabetes & Endocrinology 2018; 6: 114–121.

79 Onady GM, Stolfi A. Insulin and oral agents for managing cystic fibrosis-related diabetes. Cochrane Database of Systematic Reviews 2016. doi:10.1002/14651858.CD004730.pub4.

80 Gnanapragasam H, Mustafa N, Bierbrauer M, Andrea Providence T, Dandona P. Semaglutide in Cystic Fibrosis-Related Diabetes. The Journal of Clinical Endocrinology & Metabolism 2020; 105: 2341–2344.

81 Tsabari R, Elyashar HI, Cymberknowh MC, Breuer O, Armoni S, Livnat G et al. CFTR potentiator therapy ameliorates impaired insulin secretion in CF patients with a gating mutation. Journal of Cystic Fibrosis 2016; 15: e25–e27.

82 Li A, Vigers T, Pyle L, Zemanick E, Nadeau K, Sagel SD et al. Continuous glucose monitoring in youth with cystic fibrosis treated with lumacaftor-ivacaftor. Journal of Cystic Fibrosis 2019; 18: 144–149.

83 Mehfooz A, Zeb M, Morey-Vargas O. SUN-LB026 Do CFTR Modulators Treat Cystic Fibrosis-Related Diabetes? J Endocr Soc 2019; 3. doi:10.1210/js.2019-SUN-LB026.

84 Perano SJ, Couper JJ, Horowitz M, Martin AJ, Kritas S, Sullivan T et al. Pancreatic Enzyme Supplementation Improves the Incretin Hormone Response and Attenuates Postprandial Glycemia in Adolescents With Cystic Fibrosis: A Randomized Crossover Trial. The Journal of Clinical Endocrinology & Metabolism 2014; 99: 2486–2493.

85 Kuo P, Stevens JE, Russo A, Maddox A, Wishart JM, Jones KL et al. Gastric Emptying, Incretin Hormone Secretion, and Postprandial Glycemia in Cystic Fibrosis—Effects of Pancreatic Enzyme Supplementation. The Journal of Clinical Endocrinology & Metabolism 2011; 96: E851–E855.

86 Brennan A, Elisaus P, Bianco B, Cottam S, Pickles J, Tofeec K et al. P301 Metformin tolerability in patients with cystic fibrosis. Journal of Cystic Fibrosis 2019; 18: S142.

87 Heather Spain AP. Use of Dipeptidyl Peptidase-4 Inhibitors in a Subset of Patients with Cystic Fibrosis Related Diabetes. Journal of Diabetes & Metabolism 2015; 06. doi:10.4172/2155-6156.1000501.

88 de Bray AY, Sunsoa H, McKemey E, Kempegowda P, Nash EF, Syed A. P300 Outcomes for patients using mono-or dual DPP4-inhibitor therapy for Cystic Fibrosis-Related Diabetes - a regional centre's 2-year experience. Journal of Cystic Fibrosis 2019; 18: S142.

89 Belle-van Meerkerk G, de Valk HW, Stam-Slob MC, Teding van Berkhout F, Zanen P, van de Graaf EA. Cystic Fibrosis-Related Diabetes with strict glycaemic control is not associated with frequent intravenous antibiotics use for pulmonary infections. Diabetes Res Clin Pract 2016; 116: 230–6.

90 Adler AI, Shine B, Haworth C, Leelarathna L, Bilton D. Hyperglycemia and Death in Cystic Fibrosis–Related Diabetes. Diabetes Care 2011; 34: 1577–1578.

91 Haliloglu B, Gokdemir Y, Atay Z, Abali S, Guran T, Karakoc F et al. Hypoglycemia is common in children with cystic fibrosis and seen predominantly in females. Pediatric Diabetes 2017; 18: 607–613.

92 Lee J, Speight L, George L, Duckers J, Lau D, Ketchell RI et al. 277 Hypoglycaemia in cystic fibrosis in the absence of diabetes at the All Wales Adult CF Centre (AWACFC). Journal of Cystic Fibrosis 2017; 16: S132.

93 Radike K, Molz K, Holl RW, Poeter B, Hebestreit H, Ballmann M. Prognostic Relevance of Hypoglycemia Following an Oral Glucose Challenge for Cystic Fibrosis–Related Diabetes. Diabetes Care 2011; 34: e43–e43.

94 Cheung MS, Bridges NA, Prasad SA, Francis J, Carr SB, Suri R et al. Growth in children with cystic fibrosis-related diabetes. Pediatric Pulmonology 2009; 44: 1223–1225.

95 Bizzarri C, Montemitro E, Pedicelli S, Ciccone S, Majo F, Cappa M et al. Glucose tolerance affects pubertal growth and final height of children with cystic fibrosis. Pediatric Pulmonology 2015; 50: 144–149.

96 Stallings VA, Stark LJ, Robinson KA, Feranchak AP, Quinton H. Evidence-Based Practice Recommendations for Nutrition-Related Management of Children and Adults with Cystic Fibrosis and Pancreatic Insufficiency: Results of a Systematic Review. J Am Diet Assoc 2008; 108: 832–839.

97 Cystic Fibrosis Trust. Nutritional Management of Cystic Fibrosis. London, 2016.

98 Calder PC. Long-chain fatty acids and inflammation. Proceedings of the Nutrition Society 2012; 71: 284–289.

99 Perrin FM, Serino W. Ischaemic heart disease - a new issue in cystic fibrosis? J R Soc Med 2010; 103: 44–48.

100 Smith C, Winn A, Seddon P, Ranganathan S. A fat lot of good: Balance and trends in fat intake in children with cystic fibrosis. Journal of Cystic Fibrosis 2012; 11: 154–157.

101 NICE. Cardiovascular disease prevention (PH25). 2010. Available at: **https://www.nice.org.uk/guidance/ph25/chapter/1-recommendations** (accessed Sept 2022).

102 Maqbool A, Schall JI, Gallagher PR, Zemel BS, Strandvik B, Stallings VA. Relation Between Dietary Fat Intake Type and Serum Fatty Acid Status in Children With Cystic Fibrosis. Journal of Pediatric Gastroenterology & Nutrition 2012; 55: 605–611.

103 Paterson MA, Smart CEM, Lopez PE, McElduff P, Attia J, Morbey C et al. Influence of dietary protein on postprandial blood glucose levels in individuals with Type 1 diabetes mellitus using intensive insulin therapy. Diabetic Medicine 2016; 33: 592–598.

104 Marathe CS, Rayner CK, Jones KL, Horowitz M. Relationships Between Gastric Emptying, Postprandial Glycemia, and Incretin Hormones. Diabetes Care 2013; 36: 1396–1405.

105 Bell KJ, Smart CE, Steil GM, Brand-Miller JC, King B, Wolpert HA. Impact of Fat, Protein, and Glycemic Index on Postprandial Glucose Control in Type 1 Diabetes: Implications for Intensive Diabetes Management in the Continuous Glucose Monitoring Era. Diabetes Care 2015; 38: 1008–1015.

106 Matel JL. Nutritional Management of Cystic Fibrosis. Journal of Parenteral and Enteral Nutrition 2012; 36: 60S-67S.

107 Ode KL, Brunzell C. Nutrition in Cystic Fibrosis: A Guide for Clinicians. Springer International Publishing: Cham, 2015.

108 DAFNE Study Group. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. BMJ 2002; 325: 746–746.

109 Robb L, Richardson M, Johnston S, Innes JA. Carbohydrate counting and insulin adjustment in Cystic Fibrosis related Diabetes. Journal of Cystic Fibrosis 2009; 8: S82.

110 Collins S, Watson K, Elston C, Gyi KM. 249 Diabetes in cystic fibrosis – education (DICE) – the impact of a structured education programme for the management of cystic fibrosis related diabetes (CFRD) on quality of life. Journal of Cystic Fibrosis 2015; 14: S122.

111 Still J, Philip S. 335 Carbohydrate counting in cystic fibrosis related diabetes mellitus (CFRDM): is it useful? Journal of Cystic Fibrosis 2017; 16: S148.

112 Diabetes UK. Glycaemic index and diabetes. Available at: **https://www.diabetes.org.uk/guide-to-diabetes/enjoy-food/carbohydrates-and-diabetes/glycaemic-index-and-diabetes?gclid=EAIaIQobChMI1Z7_xdOm3wIVSgOGCh3q2QbqEAAYASAAEgKR2fD_BwE** (accessed Sept 2022).

113 Balzer BWR, Graham CL, Craig ME, Selvadurai H, Donaghue KC, Brand-Miller JC et al. Low Glycaemic Index Dietary Interventions in Youth with Cystic Fibrosis: A Systematic Review and Discussion of the Clinical Implications. Nutrients 2012; 4: 286–296.

114 Cystic Fibrosis Trust. Standards of Clinical Care for Children and Adults with Cystic Fibrosis in the UK. . London, 2011.

115 Turck D, Braegger CP, Colombo C, Declercq D, Morton A, Pancheva R et al. ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children, and adults with cystic fibrosis. Clinical Nutrition 2016; 35: 557–577.

116 Middleton PG, Wagenaar M, Matson AG, Craig ME, Holmes-Walker DJ, Katz T et al. Australian standards of care for cystic fibrosis-related diabetes. Respirology 2014; 19: 185–192.

117 Bridges N, Rowe R, Holt RIG. Unique challenges of cystic fibrosis-related diabetes. Diabetic Medicine 2018; 35: 1181–1188.

118 NICE. Cystic fibrosis: diagnosis and management (NG78). 2017. Available at: **https://www.nice.org.uk/guidance/ng78** (accessed Sept 2022).

119 Hanna RM, Weiner DJ. Overweight and obesity in patients with cystic fibrosis: A center-based analysis. Pediatric Pulmonology 2015; 50: 35–41.

120 Stephenson AL, Mannik LA, Walsh S, Brotherwood M, Robert R, Darling PB et al. Longitudinal trends in nutritional status and the relation between lung function and BMI in cystic fibrosis: a population-based cohort study. The American Journal of Clinical Nutrition 2013; 97: 872–877.

121 González Jiménez D, Muñoz-Codoceo R, Garriga-García M, Molina-Arias M, Álvarez-Beltrán M, García-Romero R et al. Excess weight in patients with cystic fibrosis: is it always beneficial? Nutrición Hospitalaria 2017; 34: 578.

122 Edenborough FP, Borgo G, Knoop C, Lannefors L, Mackenzie WE, Madge S et al. Guidelines for the management of pregnancy in women with cystic fibrosis. Journal of Cystic Fibrosis 2008; 7: S2–S32.

123 HAPO Study Cooperative Research Group. Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) Study: associations with maternal body mass index. BJOG: An International Journal of Obstetrics & Gynaecology 2010; 117: 575–584.

124 Girault A, Blanc J, Gayet V, Goffinet F, Hubert D. Maternal and perinatal outcomes of pregnancies in women with cystic fibrosis – A single centre case-control study. Respiratory Medicine 2016; 113: 22–27.

125 Reynaud Q, Poupon-Bourdy S, Rabilloud M, al Mufti L, Rousset Jablonski C, Lemonnier L et al. Pregnancy outcome in women with cystic fibrosis-related diabetes. Acta Obstetricia et Gynecologica Scandinavica 2017; 96: 1223–1227.

126 NICE. Diabetes in pregnancy: management from preconception to the postnatal period (NG3). 2015. Available at: **https://www.nice.org.uk/Guidance/NG3** (accessed Sept 2022).

127 Stephenson AL, Sykes J, Berthiaume Y, Singer LG, Aaron SD, Whitmore GA et al. Clinical and demographic factors associated with post–lung transplantation survival in individuals with cystic fibrosis. The Journal of Heart and Lung Transplantation 2015; 34: 1139–1145.

128 Koutsokera A, Varughese RA, Sykes J, Orchanian-Cheff A, Shah PS, Chaparro C et al. Pre-transplant factors associated with mortality after lung transplantation in cystic fibrosis: A systematic review and meta-analysis. Journal of Cystic Fibrosis 2019; 18: 407–415.

129 Hayes D, Patel A v., Black SM, McCoy KS, Kirkby S, Tobias JD et al. Influence of diabetes on survival in patients with cystic fibrosis before and after lung transplantation. The Journal of Thoracic and Cardiovascular Surgery 2015; 150: 707-713.e2.

130 Diabetes UK. Diabetes education: the big missed opportunity in diabetes care. 2015. Available at: **https://diabetes-resources-production.s3-eu-west-1.amazonaws.com/diabetes-storage/migration/pdf/Diabetes%2520UK_Diabetes%2520education%2520-%2520the%2520big%2520missed%2520opportunity_updated%2520June%25202016.pdf** (accessed Sept 2022).

131 NICE. Type 1 diabetes in adults:diagnosis and management (NG17). 2016. Available at: **https://www.nice.org.uk/guidance/ng17** (accessed Sept 2022).

132 NICE. Type 2 diabetes in adults: management (NG28). 2017. Available at: **https://www.nice.org.uk/guidance/ng28** (accessed Sept 2022).

133 GOV.UK. Diabetes and driving. 2018. Available at: **https://www.gov.uk/diabetes-driving** (accessed Sept 2022).

134 Diabetes UK. Driving and diabetes. 2019. Available at: **https://www.diabetes.org.uk/Guide-to-diabetes/Life-with-diabetes/Driving** (accessed Sept 2022).

135 NICE. Diabetes (type 1 and type 2) in children and young people: diagnosis and management (NG18). 2016. Available at: **https://www.nice.org.uk/guidance/ng18/chapter/1-Recommendations** (accessed Sept 2022).

136 Battezzati A, Mari A, Zazzeron L, Alicandro G, Claut L, Battezzati PM et al. Identification of insulin secretory defects and insulin resistance during oral glucose tolerance test in a cohort of cystic fibrosis patients. European Journal of Endocrinology 2011; 165: 69–76.

137 van den Berg JMW, Morton AM, Kok SW, Pijl H, Conway SP, Heijerman HGM. Microvascular complications in patients with cystic fibrosis-related diabetes (CFRD). J Cyst Fibros 2008; 7: 515–9.

138 Quon BS, Mayer-Hamblett N, Aitken ML, Smyth AR, Goss CH. Risk Factors for Chronic Kidney Disease in Adults with Cystic Fibrosis. American Journal of Respiratory and Critical Care Medicine 2011; 184: 1147–1152.

139 Wilcock MJ, Ruddick A, Gyi KM, Hodson ME. Renal diseases in adults with cystic fibrosis: a 40 year single centre experience. Journal of Nephrology 2015; 28: 585–591.

140 Lind-Ayres M, Thomas W, Holme B, Mauer M, Caramori ML, Moran A. Microalbuminuria in Patients With Cystic Fibrosis. Diabetes Care 2011; 34: 1526–1528.

141 National Kidney Foundation. Screening for Microalbuminuria in Patients with Diabetes. 2007 Available at: **https://www.kidney.org/sites/default/files/12-10-2089_ScreeningForMicroalbuminuriaDiabetes.pdf** (accessed Sept 2022).

142 Kelly A, Moran A. Update on cystic fibrosis-related diabetes. Journal of Cystic Fibrosis 2013; 12: 318–331.

143 Kayani K, Mohammed R, Mohiaddin H. Cystic Fibrosis-Related Diabetes. Frontiers in Endocrinology 2018; 9. doi:10.3389/fendo.2018.00020.

144 NICE. Cardiovascular disease: risk assessment and reduction, including lipid modification (CG181). 2016. Available at: **https://www.nice.org.uk/guidance/cg181/chapter/2-Implementation-getting-started#measuring-non-high-density-lipoprotein-cholesterol-when-lipid-profiling-for-the-primary-prevention** (accessed Sept 2022).

145 NICE. Hypertension in adults: diagnosis and management (NG136). 2022. Available at: **https://www.nice.org.uk/guidance/ng136** (accessed Sept 2022).

146 Quittner AL, Abbott J, Georgiopoulos AM, Goldbeck L, Smith B, Hempstead SE et al. International Committee on Mental Health in Cystic Fibrosis: Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus statements for screening and treating depression and anxiety. Thorax 2016; 71: 26–34.

147 Wang X, Liu Z, Li Y, Li G, Huang Y. Association of comorbidity of mood and anxiety disorders with suicidal behaviors. Journal of Affective Disorders 2018; 227: 810–816.

148 Kyrios M, Nankervis A, Reddy P, Sorbello LM. The Relationship of Depression to Treatment Adherence, Quality of Life and Health Outcomes in Type 1 Diabetes Mellitus. E-Journal of Applied Psychology 2006; 2: 3–14.

149 Maercker A, Lorenz L. Adjustment disorder diagnosis: Improving clinical utility. The World Journal of Biological Psychiatry 2018; 19: S3–S13.

150 Zelviene P, Kazlauskas E. Adjustment disorder: current perspectives. Neuropsychiatric Disease and Treatment 2018; Volume 14: 375–381.

Cystic Fibrosis Trust

Cystic Fibrosis Trust is the charity uniting people to stop cystic fibrosis. Our community will improve care, speak out, support each other and fund vital research as we race towards effective treatments for all.

We won't stop until everyone can live without the limits of cystic fibrosis.

Cystic Fibrosis Trust
One Aldgate
2nd Floor
London EC3N 1RE

020 3795 1555

cysticfibrosis.org.uk

We welcome your feedback on our resources. You can also ask for this resource in large print or as a text file.

Email **infoteam@cysticfibrosis.org.uk**

Uniting for a life unlimited