LRI Children's Hospital

Cystic Fibrosis Related Diabetes UHL Children's Hospital Guideline

Staff relevant to:	Clinical staff working within the UHL Children's Hospital.
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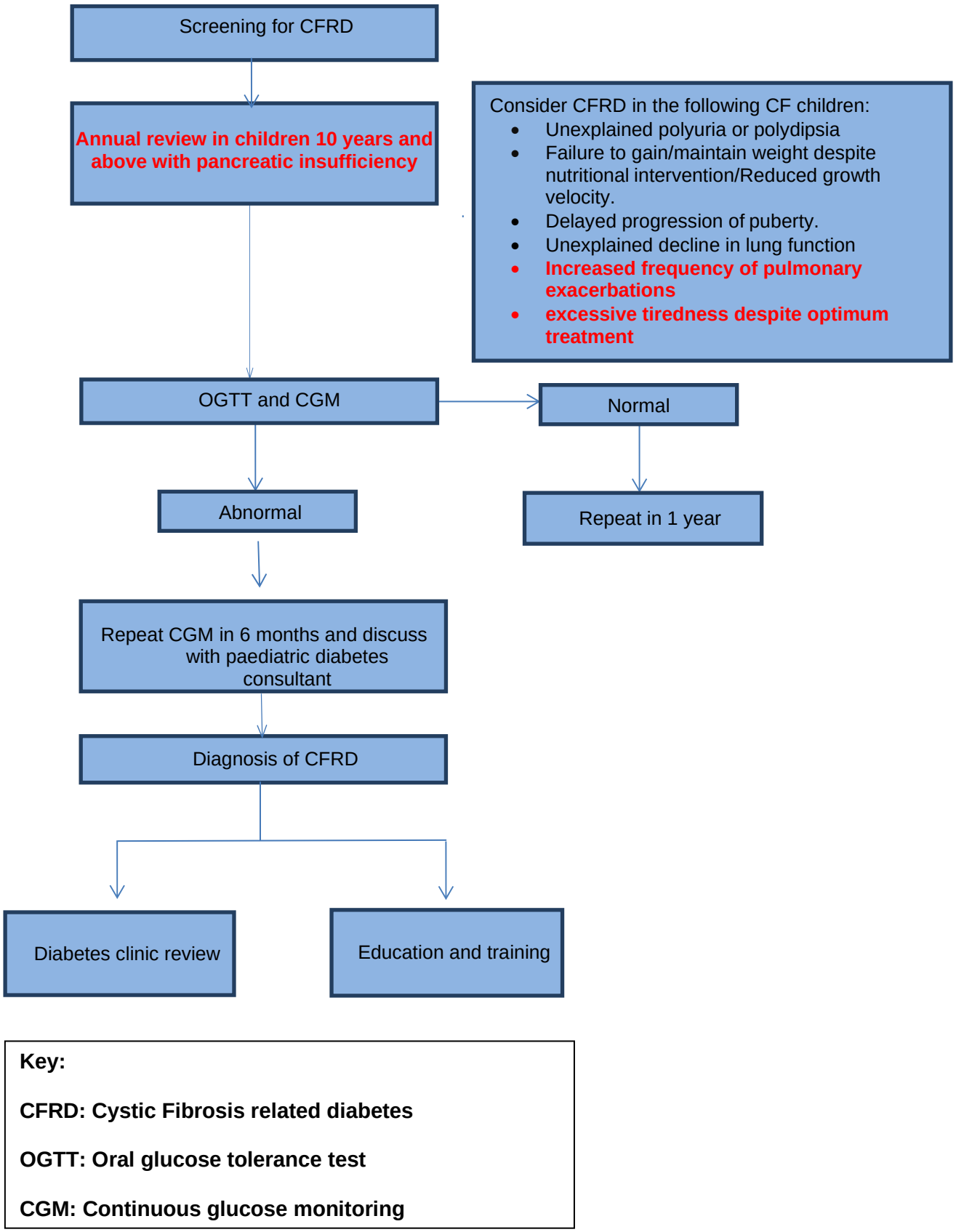
1. Introduction and Scope

Cystic Fibrosis is the most common autosomal recessive inherited condition in the white population, with a gene carrier rate of 1 in 25 people and affecting around 1 in 2500 new-borns in the UK. With increasing age, patients are facing new challenges and the prevalence of comorbidities have significantly increased. Cystic fibrosis–related diabetes (CFRD) is one of the most common comorbidities in people with cystic fibrosis (CF), occurring in about 20% of adolescents and 40–50% of adults. The pathophysiology of CFRD is different from both type 1 and type 2 diabetes; however, insulin is the mainstay of treatment of CFRD.

Cystic fibrosis–related diabetes (CFRD) is the most common comorbidity in people with cystic fibrosis (CF). CFRD can develop insidiously and patients may be asymptomatic for years. CFRD may first present during acute pulmonary infection or glucocorticoid therapy, or during high-carbohydrate food supplementation. In recent years, several lines of evidence have demonstrated that pulmonary function, microbiological colonization and nutritional status start to worsen several years prior to the diagnosis of CFRD Early detection of pre-diabetes, defined in CF patients by the presence of abnormal glucose tolerance (AGT), impaired glucose tolerance (IGT), impaired fasting glucose (IFG) or indeterminate glycaemia (INDET) is therefore essential, although to date few studies have focused on pre-diabetes and its negative significant impact on the course of CF [(29)].

Contents

UHL CYP CFRD referral pathway



Key:

CFRD: Cystic Fibrosis related diabetes

OGTT: Oral glucose tolerance test

CGM: Continuous glucose monitoring

Table 1: Pathophysiology of CFRD, Type 1 and Type 2 diabetes

	Type 1 diabetes	Type 2 diabetes	CFRD
Onset	Usually Acute	Insidious	Insidious
Peak age of onset	Children, youth	Adults	18-24 years
Body habitus	Normal	Obese	Normal-underweight
Antibody (+)	Yes	No	Probably No
Insulin deficiency	Nearly complete	Partial, variable	Severe, not complete
Insulin sensitivity	Somewhat decreased	Severely decreased	Somewhat decreased
Ketones	Yes	Rare	Rare
Treatment	Insulin	Diet, oral meds, insulin	Insulin
Microvascular complications	Yes	Yes	Yes
Macrovascular complications	Yes	Yes	No
Metabolic syndrome	No	Yes	No
Cause of death	Cardiovascular	Cardiovascular	Pulmonary

2.1 Definitions

CFRD is part of a spectrum of progressive glucose tolerance abnormalities identified by a standard oral glucose tolerance test (OGTT). Normal fasting blood glucose levels characterize the early stage of diabetes, but over time fasting hyperglycaemia develops. Few individuals with CF have truly normal glucose tolerance. Even when the fasting and 2-hour OGTT glucose levels are normal, variable and intermittent post-prandial hyperglycaemia can often be detected at home by continuous glucose monitoring system (CGM). Abnormal glucose tolerance (AGT) is the collective term of all three CFRD, IGT and INDET.

The North American CFRD Consensus Conference in 2009 defined glucose tolerance in individuals with a 1 hour plasma glucose (PG1) >200 mg/dL as indeterminate glycemia (INDET), the significance of which is not completely understood. In CF, isolated elevations of the PG1 during OGTT are common, and cross-sectional data suggest that higher glucose may be associated with poor clinical outcome in CF patients. Data are still lacking on the benefits of interventions targeting the PG1 [(6)]

The CFRD Guidelines Committee defined the onset of CFRD as the first time a patient meets the diagnostic criteria for diabetes, even if glucose tolerance subsequently improves, as the long-term outcomes in microvascular disease and mortality correlate with the duration of diabetes that includes these early years. Factors specific to CF that cause fluctuations in glucose metabolism include: respiratory infection and

inflammation, increased energy expenditure, malnutrition, glucagon deficiency, and gastrointestinal abnormalities (malabsorption, altered gastric emptying and intestinal motility and liver disease).

2.2 Clinical presentation of CFRD

Clinical symptoms, which may indicate the presence of CFRD are as follows:

- Unexplained polyuria or polydipsia
- Failure to gain or maintain weight despite nutritional intervention
- Reduced growth velocity
- Delayed progression of puberty
- Unexplained chronic decline in pulmonary function
- increased frequency of pulmonary exacerbations
- There may be no symptoms and so screening is essential

CFRD develops insidiously and patients may be asymptomatic for years. This may first present during situations where insulin resistance is increased, such as acute pulmonary infection or glucocorticoid therapy, or during high-carbohydrate food supplementation such as continuous enteral feeding. Diabetes is common in the setting of lung transplantation and liver disease.

Diabetic ketoacidosis (DKA) is rare, most likely because of the persistence of endogenous insulin secretion or because glucagon secretion is also impaired. Hypoglycaemia is more common and more concerning in CF patients with liver disease. In the absence of liver disease, fasting hypoglycaemia is generally only seen in malnourished patients and the very young.

Screening for CFRD at annual review should be performed for all children 10 years and above. Oral glucose tolerance test (OGTT) and continuous glucose monitoring (CGM) are useful screening tools. HbA1C and random glucose measurements are not reliable tools to diagnose CFRD.

2.3 Survival and prognosis

The presence of CFRD is associated with worse lung function, poorer nutritional status, and decreased survival compared to non-diabetic CF patients. Diabetes has been directly implicated in the pathophysiology of CF lung function decline because of both the catabolic effect of insulin insufficiency on nutritional status and muscle mass and the negative impact of chronic hyperglycaemia on lung function.

Microvascular complications have been described in CFRD patients, sometimes with significant morbidity. No microvascular complications were found in CFRD patients who never had any previous evidence of fasting hyperglycaemia. Death from macrovascular complications has not been reported in CF.

As we enter an era of widespread use of highly effective modulator therapies, ongoing research to assess the impact of these treatments on CFRD prevalence and complications, including microvascular and potentially macrovascular outcomes are

needed.

2.4 Investigations for abnormal glucose tolerance and diabetes in CF

Children with CF should be investigated for CFRD in the following situations:

- Annual review for all children 10 years and above
- Clinical concerns (as detailed below section 2.2)
- Finding of high random blood glucoses in any individual (Blood glucose > 11.1 mmol/L)
- High HbA1c >6.5% (IFCC HbA1c >48 mmol/mol)
- Symptoms of hyperglycaemia
- Prior to starting high dose steroids, enteral feeds, or before major surgery

The investigations for diagnosing CFRD are as follows:

- OGTT & CGMS as screening tool annually for 10 years and above as part of CF annual review
- CGM prior to starting insulin therapy

All screening tests should be done during period of stable health.

Oral glucose tolerance test (OGTT):

The 2-hour OGTT is considered the gold standard for screening of CFRD.

For an OGTT, the child is fasted from midnight although drinks of plain water are allowed. 1.75 g/kg glucose to a maximum of 75 g, as glucose monohydrate diluted in water (200-300 mls) is given as a glucose drink. The blood sampling should be organised along with the annual review bloods. Sampling is done as follows:

- Take blood for glucose at 0 minutes (fasting)
- Give the glucose drink
- Take blood for glucose at 120 minutes

CFRD is part of a spectrum of progressive glucose tolerance abnormalities defined by a standard OGTT (Table 2). Few individuals with CF have truly normal glucose tolerance (NGT). Even when the fasting and 2-hour OGTT glucose levels are normal, variable, intermittent postprandial hyperglycaemia can often be detected at home by continuous glucose monitoring (CGM). With time, as glucose tolerance worsens, indeterminate glycaemia develops (INDET, mid-OGTT glucose ≥11.1 mmol/L), followed by impaired glucose tolerance (IGT) and finally diabetes. Early diabetes is characterized by normal fasting glucose levels, but over time fasting hyperglycaemia develops. Isolated-impaired fasting glucose (IFG) is sometimes present in persons with CF but the significance is unclear.

Table 2: Abnormal glucose tolerance categories in CF

Category	FPG (mmol/L)	2 hr glucose (mmol/L)	Notes
Normal (NGT)	<7	<7.8	All glucose levels <11.1 mmol/L
Indeterminate (INDET)	<7	<7.8	1 hour plasma glucose >11.1mmol/L
Impaired (IGT)	<7	7.8-11.1	
CFRD FH−	<7	≥11.1	
CFRD FH+	≥7.0	≥11.1	
IFG	6.1-6.9	<7.8	All glucose levels < 11.1 mmol/L

FPG, fasting plasma glucose; FH, fasting hyperglycaemia; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test.

Responses to OGTT results

- Normal glucose tolerance : Repeat OGTT in 1 year
- Impaired glucose tolerance: CGM and review
- INDET: these are not identified by our OGTT protocol. If clinically needed then to consider discussion with diabetes consultant (Consider joint review in clinic)
- Plasma Glucose ≥ 8.2 and clinical concern at any stage during OGTT: Discuss with Diabetes consultant

2.6 CGM (continuous glucose monitoring):

CGM work by sensing glucose levels in the body's interstitial fluid using a subcutaneous sensor. These are tested every few minutes and the results are sent to a receiver. A subcutaneous sensor gives a profile of glucose levels for up to 7 days. CGM give a profile and statistical breakdown of the glucose levels and a very comprehensive picture of glucose status over a number of days.

CGM has been validated and proven to be useful in measuring glycaemia in children and adolescents. Its role in CF patients who do not have diabetes is less clear. CGM is not licensed for diagnosing diabetes. Furthermore, while it is well known that postprandial glycaemic abnormalities that can be detected by CGM exist in patients with CF prior to OGTT results moving from NGT to IGT or diabetes, the clinical significance of these brief elevations in glucose excursion remains unknown. It is therefore suggested that CGM should

be considered a useful tool for insulin dosage adjustment and to alert the patient to hypoglycaemia, but there is no current available evidence for its use in diagnosis of CFRD.

The NICE Guideline on diagnosis and management of cystic fibrosis has suggested use of CGM and serial glucose testing over several days in addition to OGTT for diagnosis of CFRD.

Once a decision to organise a CGM is taken by the CF or the CF diabetes team:

- The CF specialist nurse will contact the family and arrange for the CGM to be done.
- CGM will be done along with a food diary and pre-meal blood glucose recording for 5-7 days.
- The CGM report will be downloaded by the CF team and if abnormal, forwarded on to the diabetes consultant along with the referral form (Appendix 3)

2.7 HbA1C:

If the HbA1c is over 6.5% (48mmol/mol), glucose levels are not likely to be normal and OGTT and CGM are indicated. An elevated HbA1c is suggestive of CFRD but is a late occurrence and people with CF often have spuriously low HbA1c levels, therefore the test is not a reliable tool for diagnosis. It can be prone to false negatives due to the increased red blood cell turnover that occurs in people with CF.

2.8 Special circumstances:

- The diagnosis of CFRD can be made in CF patients with acute illness (intravenous antibiotics in the hospital or at home, systemic glucocorticoid therapy) when fasting plasma glucose (FPG) levels ≥7.0 mmol/L or 2-hour post-prandial plasma glucose levels 11.1 mmol/L persist for more than 48 hours.
- The diagnosis of CFRD can be made in CF patients on enteral feedings when mid- or post-feeding plasma glucose levels exceed 11.1 mmol/L on two separate days.

2.9 Medical management

Insulin therapy is the only recommended therapy for CFRD and should be started following discussion with the paediatric diabetes team. Education and training on diabetes management for the child and the family shall be arranged by the diabetic team. Maintaining adequate nutrition is a priority and families will have input from the paediatric CF dietitian at UHL.

The commencement of insulin may improve lung function and nutritional status.

<u>Insulin therapy (This will need to be discussed and confirmed with the diabetes consultant)</u>

When starting insulin, look at the pattern of glucose abnormalities on OGTT and CGM:

- The fasting glucose levels are normal but there is evidence of postprandial hyperglycaemia after main meals- Start Novorapid before meals.
- The fasting glucose levels are normal with random elevated glucose levels during the day but no fixed pattern noted with meals - Start Levemir.
- The fasting glucose levels are elevated and high glucose levels noted through the day -Start MDI: Levemir once a day and Novorapid with meals.
- Children on overnight feeds with elevated glucose levels during the night - Start Levemir given 1-2 hours before the feed starts. Check blood glucose at 4-5 hours during the feed and at the end of the feed. Alternatively pre-mixed insulin with short and intermediate acting insulin can be used (e.g. Novomix 30).
- Children on steroid treatment - Start Levemir and adjust the dosage as per response, consider BD Levemir if persisting hyperglycaemia.
- If the child has irregular eating habits or if there is random hyperglycaemia with no specific pattern - Start Levemir given in the morning and adjust then add in Novorapid if needed.

Insulin therapy may be considered in cases of INDET and IGT after joint review in CF clinic with paediatric diabetes consultant (suggested Levemir 0.1 units/kg).

Recommended doses (according to ISPAD guidelines 2018)

- Total Insulin dose: 0.5-0.8 unit/kg/day
- Basal Insulin: 0.25 unit/kg (start with 0.125 unit/kg of total insulin with Levemir and increase the dose gradually depending on blood glucose).
- Rapid acting 0.5-1 unit: 15 grams carbohydrate (start insulin carb ratio 1:30)
- Corrections: 0.5-1 unit: 2.8mmol/L; Target Glucose: 8.3mmol/ (start Insulin sensitivity Factor 1:5.8)
- Fixed doses of insulin for meal time and corrections can also be considered until the family are educated by the Diabetes/CF Dietitian on carbohydrate counting.

Once full multiple daily injections regimen is established and patients are competent in carbohydrate counting consideration of insulin via subcutaneous pump should be given to improve quality of life.

2.10 Medical nutritional therapy

The family should have input from the paediatric CF dietitian at UHL. It is important that children and their carers understand that the dietary management is not the same as in other forms of diabetes and they do not need to adopt a “diabetic” diet. Families should be discouraged from reducing calorie intake to avoid starting insulin treatment.

Calorie intake: In CFRD maintaining adequate nutrition remains the priority and a high fat

diet must be considered. Children should avoid high sugar snacks and drinks between meals (i.e. regular fizzy drinks, juices and squashes, jellied sweets etc.) and substitute with no-sugar-added drinks (i.e. diet fizzy drinks and squashes).

Regular eating: Encourage regular meals and snacks (including breakfast if possible) because this makes the diabetes easier to control and improves weight gain. Food intake should not be reduced to try to control glucose levels; meals and snacks must be given whatever the blood glucose.

2.11 Long-term management of CFRD

Regular outpatient review in both CF and Diabetes Clinics (once stable):

- CF clinic 2 monthly; with monitoring of pulmonary function and nutritional status
- Diabetic clinic 3 monthly: Monitor HbA1C [aim < 7.0% (53mmol/mol)] and Blood pressure; Higher or Lower target HbA1C may be considered

Annual review to detect microvascular complications:

- Retinopathy: This is done in the community with retinopathy screening.
- Nephropathy: Microalbuminuria, early morning urine albumin/creatinine ratio, blood pressure
- Neuropathy: sensory and vibration sense examination

2.12 Surgery

Prior to any general anaesthetic a plan must be made by the diabetes team and anaesthetist should be informed in advance.

2.13 DKA

DKA is rare in CFRD but it can still happen. DKA should be managed according to UHL guidelines.

Contact details:

Diabetes Consultants – Extension 15027
CF Consultants – Extension 16694
Paediatric Diabetic Specialist Nurses (PDSN's): Extension 16786
Children's Specialist Diabetes Dietitian - Extension 15400
CF Dietitian - Extension 15400

3. Education and Training

CF specialist nurses on CGM insertion

Dietitian on CGM insertion

4. Monitoring and Audit Criteria

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Diagnosis and management of CFRD	• Internal Audit • Service evaluation • Peer Review	Paediatric consultant CF lead	Internal audit and Evaluation 2 yearly. Peer review 5 yearly.	Local clinical audit group

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6. Key Words

Cystic Fibrosis, Diabetes, Glucose tolerance test, Blood glucose, Continuous glucose monitoring, HbA1c, Insulin therapy, Children

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The Trust recognises the diversity of the local community it serves. Our aim therefore is to provide a safe environment free from discrimination and treat all individuals fairly with dignity and appropriately according to their needs.
As part of its development, this policy and its impact on equality have been reviewed and no detriment was identified.

Contact and review details	
Guideline Lead (Name and Title) **Tahera Doctor: Consultant** Imad Ahmed : Consultant Sonal Kapoor: Consultant Erol Gaillard: Consultant James Greening: Consultant Prem Sundaram: Consultant Anne Rogers: Children's Specialist Diabetes Dietitian Rachel Fox: CF Dietitian:	**Executive Lead** Chief Medical Officer
Details of Changes made during review: **Introduction has paragraph regarding pre diabetes** **2.1 Definition Added paragraph in introduction regarding pre diabetes** **Referral pathway –** **Children 10 years and above rather than just >10 yr** **2.2 Added increased frequency of pulmonary exacerbations and excessive tiredness to list of clinical presentations** **2.3 added paragraph regarding modulator drugs** **Clinical procedure- removed first paragraph which was repeat in 2.4 section** **OGTT – Interpretation regarding INDET** **Reformatted throughout and updated references**	

Glossary

Glucagon	Hormone that plays an active role in allowing the body to regulate the utilisation of glucose and fats and is released in response to low blood glucose levels
HbA1C	Glycated haemoglobin – a form of haemoglobin that is measured primarily to identify the three-month average plasma glucose concentration
Hyperglycaemia	Elevated blood glucose levels -symptoms include increased thirst, frequent urination, fatigue, headache, blurred vision and weight loss despite increased food intake
Indeterminate glycaemia	When your fasting and two-hour OGTT results are normal, but a high blood glucose noted in the middle of the OGTT
Levemir	Long acting insulin
Metabolic syndrome	a cluster of biochemical and physiological abnormalities associated with the development of cardiovascular disease and type 2 diabetes
Novorapid	Short acting insulin
Polydipsia	Abnormally great thirst as a symptom of disease
Polyuria	Excessive or abnormally large production or passage of urine
Post-prandial hyperglycaemia	Elevated blood glucose levels after food
Neuropathy	Damage to the nervous system from uncontrolled blood sugar over time

Abbreviations

ADA	American Diabetes association
CF	Cystic fibrosis
CFRD	Cystic fibrosis related diabetes
CGM	Continuous glucose monitoring
IGT	Impaired Glucose Tolerance
INDET	Indeterminate glycaemia
OGTT	Oral glucose tolerance test
FPG	fasting plasma glucose
FH	fasting hyperglycaemia
IFG	impaired fasting glucose
NGT	normal glucose tolerance

Appendix 2: UHL CFRD referral pathway

Consider CFRD in the following children with Cystic fibrosis:

- **Unexplained polyuria or polydipsia**
- **Failure to gain or maintain weight despite nutritional intervention**
- **Reduced growth velocity**
- **Delayed progression of puberty**
- **Unexplained chronic decline in pulmonary function**
- **Increased frequency of pulmonary exacerbations**

- **Screening for CFRD with OGTT and CGM at annual review for all children 10 years and above;**
- **If OGTT is abnormal: CGM to guide insulin therapy**
- **HbA1C>6.5%: proceed to OGTT and CGM**

- **CGM report downloaded by the paediatric CF team and if abnormal, forwarded on to the paediatric diabetes consultant along with the referral form**
- **CGM report to be discussed with the paediatric diabetes team and a management plan to be formulated**
- **Liaising with diabetes consultant on call for their availability on CF clinic days and arranging appointment for the child to see the diabetic team in the CF clinic**
- **Child and family to receive education and training on diabetes management**

Appendix 3- CGM Referral form

Name of patient: **Hospital no:**

Date of Birth: **Address:**

Diagnosis:

Indications for CGM:

Annual review		**Symptoms of hyperglycaemia**	
Clinical concerns		**Prior to starting high dose steroids**	
High random glucoses		**Before major surgery**	
High HbA1c		**Overnight feeds**	
Other (please give details):			

Previous CGM /OGTT results:

Previous diabetes team review and plan:

Recent Lung function:

Date: ……. FEV1 :……L (..... % pred) FVC: :….L (……% pred)

On CF Modulator YES/NO

Weight: **Centile:**

Investigations: **Date**

Glucose

HbA1C

Referrer: **Grade:**

Signature: **Date of referral:**