CHAPTER 12 CYSTIC FIBROSIS RELATED DIABETES

A. Matson & T. Katz

CF-related diabetes shares features of type 1 and type 2 diabetes but is a distinct form of diabetes classified as "other forms of diabetes" or pancreatogenic diabetes [145,146]. This form of diabetes occurs at the end of a spectrum of progressive glucose tolerance abnormalities; it may occur intermittently, and few people with CF demonstrate completely normal glucose tolerance [147,148].

Comparison bewteen type 1 and type 2 diabetes and CF-related diabetes has been summarised in clinical reviews [604,605]. Type 1 diabetes arises from β-cell destruction primarily due to autoimmune aetiology with islet cell antibodies (ICA), glutamic acid carboxylase (GAD) or tyrosine phosphatase (1A-2A) antibodies present in 85% of cases [606]. CF-related is not an autoimmune condition (no autoimmune antibodies are present) , hence if a patient presents acutely with polyuria, polydipsia, lethargy, weight loss, hyperglycaemia, blood and urinary ketones; patients should be tested for the rare occurrence of type 1 diabetes co-occuring with cystic fibrosis by testing for autoimmune antibodies.

As the CF population increases in age, those with milder disease who are pancreatic sufficient and possibly overweight may also experience age related β-cell decline (and / or islet destruction secondary to pancreatitis), this may obscure the distinction between type 2 diabetes and CF-related diabetes [604]. Treatment should be tailored towards the individual in these cases aiming to improve BMI, glycaemia, lipidaemia and hypertension.

Prior to the clinical diagnosis of CF-related diabetes, abnormal glucose tolerance may adversely impact on pulmonary function and nutritional status with many studies demonstrating increased morbidity and mortality, especially in females [239]. If not recognised, or inadequately controlled, diabetes can contribute to energy deficits through glycosuria and loss of protein anabolism from insulinopaenia [607,608].

Less mortality has been observed in people with CF and CF-related diabetes with screening by annual two hour oral glucose tolerance tests (OGTT) from age 10, and early commencement of insulin therapy [145,609]. Insulin management has also been observed to reverse a decline in lung function and BMI in individuals with CF [238,610,611]. Despite these improvements, research to enhance understanding of optimal screening, diagnosis and treatment practices for early detection and management of CF-related diabetes is ongoing.

It is important to note that the methodology used to create this chapter is different from the rest of the guideline document. Data from the 2 most recent Australian and NZ CF dietitian surveys [180,612] indicates that practice in managing CF-related diabetes is amongst the most inconsistent. In an attempt to improve consistency of practice where possible (and rather than performing a full systematic review), existing guideline paper recommendations have been emphasised when they are applicable to the Australian and NZ context.

Disease Aetiology

The primary defect in CF-related diabetes is reduced β-cell mass leading to insulin deficiency, in part caused by fibrosis of pancreatic cells due to the CFTR defect. More recently the CF mutated gene has been identified as having a role in regulating insulin secretion in beta cells [613], a function that can be recovered by those treated with Ivacaftor [614]. Insulin resistance, especially during periods of acute illness, in patients with liver disease, during pregnancy and when prescribed systemic glucocorticoids may also play a causal role. Genetic variants for type 2 diabetic susceptibility genes have also been linked with development of CF-related diabetes [615]. Further research continues into the pathophysiology of CF-related diabetes.

Prevalence of CF-related diabetes increases with age and affects approximately 50% of people with CF by the age of 40 [238,615]. The 2014 Australian Data Registry reported on the rates of chronic CF-related diabetes requiring insulin as:

- young and older children - 6.8%
- adolescents - 26.7%
- adults (>30 years) - 27.2% [188]

Recent data from NZ reports a slightly higher prevalence (8.6%) in children under 11 years of age [189].

Centres not routinely performing annual OGTT screening may underestimate the prevalence of CF-related diabetes [616]. People with severe CF disease, pancreatic insufficiency and Type 2 Diabetes susceptibility genes may have greater incidence of CF-related diabetes, although pancreatic sufficient individuals can also be affected [617].

Comparison of type 1 and type 2 diabetes and CF-related diabetes has been summarised in clinical reviews [604,605]. Type 1 diabetes may be differentiated from CF-related diabetes by testing autoimmune antibodies, although rare type 1 diabetes and CF can co-exist. Type 2 diabetes may occur in people with CF and pancreatic sufficiency, those at risk are overweight individuals with metabolic syndrome and treatment should be individualised.

Assessment

DIET

At CF-related diabetes diagnosis a complete nutritional assessment should be undertaken as per Chapter 5 and the Australian CF standards of Care Recommendations [2]. The dietary assessment should be conducted within the context of overall health, lifestyle, exercise and eating patterns. Particular focus should assess the quantity (e.g. grams of carbohydrate consumed at usual meals / snacks / supplements) and quality of carbohydrate intake (the glycaemic index (GI)) at meals and snacks. The blood glucose levels pre-meal and 2 hours post-meals should be assessed to assist with planning an insulin regimen with the Endocrinologist and planning diet modifications.

Pancreatic enzyme replacement therapy (PERT) should be assessed as described in chapter 10. Maximising PERT efficacy has been demonstrated to improve glucose excursions [618].

CLINICAL

CF-RELATED DIABETES SCREENING

Screening for CF-related diabetes has been demonstrated to reduce morbidity and mortality rates by enabling early identification and intervention [145,609].

During a time of clinical stability (at least 6 weeks since an acute exacerbation, after an 8 hour fast, and consumption of 150g carbohydrate /d for 3 days prior to the OGTT), routine screening should be performed using a 2 hour OGTT with 75g of oral glucose (or 1.75g/kg in children) with blood glucose measures taken at 0, 1 and 2 hours [238,615,619]. The glucose dose can be given via gastrostomy if more acceptable.

Exceptions to screening with OGTT are an individual with CF presenting with classical symptoms of polyuria and polydipsia in the presence of a glucose level >11.1 mmol/l or an individual with CF having two more diagnostic criteria for diabetes (such as both fasting and 2-h glucose elevation or a diabetes pattern on OGTT in the presence of a HbA1C level >6.5%).

Glycosylated haemoglobin (HbA1c) is not recommended for routine screening, as HbA1c may be lower in patients with CF possibly due to increased red blood cell turnover and inflammation [238,615,619]. Recently Burgess et al (2016) suggested the use of HbA1c greater than or equal to 5.8% as a quick CF-related diabetes screening tool [620], however concern has been expressed in patients with advanced CF lung disease [621,622] due to the risk of insulinopaenia and the risk of failing to identify patients with early glucose abnormalities by relying on this method. Research continues as to the optimal early diagnosis criteria and management strategies specifically related to CF-related diabetes.

Table 12a. Screening considerations for people not known to have CF-related diabetes*

	Considerations
Routine screening	During a time of clinical stability (at least 6 weeks since an acute exacerbation, after an 8 hour fast, and consumption of 150g carbohydrate /d for 3 days prior to the OGTT) a 2 hour OGTT with 75g of oral glucose (or 1.75g/kg in children) with BGLs measured at 0, 1 and 2 hours should be performed. Annual screening for CF-related diabetes should begin by age 10 in all people with CF. Children < 10 years of age should only be screened if clinically indicated e.g acute loss of lung function and / or weight, symptomatic polyuria, polydipsia, or hyperglycaemia on routine blood testing.
Illness	In those with acute pulmonary exacerbation requiring intravenous antibiotic and/or systematic glucocorticoids, the risk of hyperglycaemia is increased. People with CF who are unwell may develop hyperglycaemia intermittently. Fasting and 2hr post prandial plasma glucose levels should be checked for the first 48 hours of admission.

...table continued overleaf

Enteral feeding	To maximise provision of high caloric enteral feeds in malnourished individuals with CF and to assist weight gain, screening for BGLs >11.1 mmol / l is advised. Plasma glucose levels should be checked once midway through feed provision and immediately post feeds. This should occur at the time of gastrostomy tube insertion and then monthly.
Pregnancy (Chapter 14)	Women with CF who are planning a pregnancy or confirmed to be pregnant should be screened for pre-existing CF-related diabetes if they have not been screened in the previous 6 months. Screening for gestational diabetes via a 2 hour OGTT is recommended at both 12-16 week and 24-28 weeks of gestation in pregnant women with CF not known to have CF-related diabetes. Post pregnancy screening for CF-related diabetes is recommended 6-12 weeks post-partum for those who had gestational diabetes.

*Adapted from [238,615,619]

CF-RELATED DIABETES DIAGNOSIS

The most current criteria for the diagnosis of CF-related diabetes based on the 2014 *'International Society for Diabetes and Adolescent Diabetes (ISPAD) clinical practice consensus guidelines: management of CF-related diabetes in children and adolescents'* [238] is summarised in table 12b with considerations for diagnosis under various circumstances shown in table 12c. Various Australian and international guidelines recommend an annual formal fasting 75 gram 2 hour OGTT (or 1.75g/kg in children) to screen for and diagnose diabetes [615,623].

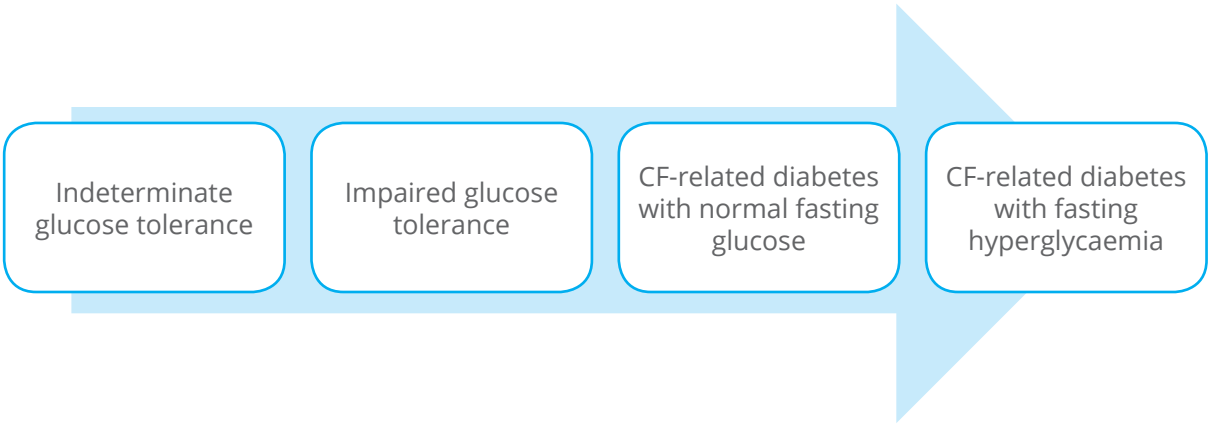

Figure 1. Diabetes in CF is part of a progressive spectrum of glucose tolerance abnormalities

Table 12b. Diagnostic criteria* for glucose abnormalities in individuals with CF

Category	Fasting plasma glucose (FPG) (mmol/L)	1 hour plasma glucose (mmol/L)	2 hour plasma glucose (mmol/L)
Normal glucose tolerance	< 7.0	-	< 7.8
Indeterminate glucose tolerance	< 7.0	≥ 11.1	< 7.8
Impaired glucose tolerance	< 7.0	-	7.8 - < 11.1
CF-related diabetes without fasting hyperglycaemia	< 7.0	-	≥ 11.1
CF-related diabetes with fasting hyperglycaemia	≥7.0	-	-

* Adapted from [238,615]

Table 12c. Considerations* for CF-related diabetes under various circumstances

Diagnostic criteria and considerations	
Clinical stability (healthy baseline)	Diagnosis is based on one or more of the following criteria at a time of clinical stability: • 2hr OGTT plasma glucose with a 120min BGL ≥11.1mmol/L • Fasting plasma glucose levels ≥7mmol/L • HbA1c ≥6.5% • random glucose measures ≥11.1mmol/L with symptoms of polyuria and/or polydipsia The first 3 measures listed above should be repeated on 2 separate days to confirm diagnosis.
Acute illness	Diagnosis may be made on one (or more) of the following criteria: • Fasting plasma glucose levels ≥7mmol/L • 2 hour post prandial plasma glucose levels ≥11.1mmol/L Either type of hyperglycaemia must persist more than 48 hours. An OGTT is not necessary as plasma blood glucose levels at the fasting and / or 2 hours post prandial time points may be used diagnostically during acute illness. CF-related diabetes diagnosed at this time may be intermittent or long term.
Enteral Feeding	Diagnosis made when blood glucose levels are ≥11.1mmol/L mid or immediately post enteral feeding on two separate days. • confirm via laboratory plasma glucose measurement • CF-related diabetes may occur in relation to the high carbohydrate load of an enteral feed; an OGTT will not identify this and hence plasma blood glucose mid or post feed can be used to make this diagnosis.
Pregnancy (Chapter 14)	Women with CF are at increased risk of gestational diabetes mellitus. Gestational diabetes is diagnosed using lower glycaemic thresholds of a 2 hour OGTT and is based on one or more of the following criteria • Fasting plasma glucose levels ≥5.1mmol/L • 1 hour plasma glucose ≥ 10mmol/L • 2 hour plasma glucose ≥ 8.5mmol/L

*adapted from [238,615,619,624,625]. Point of care capillary blood glucose (e.g. glucometer) is not recommended for screening/diagnosing diabetes.

CF-RELATED DIABETES AND HYPOGLYCAEMIA

Insulin induced hypoglycaemia can occur in CF-related diabetes as in any other patient on insulin therapy. However, hypoglycaemia (BGL less than or equal to 3.9 mmol/l or low enough to cause symptoms) is also recognised as a phenomenon in people with CF in the absence of diabetes or glucose lowering medications [615,626]. Fasting hypoglycaemia may reflect malnutrition and/or increased energy needs due to inflammation and infection [627]. Reactive or postprandial hypoglycaemia may be related to delayed or disordered insulin secretion.

Non CF-related diabetes hypoglycaemia is generally mild because patients have poor glucagon response to hypoglycaemia [628] but have a brisk catecholamine response [628] and normal hypoglycaemia awareness. Limited research on hypoglycaemia in the absence of diabetes or glucose lowering medications has been published, and further research is crucial to understanding the aetiology and management strategies to assist treatment.

CF-RELATED DIABETES AND DIABETIC KETOACIDOSIS

Diabetic ketoacidosis is uncommon in people with CF and thus, ketones are not routinely measured. [615]. If an individual with CF presents with diabetic ketoacidosis they should be screened for auto-immune antibodies to exclude type 1 diabetes mellitus occurring concurrently with CF e.g. islet cell antibodies (ICA), glutamic acid carboxylase (GAD) or tyrosine phosphatase (1A-2A) antibodies.

BIOCHEMICAL AND LABORATORY DATA

The biochemical criteria for the medical diagnosis of CF-related diabetes are outlined in tables 12b and 12c above.

Intervention

CF-related diabetes should be managed by an interdisciplinary team with knowledge in CF, including but not limited to an endocrinologist, CF physician, credentialed diabetes educator (CDE), dietitian, nurse and psychologist. The diabetes team should be familiar with CF-related diabetes, recognising the differences between this and Type 1 and 2 diabetes pathophysiology and treatment. Good communication between diabetes and CF care providers is essential [615].

MEDICAL MANAGEMENT

Principal goals in management of CF-related diabetes are symptom control, optimisation of nutritional status and lung function, avoidance of hypoglycaemia and hyperglycaemia, prevention of microvascular diabetic complications and psychological support to manage CF-related diabetes in combination with complexities of CF management. Table 12d provides an illustrative example of BGL treatment targets.

Insulin is the treatment of choice as the primary problem in CF-related diabetes is insulin insufficiency [238,615,619]. Oral diabetic agents are not currently recommended except as part of research trials [238,615].

Insulin is the only recommended medical treatment for CF-related diabetes with options for insulin delivery being single or multiple insulin injections (MDI) or continuous subcutaneous insulin infusion (CSII) via an insulin pump. Insulin regimen decisions are based on achieving normo-glycaemia, balanced with patient acceptance of the insulin regimen.

There are no guidelines regarding the use of insulin pump therapy in treatment for CF-related diabetes, however a number of case reports and non – randomised studies [629] have reported improvement of glycaemic control and quality of life from insulin pump therapy. Pump therapy in CF-related diabetes management is not as widely used compared to as in type 1 diabetes [630], however this may change over time. Individuals should consult with their care teams regarding eligibility for insulin pump therapy and specialist management services available.

Table 12d. Example of treatment targets and goals for individuals with CF-related diabetes*

	Optimal Control	**Modified Control** (people at high risk of hypoglycaemia)	**Symptomatic Control** (when end-stage CF care is appropriate)
Fasting glucose	4-6 mmol/L	4-7 mmol/L	No BGL targets. Avoidance of hypo / hyperglycaemia for comfort measures are assessed on an individual basis.
2hr post meal glucose	4-7 mmol/L	7-10 mmol/L	No BGL targets. Avoidance of hypo / hyperglycaemia for comfort measures are assessed on an individual basis
Hypoglycaemia	Mild daytime hypos only	Aim for none	No BGL targets. Avoidance of hypoglycaemia for comfort measures are assessed on an individual basis
HbA1c	<7%	<8%	no HbA1c targets

*adapted from [631,632]

Medical management and insulin requirements may vary in some situations, and should be designed for the individual, in conjunction with relevant expert management teams

- **Enteral feeds -** extra insulin may be required during feeding sessions to cover the carbohydrate load, improve glycaemia and promote weight gain. Additional blood glucose monitoring before, during and after enteral nutrition will assist in determining the effects of enteral feeding on glycaemia and how best to adjust the insulin regimen.
- **Post lung transplant -** it is common for those post lung transplant to have changing nutritional and insulin requirements [238]. Refer to Chapter 16 for further information.
- **Genetic potentiator treatments (e.g. Ivacaftor) -** nutritional requirements may change and / or insulin secretion may improve [163]. Genetic potentiators are discussed in Chapter 14.
- **Exacerbations and infections -** acute illness may increase the risk of hyperglycaemia and insulin requirements may increase up to four times that required normally. Insulin doses must be reduced as the individual improves clinically to avoid hypoglycaemia, this may take a couple of months [238].

- **Pregnancy -** women with established CF-related diabetes, who are planning a pregnancy, or who are already pregnant, should optimise blood glucose control in accordance with advice from specialist endocrine and obstetric teams [633]. The Australasian Diabetes in Pregnancy Society (ADIPS) has recommended BGL targets at fasting, one and two hours post prandial, as follows [625]: Refer to Chapter 14 for further information.
    - Fasting capillary BGL: ≤5.0 mmol/L
    - 1 hour after commencing meal BGL: ≤7.4 mmol/L
    - 2 hours after commencing meal BGL: ≤6.7 mmol/L

Registration with the National Diabetes Service Scheme (NDDS) in Australia provides subsidised products (test strips, syringes, and pen needles) for diabetes requiring insulin and caused by CF. Registered medical and nurse practitioners, and credentialed diabetes educators can certify the NDSS form. Currently in Australia, continuous subcutaneous insulin infusion (CSII) via insulin pumps and related consumable products are government funded only for type 1 diabetes or available at full or subsidised cost through some private health funds. Individuals should contact their private health provider for eligibility criteria and discuss suitability with their Diabetes / CF health care teams.

In NZ Pharmac funds all products for diabetes management including CSII insulin pumps and consumables and registration is not required. International recommendations state that people with CF-related diabetes should be commenced on an individually tailored insulin regimen guided by the degree of glucose tolerance, eating habits and lifestyle [631,634-637]. There is no evidence that one type of insulin is superior to another.

SELF-MANAGEMENT OF CF-RELATED DIABETES

Practitioners should provide ongoing self-management education that meets national standards e.g. Australian Diabetes Educator Association guidelines and standards [638]. Education should include [639]:

- Self-monitoring of blood glucose
- Medications (i.e. insulin actions, timing, side effects, interactions)
- Relationship between CF-related diabetes and other health problems (e.g. weight, lung function, corticosteroids, sick days)
- Nutrition education as appropriate
- Carbohydrate counting as appropriate
- Exercise considerations
- Alcohol education
- Hypoglycaemia prevention and management, including use of glucagon

Self-monitoring of blood glucose levels should occur to assist in reviewing management goals [238,615]. Whilst establishing an insulin regimen, monitoring pre and 2 hours post prandial blood glucose levels provides information to assist insulin adjustment. Once established on an insulin regimen, pre-prandial and before bed time monitoring is usually sufficient to review blood glucose targets.

MEDICAL MANAGEMENT OF IMPAIRED GLUCOSE TOLERANCE

Small studies to treat indeterminate glucose tolerance and impaired glucose tolerance have demonstrated benefits in the early introduction of insulin [238]. Australian research has also demonstrated improved weight gain and lung function following once daily insulin treatment in these sub-population groups [640]. However, at present no definitive data has been published and this research area is of high priority.

NUTRITIONAL MANAGEMENT OF CF-RELATED DIABETES

There are currently no randomised controlled diet intervention trials in the management of CF-related diabetes. Recommendations are based on cohort studies and current clinical consensus guidelines [145,238,609,615,619]. A CF- related diabetes diagnosis does not alter usual CF dietary recommendations, the goal is to achieve and maintain good nutritional status and optimise blood glucose levels. A comparison between dietary considerations for people with Type 1 and 2 diabetes and CF-related diabetes is outlined in table 12e.

Specific energy and macronutrient considerations in CF-related diabetes compared to type 1 / type 2 diabetes include:

- **Energy** - whilst dietary restrictions are common in Type 1 and 2 diabetes, the majority of people with CF-related diabetes require higher energy intakes of 110-200% of the general population targets [619]. Energy requirements are reviewed in Chapter 7.

- **Protein** - protein requirements are 15-20 percent of total energy requirement and are discussed in Chapter 7.
- **Fat** - fat intake from all sources is usually not restricted in CF-related diabetes compared to type 1 and 2 diabetes. Quality and quantity of total fat intake should be individualised based on age, BMI and overall health status. See chapter 7 for further information.
- **Carbohydrate** – the high energy requirements of CF, combined with individual preference, somtimes demand the inclusion of refined sugars such as sweet foods and beverages. These foods should be as part of a meal or substantial snack as they can cause rapid rises in blood glucose if eaten in isolation [631]. Hyperglycaemia is known to perpetuate B-cell destruction hence diet related glucose elevations should be minimised by diet modification (the reduction and / or spreading of refined sugars throughout the day, and /or inclusion with mixed meals rather than eaten alone). When malnutrition necessitates the inclusion of refined sugar products, insulin therapy should be adjusted to match bolus insulin dose to the refined sugar carbohydrate quantity. Where possible, carbohydrate foods with low glycaemic index should be encouraged and distributed evenly and consistently throughout the day to help optimise blood glucose control, provided that these changes do not cause an unwanted reduction in the total caloric intake. A flexible dietary intake can be managed by altering the insulin dose using individually determined insulin to carbohydrate ratios [634].

Table 12e: Comparison of dietary management between type 1 and 2 diabetes in the general population and CF-related diabetes

Nutrient	Type 1 & 2 diabetes	CF-related diabetes
Energy (calories)	Individualised for growth, weight maintenance or reduction. To prevent overweight and obesity caloric restriction of <100% of normal requirements for age and gender may be used.	Individualised for growth, weight maintenance or reduction. Usually require 110-200% of normal caloric intake for age and gender to prevent undernutrition.
Protein	15-20% of total energy from protein Reduce to 0.8-1g/kg with nephropathy	15-20% of total energy from protein
Fat	<35% total energy from fat <7% total energy from saturated fat	Unrestricted: adequate fat to meet energy targets No restriction on type of fat
Total Carbohydrate	Individualised. Monitor to achieve glycaemic control. Total energy approximately 45-60% from carbohydrate. Artificial sweeteners may be used to assist glycaemic control and/or weight management in overweight/obese people.	Individualised. Monitor to achieve glycaemic control. Total energy approximately 45-65% from carbohydrate. Artificial sweeteners may be used to assist glycaemic control and / or weight management in overweight / obese people.
Dietary Fibre	Approximately 30g per day	Encouraged in the well-nourished CF population but not at the expense of other nutrients.
Salt	Restriction to approximately <2300mg per day for control of hypertension.	No restriction. Sodium requirements for CF are discussed in chapter 9.

Carbohydrate intake plays an important role in management. In addition to the advice provided around general dietary intake, as outlined in chapter 7, basic education on carbohydrate intake and recognition is required. People with CF-related diabetes should also be advised how they can integrate insulin regimens (i.e. taking into consideration the amount and distribution of carbohydrates) into their usual eating patterns and physical activity habits. For some people it may be appropriate to provide complex education regarding individualised insulin to carbohydrate ratios to assist in glycaemic control and carbohydrate counting skills.

Monitoring and evaluation

People with CF-related diabetes require review from a diabetes perspective at least quarterly by the combined inter-disciplinary team (i.e. CF and diabetes teams). Some people may require more frequent review after initial diagnosis or if their clinical condition changes [615]. Aim to review trends in daily blood glucose levels at every appointment and to monitor HbA1c every 3 months to help guide insulin therapy decisions [238,619]. Routine measurement of weight, body mass index, lung function, bone mineral density and vitamin status should also occur [2,3].

HbA1c reflects average glycaemia over the preceding 6–8 weeks. [632]. In most people with CF-related diabetes, HbA1c treatment goal is <7% or 53 mmol/mol (although diabetes targets for type 1 diabetes have recently lowered to 6.5% or 48mmol/mol in the UK) to reduce risk of vascular complications [615,641,642]. However, an individualised approach is encouraged.

Further research into CF-related diabetes management may alter HbA1c and /or BGL targets however until then individualised targets should be balanced with overall health status.

Refer to chapter 16 for discussion of diabetes treatment targets are lung transplant.

SCREENING FOR COMPLICATIONS

Whilst macrovascular complications are rarely reported in people with CF-related diabetes, microvascular complications such as retinopathy, neuropathy and nephropathy can develop [643]. Available data suggest that complications are rare within the first five years of the onset of CF-related diabetes but, may become more common as individuals with CF- related diabetes progress into the fifth and sixth decades of life.

Accordingly, screening plays a crucial role in the identification of diabetic complications and is therefore strongly recommended [146,238,619]. The following tests should be undertaken:

- **Hypertension** - measurement of blood pressure is recommended at every diabetes clinic review [238].
- **Lipids** - complete lipid profiles are recommended annually, and are of particular significance for people with CF who are pancreatic sufficient, obese, or have a family history of cardiovascular disease or prescribed immunosuppressive therapy following transplant [238].
- **Neuropathy** - neurologic assessment and foot evaluation are recommended annually. Gastroparesis is common in CF patients and may make good glycaemic control difficult to achieve.

Every 5 years (after initial diagnosis) of CF-related diabetes, the following should be screened:

- **Retinopathy** - by ophthalmic assessment with dilated retinal examination [146].
- **Nephropathy** - via urinalysis [146]. Tight glycaemic control and treatment of microalbuminuria with ACE inhibitors or angiotensin receptor blockers combined with optimal control of hypertension, delay progression of diabetic renal disease in the general diabetes population [615]. They are assumed to also be beneficial for the relevant CF population although there are no specific data in this population.