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MANAGEMENT OF CYSTIC FIBROSIS RELATED DIABETES MELLITUS

Report of the UK Cystic Fibrosis Trust Diabetes Working Group

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* Printed with permission from Driver and Vehicle Licensing Agency Swansea
Grading scheme for recommendations used in the Management of Cystic Fibrosis Related Diabetes Mellitus (CFRD)

The criteria for the grading of recommendations in this document are based upon a paper by Petrie et al published on behalf of the Scottish Intercollegiate Guidelines Network.

### Levels of evidence

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<tr>
<th>Level</th>
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<td>Ia</td>
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<tr>
<td>IIa</td>
<td>Evidence obtained from at least one well designed controlled study without randomisation.</td>
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<td>IIb</td>
<td>Evidence for at least one other type of quasi-experimental study.</td>
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<td>III</td>
<td>Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies.</td>
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<td>IV</td>
<td>Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.</td>
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<td>A (levels Ia, Ib)</td>
<td>Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.</td>
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<td>B (levels IIa, IIb, III)</td>
<td>Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of the recommendation.</td>
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<tr>
<td>C (level IV)</td>
<td>Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality.</td>
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MANAGEMENT OF CYSTIC FIBROSIS RELATED DIABETES MELLITUS

SUMMARY

Numbers refer to Sections in the main document.

1. The prevalence of cystic fibrosis related diabetes (CFRD) rises as age of survival increases. CFRD is a distinct type of diabetes with features of both Type 1 and Type 2 diabetes. The onset is insidious and the glycaemic status varies being influenced by the clinical state of the patient. Delaying the diagnosis can result in an avoidable deterioration in both pulmonary function and clinical status – hence the need for regular screening by annual glucose tolerance tests after the age of 12 years. Resources of both the Specialist CF and Diabetes Teams are essential for optimal management.

2. Progressive fibrosis and fatty infiltration of the exocrine pancreas lead to progressive disruption and destruction of islet architecture leading to loss of endocrine cells secreting insulin, glucagon and pancreatic polypeptide.

3. The development of CFRD is associated with worse lung function and poorer nutritional status when compared to non-diabetic patients with cystic fibrosis. Recent prospective data found that patients with CFRD have a median survival age of 24 years as compared to 34 years in non-diabetic controls with cystic fibrosis. The diagnosis of CFRD can be difficult to establish in the early stages, but early intervention in CFRD can have a profound impact on patient wellbeing and protects against weight loss and deterioration in lung function. Oral glucose tolerance tests (OGTT) and serial glucose monitoring are the most specific and sensitive tools presently available for screening for CFRD, as fasting and random glucose levels and glycosylated haemoglobin (HbA1c) measurements have reduced sensitivity and specificity. The glycaemic status of a child or adult with CF should be investigated at any time or age if there are symptoms of hyperglycaemia, deterioration in respiratory function, unexplained weight loss or growth failure, before commencing supplemental tube feeds, during infective episodes, during steroid therapy, before major surgery, pregnancy and with symptoms of hypoglycaemia.

4. Treatment aims at eradicating symptoms of hyperglycaemia, maintaining adequate nutrition, growth and respiratory function and should be commenced in those with a diabetic OGTT and/or regular hyperglycaemia. Treatment should also be considered when an impaired OGTT is associated with weight loss or deteriorating clinical condition or with high blood glucose levels. It is important to determine any factors that may have affected the OGTT result e.g. concomitant infection or steroid treatment. Insulin remains the treatment of choice although some patients may be controlled with oral tablets initially or where there are practical problems with taking insulin. Good control will reduce the chances of long-term complications. Referral to a Diabetologist or Physician with experience in management of CFRD should be made for all patients diagnosed as having CF related diabetes.

5. A diet, advised by a Dietitian experienced in CFRD, will be high in energy, high in fat and with planned use of refined carbohydrates. Conflicts between dietary therapy of CF and diabetes should usually be resolved in favour of the CF diet and the insulin regimen adjusted to the diet rather than the diet to the insulin.
6. Knowledge of and success with the practical management of insulin administration, glucose monitoring, hypoglycaemia, exercise and intercurrent illness are extremely important and determine the degree of control achieved in the management of the CF related diabetes.

7. Annual Review of the patient with CF should include additional features relating to the control and effects of the CF related diabetes.

8. Diabetic ketoacidosis is very rare in CFRD and should be treated according to local protocols as recommended by Diabetes UK (http:www.diabetes.org.uk/dka_paed/index.html). Chronic microvascular ocular and renal complications have been reported in CFRD and all patients should receive annual screening of these systems.

9. Women with CFRD should optimise their diabetic control in the preconceptional period and during pregnancy and be managed in close collaboration between the CF, Diabetes and Obstetric Teams. Glycaemic status of all pregnant women with CF should be determined – preferably before they become pregnant.

10. Psychological problems are common in children and adults with CFRD and may require input from the psychologist in adjusting to the diagnosis of diabetes and coping with the management of both CF and CF related diabetes.

11. People receiving treatment for CFRD with insulin or oral hypoglycaemics qualify for free NHS prescriptions for all their medications.
Cystic fibrosis (CF) is the most common, life-threatening, recessively inherited disease of Caucasian populations, with a carrier rate of 1 in 25 and an incidence of 1 in 2,500 live births. In 1992 there were over 6,500 people with CF in the United Kingdom, with 65% under 16 years. Births of slightly over 300 per year outnumber deaths by 160, which suggest an estimated population of over 7,500 patients in the UK at present (Dodge et al, 1997 [III]). The proportion and number who are adults is increasing and now equals the number of children. Median survival has improved dramatically and has been predicted to be at least 40 years for children born in the 1990s (Elborn et al, 1991 [III]).

Cystic fibrosis is the result of mutations affecting a gene, which encodes for a chloride channel known as the cystic fibrosis transmembrane conductance regulator (CFTR), which is essential for the regulation of salt and water movements across cell membranes (Rommens et al, 1989 [III]; Riordan et al, 1989 [III]; Kerem et al, 1989 [III]). Improper or faulty regulation results in thickened secretions in organs such as the lung and pancreas. In the respiratory tract this impairs the clearance of microorganisms leading to recurrent infection, bronchial damage, bronchiectasis and eventually death from respiratory failure. In the pancreas, the exocrine ducts become blocked and there may be severe damage even before birth (Andersen, 1938 [III]; Imrie et al, 1979 [III]). Most men with CF are infertile due to failure of the vas deferens, seminal vesicle, ejaculatory duct and body and tail of the epididymis to develop (Oppenheimer & Esterly, 1969 [III]).

There is a wide range of clinical presentation and severity. The majority present in early childhood with respiratory tract infections, which are slow to clear or persistent, or with intestinal malabsorption and failure to thrive. Some infants (c.15%) present at birth with meconium ileus. A few patients are diagnosed in adult life. Most of the morbidity and more than 90% of the mortality of CF is related to chronic pulmonary sepsis and its complications. Eventual infection with *Pseudomonas aeruginosa* is almost inevitable for reasons that are ill understood although with early antibiotic treatment the organism can be eradicated in many patients and chronic *P. aeruginosa* infection and respiratory deterioration are not inevitable and can be prevented or delayed for many years (Littlewood et al, 1985 [IV]; Valerius et al, 1991 [Ib]). Thus, the provision of optimal respiratory care is essential from an early age if infections are to be identified promptly, treated early and effectively to avoid chronic infection. The maintenance of a good nutritional state also plays a major part in maintaining respiratory health (Corey et al, 1988 [III]).

With increasing age patients may suffer a variety of complications including diabetes mellitus (DM), osteoporosis, oesophageal reflux and oesophagitis, nasal polyposis, episodic and chronic distal intestinal obstruction syndrome, chronic liver disease, portal hypertension, gallstones, pneumothorax, haemoptysis, allergic bronchopulmonary aspergillosis (ABPA), respiratory and cardiac failure, inflammatory arthritis, and male infertility. Behavioural and psychological problems are common in both children and adults.

Diabetes mellitus is a well-recognised complication of cystic fibrosis. As survival in CF increases the prevalence of cystic fibrosis related diabetes (CFRD) increases so that CFRD is now a common, expected complication. As individuals with CFRD survive longer they are at increasing risk of the complications of diabetes: also the nature of CFRD changes, usually becoming more complex and requiring more treatment.
1.2 Prevalence of CFRD and impaired glucose tolerance in cystic fibrosis

Cystic fibrosis related diabetes develops in individuals with CF as a consequence of pancreatic pathology. It is more common and develops at an earlier age in individuals who are pancreatic insufficient. The prevalence of CFRD increases with age. The median age of diagnosis is reported as being between 18 and 21 years of age (Lanng et al, 1995 [III]; Koch et al, 2001a [IV]). Reported prevalence may be influenced by undetected cases. As survival in CF improves the number of individuals with CFRD has increased. Life table analysis suggests that 70–90% of individuals surviving to age 40 would have diabetes (dependent on the proportion of pancreatic insufficient individuals) (Lanng et al, 1995 [III]).

1.3 Clinical difficulties in the diagnosis of CFRD

Cystic fibrosis related diabetes is a distinct type of diabetes but shares certain clinical features of both Type 1 and Type 2 diabetes. It differs from Type 1 (Insulin Dependent or Juvenile Onset Diabetes) in that onset is usually insidious; many individuals are asymptomatic at diagnosis. In others the first sign may be a decline in pulmonary function (Milla et al, 2000 [III]). It differs from Type 2 diabetes in that weight loss is often an early feature and reactive hypoglycaemia is not unusual. Particular difficulties may arise in the diagnosis of CFRD in that the clinical status or treatment of an individual may alter the glycaemic status, so that an individual who has overt diabetes during an infective exacerbation may return to normal glucose tolerance (NGT) weeks or months later (Hardin et al, 1997 [III]).

1.4 Effect of CFRD on the health of individuals with cystic fibrosis

There is clear evidence that early identification of CFRD impacts on health status. Delaying the diagnosis can result in an unnecessary deterioration in both pulmonary function and clinical status. Several studies have also shown that a long-standing deterioration in glucose tolerance and an insidious decline in clinical status frequently occur in patients with CF before the diagnosis of CFRD is made (Lanng et al, 1992 [III]; Milla et al, 2000 [III]; Nousia-Arvanitakis et al, 2001 [III]; Rolon et al, 2001 [III]).

Studies have demonstrated a relationship between the development of CFRD and poor nutritional and respiratory status (Peraldo et al, 1998 [III]; Rosenecker et al, 2001 [III]). A more rapid deterioration in the respiratory status is seen in individuals who are symptomatic with more severely impaired insulin secretion (Rolon et al, 2001 [III]). The deterioration in respiratory status may predate the diagnosis of CFRD (Milla et al, 2000, [III]). Growth rate is reduced in adolescents with CFRD or impaired glucose tolerance (IGT) (Ripa et al, 2002 [III]). Inadequate treatment of diabetes results in symptoms related to hyperglycaemia (polydipsia, polyuria and weight loss). Clinical improvement and reversal of decline in pulmonary function tests has been documented when the diabetes is treated with insulin (Lanng et al, 1994a [III]; Nousia-Arvanitakis et al, 2001 [III]; Dobson et al, 2002a [III]). The development of CFRD also has an adverse impact on survival (Lanng et al, 1992 [III]).

The onset and diagnosis of diabetes in patients with CF represents the development of a second chronic disease with its own burden of monitoring and treatment. This often has significant physical and important psychological implications for many individuals. It is clear that following the diagnosis of CFRD appropriate psychosocial support should be available. The medical team needs to allow the patient a period of adjustment where CFRD control may be erratic whilst they adjust and adapt to the new treatment challenges. This highlights the need for individual assessment of the patient (and family) and the need for individualized treatment plans which progress at an appropriate rate.
1.5 Management of CFRD

Treatment of CFRD differs from the treatment of Type 1 or Type 2 diabetes in that the dietary requirements of CF have to be incorporated into the treatment strategy. In addition, as insulin deficiency is a key feature of CFRD, insulin is often used early in the treatment (Cucinotto et al, 1994 [III]; Holl et al, 1997 [IIb]; Nousia-Arvanitakis et al, 2001 [III]). Treatment requirements for CFRD often change with clinical status so that an individual may require insulin treatment for optimal management only during an infective exacerbation. Education and self-monitoring are key elements in the treatment of diabetes.

1.6 Shared care arrangements

The resources of both the CF and Diabetes Teams are essential for the management of people with CF related diabetes. Good communication between teams with clear roles, responsibilities and treatment aims are needed for optimal management particularly at times of intercurrent illness and during admissions to hospital and to ensure that all elements of the Annual Review are carried out and acted upon as indicated.

1.7 Complications of CFRD and its treatment

As in other forms of diabetes there is a risk of long-term complications. Microvascular complications are reported and, as in other forms of diabetes, appear to correlate with duration and control of the hyperglycaemia. Reported complications of diabetes are likely to become more common as the survival of individuals with CFRD increases. Macrovascular complications are rare but may become more common as patients with CFRD progress into the 5th and 6th decades of life. Hypoglycaemia may occur as a side effect of insulin treatment.

1.8 Cross-infection issues

Increasing realisation of the risk of cross-infection between people with CF who are chronically infected with a variety of different pathogenic organisms has led to strict segregation according to microbiological status in many Specialist CF Centres. Similar precautions, of segregating people with CF according to their microbiological status, will need to be observed when they attend all clinics including a diabetes clinic. This will put restrictions on group education sessions (Pseudomonas aeruginosa Infection in People with Cystic Fibrosis. Suggestions for Prevention and Infection Control. Cystic Fibrosis Trust, 2001 [IV]); The Burkholderia cepacia Complex. Suggestions for Prevention and Infection Control. Cystic Fibrosis Trust, 2004 [IV]).
2. PATHOPHYSIOLOGY OF CF RELATED DIABETES MELLITUS

2.1 Differences from Type 1 and Type 2 diabetes mellitus

The primary cause of glucose intolerance in CFRD is insulinopenia with variable insulin resistance (Lanng et al, 1993b [III]; Moran et al, 1994 [IIb]; Lanng et al, 1994a [III]; Holl et al, 1995 [III]; Hardin et al, 1997 [IIa]; Moran et al, 1998 [IV]; Yung et al, 2002 [III]). Pathogenesis of CFRD is still not fully understood. It is distinctly different from Type 1 or Type 2 diabetes but shares some features of both. The reason for these differences is that glucose metabolism is variably affected by the state of the respiratory infection, increased energy expenditure, malnutrition, glucagon deficiency and gastrointestinal abnormalities. It is recognised as a distinct entity by the World Health Organisation (WHO/NCD/NCS/99.2 [IV]).

2.2 Relation to CF mutation

Cystic fibrosis transmembrane regulator (CFTR) mutations occur in six main classes (Vankeberghen et al, 2002 [IV]) and CFRD mainly occurs in people with severe class I–III mutations with background exocrine pancreatic deficiency. The European Epidemiologic Registry of Cystic Fibrosis (ERCF) reported 20% of patients carrying class I, II or III gene mutations developed CFRD in contrast to only 1.5% of patients carrying class IV and V mutations (Koch et al, 2001a [IV]).

2.3 Pancreatic pathology

The product of the CF gene, CFTR mRNA, is present in the centroacinar cells of the intercalated duct in the pancreas (Marino et al, 1991 [IIb]). Deficiency or abnormal function of CFTR results in thick viscous secretions causing obstructive damage to the pancreas. The underlying pathology is progressive fibrosis and fatty infiltration of the exocrine pancreas resulting in disruption and destruction of islet architecture leading to loss of endocrine secreting cells i.e. insulin producing beta cells, glucagon producing alpha cells and pancreatic polypeptide producing cells (Oppenheimer & Esterly, 1975 [III]; Kopito & Shwachman, 1976 [III]; Iannucci et al, 1984 [IV]; Abdul-Karim et al, 1986 [III]; Lohr et al, 1989 [III]; Couse et al, 1996 [III]). The correlation between degree of beta cell destruction and development of diabetes is poor. Autopsy studies failed to show a greater loss of pancreatic islets in patients with CFRD compared to non-diabetic patients with cystic fibrosis. Islet amyloid polypeptide (IAPP) which is characteristic of Type 2 diabetes was found in 17% of borderline CF diabetic cases and 69% of the patients with full CFRD but absent in CF patients without diabetes (Couse et al, 1996 [III]). It is not clear whether it contributes to the beta cell destruction or is simply a marker of the disease. There is no strong association with positive family history or HLA class II blood group gene (Lanng et al, 1993a [III]). Islet cell cytoplasmic antibody (ICCA), which is present in 60–80% of newly diagnosed Type 1 diabetes occurred in some patients with CFRD but failed to show consistent association (Lanng et al, 1993b [III]; Geffner et al, 1988 [III]). Glutamic acid decarboxylase (GAD) and islet cell (IA2) antibody have been detected in patients with CFRD suggesting that immune factors may play a role (Nousia-Arvanitakis et al, 2000 [III]). The association of CFRD with the rise and fall of hsp60 autoimmunity suggests that the pathogenesis of the diabetes may not be merely mechanical but related to bacterial hyperimmunisation (Jensen et al, 2001 [III]).

2.4 Pathophysiology of insulin secretion

In people with CF, both with and without glucose intolerance, there is a reduction in beta cell mass and evidence of beta cell dysfunction. Fasting insulin and proinsulin levels are normal or reduced.
and the C-peptide level is reduced in non-CFRD patients with pancreatic insufficiency (Lanng et al, 1993b [III]; Holl et al, 1997 [III]). There is delayed and blunting of peak insulin secretion following oral glucose tolerance test (OGTT) in people with CF compared to healthy controls (Holl et al, 1995 [III]). The time to peak insulin secretion is increasingly delayed from the 30–60 minutes in healthy subjects to 90–120 minutes in people with CF related diabetes (Lanng et al, 1993b [III]). This effect is more pronounced with worsening glycaemic status (De Schepper et al, 1992 [III]; Lanng et al, 1993b [III]; Hamidi et al, 1993 [III]; Yung et al, 2002 [IIb]). Following oral glucose, glucagon suppression is also impaired (Lanng et al, 1993b [III]). An elevation in hepatic glucose production may also contribute to glucose intolerance in patients with CF related diabetes (Hardin et al, 1999a [IIb]).

2.5 The role of insulin sensitivity

The role of insulin sensitivity in development of CFRD remains unclear and results are conflicting. In people with CFRD insulin sensitivity has been found to be variable and usually normal or decreased (Lanng et al, 1994b [III]; Moran et al, 1994 [III]; Ahmad et al, 1994 [IIb]; Hardin et al, 2001 [IIa]; Yung et al, 2002 [IIa]). Possible reasons for variable results are different glycaemic clamp techniques, different clinical and glycaemic status of patients and different method of calculation of insulin sensitivity. Other factors, which influence the development of insulin resistance, include steroid therapy, pregnancy, liver dysfunction and exacerbations of lung infection. Decreased insulin sensitivity is associated with elevation in tumour necrosis factor alpha (TNF alpha), indicating pulmonary inflammation may play a role. As the clinical status varies considerably the course of CFRD is also variable.

It is thought that insulin resistance is probably not of primary pathological importance in the development of CFRD (Lanng et al, 2001 [IV]). Among the patients with CF who have glucose intolerance some may progress to diabetes and some revert to normal glucose tolerance (Lanng et al, 1995 [IV]).

Current opinion is that progressive exocrine damage leads to reduction in beta cell mass and function causing primary insulin deficiency. Insulin resistance occurs as a result of changing clinical status exacerbated by recurrent infection and corticosteroids. Combined insulin deficiency and insulin resistance predispose normal glucose tolerance to deteriorate to impaired glucose tolerance with resulting hyperglycaemia. Hyperglycaemia itself can also cause beta cell exhaustion (Marshak et al, 1999 [III]). As not all pancreatic insufficient people with CF develop CFRD it is thought that there may be a genetic predisposition in some CF patients who progress to permanent overt diabetes (Moran et al, 2000 [IV]; Lanng et al, 2001 [IV]).
3. EPIDEMIOLOGY, DEFINITION AND DIAGNOSIS

3.1. Definition

The term diabetes mellitus describes a metabolic disorder of multiple aetiology characterised by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both (WHO/NCD/NCS/99.2 1999 [IV]).

3.2 Prevalence

Cystic fibrosis related diabetes is a common and well-recognised complication of cystic fibrosis (Finkelstein et al, 1988 [III]; Hodson, 1992 [IV]; Lanng et al, 1994b [III]; Hayes et al, 1994 [III]; Lanng et al, 1995 [III]; Moran et al, 1998 [IV]; Koch et al, 2001a [IV]). It occurs in around 10–15% of all people with cystic fibrosis. In one study of 278 patients aged over 2 years, 13.7% had impaired glucose tolerance (IGT) and 14.7% CFRD (Lanng et al, 1994b [III]); in the same Danish clinic the prevalence of CFRD increased from 11% to 24% over 5 years with an age-dependant incidence of 5 per cent. The prevalence increased significantly with age and 50% of patients had developed CFRD by 30 years of age (Lanng, 2001 [III]). The median age of onset is between 18 and 21 years (Lanng et al, 1995 [III]; Koch et al, 2001a [IV]). Cystic fibrosis related diabetes is usually associated with pancreatic exocrine dysfunction; the use of oral corticosteroids will increase the tendency to develop diabetes. The incidence and prevalence of glucose intolerance in patients with CF is much higher than any other age matched control group (Lanng et al, 1991 [III]). The incidence of CFRD is higher in those with CF liver disease (Holstein et al, 2002 [IV]).

Reported prevalence of diabetes in children with cystic fibrosis under 10 years of age is low. There are only a few studies where small numbers of children have been screened using variable criteria. In this age group children with Type 1 diabetes will disproportionately increase the apparent prevalence of diabetes. One study screened 5 to 9 year old children with CF using an OGTT and found that as many as 9% had diabetes and 34% abnormal glucose tolerance (Moran et al, 1998 [IV]). These findings have not been repeated but do indicate that young age does not preclude the diagnosis of CF related diabetes.

After 10 years of age there is an age related increase in the prevalence of CFRD of 5% per year with 24% of people having CFRD by age 20 years (Lanng et al, 1995 [III]). An Australian study found a prevalence of 5.5% in 18 young adolescents (aged 9.5–15 years) screened by OGTT (Ripa et al, 2002 [III]). The European Epidemiologic Registry of Cystic Fibrosis reported diabetes in 5% and 12.6% in age groups 10–14 and 15–19 respectively but ascertainment of diagnosis was variable (Koch et al, 2001a [IV]). Cystic fibrosis related diabetes appears to present at a younger age in girls (Lanng et al, 1995 [III]) which is probably a reflection of their earlier onset of puberty and the associated increase in insulin resistance at this time.

3.3 The problems of diagnosis in CFRD

Cystic fibrosis related diabetes is distinct from Type 1 or Type 2 diabetes but has features of both (see Section 2.1). The diagnosis in the early stages may be difficult to establish. It should be borne in mind that the WHO definition and diagnostic criteria have changed over time to reflect the risk of microvascular and macrovascular complications (see Appendix – Section 12.2). For people with CFRD other consequences of insulin deficiency are relevant e.g. nutrition, lung function and ultimately survival.
In non-CF individuals diabetes mellitus is diagnosed by finding either an elevated random blood glucose or an elevated fasting blood glucose or a diabetic glucose tolerance test (see Section 3.5). These methods are helpful in making the diagnosis of Type 1 and Type 2 diabetes but are not wholly appropriate for patients with cystic fibrosis. Patients with CF can have transient elevation of random and fasting glucose levels without having a diabetic OGTT (the opposite situation can also occur). This means that fasting glucose and random glucose measurements, which are routinely used for the diagnosis of Type 1 and Type 2 diabetes, have reduced sensitivity and specificity in cystic fibrosis. Glucose tolerance and insulin resistance often vary in CF, being influenced by factors such as nutritional status, infection and liver dysfunction.

The consensus published opinion would suggest that the routine use of OGTT and serial glucose monitoring appears to be the most specific and sensitive tool presently available for screening for CF related diabetes (Garagorri et al, 2001 [III]; Lanng et al, 1995 [III]; Peraldo et al, 1998 [III]; Cucinotta et al, 1994 [III]; Solomon et al, 2003 [IV]; Yung & Hodson, 1999 [III]; Etherington et al, 2000 [III]; Verma et al, 2000a [III]).

### 3.4 The reasons for regular screening for CFRD

There is clear evidence that early identification and treatment of CFRD impacts on health status. Delaying regular screening for CFRD can result in an unnecessary deterioration in both pulmonary function and clinical status.

Several studies have also shown that a long-standing deterioration in glucose tolerance and an insidious decline in clinical status frequently occur in patients with CF before the diagnosis of CFRD is made (Lanng et al, 1992 [III]; Milla et al, 2000 [III]; Nousia-Arvanitakis et al, 2001 [III]; Rolon et al, 2001 [III]). This deterioration can be indolent and may occur for up to several years before the diagnosis is made. Patients who develop overt symptoms of hyperglycaemia on presentation have been found to have a relatively greater decline in pulmonary function and weight loss as compared to those identified on screening (Lanng et al, 1992 [III]; Nousia-Arvanitakis et al, 2001 [III]; Rolon et al, 2001 [III]). Therefore the 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 CF related diabetes. The presence of CFRD is associated with worse lung function and poorer nutritional status when compared to non-diabetic patients with cystic fibrosis (Lanng et al, 1992 [III]; Lanng et al, 1994b [III]; Milla et al, 2000 [III]; Rosenecker et al, 2001 [III]; Navarro et al, 2001 [IV]; Schaedel et al, 2002 [III]). Cystic fibrosis related diabetes is an important determinant of severity of lung disease and a marker of excess mortality (Koch et al, 2001b [IV]). Recent prospective data found that patients with CFRD have a median survival age of 24 years as compared to 34 years in non-diabetic controls with cystic fibrosis (Koch et al, 2001b [IV]). Early intervention in CFRD can have a profound impact on patient wellbeing and protects against weight loss and deterioration in lung function (Lanng et al, 1992 [III]; Rolon et al, 2001 [III]; Nousia-Arvanitakis et al, 2001 [III]). Microvascular complications such as retinopathy, nephropathy and neuropathy are being reported with increasing frequency in patients with CF related diabetes (Chazan et al, 1970 [III]); Sullivan et al, 1989 [IV]; Lanng et al, 1994b [III]; Yung et al, 1998 [IV]; Moran et al, 1999 [IV].

### 3.5 Routine assessment of glucose status in cystic fibrosis

In most Specialist CF Centres older children, adolescents and adult patients with CF undergo regular, usually annual, screening for CFRD, and in some clinical situations (discussed below) detailed assessment of glycaemic status is required between Annual Reviews.
Random or fasting glucose levels, HbA1c or OGTTs are used as part of the assessment of glycaemic status in people with CF not known to have diabetes. Monitoring for glycosuria has poor sensitivity and is not routinely used as a screening tool. The diagnosis should not be based solely on the presence of glycosuria, raised capillary blood glucose values or elevated glycosylated haemoglobin (HbA1c).

### 3.5.1 Fasting plasma glucose

A fasting venous plasma glucose of greater than 7 mmol/l indicates diabetes in the non-CF population but fasting glucose levels may not reliably identify early CF related diabetes. According to the WHO definition, only 16% of patients with CFRD would be identified using this method as many adults with CFRD do not have fasting hyperglycaemia and would be missed if only the fasting venous plasma glucose was used as a screening tool (Lanng et al, 1995 [III]; Hardin & Moran, 1999b [III]).

### 3.5.2 Glycosylated haemoglobin

Glycosylated haemoglobin (HbA1c) has been used as a screening test for diabetes but is severely limited by the fact that levels are often normal at the time of diagnosis (Lanng et al, 1995 [III]; Etherington et al, 2000 [III]; Garagorri et al, 2001 [III]; Verma et al, 2002a [III]). HbA1c does not appear to differentiate between patients with an impaired and normal oral glucose tolerance test (Garagorri et al, 2001 [III]). An elevated HbA1c has a specificity of 78% in the diagnosis of CF related diabetes. In the Danish study only 16% of patients had elevated HbA1c values at the time of diagnosis, while 14% of those with established CFRD had normal HbA1c values (Lanng et al, 1995 [III]); similar results have been described by other authors (Holl et al, 2000 [III]).

### 3.5.3 Oral glucose tolerance test

The OGTT (see also Appendix – Section 12.1) is well established as the gold standard for the diagnosis of diabetes mellitus and is also the accepted screening test for CF related diabetes (Lanng et al, 1995 [III]; Etherington et al, 2000 [III]; Verma et al, 2002a [III]).

However, in a person with CF, a “diabetic OGTT” does not mean that the individual necessarily has diabetes, but has, at that time, abnormal glucose handling.

Some people with CF who have a diabetic OGTT will revert to normal with time and they will require careful ongoing assessment. The finding of impaired glucose tolerance (IGT) is common and may progress to a diabetic OGTT or, in 58% of cases, revert to normal (Lanng et al, 1995 [III]); but an impaired OGTT implies a higher risk for developing diabetes than does normal glucose tolerance (NGT). The risk is related to an increased glucose area under the curve during OGTT and deterioration in glucose tolerance over time (Cucinotta et al, 1999 [III]).

### 3.5.4. Table – World Health Organisation protocol for the oral glucose tolerance tests (see also Appendices – Sections 12.1 and 12.2)

<table>
<thead>
<tr>
<th>120 min venous blood sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma venous sample</td>
</tr>
<tr>
<td>&lt;7.8 mmol/l</td>
</tr>
<tr>
<td>≥7.8 mmol/l to &lt;11.1 mmol/l</td>
</tr>
<tr>
<td>≥11.1 mmol/l</td>
</tr>
</tbody>
</table>
3.6 Assessment on clinical indications
Glucose tolerance can change in CF in relation to altered clinical status.

Recommendations
Assessment of glycaemic status between Annual Reviews should be considered in the following circumstances:

- If there are symptoms of hyperglycaemia: polyuria, polydipsia, glycosuria and weight loss should be investigated fully [B].
- Unexplained deterioration in respiratory function [B].
- Unexplained weight loss or growth failure [B].
- Prior to commencing supplemental enteral tube feeding (see Section 5) [B].
- During infective exacerbations or systemic corticosteroid use [B].
- Before major surgery [B].
- Symptoms of hypoglycaemia [B].
- Pregnancy (see Section 9) [B].

A profile of blood glucose monitoring, before and 1.5 to 2 hours after meals and during overnight feed will need to be undertaken to define the extent of hyperglycaemia, before therapy can be instituted (Lanng et al, 1995 [III]).

3.6.1 Table – Possible action on the results of the routine oral glucose tolerance test

<table>
<thead>
<tr>
<th>Possible action on results of screening OGTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal glucose tolerance (NGT)</td>
</tr>
<tr>
<td>Impaired oral glucose tolerance (IGT)</td>
</tr>
<tr>
<td>Diabetic glucose tolerance (CFRD) in person who is asymptomatic</td>
</tr>
</tbody>
</table>

3.7 Criteria for starting treatment in CFRD
The decision to treat should be based on consideration of blood glucose levels, and of the impact of glucose intolerance on the individual's overall condition. Patients should be referred to a Consultant experienced in the management of CF related diabetes.
Recommendations (see also Section 4.7)

Treatment should be considered:

- When impaired glucose tolerance on OGTT is associated with weight loss or deteriorating clinical condition [B].
- When there are episodes of transient hyperglycaemia [B].
- When a diabetic glucose tolerance on OGTT, but normal glucose monitoring, is associated with weight loss or deteriorating clinical condition [B].

Definite indications for initiating treatment are:

- CF related diabetes i.e diabetic OGTT and/or regular hyperglycaemia.
- Pregnancy with impaired glucose tolerance or diabetes (see Section 9).

3.8 Summary and comment

The consensus published opinion would suggest that the routine use of the OGTT and serial glucose monitoring appears to be the most specific and sensitive tool presently available for screening for CF related diabetes. An annual OGTT, carried out at a time of clinical stability, is the most reliable method for detecting CFRD and should be part of routine clinical practice for patients over 12 years (Standards for the Clinical Care of Children and Adults with Cystic Fibrosis. Cystic Fibrosis Trust, May 2001 [IV]).

Elevated fasting or random plasma glucose levels with abnormal serial glucose monitoring, symptoms of hyperglycaemia or elevated HbA1c would also indicate CF related diabetes. It should be remembered that IGT/CFRD can be transient and may resolve albeit temporarily. Close monitoring of patients with such features should follow.

Insulin treatment is indicated where there is biochemical evidence of a diabetic OGTT and/or regular hyperglycaemia associated with a clinical decline, but may be withdrawn if insulin deficiency and insulin resistance normalise. There should be a low threshold for introducing insulin therapy for patients with regular hyperglycaemia even without clinical signs or symptoms of CFRD, in order to minimise any consequent deterioration of pulmonary or nutritional state.

Recommendations

- All people with CF over the age of 12 years should be screened annually, usually by performing an OGTT [B].
- An abnormal OGTT should be followed by a period of home blood glucose monitoring [C].
- Staff should be aware that, with an OGTT, people with CF can only be identified as having a normal, impaired or diabetic glucose tolerance and may move between these states [B].
- It is important to consider any factors that may have affected the OGTT result e.g. concomitant infection, use of steroid treatment etc. and consider further blood glucose monitoring before a diagnosis of CFRD is made [C].
- Referral to a Consultant Diabetologist or Physician with experience in management of CFRD should be made for all patients considered to have CFRD [C].
4. MEDICAL TREATMENT OF CFRD

4.1 Background
Over the past decade, large scale, long-term randomised control studies comparing treatments for patients with Type 1 and Type 2 diabetes have been published. The Diabetes Control and Complications Trial (DCCT) compared the effect of intensive and standard treatment in 1441 individuals with Type 1 diabetes (Diabetes Control and Complications [DCCT] Research Group, 1993 [Ib]).

In the United Kingdom Prospective Diabetes Study (UKPDS) patients with Type 2 diabetes were randomised to either intensive blood glucose control strategies using sulphonylureas or insulin and compared with those receiving conventional treatment (UK Prospective Diabetes Study Group, 1998 [Ib]). To date there have been no large-scale long-term randomised control studies to compare treatment strategies for CF related diabetes. Cystic fibrosis related diabetes differs from both Type 1 and Type 2 diabetes in its aetiology and pathogenesis (see Section 2.1). However, there are clinical features that are shared between the conditions and certain key differences, which can guide the management of CF related diabetes.

4.2 Principles of treatment in diabetes
In the simplest terms treatment of diabetes is based on 3 core aims:

- The relief of symptoms and avoidance or treatment of acute (metabolic) complications.
- The prevention of long-term (microvascular and macrovascular) complications of diabetes.
- Avoidance of side effects of treatment (which involves balancing the risks and benefits of treatments for each individual).

In both Type 1 and Type 2 diabetes the onset and progression of complications correlate strongly with duration and control of the diabetes and the coexistence of other risk factors such as hypertension and hypercholesterolaemia.

It is now clear that patients with CFRD are at risk of all the microvascular complications of diabetes (see Sections 7 and 8). Although, as yet, there are no long-term randomised control trials examining the effect of improvements in control on the onset and progression of complications, it is likely that improvements in the control of diabetes will delay their onset and reduce their incidence.

4.3 Objectives of treatment
These will vary according to symptoms, risk of complications of diabetes and risk of side effects of treatment. In some individuals with greatly reduced life expectancy symptomatic treatment alone may be appropriate. In others, particularly individuals expected to survive more than 5–10 years from diagnosis of CFRD or women planning for pregnancy, optimal control may minimise the risk of long-term complications. Finally, for those individuals at high risk of hypoglycaemia, modified targets may be used.

4.4 Symptoms of hyperglycaemia
Symptoms of hyperglycaemia (high blood glucose level) include thirst, polyuria, weight loss, visual disturbance, and increased susceptibility to infection. Blood glucose levels do not correlate strongly with symptoms. Symptoms of hyperglycaemia generally do not occur when blood glucose levels are
less than 10 mmol/l; symptoms usually occur with blood glucose levels over 13–15 mmol/l. Many patients remain asymptomatic despite persistently raised blood glucose levels, seldom developing thirst, polyuria or polydipsia. Weight loss or decline in clinical status may be the only features noted. Blood glucose levels of ≥13 mmol/l exceed the renal threshold and may compromise nutrition.

4.5 Hypoglycaemia

Hypoglycaemia (low blood glucose level of <4 mmol/l) is not uncommon in people with CF, both before treatment (reactive hypoglycaemia) and on oral hypoglycaemic agents or insulin (treatment related). In the Diabetes Control and Complication Trial (DCCT) the frequency of hypoglycaemia increased with efforts to optimise the control of the diabetes (DCCT Research Group, 1997 [Ib]). The occurrence of severe hypoglycaemia or loss of awareness of hypoglycaemia is a major, potentially life-threatening complication of diabetes (see Sections 4.9.1, 6.1, 6.8 and 8.5.1).

4.6 Blood glucose levels

Capillary glucose levels should be monitored using a blood glucose monitor that is regularly subject to quality control measures (see Section 6.5). Blood glucose levels should be checked and recorded at different times of the day to ensure that treatment is correctly tailored; many machines have a downloadable facility.

4.6.1. Table – Illustrative example of treatment targets for individuals with CFRD

<table>
<thead>
<tr>
<th></th>
<th>Optimal control</th>
<th>Modified control – people at high risk of hypoglycaemia</th>
<th>Symptomatic Control – when palliative care is appropriate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose</td>
<td>4–6 mmol/l</td>
<td>4–7 mmol/l</td>
<td>&lt;10 mmol/l if pulmonary function tests stable and weight loss not a problem</td>
</tr>
<tr>
<td>2 hour post meal glucose</td>
<td>4–7 mmol/l</td>
<td>7–10 mmol/l</td>
<td>&lt;10 mmol/l if pulmonary function tests stable and weight loss not a problem</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>Mild daytime hypo only</td>
<td>Aim for none</td>
<td>Aim for none</td>
</tr>
<tr>
<td>HbA1c (DCCT aligned)</td>
<td>&lt;7.0%</td>
<td>&lt;8.0%</td>
<td>Irrelevant</td>
</tr>
</tbody>
</table>

4.7 Treatment strategies

In CFRD, as in Type 1 and Type 2 diabetes, the underlying disease state changes with time, with progressive loss of beta cell function and variation in insulin sensitivity. This effect is more marked in CFRD where dramatic changes in insulin sensitivity may occur over a short period of time (such as during an infective exacerbation). Thus, treatment strategies have to take account of the stage of the disease and factors influencing insulin sensitivity. It is important to realise that the need for treatment may vary significantly with time. For example many patients may require insulin treatment during infective exacerbations but no longer require insulin treatment when their infection has settled.
Oral hypoglycaemic agents are the usual first line treatment of Type 2 diabetes, with insulin usually being reserved for the later stages of the disease when oral agents may be insufficient to achieve symptomatic relief or satisfactory glycaemic control. However, in contrast, in CFRD, insulin is the mainstay of treatment.

### 4.7.1 Table – Classification of clinical categories of CF related diabetes mellitus

<table>
<thead>
<tr>
<th>Stage of disease</th>
<th>Pre-meal sugars</th>
<th>Post-meal sugars</th>
<th>Symptoms</th>
<th>Microvascular complication risk</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactive hypoglycaemia (see Section 4.9.1)</td>
<td>Normal</td>
<td>Low</td>
<td>Hypoglycaemia after meals</td>
<td>Unknown-likely to be very low</td>
<td>1</td>
</tr>
<tr>
<td>Impaired glucose tolerance (see Section 4.9.2)</td>
<td>Normal</td>
<td>Intermittently raised</td>
<td>None or weight loss or clinical decline</td>
<td>Unknown-likely to be low</td>
<td>1,2 Consider insulin or tablets with meals</td>
</tr>
<tr>
<td>CFRD without fasting hyperglycaemia (see Section 4.9.3)</td>
<td>Normal</td>
<td>Mostly raised</td>
<td>None or thirst, polyuria, weight loss, or clinical decline</td>
<td>Unknown-likely to be related to duration, control and risk factors</td>
<td>1,2 Insulin or tablets with meals</td>
</tr>
<tr>
<td>CFRD with fasting hyperglycaemia (see Section 4.9.4)</td>
<td>Mostly raised</td>
<td>Mostly raised</td>
<td>Thirst, polyuria, weight loss, or clinical decline</td>
<td>Unknown -likely to be related to duration, control and risk factors</td>
<td>1,2 Insulin or tablets with meals Basal insulin</td>
</tr>
</tbody>
</table>

1. Patients in all these categories must be assessed and advised by a Dietitian experienced in the management of CFRD.
2. Treatment is usually with insulin but may be with tablets in certain circumstances (see Section 4.8)

### 4.8 Treatment Agents

#### 4.8.1 Diet (see also Section 5)

Although dietary regulation is the cornerstone of diabetes management in Type 1 and Type 2 diabetes, the dietary requirements for CFRD have to take into account the other considerations of cystic fibrosis. The standard “healthy eating” low fat, low refined carbohydrate, high fibre diet currently recommended for Type 1 and Type 2 diabetes is inappropriate for the majority of people with CF who often have difficulty maintaining their weight. Changes in insulin secretion in CF and CFRD mean that highly refined carbohydrates and in particular liquid carbohydrates are poorly matched by insulin secretion. Any dietary changes should be discussed with a CF Specialist Dietitian.
4.8.2 Insulin

Insulin secretion is altered in cystic fibrosis (see Sections 2.3, 2.4, 2.5). In one study, comparing 71 patients with CF with 56 normal controls, insulin secretion during an oral glucose tolerance test was delayed in individuals with CF irrespective of glucose tolerance (Holl et al, 1997 [III]). Sequential studies showed a progressive decline in insulin secretion over time in 14 individuals with CF irrespective of glucose tolerance (Arrigo et al, 1993 [Ila]). In individuals with CFRD pulmonary function declines over time particularly prior to the onset of diabetes. Lanng et al, examined the effects of treatment with insulin on lung function and lung infections in 18 individuals with CFRD and 18 matched controls. Decreases in body mass index (BMI) and lung function observed in the 3 months prior to insulin treatment were reversed within 3 months of starting insulin treatment. In addition the percentage of sputum examinations positive for *Haemophilus influenzae* and *Streptococcus pneumoniae* decreased in the patients with CF related diabetes (Lanng et al, 1994c [Iib]).

There are no published data on the use of different insulins in CFRD or on the use of continuous subcutaneous insulin infusion (CSII). However, insulin remains the treatment of choice for patients with CF related diabetes. The choice of treatment regimen depends on the stage of the disease, risks and specific treatment goals for the patient.

4.8.3 Metformin

Metformin is a biguanide that acts principally by improving hepatic insulin sensitivity. There are no published studies of its use in CFRD and it is contraindicated in renal impairment and in situations where tissue hypoxia is likely due to a risk of lactic acidosis. Metformin is not currently recommended for use in CF related diabetes.

4.8.4 Sulphonylureas and other insulin secretagogues

Sulphonylureas act by increasing insulin secretion. They are commonly used alone or in conjunction with metformin in the treatment of Type 2 diabetes. Concern has been expressed over the use of sulphonylureas in CFRD because of evidence that they bind to and inhibit CFTR (Sheppard & Welsh, 1992 [Iib]). There are many case reports and small studies examining the use of sulphonylureas in CF related diabetes (Moran et al, 2001 [Ila]) but there are no studies of long-term efficacy or risk of side effects in such patients. Sulphonylureas and glitinides are sometimes used as a bridge to insulin therapy or where there are practical difficulties using insulin therapy.

4.8.5 Peroxisome proliferator-activated receptor (PPAR) antagonists

These agents are currently recommended for use as second or third line agents in patients with Type 2 diabetes. They act by improving insulin sensitivity. Side effects include risk of hypoglycaemia, abnormality of liver function tests and fluid retention. There are no published studies of their efficacy or safety in patients with CFRD and they are not recommended at present.

4.9 Management of different categories of patient (see Table – Section 4.7.1)

All patients with changes in their glucose tolerance should receive appropriate assessment, education, advice and treatment.

Recommendations for baseline assessment at diagnosis

- **History** – looking for symptoms of diabetes and its complications [C].
- **Assessment of weight and BMI and any recent changes in weight or pulmonary function** [C].

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- Assessment of pubertal status in older children and teenagers [C].
- Physical examination – looking for complications of diabetes [C].
- Confirmation of the diagnosis [B].
- A detailed dietetic assessment (of meal pattern, refined carbohydrates, supplements, nasogastric and gastrostomy feeds) [C].
- Explanation of the diagnosis should be given [C].
- Patients should be informed of relevant issues with regards to self-management and screening for complications [C].

4.9.1 Reactive hypoglycaemia

Patients with reactive symptomatic hypoglycaemia after meals, which results from dysfunctional endogenous insulin secretion, often benefit from a reduction in refined carbohydrates, particularly when taken in isolation between meals. Patients should discuss such changes with a Dietitian with experience in the management of CF to ensure adequate calorie intake is maintained. Symptomatic hypoglycaemia usually relents before development of impaired glucose tolerance (Brun et al, 2000 [III]).

4.9.2 Impaired glucose tolerance

Decline in pulmonary function is well documented in patients with CF with impaired glucose tolerance (IGT). Studies are underway comparing treatment strategies in individuals with impaired glucose tolerance. In many individuals with IGT who are asymptomatic, with stable weight, pulmonary function and a normal HbA1c, treatment may not be indicated at this stage.

In some individuals where weight loss is a problem or there is a persistent decline in pulmonary function, further treatment may be indicated. In view of the risk of hypoglycaemia, short acting insulin analogues Lispro (Humalog Lilly) or Insulin Aspart (NovoRapid Novo Nordisk) are sometimes given with meals known to raise the blood glucose levels. This parallels the situation in gestational diabetes where women with impaired glucose tolerance are given short acting insulin to cover meals which cause hyperglycaemia. There are no long-term studies examining the outcome of individuals with CF treated with insulin for impaired glucose tolerance.

4.9.3 CFRD with normal fasting glucose

Patients should be taught to monitor capillary glucose levels by home blood glucose monitoring (HBGM) (see Section 6.5). They should be treated if they are hyperglycaemic, have a raised HbA1c or decline in pulmonary function or weight less than target weight. There are theoretical benefits to the use of short acting analogues as many patients retain a delayed secretion of insulin after meals. Short acting insulin should be given with meals that have been shown to cause hyperglycaemia on home blood glucose monitoring. The dose of insulin should be titrated so that the post meal reading is <7 mmol/l or the post meal reading is 0–2 mmol/l higher than the pre-meal reading.

4.9.4 CFRD with raised fasting glucose

These patients require both basal insulin and extra mealtime insulin in order to achieve tight control. Patients with predictable meal times and reliable food intake can sometimes be managed...
on twice daily mixed insulin. Many people with CF have variable food intake due to loss of appetite, nausea and the need to fit in other treatments especially in the mornings. Patients with variable food intake usually require a “basal bolus regimen”, where rapid acting insulin is given with meals and intermediate or long acting insulin at bedtime.

4.9.5 Management of children and adolescents

Good management of diabetes in children is essential to ensure that this complication does not impact adversely on growth, as well as nutrition and lung function. Optimal control is desirable because the potentially longer lifetime duration of diabetes will increase the risk of developing complications as adults. Data on the use of oral agents in children are limited and insulin should be considered first line therapy. Insulin has an anabolic effect, which may be of additional benefit for those with growth and nutritional failure.

Unfortunately optimal control may be difficult to achieve in this age group – there may be issues with eating behaviour and compliance, and practical problems because they will be less able or inclined to participate in the management of their diabetes. Insulin doses will need adjustment to keep pace with growth.

In children and adolescents there are a number of factors, which may influence management of diabetes:

- The insulin regimen must be individualised to take account of the degree of glucose intolerance and the eating habits and lifestyle of the child or adolescent.
- Some children and adolescents may already have a disordered eating pattern and use of twice daily, mixed insulin may lead to heightened anxieties for parents about achieving adequate calorie intake, thereby perpetuating battles over mealtimes. Short acting insulin analogues (Lispro or Aspart) have the advantage that a variable dose of fast acting insulin analogue can be more readily adjusted according to amount of food eaten (and may be given after eating if necessary). This will give better control of blood glucose when the patient’s appetite or eating behaviour is unpredictable.
- Injections and blood testing during the day may be difficult for those in full-time school.
- Younger children with diabetes may not be able to recognise hypoglycaemia, and may not be able to treat it without adult intervention. Blood glucose targets may need to be relaxed to avoid unacceptable hypoglycaemia.
- In all adolescents with diabetes, adherence with insulin, diet and other treatments is an issue. Better adherence and control may be achieved with a simple regimen than with a complex and demanding one, which may not be adhered to.
- A pragmatic approach is essential, accepting that in some cases treatment and blood testing will be erratic.

4.10 Adjustment of treatment during infection

Insulin requirements usually rise during infective exacerbations even when food intake reduces due to loss of appetite. Many patients with diabetic glucose tolerance, which is well controlled off insulin between infective exacerbations, require insulin during infection to maintain diabetes control and minimise weight loss. Patients with normal glucose tolerance when stable may have raised blood glucose levels in the diabetes range during infective exacerbations or whilst on steroid treatment.
Recommendations

- **Patients should have a blood glucose level measured on admission [C].**

- **If this is <6 mmol/l, and the patient is not known to have CFRD, capillary blood glucose levels should be checked after the main meal of the day to ensure that calorie intake is being covered by the patient's own insulin production [C].**

- **Patients with an admission blood glucose ≥6 mmol/l, patients with known CFRD and those on steroids should have pre- and post-meal blood glucose levels checked [C].**

- **Patients should be considered for insulin if blood glucose levels are persistently raised at any time of the day [C].**

- **Blood glucose targets are as described in Table 4.6.1 [C].**

### 4.10.1 Table – Adjustment of treatment during infection – an example of a protocol for adults

<table>
<thead>
<tr>
<th></th>
<th>Not known to have CFRD</th>
<th>CFRD on tablets</th>
<th>CFRD on insulin with meals</th>
<th>CFRD on basal bolus regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Raised glucose after meals</strong></td>
<td>Add fast acting analogue with meals e.g 2 to 6 units depending on meal size</td>
<td>Add fast acting analogue with meals</td>
<td>Increase meal time doses by 2 units or 10%, whichever is the greater</td>
<td>Increase meal time doses by 2 units or 10%</td>
</tr>
<tr>
<td><strong>Fasting glucose raised</strong></td>
<td>Add intermediate or long acting insulin at bedtime e.g 8 units</td>
<td>Add intermediate or long acting insulin at bedtime e.g 8 units</td>
<td>Add intermediate or long acting insulin at bedtime e.g 8 units</td>
<td>Increase bed time intermediate or long acting insulin doses by 2 units or 10%</td>
</tr>
<tr>
<td><strong>Hyperglycaemia oral steroids</strong></td>
<td>Add intermediate acting insulin at same time as steroids are given e.g 8 units at 9am</td>
<td>Add intermediate acting insulin at same time as steroids are given e.g 8 units at 9am</td>
<td>Add intermediate acting insulin at same time as steroids are given e.g 8 units at 9am</td>
<td>Add intermediate acting insulin at same time as steroids are given e.g 8 units at 9am</td>
</tr>
</tbody>
</table>

(Based on an example from Manchester Adult CF Centre Protocol, 2003)

It is important to remember that insulin doses may need to be lowered rapidly as the patient’s health improves and activity levels increase, and thus insulin resistance drops.
4.10.2 Adjustment of treatment during infection – children and adolescents

The principles of management of children and adolescents are similar to those outlined above (see Section 4.10.1), but insulin doses must be tailored to the size of the patient. For children managed on twice or three times daily insulin, it may be preferable to change to a basal bolus regimen if eating is erratic during illness or if control becomes a problem during steroid treatment. Doses of fast acting analogue insulin can be adjusted according to the amount of food eaten and can be given soon after meals if needed. As discussed above, CFRD may present for the first time in children and adolescents during exacerbations of their chest infection or when steroid treatment is commenced.

4.11 Adjustment of treatment to cover enteral tube feeds

Patients on enteral tube feeding may require additional insulin to cover their enteral tube feed and optimise nutritional status. Capillary blood glucose level should be monitored at the start, end and at least once during the feed to determine whether additional insulin (usually short and medium acting preparations depending on the individual patient) is required (see Section 5.3.2).

4.12 Adjustment of treatment after lung or liver transplant

Insulin requirements often change after transplantation and are difficult to predict for any individual. Many medications used for immunosuppression are known to increase insulin resistance or be damaging (transient or permanent) to beta cell function, and weight gain following transplantation may also increase insulin requirements. Paradoxically there are several case reports of individuals with known CFRD who return to normal glucose tolerance following transplantation (Ashworth, et al 2000 [IV]).

Key recommendations

- Insulin is the mainstay of treatment for CF related diabetes [B].
- In all individuals with CFRD, treatment must aim to eradicate symptoms of hyperglycaemia and maintain adequate nutrition, growth and respiratory function [C].
- Optimal control of diabetes will reduce the chances of long-term complications and is the aim in most patients [A].
- Optimal control is the aim in children and adolescents, but practical and psychological factors may make this difficult [C].
- Treatment adjustments may be required during respiratory exacerbations, steroid therapy and enteral tube feeding [C].
5. DIETARY/NUTRITIONAL TREATMENT

5.1 Introduction

There are no meta-analyses or randomised controlled trials of dietary intervention in cystic fibrosis related diabetes (Wilson et al, 2000 [IV]). As a consequence, recommendations for the nutritional management of CFRD are based on the relatively weak evidence of cohort studies and current clinical practice reported in clinical consensus guidelines. These consensus guidelines tend to reflect national practice that varies from country to country (Moran et al, 1999 [IV]).

Poor clinical outcomes are associated with under nutrition in patients with cystic fibrosis (Corey et al, 1988 [III]; Kerem et al, 1992 [III]; Beker et al, 2001 [III]). The management of the co-existing conditions CF and CFRD should enhance rather than interfere with the achievement of a good nutritional status (Moran et al, 1999 [IV]).

The primary aim of the nutritional management of CFRD is to achieve a normal nutritional status (Moran et al, 1999 [III]; Wilson et al, 2000 [III]). In children, nutritional management of CFRD should also promote the maintenance of normal growth and development. In adults there should be optimal nutrition and the maintenance of a good nutritional status.

Poor glycaemic control can lead to a deterioration in nutritional status hence avoidance of hyperglycaemia is a key feature of the dietary and medical management of CF related diabetes. Good glycaemic control is needed to avoid the acute symptoms of polyuria, polydipsia and weight loss associated with hyperglycaemia in CF related diabetes. Evidence of microvascular complications (Sullivan & Denning, 1989 [IV]; Lanng et al, 1994b [III]; Yung et al, 1998 [IV]) and a need to reduce the potential risk of chronic complications are also important reasons for ensuring optimal control. Dietary management whilst focusing on nutritional status and control of hyperglycaemia should also minimise the risk of, and include education of patients about the avoidance of hypoglycaemia.

Dietary advice should take into consideration the individual’s appetite and nutritional status but other influences on food intake such as socio-economic factors, psychological factors (see Section 10) and social/lifestyle/economic factors need to be taken into account. An experienced CF Specialist Dietitian should advise the patient on an individualised, achievable dietary plan. It is important that there is close liaison between the CF Specialist Dietitian, the CF Team and the Endocrinologist/Diabetologist and Diabetes Team to ensure coordination of care.

Recommendations

- *An experienced CF Specialist Dietitian should advise the patient on an individualised dietary plan [C].*

- *Conflicts between dietary therapy of CF and diabetes mellitus should usually be resolved in favour of the CF diet [C].*

- *In most instances, medical management, i.e. insulin therapy, should be tailored to the patient’s needs rather than the diet being tailored to the insulin regimen [C].*
5.2 Dietary recommendations for CFRD

The aim of this section is to discuss the rationale of the dietary treatment for CF related diabetes. For more detailed information on the nutritional needs of people with CF please refer to:

- *Nutrition in Patients with Cystic Fibrosis: a European Consensus* (Sinaasappel et al, 2002 [IV]).
- *Consensus Report on Nutrition for Pediatric Patients with Cystic Fibrosis* (Borowitz et al, 2002 [IV]).

The dietary recommendations for people with diabetes mellitus and those with CF are conflicting. Conflicts between dietary therapy of CF and diabetes mellitus should usually be resolved in favour of the CF diet.

5.2.1 Table – Differences in the dietary management of non-CF related diabetes mellitus (DM) and CF related diabetes mellitus (CFRD)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy</td>
<td>100% of normal if the BMI is 18.5–25</td>
<td>Individualised 120-150% of normal depending on nutritional state</td>
</tr>
<tr>
<td>Fat</td>
<td>&lt;35% of total energy</td>
<td>40% of total energy</td>
</tr>
<tr>
<td>Refined Sugars</td>
<td>Up to 10% of total energy</td>
<td>Allow throughout the day</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>45-60% of total energy</td>
<td>45-50% of total energy</td>
</tr>
<tr>
<td>Dietary Fibre</td>
<td>No quantitative recommendation but encouraged due to beneficial effects</td>
<td>Encouraged in the well nourished, but in poorly nourished patients may compromise energy intake</td>
</tr>
<tr>
<td>Protein</td>
<td>10-20% of total energy Not &gt;1g per kg body weight</td>
<td>200% of Reference Nutrient Intake (RNI)</td>
</tr>
<tr>
<td>Salt</td>
<td>Low intake ≤6g sodium chloride/day</td>
<td>Increased requirement</td>
</tr>
<tr>
<td>Snacks</td>
<td>Scheduled meal plan including some snacks</td>
<td>Ad-lib</td>
</tr>
</tbody>
</table>

(Adapted from Ashworth et al, 1999 [IV].)
5.2.2 Energy

In order to achieve weight maintenance or weight gain, people with CF need to ensure that their absorbed energy intake is equal to or greater than their energy expenditure. The need for high-energy requirements in CF is explained in more detail elsewhere (Nutritional Management of Cystic Fibrosis. UK CF Trust Nutrition Working Group. Cystic Fibrosis Trust, 2002 [IV]; Sinaasappel et al, 2002 [IV]; Pencharz & Durie, 2000 [IV]; Borowitz et al, 2002 [IV]).

People with cystic fibrosis require a high-energy diet usually providing 120–150% of that required by healthy individuals of the same age, sex and size (Pencharz et al, 1984 [III]; Vaisman et al, 1987 [III]). However, requirements do vary and in the clinical situation energy requirements are determined individually following a full nutritional assessment and consideration of the individual’s nutritional and clinical state.

Studies in children and adults with CF indicate the high-energy intake is difficult to achieve (Morrison et al, 1994 [III]; Kawchak et al, 1996 [III]; Morton et al, 2001 [III]). This is particularly true for patients with CFRD who have a lower energy intake than patients who do not have CFRD (Morton et al, 2001 [III]). More invasive methods of nutritional support are often used to prevent or resolve negative energy balance. Dietary recommendations for non-CF diabetes mellitus (DM) promote the use of foods that are low in fat and refined carbohydrate (and hence have a lower energy density). In contrast, people with CFRD need to increase their consumption of foods with a high-energy density if they are to meet their energy requirements.

Recommendation

- People with CFRD require a high-energy diet usually providing 120–150% of estimated average requirement (EAR) [B].

5.2.3 Fat

Dietary recommendations for DM advise a fat intake that provides 25–35% of the total energy intake. There is also an emphasis on reduction of saturated and polyunsaturated fat and promotion of monounsaturated fat. The restriction in the amount and types of fat is aimed at preventing obesity, hyperlipidaemias, and macrovascular disease (Diabetes Nutrition Study Group [DNSG], 2000 [IV]; Connor et al, 2003 [IV]). In contrast to people with DM, obesity is rare in people with CF who may be undernourished. In the UK only 7.6% of adults with cystic fibrosis had a BMI that fell above the 90th centile whilst 24.8% of adults had a BMI less than 19.0 kg/m² (UK CF Database, 2002 [IV]).

Although hyperlipidaemia has been reported in patients with CF (Stewart et al, 1997 [III]), no relationship has been found between plasma lipid levels and glucose intolerance or CF related diabetes (Jackson et al, 2002 [III]; Figueroa et al, 2002 [III]).

In a survey of the UK Dietitians’ CF Interest Group, 100% of respondents reported they would not recommend reducing fat intake if the patient developed CF related diabetes (Ashworth et al, 1999 [IV]). This high intake of fat is required to help achieve the increased energy requirements needed to maintain a positive energy balance in people with CF related diabetes. Dietary recommendations in CFRD are therefore to advise to continue a high fat intake.

Some Dietitians in the UK survey stated that they may recommend a further increase in fat intake to allow for a more moderate use of refined carbohydrates (Ashworth & Leonard, 1995 [IV]). Fat slows absorption of glucose from the intestine thus avoiding rapid rises in blood glucose levels.
It may be prudent to encourage a variety of different types of fat especially monounsaturated and polyunsaturated fats to ensure a supply of essential fatty acids.

**Recommendations**

- **A high fat intake – aiming to achieve 40% of total daily calories as fat [C].**
- **With increased longevity it may be prudent to review the types of dietary fat promoted [C].**

### 5.2.4 Carbohydrate

The glycaemic response to a food is affected by many factors other than the mono- or disaccharide content. Factors affecting the glycaemic response of an individual food are; the method of cooking or processing, its degree of ripeness, the overall meal size and the effect of other foods eaten at the same time. As a result mono- and disaccharides (refined carbohydrate) can be incorporated in diets used in the treatment of diabetes.

Current dietary recommendations for DM advise a carbohydrate intake that provides 45–60% of the total energy intake; within these refined carbohydrates should not exceed 10% of the total energy intake. The use of carbohydrates, which have a low glycaemic index and high fibre foods, are encouraged (Diabetes Nutrition Study Group [DNSG], 2000 [IIa]). These recommendations reduce the likelihood of hypertriglyceridaemia and obesity whilst helping to achieve normoglycaemia. However, many people with CF who have a poor nutritional status, rely heavily on refined sugary foods as a major source of energy and restricting the use of refined carbohydrates in CFRD may therefore seriously affect their total energy intake and nutritional status.

The amount, type and timing of carbohydrate intake are major considerations when tailoring dietary advice to the individual. There needs to be a balance between carbohydrate intake, hypoglycaemic medication (tablets or insulin) and activity levels.

Different approaches to dietary modification have been used in the treatment of diabetes mellitus. Traditionally the exchange system was used where foods containing a defined amount of carbohydrate were substituted for one another. This system tended to be very prescriptive and regulated or restricted the amount of carbohydrate consumed at each meal and snack whilst the insulin regimen remained fixed; it did not consider other aspects of the diet and it assumed that equal quantities of carbohydrate had equal glycaemic effects.

The exchange system is not used in the treatment of CF related diabetes (Ashworth & Leonard, 1995 [IV]). In CFRD, UK Dietitians recommend that refined carbohydrates should be taken with or just after eating other foods. This enables an even distribution of sugar intake throughout the day instead of binges that could cause sudden peaks in blood glucose levels (Ashworth & Leonard, 1995 [IV]). Patients are also advised to eat regular meals and snacks containing complex carbohydrates in order to maintain normoglycaemia.

In contrast, Dietitians treating CFRD in the USA make no distinction between refined and complex carbohydrates and recommend a carbohydrate counting system (Moran et al, 1999 [IV]), where the total amount of carbohydrate in a meal or snack is calculated and the patient is taught to alter their short acting insulin dose using an individually determined insulin to carbohydrate ratio.

Carbohydrate counting was used in the DAFNE study (Dose Adjustment for Normal Eating). DAFNE educates people with Type 1 diabetes via an intensive 5-day group course on how to adjust their insulin injections to fit their life and diet rather than the other way around. The approach
relies on multiple injections of both short and intermediate acting insulin. Evaluation of DAFNE has shown promotion of dietary freedom, improved quality of life and improved glycaemic control (DAFNE Study Group, 2002 [Ib]).

Unfortunately education programmes used in CFRD have not been evaluated. There is a need to evaluate any dietary education programmes that are used in the treatment of CF related diabetes.

Recommendations

- **Refined carbohydrates should not be routinely restricted in CFRD as this may adversely affect total energy intake and nutritional status [C].**
- **There should be a balance between amount, type and timing of carbohydrate, hypoglycaemic medication and activity levels [B].**

### 5.2.5 Dietary fibre

Foods containing dietary fibre tend to have a low energy density and provide bulk to a meal to promote fullness and satiety. Foods high in soluble fibre have been shown to delay the rate of postprandial glucose absorption and have beneficial effects on lipid metabolism (Jenkins et al, 1987 [III]; Brown et al, 1999 [III]). In the treatment of people with DM a diet high in fibre is used to treat obesity, improve glycaemic control and promote normal blood lipid levels. As discussed (see Section 5.2.2) obesity and hyperlipidaemia are not currently major problems in CF related diabetes. Advocating a diet high in dietary fibre for people with CFRD may further compromise nutritional status by reducing energy intake.

**Recommendation**

- **A moderate increase in fibre intake is appropriate for well-nourished people with CF related diabetes [C].**

### 5.2.6 Protein

Protein metabolism is affected in CF related diabetes. Studies have shown that proteolysis is increased in patients with CFRD and/or with impaired glucose tolerance (Hardin et al, 1998 [III]; Moran et al, 2001 [III]).

Dietary protein requirements in CF have not been well researched but it is generally accepted that protein intake should be higher than average to compensate for nitrogen losses in faeces and sputum and ensure sufficient for growth.

Protein restriction (0.3–0.8 g/kg/day) in people with insulin dependent diabetes has been shown to slow the progression of diabetic nephropathy towards renal failure (Waugh & Robertson, 2004 [III]). Reduction in protein intake in people with CFRD will decrease protein synthesis while uncontrolled hyperglycaemia will increase protein breakdown resulting in catabolism of body protein stores.

**Recommendation**

- **Restriction of dietary protein intake in CFRD with or without nephropathy may be inappropriate and should be avoided [C].**
5.2.7 Sodium

A salt intake of \( \leq 6 \) g/day is recommended for people with diabetes mellitus (Diabetes Nutrition Study Group, 2000 [IV]; Connor et al, 2003 [IV]). This is based on general recommendations for the UK population to reduce the average intake of salt from 9 g/day to 6 g/day (Committee on the Medical Aspects of Food and Nutrition [COMA], 1994 [IV]). A further restriction in salt intake may be advised for those people with hypertension.

Cystic fibrosis results in an abnormally high concentration of sodium and chloride being excreted in sweat. As a result salt requirements are greater in people with cystic fibrosis. Salt losses are further increased in conditions that cause excessive sweating. In these situations salt supplementation may be necessary to avoid salt depletion. Appropriate daily sodium chloride supplements are – for children less than 1 year old 500 mg, for those 1–7 years 1 g, and for those more than 7 years 2 g to 4 g in divided doses (Details in Nutritional Management of Cystic Fibrosis. UK CF Trust Nutrition Working Group, 2002 Section 3.7: Page 17 [IV]).

Recommendations

- Salt intake should not be restricted [B].
- Salt supplementation is advisable in hot weather or when excessive sweating is likely to occur [B].

5.2.8 Alcohol

Alcohol suppresses gluconeogenesis and so has a hypoglycaemic effect (Lieber, 1994 [IV]). In patients taking insulin, alcohol can cause hypoglycaemia of such severity that it can result in death or brain damage (Laing et al, 1999 [IV]). In addition, patients with CFRD may have liver disease that may further affect glucose homeostasis. If the patient is taking certain CF medications that interact with alcohol they may be better avoiding alcohol. Individualised advice should be given to patients with CF related diabetes.

Patients with CFRD should understand the effects of alcohol on their blood glucose levels. Initially blood glucose levels may be increased due to the carbohydrate content of the alcoholic beverage or due to the sugar content of mixers. However, alcohol may make the blood glucose fall rapidly later. This is because normally when alcohol has not been drunk the liver releases glucose into the bloodstream to prevent the blood glucose level dropping too low. When alcohol has been drunk the liver breaks down the alcohol and therefore releases less glucose into the bloodstream increasing the risk of hypoglycaemia.

Recommendations

- People with CFRD should check with their CF Consultant and Dietitian whether there are any reasons they should not drink alcohol [C].
- Have no more than 2 to 3 units of alcohol at any time [C].
- Never drink alcohol on an empty stomach; try to have a snack (crisps or nuts) before drinking alcohol [C].
- At bedtime always have a carbohydrate-containing snack to reduce the risk of nighttime hypoglycaemia [C].
- Check blood glucose after drinking alcohol to determine the effect of the alcohol [C].

Note: A unit of alcohol is: ½ pint of ordinary beer, lager or cider or 1 pub measure of spirits or 1 small (100 ml) glass of wine or ½ a bottle of Alcopop or a small (50 ml) glass of sherry.
5.3 Nutritional support in CFRD

Nutritional support, with regular advice from a Dietitian experienced in CF and CFRD should be an integral part of overall care for any patient with cystic fibrosis. There is a paucity of published studies investigating nutritional support in patients with CF related diabetes.

5.3.1 Nutritional supplements

Oral calorie supplements are widely used in CF care, however, their effectiveness has not been assessed by adequate clinical trials (Smyth & Walters, 2004 [IV]). In practice, CF Specialist Dietitians and CF Clinicians continue to prescribe nutritional supplements to patients with CF and CF related diabetes. The complete range of dietary supplements may be prescribed but caution is usually applied to the use of glucose polymers (Ashworth & Leonard, 1995 [IV]).

Further details can be found in Section 6.15 of Nutritional Management of Cystic Fibrosis. UK CF Trust Nutrition Working Group. Cystic Fibrosis Trust, 2002 [IV].

A variety of nutritional supplements can be incorporated into an individual dietary plan.

- **Glucose polymers** e.g. Polycal liquid, Maxijul powder, Maxijul liquid and Caloreen are rapidly absorbed and may cause a rapid increase in blood glucose levels. In practice they tend to be reserved for patients who cannot tolerate the polymeric nutritionally complete supplements. They should be taken at mealtimes (if possible) to reduce the rate of absorption and the consequent rapid rise in blood glucose levels. Appropriate insulin therapy can allow for the inclusion of glucose polymers as part of the diet.

- **Juice-based sip feeds** e.g. Enlive, Fortijuce and Provide are high in carbohydrate and fat free. They are also quickly absorbed and may cause a rapid increase in blood glucose levels. Again they can be taken alongside food or at a time when insulin therapy will cover the carbohydrate load.

- **Milk-based polymeric sip feeds** e.g. Ensure Plus, Scandishake, Fortisip, and Fresubin are the most widely used group of products used to supplement the diet of patients with CFRD (Ashworth & Leonard, 1995 [IV]). Again, these products contain simple sugars which will impact on blood glucose levels, however the presence of fat and protein and the lower carbohydrate content of these products may lead to a less dramatic rise in blood glucose levels.

Close liaison between the CF Team and the Diabetologist regarding the patient’s dietary needs is essential. Appropriate patient education can enable patients to adjust their insulin therapy in response to dietary intake and this approach can simplify the inclusion of dietary supplements within the agreed, individualised dietary plan.

**Recommendations**

- Dietary supplements should be incorporated in the diet in a regulated manner if indicated [C].
- Milk-based polymeric sip feeds are the preferred supplement [C].
- Insulin should be adjusted accordingly [C].
5.3.2 Tube feeding

Nasogastric or gastrostomy feeding may be necessary in patients with CFRD to improve and maintain their nutritional status. (Further details can be found in Sections 6.3 – 6.12 of *Nutritional Management of Cystic Fibrosis*. Report of the UK CF Trust Nutrition Working Group. Cystic Fibrosis Trust, 2002 [IV]).

Early reports of enteral tube feeding in CF suggested that hyperglycaemia associated with commencement of nocturnal feeding was common, occurring in 64% of patients in one series (Smith et al, 1994 [IV]). In populations screened for CFRD using the OGTT the incidence of CFRD presenting as a consequence of enteral tube feeding is much lower than 64% (Etherington et al, 2000 [IV]). Enteral tube feeding may be a risk factor for developing cystic fibrosis related diabetes.

The introduction of enteral tube feeding to any patient with CF should be closely monitored. Ideally an oral glucose tolerance test should be performed in patients who are being considered for enteral tube feeding to exclude undiagnosed CFRD as a cause of their poor nutrition (see Section 3). Even in patients who have recently undergone an OGTT with normal results, monitoring of blood glucose pre- and post-feed and once during the feed should be routine practice to assess effects of enteral tube feeding on nocturnal glycaemia. Some patients do develop nocturnal hyperglycaemia and may require insulin to cover their overnight feed only.

In patients known to have CFRD, the introduction of enteral tube feeding should be closely monitored and insulin therapy adjusted accordingly. In practice, a variety of insulin regimens are used depending upon feed type, feed duration, current insulin therapy and glycaemic control. Dietitians and CF Physicians use a wide variety of enteral tube feed preparations and there is no one specific feed used for enteral tube feeding in patients with CF related diabetes (Ashworth & Leonard, 1995 [IV]).

Patients with CFRD and their carers need practical education about CFRD and tube feeding. Potential problems that can arise such as pump failure following the injection of insulin or vomiting need to be addressed in the individualised dietary management plan.

**Recommendations**

- **Glycaemic status should be determined by OGTT before commencing enteral feeding [B].**
- **Blood glucose should be monitored pre- and post-feed and at least once during feed to assess the effects of enteral tube feeding on nocturnal glycaemia (see Section 4.11) [C].**
- **Introduction of enteral tube feeding in patients with CFRD should be closely monitored and insulin therapy adjusted accordingly [C].**
- **Patients with CFRD and carers need practical education about CFRD, tube feeding and potential problems that can arise [C].**

5.3.3 Parenteral nutrition

Parenteral nutrition in CF is rarely indicated as a means of routine nutritional support and should be reserved for short-term use in patients with specific indications e.g. complications of short gut, post-operative management of patients following major gastrointestinal surgery (Sinaasappel et al, 2002 [IV]). Patients with CFRD receiving parenteral nutrition should be closely monitored (as indicated in local guidelines). In practice this usually means initially hourly and then 4 to 6 hourly blood glucose measurements being performed and a sliding scale insulin or insulin infusion being titrated against blood glucose levels.
Recommendations

- Parenteral nutrition in CFRD should be reserved for short-term use e.g. after gastrointestinal surgery or complications of short gut syndrome [C].
- Patients with CFRD receiving parenteral nutrition should be closely monitored [C].

5.4 Provision of dietary education in CFRD

Dietary education should be part of a whole education package provided by a multidisciplinary team who are experienced in the treatment of CF related diabetes. The Specialist CF Dietitian is often best placed to provide this dietary education but close links with the Diabetes Team are necessary.

At present, there is poor evaluation of dietary education in CFRD and a lack of patient education literature specific to CF related diabetes.

Recommendation

- A Specialist Dietitian experienced in the management of CFRD should provide dietary education [C].

5.5 Summary recommendations – dietary/nutritional treatment

Section 5.1 – Introduction

- An experienced CF Specialist Dietitian should advise the patient on an individualised dietary plan [C].
- Conflicts between dietary therapy of CF and diabetes mellitus should usually be resolved in favour of the CF diet [C].
- In most instances, medical management, i.e. insulin therapy, should be tailored for the patient’s needs rather than the diet being tailored to the insulin regimen [C].

Section 5.2.2 – Energy

- People with CFRD require a high-energy diet usually providing 120–150% of estimated average requirement (EAR) [B].

Section 5.2.3 – Fat

- A high fat intake – aiming to achieve 40% of total daily calories as fat [C].
- With increased longevity it may be prudent to review the types of dietary fat promoted [C].

Section 5.2.4 – Carbohydrate

- Refined carbohydrates should not be routinely restricted in CFRD as this may adversely affect total energy intake and nutritional status [C].
- There should be a balance between amount, type and timing of carbohydrate, hypoglycaemic medication and activity levels [B].

Section 5.2.5 – Dietary fibre

- A moderate increase in fibre intake is appropriate for well-nourished people with CF related diabetes [B].
Section 5.2.6 – Protein

- Restriction of dietary protein intake in CFRD with or without nephropathy may be inappropriate and should be avoided [C].

Section 5.2.7 – Sodium

- Salt intake should not be restricted [B].
- Salt supplementation is advisable in hot weather or when excessive sweating is likely to occur [B].

Section 5.2.8 – Alcohol

- People with CFRD should check with their CF Consultant and Dietitian whether there are any reasons they should not drink alcohol [C].
- Have no more than 2 to 3 units of alcohol at any time [C].
- Never drink alcohol on an empty stomach; try to have a snack (crisps or nuts) before drinking alcohol [C].
- At bedtime always have carbohydrate-containing snack to help prevent nighttime hypoglycaemia [C].
- Check blood glucose after drinking alcohol to determine the effect of the alcohol [C].

Section 5.3.1 – Nutritional supplements

- Dietary supplements should be incorporated in the diet in a regulated manner if indicated [C].
- Milk-based polymeric sip feeds are the preferred supplement [C].
- Insulin should be adjusted accordingly [C].

Section 5.3.2 – Tube feeding

- Glycaemic status should be determined by OGTT before commencing enteral feeding [B].
- Blood glucose should be monitored pre- and post-feed and at least once during feed to assess the effects of enteral tube feeding on nocturnal glycaemia (see Section 4.11) [C].
- Introduction of enteral tube feeding in patients with CFRD should be closely monitored and insulin therapy adjusted accordingly [C].
- Patients with CFRD and carers need practical education about CFRD, tube feeding and potential problems that can arise [C].

Section 5.3.3 – Parenteral nutrition

- Parenteral nutrition in CFRD should be reserved for short-term use e.g. after gastrointestinal surgery or complications of short gut syndrome [C].
- Patients with CFRD receiving parenteral nutrition should be closely monitored [C].

Section 5.4 – Provision of dietary education in CFRD

- A Specialist Dietitian experienced in the management of CFRD should provide dietary education [C].
6. MANAGEMENT ISSUES AND PATIENT EDUCATION

In its latest guidance document the National Institute for Clinical Excellence recommends that structured patient education is made available to all people with diabetes at diagnosis and then as required on an ongoing basis (Diabetes UK, 2002a [IV]).

Close liaison between the CF Team and the Diabetes Team and Diabetologist to ensure co-ordination of patient education and care is of paramount importance. The CF Nurse Specialist serves a pivotal role in liaising with both teams in educating and supporting the newly diagnosed patient both in hospital and at home, helping the patient and the family to cope physically and psychologically in managing this additional CF-related complication (Ashworth et al, 1999 [IV]).

The start of patient education should begin at the diagnosis of CFRD and each should undergo a baseline assessment. As part of this assessment it is important to also address the patient’s perception and understanding surrounding the diagnosis, the impact and implications of the disease (Diabetes Attitudes Wishes and Needs [DAWN] Study, 2002 [IV]). Discussing any preconceived ideas, fears or anxieties such as; the need for insulin therapy, burden of monitoring, management of CF/diabetes, needle fear/phobia or in some cases just anticipatory fear and distress of self injection where psychological intervention may be required.

6.1 Insulin injections

There are three key factors which influence insulin absorption – injection depth, site and technique which are as important to good glucose control as the type and dose of insulin or device used (Strauss et al, 2002a [IV]). Other key variables are age, sex, body mass index (BMI) of the patient and the use of the pinch-up technique (Insulin Injection Technique. The First International Insulin Injection Technique Workshop, 1998 [IV]).

A low BMI is associated with reduced subcutaneous tissue limiting suitable injection sites. It is important to avoid the risk of intra-muscular injection, which can lead to increased absorption causing erratic control, hypoglycaemia or bleeding. Intradermal injection may cause pain or insulin leakage and lumps at sites immediately after injection (Wilbourne, 2002 [IV]).

6.1.1 Injection depth

The use of 8 mm and 12.7 mm needles were compared in 50 children and the occurrence of intra-muscular injections identified using ultrasound. The 8 mm needles significantly reduced the risk of intra-muscular insulin injection in both thin and normal children and adolescents; even shorter needles are appropriate depending on the site (Polak et al, 1996 [III]).

Another comparison of safety and efficacy of the 5 mm and 8 mm needles, both with a pinch up of the skin, found the pain of injection was lower with 5 mm needles; there were no differences in leaking or bleeding at the site. Guidelines were suggested for the size of needles to use in specific patient populations (Strauss et al, 1999 [IV]). A pinched up skin fold when injecting insulin should be made with the thumb and index finger and be maintained throughout the injection and up to 10 seconds afterwards, before removing needle (Insulin Injection Technique. The First International Insulin Injection Technique Workshop, 1998 [IV]).

Recommendations

- Patients, carers and health professionals need to be made aware of the key factors that affect insulin absorption i.e. injection depth, site and technique [B].
• Appropriate needle lengths for people with CFRD are either an 8 mm needle (with a pinched skin fold) for normal weight adults and a 5 or 6 mm needle (with or without a pinched skin fold) for children and adolescents [B].

• Normal to thin adults may use 5 mm needle with a pinched up fold only under supervision of their Health Care Professional [C].

6.2 Injection sites

People with CF may have limited injection sites. As there may be parts of their body they prefer not to use, it is important to explain to patients/carers that each site has its own pattern of insulin absorption according to, type, frequency and timing of injection (Wilbourne, 2002 [IV]). If any type of exercise is undertaken injection sites should be away from the area used as it may increase the absorption of insulin.

Recommendations

• Choose the appropriate area according to type of insulin used [C]:
  – Abdomen: Fast absorption. Inject a hand’s breadth either side of belly button. Insulins such as analogues, soluble or combined.
  – Buttocks: Slow absorption. Inject into top area. Use as alternative to thighs. Encourage long acting insulins.
  – Arms: Medium to fast absorption. Inject into upper external area. Soluble insulins. (Not recommended for self-injection, Diabetes UK.)

• Inject into the same area at the same injection time to ensure a reliable absorption (Insulin Injection Technique. The First International Insulin Injection Technique Workshop, 1998 [IV]) [C].

• Provide patients with written and illustrated educational material on injection sites [C].

6.2.1 Rotation of sites

A swelling of the fatty tissue often seen at injection sites (lipohypertrophy) may cause slow and erratic absorption of insulin. Certain patient sub-groups are vulnerable – those who re-use needles, inject into restricted injection zones, fail to rotate sites and especially those who use insulin pens (Strauss et al, 2002b [IV]). Patients who have poor metabolic control (HbA1c >8.6%) report more problems in insulin injection practices (Partanen & Rissanen, 2000 [IV]).

It should be emphasised that as well as telling patients about lipohypertrophy each must be given a personal strategy for rotation and be warned against blood glucose variations (Franzen et al, 1997 [IV]).

Recommendations:

• Use pen needles once only [B].

• Organise a rotation of injection sites to suit type of insulin (see Section 6.2) [C].
• Teach patients to space out each injection within each area, moving one fingerbreadth from the last injection site; 6–8 cm spacing is advisable when lipohypertrophy is a problem [C].

• Clearly document advice in patient’s individual education plan. Give appropriate written educational materials, diagrams and rotation charts for thighs and stomach [C].

• Alternate left and right-hand sides from one week to another [C].

• Emphasise the problems of injecting into lipohypertrophic areas [C].

• Health Care Professionals should be trained to identify lipodystrophy [C].

• At each clinic visit or admission, clearly document that injection technique sites have been inspected and palpated [C].

6.3 Devices for the administration of insulin

Most patients favour pen devices either using a re-usable or disposable insulin pen. There is a range of pens available to match each person’s individual needs. For those with needle aversion, there is a needle-free delivery device or a needle guard to hide the needle. Guidelines regarding recommended safe practice should be available to all relevant staff involved in the use of pen devices or in the education of patients regarding use, storage of insulin cartridges/pens and sharps disposal (Strauss et al, 2002b [IV]).

Recommendations

• Ensure correct cartridge being used, checking size, origin, name and type of insulin and manufacture. (Some cartridges do not fit into pens made by another manufacturer) [C].

• Unopened cartridges/pens stored in the main body of fridge at 2–8 ºC, remain usable to their expiry date [C].

• Cartridges and pens “in use” may be stored at room temperature for 1 month [C].

• Pens containing an insulin cartridge and needle must NEVER be stored in a fridge, as moving from extremes of temperature can cause insulin to expand /or contract in the cartridge, resulting in air bubbles or loss of insulin solution via the needle [C].

• Partly used cartridges should never be returned to the fridge to be reused and must be discarded [C].

• Detailed instruction in the use of pen devices and needles should be provided [C].

• Patients should be prescribed 1 litre “sharps bins” for disposal of needles, pens and lancets and safe clips to clip off the end of needles [C].

6.4 Injection technique

A recent report emphasised that current educational tools and approaches in this area are not adequate (Strauss et al, 2002b IV]). It is essential that nurses, who are in the main the principal instructors in injection technique, ensure that up to date information is incorporated into a clear, written education package instructing patients, carers and other Health Care Professionals. It is important that regular evaluation is an integral part of the Annual Review.
Recommendations

- **Health Care Professionals could consider demonstrating on themselves when teaching patients injection technique [C].**

- **Insulin should only be administered when stored at room temperature (see Section 6.3) [C].**

- **Attach the appropriate sized needle (see Section 6.1.1) and use once only [C].**

- **Neutral protamine hagedorn (NPH)/Premixed insulins: pens/cartridges should be rolled/tipped 10–20 times prior to use to mix insulin [C].**

- **Perform an “Air shot” of insulin prior to each injection [C].**

- **Select a site using the patient’s own injection site rotation pattern (see Section 6.6.2) [C].**

- **Use a “pinched up” skin fold if advised (see Section 6.1) with one hand, and continue to hold throughout injection. Holding the pen like a dart in the other hand, gently insert needle at 90 degrees to full needle depth. Depress the injector with thumb until all insulin has been administered. Wait 10 seconds to allow absorption then withdraw needle [C].**

- **Remove needle from pen to prevent air entry into pen cartridge [C].**

6.5 Blood glucose monitoring

There are many different blood glucose meters on the market. To help patients make an informed choice, a knowledgeable Health Care Professional should demonstrate and discuss various meters addressing ease of use and amount of blood required for test etc. Blood sampling is generally done by using a finger prick pen (lancet) on the side of the finger, however alternate site meters are now available which can be used on the arms and other sites. Hands must be washed for cleanliness and to increase blood flow. Depth of the lancet insertion can be adjusted for comfort. Patients will need to be educated about blood testing technique, as errors in testing have been documented (National Prescribing Centre, 2002 [IV]) such as; no hand washing, insufficient sampling, meters dirty, codes on strips and meters not matched, test strips date-expired. The meter should be regularly subject to quality control measures. For self-monitoring of blood glucose to be most useful, it should form part of a wider programme of education management. Patients should be given adequate training in self-monitoring techniques, and Health Care Professionals and patients should be clear what they hope to achieve by self-monitoring of blood glucose.

A continuous glucose monitoring system is available in some clinics (e.g. CGMS by MiniMed, Medtronic, Sylmar, CA, USA) and comprises a pager-sized glucose monitor, a sterile disposable subcutaneous glucose sensor with an external electrical connector, a connecting cable and a communication device enabling data stored in the monitor to be downloaded to a personal computer. Preliminary use of the CGMS shows that it is useful in demonstrating trends in the value of glucose levels during the day and has been shown to be valid in patients with cystic fibrosis (Dobson et al, 2003 [III]). Initial studies have shown that some patients with normal glucose tolerance tests may have glucose levels considered to be in the diabetic range by current WHO criteria (Dobson et al, 2002b [III]). The clinical significance of these observations has not yet been fully established but some authors suggest that blood glucose excursions into the diabetic range are an early sign of clinically significant insulin deficiency in cystic fibrosis (Dobson et al, 2002b [III]).
6.5.1 Educational goals for monitoring

- Competence and confidence in how to do blood glucose monitoring measurement (BGM).
- Understanding of the reasons why BGM is important.
- Know when to test and why.
- Interpretation of the results and knowledge of the appropriate action to take.
- Learning acceptable ranges for blood glucose levels (Diabetes UK, 2002a [IV]).

6.5.2 Why measuring blood glucose levels is important

- A profile of BGM is needed to define the extent of hyperglycaemia, before therapy can be instituted.
- For patients who have had an OGTT with normal results, monitoring of blood glucose pre/post-feed and once during feed should be routine to assess effects of enteral feeding on nocturnal glycaemia.
- For patients on treatment, BGM identifies if insulin dose is adequately matched to food intake.
- BGM identifies if insulin regimen is suitable or if adjustments are required because of lifestyle, introduction of exercise, changes in clinical status or medication.
- Safety: makes patients aware of their hypoglycaemic awareness, may help prevent development of very low blood glucose levels and recognise a downward trend in blood glucose before symptoms occur.
- Good control improves long-term outcomes.

6.5.3 When to check blood

In general, the more often patients test blood glucose levels, the more information is available for pattern management. Realistic goals for the number of blood tests should be discussed with the patient.

Recommendations:

- Ideally blood glucose should be checked up to 4 times a day [C].
- Recommended times should include before bed, fasting, pre and 1 1/2–2 hours post meals [C].
- Patients taking long acting insulin in the evening should occasionally check blood glucose in the middle of the night [C].
- Patients who have enteral feeding should check 1–2 times a week, at the beginning and end of feed and once during feed. If intermittent bolus feeding check 1 1/2–2 hours after the bolus [C].
- During illness check 4 times a day or more [C].
- Nine hours after taking steroids [C].
- Before and after exercise [C].
6.6 Education issues (see CFRD Check List in Appendix – Section 12.6)

6.7 Lung transplantation and CFRD

Cystic fibrosis related diabetes is not a contraindication for lung transplantation. No survival disadvantage has been seen in patients with CFRD compared to patients with CF without diabetes (Gyi et al, 2000 [IV]). In those with CFRD post-transplant treatment requirement may increase initially due to immunosuppressive drugs including corticosteroids, but when general health and exercise tolerance improve reduction in treatment can occur (Ashworth et al, 2000 [IV]). New onset CFRD after transplant is often precipitated by steroid pulses given for episodes of acute rejection and the use of high-dose cyclosporin or tacrolimus immunosuppression. The mechanism by which immunosuppressive drugs cause diabetes is complex and not fully understood (Montori et al, 2002 [III]). Bronchiectasis with Pseudomonas infection can often follow obliterative bronchiolitis and this may lead to poor diabetic control. Cyclosporin and tacrolimus can cause hypercholesterolaemia, hypertriglyceridemia and hypertension. Ten-year survival following CF lung transplantation is now approaching 40 per cent. Some people with CFRD survive long enough to develop chronic complications of their CFRD and it is important that they receive the recommended Annual Review of their CFRD (see Section 7). Successful combined islet-lung transplantation has been reported in a person with CF and CFRD (Buhler et al, 1996 [IV]).

Recommendations

- **CFRD is not a contraindication to organ transplantation** [C].
- **Annual Reviews should be performed to identify complications** [C].
- **Blood pressure should be measured regularly** [C].

6.8 Diabetes, liver disease and liver transplantation in cystic fibrosis

The occurrence of diabetes mellitus, or glucose intolerance, is greater in patients with non-CF related causes of cirrhosis, and becomes more common with advanced hepatic disease (Holstein et al, 2002 [IV]). In advanced liver disease there is also a high risk of hypoglycaemia due to reduced hepatic glycogen stores, impaired hepatic insulin extraction and impaired glucagon counter regulation and catabolism (Holstein et al, 2002 [IV]).

In view of the likely pathogenesis of CFRD, it is not surprising that there does appear to be a greater prevalence of this complication in patients with CF related liver disease compared to those without, and that it can occur at a young age (Mack et al, 1995, [III]; Noble-Jamieson et al, 1994 [III]; Pfister el al, 2002 [III]). For those CF patients with advanced hepatic disease, but without severe lung involvement, isolated liver transplantation generally has a good long-term outcome (Noble-Jamieson et al, 1994 [III]; Mack et al, 1995 [III]; John & Thuluvath, 2001 [III]; Milkiewicz et al, 2002 [III]).

Pre-existing diabetes may remit following liver transplantation for any cause (Perseghin et al, 2000 [III]; Steinmüller et al, 2001 [III]) and there is also an increased incidence of new onset, post-transplant diabetes (John & Thuluvath, 2002 [IIIb]). People with CF whose compliance with routine treatments pre-transplant is considered poor are likely to have a worse outcome following surgery. Their potential inability to cope with the extensive demands of regular medication needs to be tackled pre-operatively and may need to be considered as a relative contraindication for the procedure.
Hypertension, renal impairment and cardiovascular disease can follow organ transplantation for a number of reasons, including as a complication of the use of immunosuppressive agents (Sheiner et al, 2000 [IV]).

There are a number of reports of patients with insulin-requiring diabetes (Type 1 or Type 2) and cirrhosis that have received combined islet cell, or pancreas, and liver transplantation (Aguirrezabalaga et al, 2002 [III]; Ricordi, 2003 [IV]; Trotter et al, 2000 [IV]). Many of the patients were able to discontinue insulin post-transplant. As this procedure becomes more routine it will hopefully be available for similarly affected people with cystic fibrosis.

Recommendations

- Patients of any age with established liver disease should be screened regularly for the presence of diabetes [C].
- Tight control of blood glucose post transplant will minimise the risk of short and long-term complications and graft failure [C].
- Minimisation of nephrotoxic drug regimens is essential for patients with CFRD who have received a liver transplant, as progressive renal impairment will complicate future antibiotic treatment of the chest infections [C].
- More frequent monitoring for renal impairment and hypertension is necessary [C].

6.9 Exercise

Glycaemic changes during exercise depend largely on blood insulin levels and therefore on the type of insulin, the time since the insulin injection and the exercise. It is important that people with CFRD have an understanding of the effects of exercise on glycaemic control summarised as follows (Williams & Pickup, 1999 [IV]):

**Blood glucose decreases if:**
- Hyperinsulinaemia (high levels of insulin) exists during exercise
- Exercise is prolonged (more than 30 to 60 minutes) or intensive
- More than 3 hours have elapsed since the preceding meal
- No extra snacks are taken before or during exercise.

**Blood glucose generally remains unchanged if:**
- Exercise is brief
- Plasma insulin concentration is normal
- Appropriate snacks are taken before and during exercise
- Blood glucose is habitually high and control poor.

**Blood glucose increases if:**
- Hypoinsulinaemia (low levels of insulin) exists during exercise
- Exercise is strenuous
- Excessive carbohydrate is taken before or during exercise.

Recommendations

Patients prescribed insulin (or some of the oral hypoglycaemic agents) are recommended to consider the following:
• Injection sites should be away from areas used during the chosen form of exercise [C].
• “Fast-acting” carbohydrate snacks should be at hand during and after exercise [C].
• Blood glucose levels should be monitored before and after activity and, on the results, take any necessary steps to prevent hypoglycaemia [C].
• Measure the blood glucose response to exercise to allow greater self-management [C].
• Note that delayed hypoglycaemia can occur up to 24 to 36 hours after exercise as the muscles refuel [C].
• Pay attention to hydration before, during and after exercise [C].
• Pay attention to foot care [C].
• Consider the need for salt supplements [B].

Energy expenditure may be higher than usual for patients with CF and CFRD during periods of recovery from mild exercise or activity due to increased work of breathing consistent with higher ventilatory requirements (Ward et al, 1999 [IIb]).

6.10 Hypoglycaemia

Hypoglycaemia can occur in people with CFRD who are treated with insulin and oral hypoglycaemic agents particularly with promotion of tighter control of diabetes to avoid complications.

For practical purposes, a blood glucose level of 4 mmol/l or below should be used as an indicator of impending or increased risk of a hypoglycaemic episode (Moran et al, 1995 [III]; O’Neill, 1997 [IV]). This level enables recognition of warning symptoms and allows time for self-treatment.

When symptoms of hypoglycaemia are recognised patients should be encouraged to check their blood glucose levels in the first instance to confirm diagnosis. If this is not possible the patient should assume that they are having a hypoglycaemic episode.

The recommended dietary management of hypoglycaemia is ingestion of 15 g of sucrose or glucose followed by a starchy carbohydrate snack or meal (Slama et al, 1990 [IV]). Glucose tablets, Lucozade and sugar lumps should be recommended over mixed foods that contain some sugar, as they will work more quickly than other sugar containing foods such as chocolate. Emphasis must be made to the patient about the need for a starchy snack to avoid a second hypoglycaemic episode.

“Hypostop” dextrose gel (Bio-Diagnostics Ltd.) can also be used for the treatment of hypoglycaemia in patients who are confused or semi-conscious but still able to swallow. Hypostop gel should not be used in people who are unconscious and unable to swallow (Diabetes UK, 2002b [IV]).

People with CF may be unable to mount a spontaneous glucagon response to hypoglycaemia, but they are generally able to compensate for glucagon deficiency via catecholamines (Moran et al, 1991 [III]). The exception to this is the patient who loses their hypoglycaemia awareness, where the counter regulatory catecholamine response is lost secondary to frequent episodes of hypoglycaemia. It is imperative that these patients are advised by the Diabetologist and their carers are taught how to administer glucagon.
Recommendations

Patients and carers should be taught:

- What is meant by a hypoglycaemic episode [C].
- How to recognize the signs and symptoms of a hypoglycaemic episode [C].
- The glucose level at which a hypoglycaemic episode will occur [C].
- Appropriate management of a hypoglycaemic episode (dietary treatment and glucagon) [C].
- The importance of identifying the cause of the particular hypoglycaemic episode [C].
- To familiarise themselves with guidelines on driving and hypoglycaemia (see Appendix – Section 12.9) [C].

6.11 Acute Illness (see also Section 4.10.1)

Acute illness is associated with increased and possibly severe insulin resistance and fluctuation of any residual insulin production. It is usual for people with CFRD to require a substantial increase in their insulin dosages during acute illness. Conversely, as the illness subsides reduction of the insulin dose to the patient’s baseline levels is necessary (Moran et al, 1999 [IV]). Frequent blood glucose monitoring is required to help determine the insulin dosage during acute illness (every 4–6 hours whilst blood glucose levels are elevated).

If appetite is poor and solid food is not tolerated patients should be encouraged to take carbohydrate-containing fluids every 2–3 hours. Suitable fluids are Lucozade, milk, fruit juice, sugary drinks, and supplement drinks. Fluids that do not contain carbohydrates should also be encouraged to prevent dehydration.

If the patient is unable to tolerate anything orally, intravenous fluid and a sliding scale of insulin should be commenced until the patient is able to tolerate food.

Recommendations

- If appetite is poor and solid food is not tolerated patients should be encouraged to take carbohydrate-containing fluids every 2–3 hours [C].
- If the patient is unable to tolerate anything orally, intravenous fluid and a sliding scale of insulin should be commenced [C].
- All patients with CFRD should be encouraged to contact their CF Teams for advice, before changing their treatment regimen, if they:
  - Notice that their blood glucose levels are running higher than normal.
  - Are unable to eat normally for more than 24 hours.
  - Have diarrhoea or vomiting which lasts longer than 6 hours.
  - Have a pyrexia [B].

6.12 Driving (see Appendix – Section 12.9)
6.13 Summary of recommendations – management issues and patient education

Section 6.1.1 – Injection depth

- Patients, carers and health professionals need to be made aware of the key factors that affect insulin absorption i.e. injection depth, site and technique [B].

- Appropriate needle lengths for people with CFRD are either a 8 mm needle (with a pinched skin fold) for normal weight adults and a 5 or 6 mm needle (with or without a pinched skin fold) for children and adolescents [B].

- Normal to thin adults may use 5 mm needle with a pinched up fold only under supervision of their Health Care Professional [C].

Section 6.2 – Insulin sites

- Choose the appropriate injection area according to type of insulin [C]:
  - Abdomen: Fast absorption. Inject a hand’s breadth either side of belly button. Insulins such as analogues, soluble or combined.
  - Buttocks: Slow absorption. Inject into top area. Use as alternative to thighs. Encourage long acting insulins.
  - Thighs: Slow absorption. Inject front or side. Medium acting insulins.
  - Arms: Medium to fast absorption. Inject into upper external area. Soluble insulins. (Not recommended for self-injection by Diabetes UK.)

- Inject into the same area at the same injection time to ensure a reliable absorption (Insulin Injection Technique. The First International Insulin Injection Technique Workshop, 1998 [IV]) [C].

- Provide patients with written and illustrated educational material on injection sites [C].

Section 6.2.1 – Rotation of sites

- Use pen needles once only [B].

- Organise a rotation of injection sites to suit type of insulin (see Section 6.2) [C].

- Teach patients to space out each injection within each area, moving one fingerbreadth from the last injection site; 6–8 cm spacing is advisable when lipohypertrophy is a problem [C].

- Clearly document advice given in patient’s individual education plan. Give appropriate written educational materials, diagrams and rotation charts for thighs and stomach [C].

- Alternate left and right-hand sides from one week to another [C].

- Emphasise the problems of injecting into lipohypertrophic areas [C].

- Health Care Professionals should be trained to identify lipohypertrophy [C].

- At each clinic visit or admission, clearly document that injection technique sites have been inspected and palpated [C].
Section 6.3 – Devices for administration of insulin

- Ensure correct cartridge being used, checking size, origin, name and type of insulin and manufacture. (Some cartridges do not fit into pens made by another manufacturer) [C].

- Unopened cartridges/pens stored in the main body of fridge at 2–8°C, remain usable to their expiry date [C].

- Cartridges and pens “in use” may be stored at room temperature for 1 month [C].

- Pens containing an insulin cartridge and needle must NEVER be stored in a fridge, as moving from extremes of temperature can cause insulin to expand/or contract in the cartridge, resulting in air bubbles or loss of insulin solution via the needle [C].

- Partly used cartridges should never be returned to the fridge to be reused and must be discarded [C].

- Detailed instruction in the use of pen devices and needles should be provided [C].

- Patients should be prescribed 1 litre “sharps bins” for disposal of needles, pens and lancets and safe clips to clip off the end of needles [C].

Section 6.4 – Injection technique

- Health Care Professionals could consider demonstrating on themselves when teaching patients injection technique [C].

- Insulin should only be administered when stored at room temperature (see Section 6.3) [C].

- Attach the appropriate sized needle (see Section 6.1.1) and use only once. [C].

- Neutral protamine hagedorn (NPH)/Premixed insulins: pens/cartridges should be rolled/tipped 10–20 times prior to use to mix insulin [C].

- Perform an “Air shot” of insulin prior to each injection [C].

- Select a site using the patient’s own injection site rotation pattern (see Section 6.6.2) [C].

- Use a “pinched up” skin fold if advised (see Section 6.1) with one hand, and continue to hold throughout injection. Holding the pen like a dart in the other hand, gently insert needle at 90 degrees to full needle depth. Depress the injector with thumb until all insulin has been administered. Wait 10 seconds to allow absorption then withdraw needle [C].

- Remove needle from pen to prevent air entry into pen cartridge [C].
Section 6.5.3 – When to check blood

- Ideally blood glucose should be checked up to 4 times a day [C].
- Recommended times should include before bed, fasting, pre and 1½–2 hours post meals [C].
- Patients taking long acting insulin in the evening should occasionally check blood glucose in the middle of the night [C].
- Patients who have enteral feeding should check 1–2 times a week, at the beginning and end of feed and once during feed. If intermittent bolus feeding check 1½–2 hours after the bolus.
- During illness check 4 times a day or more.
- Nine hours after taking steroids [C].
- Before and after exercise [C].

Section 6.7 – Lung transplantation and CFRD

- CFRD is not a contraindication to organ transplantation [C].
- Annual Reviews should be performed to identify complications [C].
- Blood pressure should be measured regularly [C].

Section 6.8 – Diabetes, liver disease and liver transplantation in cystic fibrosis

- Patients of any age with established liver disease should be screened regularly for the presence of diabetes [C].
- Tight control of blood glucose post transplant will minimise the risk of short and long-term complications and graft failure [C].
- Minimisation of nephrotoxic drug regimens is essential for patients with CFRD who have received a liver transplant, as progressive renal impairment will complicate future antibiotic treatment of the chest infections [C].
- More frequent monitoring for renal impairment and hypertension is necessary [C].

Section 6.9 – Exercise

- Injection sites should be away from areas used during the chosen form of exercise [C].
- “Fast-acting” carbohydrate snacks should be at hand during and after exercise [C].
- Blood glucose levels should be monitored before and after activity and, on the results, take any necessary steps to prevent hypoglycaemia [C].
- Measure the blood glucose response to exercise to allow greater self-management [C].
- Note that delayed hypoglycaemia can occur up to 24 to 36 hours after exercise as the muscles refuel [C].
- Pay attention to hydration before, during and after exercise [C].
- Pay attention to foot care [C].
- Consider the need for salt supplements [B].
Section 6.10 – Hypoglycaemia

Patients and carers should be taught:

- What is meant by a hypoglycaemic episode [C].
- How to recognize the signs and symptoms of a hypoglycaemic episode [C].
- The glucose level at which a hypoglycaemic episode will occur [C].
- Appropriate management of a hypoglycaemic episode (dietary treatment and glucagon) [C].
- The importance of identifying the cause of the particular hypoglycaemic episode [C].
- To familiarise themselves with guidelines on driving and hypoglycaemia (see Appendix – Section 12.9) [C].

Section 6.11 – Acute illness

- If appetite is poor and solid food is not tolerated patients should be encouraged to take carbohydrate-containing fluids every 2–3 hours [C].
- If the patient is unable to tolerate anything orally, intravenous fluid and a sliding scale of insulin should be commenced [C].
- All patients with CFRD should be encouraged to contact their CF Teams for advice, before changing their treatment regimen, if they:
  - Notice that their blood glucose levels are running higher than normal
  - Are unable to eat normally for more than 24 hours
  - Have diarrhoea or vomiting which lasts longer than 6 hours
  - Have a pyrexia [B].
7. ANNUAL REVIEWS AND SURVEILLANCE FOR COMPLICATIONS

7.1 Need for a CFRD Annual Review

Ideally the CF Clinician and Diabetologist should carry out a combined general and CFRD Annual Review. In practice, it is usually more convenient for the CFRD Annual Review to be carried out at a different appointment to the general CF Annual Review. The aim of the CFRD Annual Review is to screen for and if necessary treat, early complications, to check diabetic treatment is adequate and appropriate, to assess nutritional management and to address adherence issues, diabetic education and psychosocial issues.

7.2 Screening for microvascular complications

Retinopathy, nephropathy and neuropathy can develop in patients with CFRD (see Section 8) (Sullivan & Denning, 1989 [IV]; Lanng et al, 1994b [III]; Yung et al, 1998 [III]; Scott et al, 2000 [IV]). The natural course of these complications are not as clearly established in CFRD as in Type 1 and Type 2 diabetes but available data suggest they are rare within the first five years of the onset of the CF related diabetes.

The National Screening Committee review of diabetic retinopathy screening recommends annual screening for all diabetic patients aged over 12 years, digital imaging and indirect slit-lamp ophthalmoscopy being the preferred techniques (Negi & Vernon, 2003 [III]; Squirrell & Talbot, 2003 [III]) (see Section 8.3.1).

In screening for nephropathy the impact of other potentially toxic therapeutic interventions i.e. antibiotics (aminoglycosides and polymyxins) and anti-inflammatory drugs (ibuprofen) should be considered. Annual microalbuminuria measurement is recommended (see Section 8.3.2).

7.3 Macrovascular complications

At present these are extremely rare in CFRD but there is the possibility that such complications will develop in people with CF and CFRD as survival increases.

7.4 Recommendations for Annual CFRD Review [C]

- **History**
  - Clinical course, number of admissions with reasons
  - Alcohol and smoking
  - Hypoglycaemia – identify cause and optimise treatment
  - Problems with infections, eyes, feet, skin, genitourinary
  - Sexual dysfunction
  - Episodes of distal intestinal obstruction syndrome (DIOS)
  - Exercise taken.

- **Full dietetic review**
  - Meals, snacks, enzymes, supplements, feeds.

- **Drug therapy**
  - Insulin therapy
  - Injection technique.
- Home blood glucose monitoring.
- Psychosocial counselling (if considered necessary).

Examinations
- Weight, height, BMI, centiles
- Respiratory function (FEV₁, SaO₂)
- Blood pressure
- Sensory and vibration sense
- Feet examination and pedal pulses.

Investigations
- Microalbuminuria
- HbA₁c and random glucose
- Urea and electrolytes, creatinine clearance (selected)
- Fasting lipid profile.

- Retinopathy screening referral.
8. TREATMENT OF COMPLICATIONS

8.1 Complications of diabetes

Complications of diabetes can be divided into 3 main groups:

- Acute, usually metabolic, complications.
- Chronic, micro and macrovascular complications.
- Complications of treatment and adaptation to treatment (e.g. hypoglycaemia, psychological problems).

8.2 Acute complications

8.2.1 Diabetic ketoacidosis

Type 1 diabetes can occur in individuals with cystic fibrosis. In one case report the authors describe an 11-year-old boy with cystic fibrosis who developed diabetic ketoacidosis (Atlas et al 1992, [IV]). The prevalence of Type 1 diabetes in the general population is low, estimated at approximately 0.3%, assuming simple inheritance with no adverse or advantageous effect on survival conferred by the coincidence of the two conditions this would imply that fewer than 25 individuals have the combination of CF and Type 1 diabetes in the UK.

The finding of ketonuria is well reported in the context of CFRD in a fasting subject but ketoacidosis in CFRD without Type 1 diabetes has not been reported.

- Management of diabetic ketoacidosis should be with standard guidelines such as those for children and adolescents produced by Diabetes UK: http://www.diabetes.org.uk/dka_paed/index.html

8.2.2 Hyperosmolar non-ketotic coma

The clinical syndrome of hyperosmolar non-ketotic coma (HONK) represents the extreme end of the spectrum of severe metabolic decompensation. It tends to occur in older patients with Type 2 diabetes in the context of sepsis, myocardial infarction or other intercurrent illness. The clinical picture includes confusion or coma, dehydration, and an increased risk of fits, focal neurological deficit and disseminated intravascular coagulation. The clinical diagnosis is confirmed by the biochemical findings of plasma osmolality >320 mmol/l, blood glucose >33 mmol/l in the absence of ketoacidosis. The clinical syndrome has not been reported in CFRD although many patients with CFRD present with extremely high random blood glucose levels at diagnosis and may meet the biochemical criteria for HONK without displaying the clinical features.

8.3 Chronic complications

In both Type 1 and Type 2 diabetes the onset and progression of complications correlate strongly with duration and control of the diabetes and the coexistence of other risk factors such as hypertension and hypercholesterolaemia. The same is likely to be true of CF related diabetes.
8.3.1 Microvascular complications

It is now clear that patients with CFRD are at risk of complications of diabetes (Allen et al, 1986 [IV]). In one study of 311 patients with CF microvascular complications were identified in 4 patients with CFRD (10%) with duration of diabetes mellitus of 1–17 years: (background retinopathy, diabetic nephropathy, microalbuminuria and neuropathy) (Lanng et al, 1994b [III]). In other studies an incidence of 21–23% was found (Sullivan & Denning, 1989 [III]; Wilson et al, 2000 [III]).

Recommendation

- Annual screening should be offered to identify complications [C].

8.3.2 Microalbuminuria

Microalbuminuria has been demonstrated in CFRD although it is not known whether the clinical significance of different levels of microalbuminuria can be extended from studies in Type 1 and Type 2 patients to the CFRD population. The amounts of creatinine, protein, carbohydrate and stalic acid in the urine of 19 patients with CF, 12 normal controls and 11 pathological controls with chronic lung disease were determined. The mean creatinine excretion levels of the total CF group as well as the CF subgroups were significantly decreased when compared to normal controls but comparable to pathological controls. Mean urinary protein levels appear to be increased in patients with CF compared to normal controls and pathological controls but the increased levels resulted from factors (e.g. presence of diabetes mellitus) other than CF (Guman-Wignot et al, 1989 [III]). In Type 1 diabetes patients with persistent microalbuminuria in the EUCLID (Eurodiab controlled trial of Lisinopril in insulin dependent diabetes) study treatment with an angiotensin-converting enzyme (ACE) inhibitor reduced the progression to overt nephropathy even in individuals who were not hypertensive (EUCLID Study Group, 1997 [IV]). Until further evidence is available, people with CFRD with persistent microalbuminuria or overt proteinuria should be treated with an ACE inhibitor.

Recommendations

- Annual urine testing for microalbuminuria for those over 12 years and those with diabetes for more than 5 years [B].
- People with CFRD and persistent microalbuminuria or proteinuria should be investigated and, if appropriate, treated with an ACE inhibitor [B].

8.3.3 Macrovascular complications

As far as macrovascular complications are concerned it is likely that patients with CFRD will follow the same pattern as Type 1 patients (who unlike Type 2 patients usually have a clear date of onset of diabetes and usually do not have hypercholesterolaemia or hypertension after stabilisation). In these patients overt macrovascular disease presents more than 20 years after diagnosis. Hypertension and hyperlipidaemia may develop following transplantation.

8.4 Other risk factors

8.4.1 Hyperlipidaemia

Cholesterol and triglyceride concentrations are commonly believed to be low in patients with cystic fibrosis. In one study, fasting lipid profiles were measured in 192 patients with CF in conjunction
with an oral glucose tolerance test. In most cases, hypertriglyceridemia was isolated; only 3 subjects had elevation of both cholesterol and triglycerol. Lipid concentrations were not related to body mass index, weight, glucose tolerance, the areas under the curve for glucose or insulin, or glycated haemoglobin (Figueroa et al, 2002 [III]). Isolated hypertriglyceridemia appears to be common in CF, whereas cholesterol concentrations are generally low (see Section 5.2.2) (Jackson et al, 2002 [III]; Stewart et al, 1997 [III]).

**Recommendation**

- **Fasting lipid levels should be checked annually [C].**

### 8.4.2 Hypertension

Similarly hypertension is uncommon in the CF population as a whole. However given that hypertension is a risk factor for the progression of microvascular complications (particularly diabetic nephropathy) and that microvascular complications are common in CFRD, measurement of blood pressure should be included in the Annual Review.

**Recommendation**

- **Treatment should be commenced if the systolic BP >140mm Hg or diastolic BP >80mm Hg [C].**

Thus, patients with CFRD are probably as likely to develop late diabetic complications as patients with other types of diabetes of equally long duration and comparable glycaemic control.

Patients should be screened for the complications of diabetes at diagnosis and regularly thereafter (annually for those with no complications). (see Section 7). Patients with established complications should be referred to the Specialist Diabetes Team.

### 8.5 Complications of treatment and adaptation to treatment

#### 8.5.1 Hypoglycaemia (see also Sections 4.5 and 6.10)

Hypoglycaemia is a common acute complication of intensive insulin therapy. Patients with CFRD are at increased risk of hypoglycaemia because of variations in dietary intake (without concomitant insulin adjustment) and problems with delayed absorption of food. In addition the response to hypoglycaemia is altered in CF related diabetes. Patients with CFRD are not able to mount a glucagon response to hypoglycaemia but they are generally able to mount an adequate catecholamine response (Moran et al, 1991, [III]). Thus patients with CFRD aiming for optimal control may have more frequent episodes of hypoglycaemia particularly if they do not adjust their insulin in the light of changing requirements. Frequent episodes of hypoglycaemia may lead to a reduction in catecholamine response to hypoglycaemia, this is a particularly important consideration in the case of many patients with CF who have little or no glucagon response to hypoglycaemia, and in these cases recurrent episodes of severe hypoglycaemia can occur. This situation is a diabetic emergency and patients should be admitted to hospital and an urgent opinion should be sought from the Specialist Diabetes Team.

**Recommendations (see also Sections 4.5 and 6.10)**

- **All people with CFRD should be given education on prevention and management of hypoglycaemia [C].**

- **Some individuals, particularly those on insulin, may need glucagon kits at home. If this is the case both the person with CFRD and their carers should know when and how it should be used.**
9. PREGNANCY IN CFRD AND GESTATIONAL DIABETES IN CYSTIC FIBROSIS

9.1 Diabetes UK Definition 2000

“Gestational diabetes is carbohydrate intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during pregnancy. It does not exclude the possibility that the glucose intolerance may antedate pregnancy but has been previously unrecognised. The definition applies irrespective of whether or not insulin is used for treatment or the condition persists after pregnancy” (World Health Organisation, [IV]; Diabetes UK, 2000 [IV]).

9.2 Background

As survival of patients with CF increases more women with CF wish to become pregnant. Pregnancy has a major impact on glucose tolerance. Insulin requirements are stable or reduced in the first trimester, begin to rise in the second trimester and peak in the third trimester. Insulin requirements increase by 200–300% above preconception levels by the end of the third trimester (Steel et al, 1994 [III]). Thus women with CF who are already at risk of CFRD are at high risk of gestational diabetes.

Raised blood glucose levels in the first trimester are associated with an increased risk of teratogenesis (foetal malformation) (Suhonenen et al, 2000 [III]). Raised blood glucose levels in the second and third trimester are associated with increased risks to both mother and foetus (Towner et al, 1995 [III]).

In many of the reported series of pregnancies a large proportion of patients with CF were pancreatic sufficient: outcome was assessed in a series of 11 patients with CF who had 13 completed pregnancies between 1975 and 1995. Pre-pregnancy the mean age of the group was 24 (range 17–27) years. Seven patients had pancreatic insufficiency and 7 had chest X-ray evidence of bronchiectasis. None of the patients had diabetes mellitus but 3 developed gestational diabetes (Jankelson et al, 1998 [IV]).

As more pancreatic insufficient patients reach adulthood with less severe disease the proportion of women with gestational diabetes is likely to rise. In a follow up report from the University of Toronto 71% of the pregnancies in their CF population in the 1970s were in pancreatic sufficient women, compared with 48% in the 1980s and 29% in the 1990s (as compared with 21% pancreatic sufficiency in the entire adult CF population at that time) (Gilljam et al, 2000 [IV]).

9.3 Complications of pregnancy

Complications are more common in women with CFRD and gestational diabetes. In a study of 33 successful pregnancies in 23 women, 3 were found to have diabetes requiring insulin prior to pregnancy and 7 developed gestational diabetes with 5 requiring insulin giving a prevalence of diabetes/gestational diabetes of 10/23 (43%). The most frequent complication of the pregnancies was preterm delivery, which occurred in 24% of cases. The lung function of the women was significantly lower in the preterm group than in those delivering at term. Those who went on to deliver preterm were more likely to have other CF complications including diabetes, asthma or liver disease (Odegaard et al, 2002 [III]). Few studies of pregnancy in CF describe their screening protocol for gestational diabetes. In a study where systematic screening for diabetes was used all 6 women becoming pregnant in a year at a single Specialist CF Centre were found to have CFRD or gestational diabetes (Verma et al, 2002b [III]).
9.4 Diagnosis of gestational diabetes

This is based on criteria set out by the World Health Organisation (see Section 3) and endorsed by Diabetes UK.

9.4.1 Management of women with CF who become pregnant or who wish to become pregnant

The issues surrounding pregnancy and diabetes vary according to glucose tolerance. Women with CF who wish to become pregnant may be divided into 4 groups:

- Those with established CFRD
- Those with known impaired glucose tolerance
- Those with normal glucose tolerance
- Women with unknown glycaemic status.

9.4.2 Women with established CFRD

Women with established CFRD should be advised to optimise their diabetic control prior to conception to minimise the risk of teratogenesis. Tight blood glucose control is required throughout pregnancy and there is a high risk of hypoglycaemia. They do not need a glucose tolerance test in pregnancy. The Specialist Diabetes Team should be informed immediately (ideally preconception) if a woman with CFRD wishes to become pregnant. Close liaison will be required between the Specialist CF Team, Specialist Diabetes Team and Obstetric Team to achieve the best outcome for mother and baby.

9.4.3 Women with known impaired glucose tolerance

Women with known impaired glucose tolerance prior to conception already meet the WHO criteria for the definition of gestational diabetes when they are pregnant. They do not need a glucose tolerance test in pregnancy. They should be referred to the Specialist Diabetes Team immediately where their diabetes control will be assessed and treatment initiated if appropriate. It is unknown whether there is an increased risk of teratogenesis in women with impaired glucose tolerance at conception.

9.4.4 Women with normal glucose tolerance

Women with CF with normal glucose tolerance documented in the three months prior to conception are likely to maintain normoglycaemia throughout the first trimester; insulin requirements do not rise in this time unless there is an intercurrent problem, which increases insulin resistance such as infection or initiation of steroids. However, insulin requirements start to rise in the second trimester and a formal glucose tolerance test should be carried out every trimester to 30 weeks. (An OGTT between 24 and 28 weeks of pregnancy is recommended by Diabetes UK for gestational diabetes in non-CF related diabetes but not in the latest NICE Guidelines.) Women shown to have abnormal glucose levels in pregnancy should be referred urgently to the Specialist Diabetes Team.

9.4.5 Women with unknown glycaemic status

Women with CF and unknown glycaemic status wishing to become pregnant should have an oral glucose tolerance test done before conception to determine glycaemic status. Women with CF who
become pregnant without knowing their glycaemic status and who wish to continue the pregnancy should have an oral glucose tolerance test done as soon as possible following confirmation of pregnancy.

**Recommendations**

- **Women with IGT or CFRD** should optimise their diabetic control and must be referred to the Specialist Diabetes Team before becoming pregnant [B].

- **Those with known impaired glucose tolerance** must be referred to Diabetes Team immediately for assessment [B].

- **Those with normal glucose tolerance** should have an OGTT in the first trimester and then at least between 24 and 28 weeks. If abnormal refer to the Diabetes Team.

- **Those with unknown glycaemic status** should have a OGTT before becoming pregnant [B].
10. PSYCHOLOGICAL ISSUES

10.1 Psychological support

The management of CF involves a time-consuming and often complicated treatment regimen. Although there is a paucity of evidence in the literature addressing how a second diagnosis of CFRD affects patients and carers, the need for additional and perhaps more demanding and complicated treatment may come as a heavy blow. This may present an additional burden to the person with CF and may cause additional anxiety amongst their parents and carers. The additional burden of CFRD needs to be acknowledged in patient management and care.

In both CF and Type 1 diabetes, social support is important (Skinner et al, 2000 [III]), and a variety of psychological interventions have been demonstrated to be effective (Hampson et al, 2000 [III]; Duff, 2001 [III]). In both CF and Type 1 diabetes, adolescence and the transition from paediatric care to adult care are psychologically difficult periods (Johannesson et al, 1998 [III]; Bryden et al, 2001 [III]).

10.2 Eating disorders

Eating disorders are much more common in adolescents and young people with Type 1 diabetes than in the age matched population – the problem is worst for females (Engstrom et al, 1999 [IIa]; Jones et al, 2000 [III]). During adolescence (11–19 years) female patients with Type 1 diabetes aged 13–14 years seem to be at the greatest risk of developing disordered eating patterns (Meltzer et al, 2001 [III]). For girls with Type 1 diabetes weight gain can be a problem (this may get worse with tight glycaemic control) and disordered eating patterns may be accompanied by a pattern of insulin omission in order to limit the weight gain (Khan et al, 1996 [III]). There are no reports as to the situation for individuals with CFRD – insulin omission to control weight may be less likely but not impossible.

In adolescents and young adults with CF, eating behaviour and attitudes, body satisfaction and self-esteem have been found to be similar to those of their healthy peers. Males perceive themselves as heavier than they are but also wish to be heavier still. Females with CF see themselves as thinner than they are but are happy with their perceived body image. The females with CF actually had fewer problems than their healthy peers. In this paper dissatisfaction with body image and disordered eating was reported (Abbott et al, 2000 [III]); other work has shown people with CF have no desire to be slimmer and no evidence of an increased rate of eating disorders (Sawyer et al, 1995 [III]; Raymond et al, 2000 [III]).

A study comparing eating behaviour and attitudes, body satisfaction and self-esteem in patients with CFRD and non-diabetic adults with CF found no difference between the groups relating to actual, perceived or desired body mass index. However those with CFRD reported a greater number of problems concerning food/eating behaviours with females with diabetes reporting significantly more problems than males. Both male and females with CFRD were less satisfied with their body appearance than controls. Method of treatment also had significance with patients treated with insulin reporting greater problems with food/eating behaviours and feelings of lower self-worth than those taking oral medication (Abbott et al, 1998 [III]).

Recommendations

- **Dietary and diabetes advice should take into account possible concerns about body image.**
- **Diabetes support and education should be available.**
- **Appropriate psychological support should be available.**
• **Patients should be given advice on how to manage their diabetes and information on the reasons for achieving good control [C].**

• **Perfect compliance with diabetes treatment should not be assumed [C].**

• **Difficulties should be explored in a non-confrontational way [C].**

• **Telephone advice and backup should be available [C].**

### 10.3 Adherence issues

In Type 1 diabetes in adolescents and young people psychological issues are an important element in their diabetes management, with insulin omission a frequent cause of poor glycaemic control or admission with diabetic ketoacidosis (Bryden et al, 2001 [III], Khan et al, 1996 [III]). Studies in adolescents with CF have identified that they participate in risk taking behaviour but to a lesser extent than healthy controls (Britto et al, 1998 [III]). In chronic disease a large proportion of patients do not adhere fully to treatment, even if the disorder is life-threatening as in CF (Abbott et al, 1998a [III], Skinner et al, 2000 [III]).

**Recommendations**

• **Adherence issues should be considered in the choice of insulin regimen – in adolescents, better control may be achieved with a simple regimen than with a complex and demanding one that is not adhered to [B].**

• **Perfect adherence to diabetes treatment should not be assumed. Difficulties should be explored in a non-confrontational way [B].**

• **The need for good diabetic control may need to be balanced with other clinical factors [B].**

• **Diabetes support and education should be available. Patients should be given advice on how to manage their diabetes and information on the reasons for achieving good control [B].**

• **Telephone advice and backup should be available [C].**
11. FINANCIAL ALLOWANCES

11.1 Prescription charges

There are various schemes that cover prescription charges. Some people are automatically exempt because of age, low income or because of a chronic medical condition. Unfortunately having cystic fibrosis does not mean a patient is automatically exempt. However people with cystic fibrosis related diabetes who are insulin or tablet treated do qualify for exemption from prescription charges on all their medication. Patients can get an exemption certificate by completing form FP92A (EC92A in Scotland) available from pharmacies or their doctor. These must be sent to the Primary Care Trusts.

11.2 Other benefits

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

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

- The CF Social Worker at their Specialist CF Centre.
- The CF Trust Benefits Advice Helpline ☎️ 0845 859 1000.
- Hospital Welfare Rights Service or Citizens Advice Bureau.
- The Benefits Enquiry Line (BEL) ☎️ 0800 882200, text phone 0800 243355 (in Northern Ireland ☎️ 0800 220674).
- Cystic Fibrosis Trust website www.cftrust.org.uk
12. APPENDICES

12.1 Standards for the oral glucose tolerance test (OGTT)

A patient information sheet may be helpful. This should include:

- The reason for the test.
- The procedure that is used (morning tests only).
- Information about an unrestricted diet (containing at least 150 g carbohydrate daily) and usual physical activity for at least 3 days before the test.
- Recent evidence suggests that a reasonable (30–50 g) carbohydrate containing meal should be consumed on the evening before the test.
- Information about fasting for 8–14 hours before the test (water may be drunk).
- Not taking long-term medication on the morning of the test.
- Instructions to bring a list of their current medications.
- Smoking is not permitted during the test.
- The presence of factors that influence interpretation of the results of the test must be recorded (e.g. medications, inactivity, infection, etc.).

Test Protocol

The patient must be fasting from midnight the night before the study (8–14 hours) and be clinically stable. The OGTT should NOT be performed during acute illness, shortly after major surgery or while the patient is on oral steroids.

1. The test should be performed in the morning.
2. Smoking is not allowed.
3. The patient should avoid excessive exercise during the test.
4. Take time 0 glucose in fluoride oxalate tube.
5. A glucose load should be ingested.
   a. Equivalent to 75 g anhydrous glucose in a total fluid volume of 250–300 ml.
   b. Children should be given 1.75 g anhydrous glucose per kg body weight (max. 75 g glucose).
   c. A partial hydrolysate of starch (82.5 g of glucose monohydrate) e.g. Polycal (Nutricia Clinical Care, White Horse Business Park, Trowbridge, Wiltshire, BA14 0XQ) may be used as an alternative to anhydrous glucose and has been accepted by Diabetes UK; 113 ml of Polycal liquid provides an equivalent carbohydrate load to a standard 75 g dose of anhydrous glucose.
   d. Consumed over a 5 minute period.
6. Timing for the rest of the test starts at the beginning of ingestion.
7. Take a second glucose sample at 120 minutes after beginning ingestion in a fluoride oxalate tube.
8. Preparations containing caffeine should be avoided.
9. Lucozade is NOT suitable.
10. It is not necessary to measure urine glucose for the diagnosis of diabetes.
11. Ensure that both bottles are labelled with time and date for the labs to analyse the results.

Some biochemistry laboratory services will be able to perform the OGTT.

These following criteria are recommended for the diagnosis of Type 1 and Type 2 diabetes but there are difficulties applying them to CFRD.

A. Symptoms of hyperglycaemia such as polyuria, polydipsia and unexplained weight loss with one of the following
   - Random venous plasma glucose \( \geq 11.1 \text{ mmol/l} \)
   - Fasting venous plasma glucose \( \geq 7.0 \text{ mmol/l} \)
   - 2 hour venous plasma glucose \( \geq 11.1 \text{ mmol/l} \) after 75 g anhydrous glucose (OGTT)
     Children 1.75 g/kg up to maximum of 75 g

B. Without symptoms of hyperglycaemia
   - Diagnosis should not be made on the basis of only one glucose measurement
   - At least one other glucose measurement on another day should be made
   - If fasting or random samples are not diagnostic need an OGTT

C. Because of the medical and legal implications the diagnosis should be secure, and not based solely on
   - Glycosuria
   - Capillary blood glucose
   - Elevated HbA1c

The diagnosis of diabetes should be based on plasma glucose measurements (fluoride oxalate tube). WHO guidelines also have ranges for whole blood (clotted sample).

Classification and terms

- Insulin-dependent (IDDM) and non-insulin dependent diabetes (NIDDM) will be renamed Type 1 and Type 2 diabetes
- The terms Type 1 and Type 2 process will be introduced to describe the cause of insulin dependent and non-insulin dependent diabetes respectively. Both of these pathological processes will be clinically staged by the treatment that they need – from diet to insulin
- Impaired Glucose Tolerance (IGT) is a stage of impaired glucose regulation (Fasting plasma glucose <7.0 mmol/l and OGTT two hour value \( \geq 7.8 \text{ mmol/l but <11.1 mmol/l} \)).
- Impaired Fasting Glycaemia (IFG) has been introduced to classify individuals who have fasting glucose values above the normal range but below those diagnostic of diabetes. (Fasting plasma glucose \( \geq 6.1 \text{ mmol/l but <7.0 mmol/l} \)).

Diabetes UK recommends that all those with IFG should have an OGTT to exclude the diagnosis of diabetes and are actively managed with lifestyle advice.
12.3 The National Service Framework for Diabetes

The National Service Framework for Diabetes (NSF) has been informed by the advice of an External Reference Group. It builds upon the vision of the St Vincent Declaration and was published in two stages. The document, National Service Framework for Diabetes: Standards, sets out the aims, standards, rationales and key interventions, together with the implications for planning services. The NSF for Diabetes applies to all diabetes including CF related diabetes. (http://www.doh.gov.uk and search for The National Service Framework for Diabetes.) Similar initiatives are happening in each of the 4 UK nations, although there are differences in priorities and approaches.

The following areas are specified in the English NSF document:

- Prevention of Type 2 diabetes
- Identification of people with diabetes
- Empowering children, young people and adults with diabetes
- Clinical care of adults with diabetes
- Clinical care of children and young people with diabetes, including the transition from specialist paediatric diabetes services to specialist adult diabetes services
- Management of diabetic emergencies
- Care of people with diabetes during admission to hospital
- Diabetes and pregnancy
- Detection and management of long-term complications of diabetes and the provision of integrated health and social care.
12.4 Advice for holiday travel for people with cystic fibrosis related diabetes

- Have personal identification and a letter confirming you have cystic fibrosis and diabetes.
- Diabetes UK (☎ 0845 120 2960) can provide photographic ID cards.
- Ensure at least one person you are travelling with knows you have diabetes and knows how to treat hypoglycaemia.
- Carry your supplies in your hand luggage (insulin will freeze in the aircraft hold and will then be unusable).
- In case of loss or breakages, take twice the amount of supplies than you will actually need.
- Do not ask for a diabetic meal on a flight – have the same meal as everyone else (air meals for diabetics contain too little carbohydrate).
- Always carry extra supplies of quick acting sugar and starchy carbohydrate in case of delays.
- If you are going to a hot climate your insulin may work better and therefore you may need to reduce your insulin doses. Keep your insulin and test strips cool.
- Frio packs (☎ 01437 741700) are an easy way to keep insulin at the correct temperature (Insulin goes off if frozen or above 30 degrees therefore you should always use a Frio pack if temperature likely to be outside of these parameters).
- Drink plenty of non-alcoholic fluids to prevent dehydration.
- If you are going to a cold climate ensure insulin does not freeze.
- Ensure your insurance covers pre-existing illnesses CF and diabetes.
- If you are unwell follow usual sick day rules.
12.5 Cystic fibrosis related diabetes education check list

Below is an example of a list of topics that need to be addressed.

Understanding what is CFRD and causes
- Impact on weight and lung function
- Other CF related conditions that effect the management of blood glucose
- Discuss preconceived fears and anxieties
- Medication that affects blood glucose

Blood glucose monitoring
- Meter, test strips and finger prick device
- Confidence and competence in technique
- Understands common problems causing inaccurate blood tests and reasons why blood glucose monitoring is important
- When to check glucose levels
- What the results mean and the action to take
- Recording of the results in diary
- Correct meter care and quality control tests
- Who to contact if any problems
- Acceptable ranges for blood glucose – fasting, post meals, before bed, other

Treatment Plan

Aims and Objectives
- **Tablets** – Type [ ] Action [ ] Duration [ ] Timing [ ]
- **Insulin** – Type [ ] Action [ ] Duration [ ] Timing [ ]

Type of pen device
- Confidence and competence in assembling and using device
- Dialling up and down doses

Needle size

With and without pinched skin fold

Chosen Injection sites
- Same site / same time

Injection technique
- Rotate pen 15–20 times if cloudy insulin
- Change needle every time
- Air shot 1–2 units insulin
- Dial up dose, choose site
- Pinched up skin fold if needed and why
- Inject insulin hold for 10 seconds

Rotation pattern
- Alternate sites left and right weekly

Disposal of sharps
- Safe clip and 1 Litre sharps bin
Storage of insulin/pens
- Unopened cartridges/pens – fridge
- In use – room temperature for 1 month

Dietary Assessment
- Any dietary changes
- Eating out

Hypoglycaemia
- Causes
- Symptoms
- Treatment
- Prevention
- Glucagon (if relevant)

Hyperglycaemia
- Causes
- Symptoms
- Treatment
- Prevention

Illness
- Infection
- Vomiting and diarrhoea
- Reduced appetite

Adjustment of insulin

Discuss life issues

Who to inform about diabetes
- Family/carers/partners/friends/school/college/work

Smoking

Alcohol
- Type
- Advice given on management of blood glucose

Physical activity
- Type
- When
- Advice given on adjusting food, insulin and monitoring

Cultural issues

Driving (Appendix – Section 12.9)
- Insurance company

Family planning advice
Pregnancy
Care provision by whom and when
Contact numbers

GP informed of
- Meter/test strips/finger pricking device and lancets
- Type of Insulin /pen device/needle size
- B.D Safe clip/1 litre sharps bin
- Obtaining prescriptions / supplies

Identification

Exemption certificate/prescriptions

Complications/prevention

HbA1c – what it means

Eye/foot screening

Next review by Diabetologist
12.6 Hypoglycaemia – note for patients

What is it?

Hypoglycaemia literally means a low level of glucose in the blood.

It happens when the blood glucose level is less than 4 mmol/l.

How does it make you feel?

It can be different from person to person

You may feel:
- Sweaty
- Dizzy
- Trembling
- Hungry
- Tingling sensation in the hands, lips and tongue
- Difficulty in concentration
- Irritable

What should you do?

● Take a capillary blood glucose level if this is possible.

● If the glucose level is less than 4mmol/l take a form of quick acting sugar such as 100 ml of Lucozade or 5 dextrose tablets or a glass of pure fruit juice.

● Wait 5 minutes.

● If the symptoms have gone, have some starchy carbohydrate such as 2 digestive biscuits or if a meal is due give your usual insulin (if due) and eat your meal immediately.

● If the symptoms are still present test again and if your blood glucose has not risen above 4 mmol/l repeat Lucozade/dextrose/fruit juice and review after 5 minutes.

● If the blood glucose has still not improved glucagon may be required.
12.7 Useful websites

Diabetes UK

- www.diabetes.org.uk

Diabetes UK Guidelines for treatment of diabetic ketoacidosis


Cystic Fibrosis Trust UK

- www.cftrust.org.uk

Website of the Leeds Regional Cystic Fibrosis Centres

- www.cysticfibrosismedicine.com

Diabetes Guidelines Europe (WHO definition and diagnostic criteria)

- www.staff.ncl.ac.uk/philip.home/who_dmc.htm


- www.bma.org.uk
12.8 Other publications


12.8.1 Documents published by the Cystic Fibrosis Trust, UK

These are all available at www.cftrust.org.uk or as hard copies from the Publications Manager at the CF Trust

- *Standards for the Clinical Care of Children and Adults with Cystic Fibrosis in the UK 2001*. UK Cystic Fibrosis Trust Clinical Standards and Accreditation Group. 2001.
12.9 Driver and Vehicle Licensing Authority

“These guidelines are intended for use by doctors. If you are not medically qualified, please consult your doctor about these guidelines and fitness to drive”. The applicant or licence holder must notify DVLA unless stated otherwise in the text

Chapter 3 Diabetes Mellitus

<table>
<thead>
<tr>
<th><strong>Group 1 Entitlement</strong></th>
<th><strong>Group 2 Entitlement</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insulin Treated</strong></td>
<td>New applicants on insulin or existing drivers are barred in law from driving HGV or PCV vehicles from 1/4/91. Drivers licensed before 1/4/91 on insulin are dealt with individually and licensed subject to satisfactory annual Consultant assessment. Regulation changes in April 2001 allow “exceptional case” drivers to apply for or retain their entitlement to drive class C1 vehicles (3500-7500kgs lorries) subject to annual medical examination.</td>
</tr>
<tr>
<td>Diabetic drivers are sent a detailed letter of explanation about their licence and driving by DVLA.</td>
<td>Must recognise warning symptoms of hypoglycaemia and meet required visual standards. 1, 2 or 3 year licence.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Temporary Insulin Treatment</strong></th>
<th>Legal bar to holding a licence while insulin treated. May reapply when insulin treatment is discontinued.</th>
</tr>
</thead>
<tbody>
<tr>
<td>eg gestational diabetes, post-myocardial infarction, participants in oral/inhaled insulin trials.</td>
<td>May retain licence but should stop driving if experiencing disabling hypoglycaemia. Notify DVLA again if treatment continues for more than 3 months.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Managed by Diet and Tablets</strong></th>
<th>Drivers will be licensed unless they develop relevant disabilities eg. diabetic eye problem affecting visual acuity or visual fields, in which case either recommended refusal or revocation or short period licence. If becomes insulin treated will be recommended refusal or revocation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic drivers are sent a detailed letter of explanation about their licence and their driving by DVLA.</td>
<td>Will be able to retain Till 70 licence unless develop relevant disabilities eg. diabetic eye problems affecting visual acuity or visual field or if insulin required.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Managed by Diet Alone</strong></th>
<th>Need not notify DVLA unless develop relevant disabilities eg. Diabetic eye problems affecting visual acuity or visual field or if insulin required.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need not notify DVLA unless develop relevant disabilities eg. Diabetic eye problems affecting visual acuity or visual field or if insulin required.</td>
<td>Need not notify DVLA unless develop relevant disabilities eg. Diabetic eye problems affecting visual acuity or visual field or if insulin required.</td>
</tr>
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<table>
<thead>
<tr>
<th><strong>Diabetic Complications</strong></th>
<th><strong>Group 1 Entitlement</strong></th>
<th><strong>Group 2 Entitlement</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequent hypoglycaemic episodes likely to impair driving</td>
<td>Cease driving until satisfactory control re-established, with consultant/GP report.</td>
<td>See above for insulin treated. Recommended refusal or revocation.</td>
</tr>
<tr>
<td>Impaired awareness of Hypoglycaemia</td>
<td>If confirmed driving must stop. Driving may resume provided reports show awareness of hypoglycaemia has been regained, confirmed by consultant/GP report.</td>
<td>See above for insulin treated. Recommended refusal or revocation.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Eyesight complications (affecting visual acuity or fields)</strong></th>
<th>See Section: Visual Disorders.</th>
<th>See above for insulin treated and Section: Visual Disorders.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Renal Disorders</strong></td>
<td>See Section: Renal Disorders.</td>
<td>See Section: Renal Disorders.</td>
</tr>
<tr>
<td><strong>Limb Disability e.g. peripheral neuropathy</strong></td>
<td>See Section: Disabled Drivers at Annex 1</td>
<td>As Group 1</td>
</tr>
</tbody>
</table>

The above chart is regularly updated on
http://www.dvla.gov.uk/at_a_glance/ch3_diabetes.htm 02/14/03
• If on any diabetes medication or insulin long-term (i.e. for more than 3 months) must notify DVLA and Insurance Company.

• If on a sulphonylurea or insulin treatment always test your blood glucose level before starting to drive.

• If your blood glucose level is less than 5 mmols have some carbohydrate to eat (at least 20 grammes) and do not drive until your blood glucose level has risen to above 5 mmols.

• Stop driving every 2 hours and retest your blood glucose level.

• Always carry some quick acting carbohydrate (i.e. dextrose tablets/Lucozade/sugary drink) and long acting carbohydrate (i.e. sandwich/biscuits/crisps) with you.

• If you feel hypoglycaemic whilst driving pull over as soon as it is safe to do so, switch off the engine, remove the keys from the ignition and, if possible, sit in the passenger seat to treat the hypoglycaemia (otherwise you could be charged with driving under the influence of a drug). Do not start driving again until your blood glucose level is above 5 mmols.
13. REFERENCES


John PR, Thuluvath PJ. Outcome of patients with new-onset diabetes mellitus after liver transplantation compared with those without diabetes mellitus. Liver Transplantation 2002; 8:708–713.


### 14. LIST OF ABBREVIATIONS/ACRONYMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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</thead>
<tbody>
<tr>
<td>ABPA</td>
<td>Allergic bronchopulmonary aspergillosis</td>
</tr>
<tr>
<td>ACE</td>
<td>Angiotensin-converting enzyme</td>
</tr>
<tr>
<td>BGM</td>
<td>Blood glucose monitoring</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CFRD</td>
<td>Cystic fibrosis related diabetes mellitus</td>
</tr>
<tr>
<td>CFTR</td>
<td>Cystic fibrosis transmembrane regulator</td>
</tr>
<tr>
<td>CGMS</td>
<td>Continuous glucose monitoring system</td>
</tr>
<tr>
<td>CSII</td>
<td>Continuous subcutaneous insulin infusion</td>
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<tr>
<td>COMA</td>
<td>Committee on the Medical Aspects of Food and Nutrition Policies</td>
</tr>
<tr>
<td>DAFNE</td>
<td>Dose adjustment for normal eating</td>
</tr>
<tr>
<td>DAWN</td>
<td>Diabetes attitudes wishes and needs</td>
</tr>
<tr>
<td>DCAC</td>
<td>Diabetes Care Advisory Committee</td>
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<tr>
<td>DCCT</td>
<td>Diabetes Control and Complications Trial</td>
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<tr>
<td>DIOS</td>
<td>Distal intestinal obstruction syndrome</td>
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<tr>
<td>DM</td>
<td>Diabetes mellitus</td>
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<tr>
<td>DNSG</td>
<td>Diabetes Nutrition Study Group</td>
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<tr>
<td>EASD</td>
<td>European Association for the Study of Diabetes</td>
</tr>
<tr>
<td>EAR</td>
<td>Estimated average requirement (foods)</td>
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<tr>
<td>ERCF</td>
<td>European Epidemiologic Registry of Cystic Fibrosis</td>
</tr>
<tr>
<td>EUCLID</td>
<td>Eurodiab controlled trial of lisinopril in insulin dependent diabetes</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Forced expiratory volume in one second</td>
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<tr>
<td>GAD</td>
<td>Glutamic acid decarboxylic</td>
</tr>
<tr>
<td>HbA&lt;sub&gt;1c&lt;/sub&gt;</td>
<td>Glycosylated haemoglobin</td>
</tr>
<tr>
<td>HBGM</td>
<td>Home blood glucose monitoring</td>
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<tr>
<td>HONK</td>
<td>Hyperosmolar non-ketotic coma</td>
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<tr>
<td>IAPP</td>
<td>Islet amyloid polypeptide</td>
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<tr>
<td>ICCA</td>
<td>Islet cell cytoplasmic antibody</td>
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<tr>
<td>IDDM</td>
<td>Insulin dependent diabetes mellitus</td>
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<tr>
<td>IFG</td>
<td>Impaired fasting glycaemia</td>
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<tr>
<td>IGT</td>
<td>Impaired glucose tolerance</td>
</tr>
<tr>
<td>mRNA</td>
<td>Messenger ribonucleic acid</td>
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<tr>
<td>NGT</td>
<td>Normal glucose tolerance</td>
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<tr>
<td>NICE</td>
<td>National Institute of Clinical Excellence</td>
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<tr>
<td>NIDDM</td>
<td>Non-insulin dependent diabetes mellitus</td>
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<tr>
<td>NPH</td>
<td>Neutral protamine hagedorn</td>
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<td>NSF</td>
<td>National Service Framework</td>
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<tr>
<td>OGTt</td>
<td>Oral glucose tolerance test</td>
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<tr>
<td>PPAR</td>
<td>Peroxisome proliferator-activated receptor</td>
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<tr>
<td>RNI</td>
<td>Reference Nutrient Intake</td>
</tr>
<tr>
<td>SaO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Oxygen saturation of the blood</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumour necrosis factor</td>
</tr>
<tr>
<td>UKPDS</td>
<td>UK Prospective Diabetes Study</td>
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</table>
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