# 7. CF-related diabetes

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## 1. INTRODUCTION

- ***CF-related diabetes (CFRD)*** is one of the most common complications of CF. Its prevalence increases with age and is higher in adult female patients. It occurs in approximately
  - 30% of CF patients aged 18 years and older
  - >50% of CF patients aged 50 years and older (80% of those with *CFTR* variants associated with a severe CF phenotype)
- **CFRD** is usually clinically silent making **screening** essential for timely diagnosis. *Oral glucose tolerance test (OGTT)* is the gold standard for CFRD screening and should be performed annually.
- **Milder abnormalities of glucose regulation** such as impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) usually precede CFRD.
- **Fasting asymptomatic *hypoglycemia* and postprandial reactive hypoglycemia** are common in CF and are associated with inappropriate insulin secretion control (low BMI, delayed responsiveness to hyperglycemia, lack of insulin suppression by hypoglycemia). While uncomfortable, it is in general not dangerous.

## 2. PATHOGENESIS AND RISK FACTORS OF CFRD

- The **etiology of CFRD** is complex and the mechanisms leading to its development are not fully understood:
  - CFRD is distinct from type 1 and type 2 diabetes **(Table 1)**.
  - The main defect is **insulin insufficiency** as a result of the destruction of β-pancreatic cells and decreased β-cell function: abnormal CFTR → reduced $HCO_3^-$ secretion from the pancreatic duct cells into the lumen → pancreatic enzyme precipitation, mucus accumulation → reduction of pancreatic enzyme secretion, pancreatic tissue destruction **(see also Chapter "*Pathogenesis of CF*")**.
  - **Insulin resistance** associated with infection or inflammation also contributes to CFRD. Insulin resistance transiently increases during acute pulmonary infections.
  - After transplantation the use of systemic corticosteroids and immunosuppressive agents increases the incidence of diabetes through multiple mechanisms (direct toxic effect on the β-pancreatic cells, decreased insulin secretion, increased insulin resistance).
  - The main risk factors for the development of CFRD are shown in **Table 2**.

## 3. CLINICAL MANIFESTATIONS OF CFRD AND LONG-TERM OUTCOMES

- CFRD is usually asymptomatic, its course is insidious and its diagnosis depends largely on the screening of asymptomatic patients.
  - Symptoms of hyperglycemia, such as polydipsia and polyuria, are rare.
  - Diabetic ketoacidosis is uncommon.
  - **CFRD may present as a decline of nutritional status or pulmonary function tests: in this case a high index of clinical suspicion should prompt active investigations for CFRD.**

**Table 1:** Comparison of type 1, type 2 diabetes and CFRD (adapted from[1])

| | Type 1 diabetes | Type 2 diabetes | CFRD |
|---|---|---|---|
| **Clinical features** | | | |
| Overweight | Uncommon | **Common** | Uncommon |
| Hypertension | Uncommon | **Common** | Uncommon (except after transplant) |
| Dyslipidemia | Uncommon | **Common** | Uncommon (except after transplant) |
| Ketoacidosis | **Common** | Uncommon | Uncommon |
| Microvascular complications | **Common** | **Common** | **Common** |
| Macrovascular complications | Uncommon | **Common** | Uncommon |
| **Pathophysiology** | | | |
| β-cells and islets | Autoimmune destruction of β-cell<br>Marked atrophy and fibrosis of islets | Defective function of β-cells<br>Focal atrophy and amyloid deposition of islets | Islet destruction due to exocrine tissue destruction<br>Defective function of remaining β-cells |
| Insulin status | Insulin deficiency | Insulin resistance<br>Relative insulin deficiency | Insulin deficiency<br>Variable degrees of insulin resistance (notably during exacerbations) |
| Glucagon-like peptide 1 | Normal | Normal or decreased secretion<br>Efficacy normal | Decreased secretion<br>Improved secretion with pancreatic enzyme replacement |
| Gastric inhibitory polypeptide | Normal | Normal or decreased secretion | Near normal secretion<br>Decreased efficacy |
| Hyperglucagonemia | Absent | Present | Absent |
| Oxidative stress | Increasing evidence of its role | Increasing evidence of its role | Increasing evidence of its role |
| Genetic predisposition | HLA D3 and D4 | High. Multiple variants.<br>*TCF7L2* | *CFTR* genotypes associated with pancreatic insufficiency<br>*CFTR* genotypes associated with more severe CF<br>Family history of type 2 diabetes, non-CFTR genotypes (e.g. *TCF7L2*) |

**Table 2:** Factors associated with the development of CFRD[2,3]

| |
|---|
| Increasing age |
| Female gender |
| Pancreatic insufficiency |
| Mutations causing severe CFTR dysfunction, class I and II mutations |
| Decreased pulmonary function |
| Liver impairment |
| Treatment with systemic corticosteroids |
| Treatment with immunosuppressants |
| Having a sibling with CFRD |

- Compared to CF without diabetes, CFRD is associated with lower lung function, worse nutrition, more frequent hospitalizations and a higher mortality.
- The prevalence of long-term complications depends on the duration of diabetes and the level of glycemic control.
  - **Microvascular complications**
    - ***Nephropathy:*** moderately increased albuminuria (or 'microalbuminuria') has been reported in 4-21% of CFRD cases. Kidney failure is rare except after transplant.

      *Note:* Patients with CFRD may be at greatest risk of renal tubular damage when exposed to nephrotoxic drugs **(see also Chapter "*Renal disease*")**.
    - ***Retinopathy***: has been reported in 16-36% of cases with CFRD duration of ≥10 years. Blindness has not been reported.
    - **Neuropathy**: has been reported in 55% of cases with CFRD duration of ≥10 years.
    - The prevalence of CFRD-induced ***gastroparesis*** is difficult to determine because gastroparesis may be present and is common in CF patients with and without CFRD.
  - **Macrovascular complications** (cardiovascular and cerebrovascular disease) are very uncommon in CF. Death from atherosclerotic cardiovascular disease has not been reported in CF.

## 4. DIAGNOSTIC CRITERIA

- The diagnostic criteria of CFRD are the same as for type 1 and type 2 diabetes. They are summarized in **Table 3.**
- For the diagnostic criteria during pregnancy **see paragraph 10.**

## 5. DIAGNOSTIC TOOLS

- ***Fasting plasma glucose*** **(FPG)** alone is not recommended as a screening tool for CFRD due to its low sensitivity (it will miss diagnosis in patients with CFRD without fasting hyperglycemia).

**Table 3:** Diagnostic terminology

**CFRD**
– FPG ≥7.0 mmol/l or 126 mg/dl
– 2-hour OGTT plasma glucose ≥11.1 mmol/l or 200 mg/dl
– Random glucose level ≥11.1 mmol/l (200 mg/dl) in the presence of diabetic symptoms or
– HbA1c ≥6.5%*

***Impaired fasting glucose***
– IFG =5.6-6.9 mmol/l (normal FPG < 5.6 mmol/l) (110-125 mg/dl)

***Impaired glucose tolerance***
– IGT = 2-hour OGTT plasma glucose 7.8-11.0 mmol/l (normal < 7.8 mmol/l) (140-199 mg/dl)

**Indeterminate glucose tolerance**
– Normal FPG (<5.6 mmol/l, 110 mg/dl) and 2-hour OGTT plasma glucose (<7.8 mmol/l, 140 mg/dl) but increased mid-OGTT glucose levels (≥11.1 mmol/l, 200 mg/dl)

FPG=fasting plasma glucose, IGT= impaired fasting glucose, OGTT: oral glucose tolerance test
*A normal HbA1c cannot exclude CFRD

- **Random glucose measurement** may identify CFRD but is not sufficiently accurate as a screening method.
- ***Glycosylated hemoglobin* (HbA1c):** abnormal values are diagnostic of CFRD but normal values cannot be used to exclude the diagnosis as they are usually spuriously low in CF. *It is not recommended as a screening tool for CFRD due to its low sensitivity.*
- **Oral glucose tolerance test (OGTT)**
  - **It is the gold standard for CFRD screening (beginning at least by age of 10), because results prospectively correlate with prognosis.** It should be done in the morning and during clinical stability (≥6 weeks after an exacerbation).
  - Preparation:
    – Fasting during the previous ≥8 hours (water is allowed).
    – The patient should have consumed at least 150 g/day of carbohydrate during the 3 days prior to testing (600kcal): this is usually not a problem in CF patients since they are on high calorie diets.
  - The test consists of an oral liquid glucose load of 1.75 g/kg body weight (maximum 75g), given within max 5 minutes, to fasting patients. Measurements of baseline glucose and 2-hour glucose are performed at a minimum, but 30, 60 and 90 minute glucose levels are recommended in order to assess for indeterminate glycemia. During the test the patient should not eat, drink or perform any strenuous physical activity (should stay seated).
  - Interpretation of the results is shown in **Table 4.** Current diagnostic criteria are based on fasting glucose and 2-hour glucose. Results of 1-hour glucose have unclear clinical implications (except in the case of pregnancy). An increased 1-hour glucose level is associated with markers of clinical deterioration. Prospective studies are needed.
  - Hypoglycemia during/after OGTT (called reactive hypoglycemia) has been reported in 7-29.6% of CF patients, so it is important to feed a light snack at the end.

- ***Continuous glucose monitoring systems (CGMS) or flash glucose monitoring system (FGMS)***
  - CGMS/FGMS are not recommended for the diagnosis of CFRD.
  - Essentially all CF patients would have abnormal glucose levels by CGMS/FGMS. In patients not fulfilling the diagnostic criteria of CFRD, the clinical relevance of glycemic excursions observed during CGMS/FGMS is not known.

**Table 4:** Interpretation of oral glucose tolerance testing (OGTT)

| | Fasting glucose | Mid-OGTT glucose*[1] | 2-hour glucose |
|---|---|---|---|
| Normal | **<5.6** | <11.1 | **<7.8** |
| Impaired fasting glucose | **5.6-6.9** | | |
| Impaired glucose tolerance | | <11.1 | **7.8-11.0** |
| Indeterminate glucose tolerance | | ≥11.1 | **<7.8** |
| CFRD without fasting hyperglycemia | **<7.0** | - | **>11.1** |
| CFRD with fasting hyperglycemia | **≥7.0** | - | >11.1***[2]** |

*[1]Current diagnostic criteria are based on fasting glucose and 2-hour glucose. The clinical implications of 1-hour glucose are not clear, except in the case of pregnancy.
*[2]The presence of fasting hyperglycemia allows CFRD diagnosis without the need of an OGTT.
Values expressed in mmol/L.

## 6. WHEN AND HOW TO SCREEN FOR CFRD

- **Table 5** summarizes routine screening recommendations for CFRD

**Table 5:** Routine screening recommendations (patients not known for CFRD)

| When | How |
|---|---|
| Annually during clinical stability | OGTT (baseline, 2-hour) |
| Respiratory exacerbation requiring IV antibiotics and/or systemic corticosteroids | FBG and 2-hour postprandial plasma glucose levels for the first 48 hours |
| During enteral feeding | Mid and immediate post-feeding plasma glucose levels at enteral feeding initiation for 48 hours and monthly thereafter |

*(continued)*

| Pregnancy | |
|---|---|
| Before pregnancy: when it is planned and if the last available normal OGTT was performed >6 months ago | OGTT (baseline, 2-hour) |
| During pregnancy: at 12–16 weeks and 24–28 weeks of gestation | OGTT (baseline,1-hour, 2-hour) |
| After pregnancy: at 6-12 weeks after the end of pregnancy in patients with gestational CFRD (i.e no pregestational CFRD) | OGTT (baseline, 2-hour) |
| Before lung transplantation if the last available normal OGTT was performed >6 months ago | OGTT (baseline, 2-hour) |

## 7. MANAGEMENT

- **All patients with CFRD should be referred to a diabetologist and a dietician with experience in CFRD.**
- **Insulin is the recommended treatment for CFRD.**
  - Examples of available types of insulin are shown in **Table 6.**
  - The general principles and usual strategies during insulin treatment for CFRD are shown in **Table 7.**
  - An insulin pump can be used to allow more flexibility and better insulin coverage. This can be helpful for CFRD in general and especially for patients who have several snacks, difficult glycemic control due to gastroparesis and enteral feeding on and off. Patients' concerns about image body issues (i.e. carrying a visible sign of CFRD) are the main limiting factor for their use in CFRD. However, advances in insulin pump technology allowing smaller and lighter devices to be developed may improve patient comfort.
- **Oral antidiabetics**
  - Although they are not recommended by the current guidelines for the treatment of CFRD, there is published evidence for their use in CFRD.
  - A 2016 Cochrane review concluded that there is
    - "no significant conclusive evidence that long-acting insulins, short-acting insulins or oral hypoglycemic agents have a distinct advantage over one another in controlling hyperglycemia or clinical outcomes associated with CFRD".
    - "no demonstrated advantage yet established for using oral hypoglycemic agents over insulin".
  - In clinical practice oral antidiabetics such as insulin secretagoges may be considered in cases of CFRD without fasting hyperglycemia especially if the patient is reluctant to start insulin injections. Repaglinide has been used the most. Sulfunylureas and insulin sensitizers are not recommended.
  - **Table 8** summarizes information on oral antidiabetic agents in CFRD**.**

- **Additional interventions**
  - **Self management education and hypoglycemia education** (for practical information concerning patient education see 'Managing CFRD' at https://www.cff.org/Search.aspx?topic=214)
  - **Dietary recommendations (Table 9)**
    - CF patients need a high caloric intake to compensate their energy expenditure associated to inflammation and work of breathing → **restriction of caloric intake in CFRD is NOT recommended → rather adapt insulin treatment according to caloric intake (and not the other way round).**
  - **Exercise**: regular moderate aerobic exercise is recommended for at least 150min/week. *Note*: The blood lowering effect of strenuous exercise may last several hours. Consider hypoglycemia prevention strategies such as adjusting insulin dose according to the activity level and taking a snack.
  - Management of other **risk factors** such as hyperlipidemia or hypertension.
- **Areas of investigation**
  - **CFTR modulators**
    - In patients with at least one gating mutation, treatment with ivacaftor can improve insulin secretion and glycemic control.
    - At the time of writing no data are published on the effect of lumacaftor-ivacaftor on glycemic control.
  - **Transplantation of the pancreas**
    - Currently, data are very limited concerning pancreas transplantation in CF: a recent analysis of the United Network for Organ Sharing (UNOS) database showed that among the 4600 CF patients transplanted between 1987 and 2014, only 28 received a pancreas transplant (in most cases combined with liver transplants).
    - The procedure is underused because it is not considered life-saving and in cases of combined transplantation it increases the complexity of the operation and the probability of complications.
  - **Transplantation of pancreatic islets**
    - It is a less invasive option than pancreatic transplantation. It consists of the isolation and culture of donor pancreatic islet cells → transplantation by catheterization of the portal vein or the transverse colic vein. Elevation of plasma C-peptide is measured as an indicator of islet allograft recovery.
    - There are no studies on the long-term efficacy and safety of this procedure in CF.
    - Only case reports for simultaneous or sequential lung - pancreatic islet transplantation in cases of brittle diabetes (poor glycemic control with numerous hypoglycemic episodes) in an attempt to improve glucose stability, decrease insulin requirements and eliminate hypoglycemic events.

## 8. MONITORING OF TREATED CFRD

- **Self-measurement of capillary blood glucose levels** ≥3 times/day, keeping a diary of glucose levels.
- **HbA1c** measurement 4 times/year (general target levels <7%)

**Table 6:** Examples of available insulin forms

| Type of insulin | Examples | Onset | Peak | Duration | Administration | Usual starting dose | Comment |
|---|---|---|---|---|---|---|---|
| **Rapid acting** | | | | | | | |
| Regular | Actrapid ® | 30-60 min | 2-3 h | 4-6 h | 15-30 min before meal | N/A | Higher risk of hypoglycemia compared to lispro or aspart. Prescription on a special order |
| Lispro<br>Aspart<br>Glulisin | Humalog ®<br>Novorapid ®<br>Apidra ® | <15 min | 1-2 h | 3-4 h | Less than 15 min before meal | N/A | |
| **Intermediate acting** | | | | | | | |
| NPH | Insulatard ® | 90 min | 2-12 h | 16-22 h | Mix well before injection<br>Before meals | N/A | Highly variable absorption<br>Higher risk of hypoglycemia compared to long acting insulin |
| **Long acting** | | | | | | | |
| Detemir | Levemir ® | 2 h | 6-8 h | 12-24 h depending on dose | 1-2 x/day<br>If 1x/day with evening meal or at bedtime | 10 UI/day or 0.1-0.2 UI/kg/day | |
| Glargine | Lantus ® | 2 h | Absent in low dose | 24 h | 1-2 x/day | 0.2 UI/Kg/day | |
| Degludec | Tresiba ® | 2-3 h | Absent | >24 h | 1x/day | 10 UI/day | Steady state after 3-5 days |
| **Premixed** | | | | | | | |
| Lispro | Humalog Mix ® | 10-15 min | 1-2 h | 16-22 h | Within 15 min of a meal | N/A | |
| Aspart | NovoMix ® | 10-15 min | 1-2 h | 16-22 h | Within 15 min of a meal | N/A | |

*Note:* Insulin pumps (continuous subcutaneous insulin infusion – CSII) may be used to administer rapid-acting insulin at a basal rate and, when necessary, as a bolus

**Table 7:** General principles and strategies during insulin therapy for CFRD

**General principles:**

- Adjust insulin to match patient's high calorie diet
- Adjust insulin using carbohydrate counting
- Consider patient's lifestyle (eating habits, activities)
- Self-care education has a central role in CFRD management

**Usual strategy**

- **Basal insulin (intermediate or long acting insulins)**
  Usual starting dose (for CFRD with fasting hyperglycemia): Many patients require a 50:50 basal:rapid acting insulin ratio. Some may require lower amounts of basal insulin (residual insulin secretion). Usual starting dose: 0.25 units/kg/day
  Basal insulin may not be required in CFRD without fasting hyperglycemia. In these cases, meal coverage insulin may be sufficient.
  Adjustment: based on fasting glucose level
- **Meal coverage**
  Usual starting dose: rapid acting insulin 0.5-2.0 units per 10 g of carbohydrate
  Adjustment:
  – If ≥2 units per 10 g of carbohydrate → consider increasing basal insulin
  – If glucose levels pre and 2h postprandially are almost the same → coverage dose is considered appropriate
  – If glucose levels 2h postprandially are increased → adjust by increments of 0.2-0.5 units per 10 g of carbohydrate
- **Correction dose:** depends on activity (eating, exercise)
  Usual starting dose: 1 unit of rapid-acting insulin to lower the glucose level by approximately 2- 3 mmol/l
  Adjustment: based on 2-hour post prandial glucose level

**Special situations:**

- **Nighttime gastrostomy/nasogastric tube drip feeding:**
  – Regular (or rapid insulin analog) and NPH insulin administered before the feeding**.** Glucose levels 3-4h into the feeding are used to adapt regular insulin (or rapid insulin analog) dose**.** Glucose levels at the end of feeding are used to adapt NPH insulin dose.
  – An insulin pump can also be used.
- **Infectious exacerbations:** Usually higher insulin requirements during exacerbation returning to baseline need several weeks after recovery.
- **Treatment with systemic corticosteroids**: Close monitoring at introduction of systemic corticosteroids (increase insulin dose at least 30 %), during tapering and at the end of treatment to optimize glycemic control.
- **Fasting patient** (e.g. for an exam): decrease basal insulin by one third, do not administer rapid acting insulin, consider correcting after a meal.

**Table 8:** Oral antidiabetics available in Switzerland that have been studied or are used in CFRD (adapted from [4,5])

| | Drug | Dose | Positive points | Negative points and CF-related concerns |
|---|---|---|---|---|
| **Insulin secretagoges** | | | | |
| Meglitinides | Repaglinide<br>*Novonorm®*<br>*Repaglinide®* | Starting dose 0.5 mg 3x/day taken 10 min prior to a meal<br>Dose adjusted at 1 week intervals until optimized<br>Usual dose 1-2mg 3x/day<br>Max dose 12 mg/day | -Insulin insufficiency is the main mechanism of CFRD<br>-Repaglinide is the oral antidiabetic studied the most in CFRD*<br>-Weight improvement during the first 6 months of therapy | Inconsistent efficacy<br>Laboratory data showed weak inhibition of CFTR |
| | Nateglinide<br>*Starlix®* | Starting dose 60 mg 3x/day taken prior to a meal<br>Usual dose 120 mg 3x/day<br>Maximal dose 120 mg 3x/day | Insulin insufficiency is the main mechanism of CFRD | No studies in CF<br>Laboratory data showed CFTR inhibition |

*Randomized controled trials of repaglinide vs placebo and repaglinide vs insulin

**Table 9:** Dietary recommendations for CFRD*[1]

| | |
|---|---|
| An optimal nutritional status is of major significance in CF and especially in CFRD | |
| Patients should continue their high calorie diet<br>– no diet restrictions (dietary recommendations for diabetes type 1 or 2 do not apply in CFRD)<br>– addition of oral supplements or enteral feeding may be necessary to meet the caloric requirements | |
| Carbohydrate monitoring is recommended to optimize glycemic control and insulin treatment*[2] | |
| Avoidance of sugar containing beverages between meals (preferably taken with meals or snacks) | |
| Calories | 120-150% of normal caloric intake for age and gender |
| Fat | 40% of total energy |
| Carbohydrates | 40-50% of total energy. Individualized consumption with carbohydrate monitoring |
| Protein | 200% of reference nutrient intake |
| Salt | Unrestricted intake |
| Fibre | Encouraged if it does not compromise energy intake |
| Vitamins | Routine supplementation |

*[1] See also Chapter "*Nutrition*"
*[2] For carbohydrate monitoring see https://www.cff.org/Search.aspx?topic=214

- **CGMS or FGMS** may be used in patients treated with insulin to evaluate variations of glucose levels and guide adjustments of therapy (**for more information on CGMS/ FGMS see in the Supplement S7)**. In this context, prescription of a CGMS device to a patient requires a prior request of reimbursement. Currently, in Switzerland, FGMS is reimbursed when prescribed by a diabetologist for a patient on insulin.

## 9. MONITORING AND PREVENTION OF MICROVASCULAR COMPLICATIONS AND CARDIOVASCULAR RISK FACTORS

- For patients for whom the true duration of diabetes is known, monitoring for microvascular complications should begin after 5 years of diabetes duration and should be performed yearly thereafter.
- For newly diagnosed patients who were not previously screened for diabetes (i.e. the duration of CFRD is unknown) monitoring should be performed at diagnosis and yearly thereafter.
- Annual monitoring should include the following
  - Retinal exam done by ophtalmologist
  - Unine analysis for albuminuria, proteinuria
  - Sensory foot testing
  - Lipid profile
  - Blood pressure measurement

## 10. *PREGNANCY*

- **Pregestational CFRD**
  - Preconception care to optimize glycemic control and assess for complications.
  - Close collaboration of the CF specialists, diabetologists and nutritionists.
- **Gestational CFRD**
  - Untreated gestational diabetes leads to increased maternal and perinatal morbidity.
  - Screening should be routinely performed with 75 g OGTT
    - before pregnancy: when pregnancy is planned, if the last available normal OGTT was performed >6 months ago
    - at 12–16 weeks and 24–28 weeks of gestation
    - at 6-12 weeks after the end of pregnancy in patients with gestational CFRD
  - The diagnostic criteria during pregnancy are the following (one pathological value is needed for diagnosis)
    - Fasting glucose ≥5.1 mmol/l or
    - 1-hour glucose ≥10.0 or
    - 2-hour glucose ≥8.5

## 11. LUNG TRANSPLANTATION

- At listing patients should be screened with OGTT (if the last available OGTT was performed >6 months ago).
- During the perioperative period and while the patient receives high dose corticosteroids, plasma glucose levels should be monitored closely.
- Currently, there are no CF-specific screening strategies for the diagnosis of new onset diabetes after transplantation (NODAT).
  - FBG and 2-hour postprandial plasma glucose levels should be measured routinely during the first month after transplantation.
  - FBG should be measured routinely at clinic visits.
  - In patients without fasting hyperglycemia, OGTT should be performed at least annually as done in CF patients before lung transplantation.

## 12. REFERENCES


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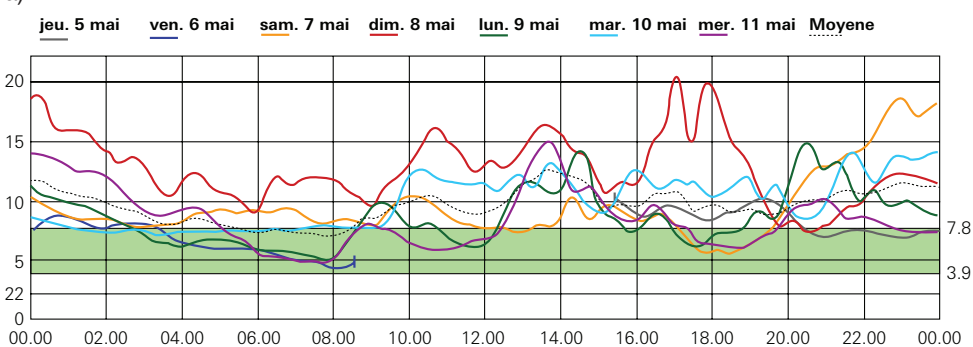
# S7. CF-related diabetes

## CONTINUOUS GLUCOSE MONITORING SYSTEMS (CGMS) OR FLASH GLUCOSE MONITORING SYSTEM (FGMS)

- Several different systems are available. In general they consist of a disposable subcutaneous glucose sensor and a glucose monitor. The glucose sensor is inserted into the subcutaneous tissue → the sensor measures the electrical current generated by the oxidation of interstitial fluid glucose by glucose oxidase every few minutes → data are stored in the glucose monitor and can be downloaded providing the pattern of glucose levels over several days (up to 14 days with FGMS).
- Capillary blood glucose measurements taken 4 times daily are used to calibrate the sensor in case of CGMS (not needed for FGMS, Freestyle libre® system).
- The patient keeps a diary of his/her activities and eating habits during the measurement period.
- CGMS/FGMS are not recommended for the diagnosis of CFRD. In patients not fulfilling the diagnostic criteria of CFRD, the clinical relevance of glycemic excursions observed during CGMS/FGMS is not known.
- CGMS/FGMS are considered useful in patients diagnosed with CFRD to evaluate variations of glucose levels and to guide insulin therapy.
- **Figure S1** shows an example of a CGMS recording.

**Figure S1: Example of a CGMS recording a)** curves obtained on each day are represented by a different color and the mean by the dotted line, **b)** descriptive statistics of daily glucose levels, **c)** percentage of time during which glucose levels are above 7.8 mmol/l, between 3.9 and 7.8 mmol/l and below 3.9 mmol/l.

a)




*(continued)*

b)

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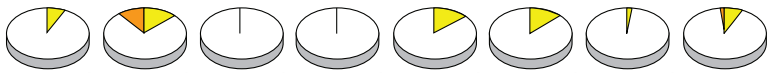
|---|---|---|---|---|---|---|---|---|
| **Nb valeurs du capteur** | 104 | 127 | 288 | 288 | 288 | 288 | 288 | 1'671 |
| **La plus élevée** | 10.4 | 12.1 | 18.7 | 20.5 | 15.0 | 14.2 | 15.2 | 20.5 |
| **La plus basse** | 7.0 | 4.3 | 5.6 | 7.4 | 5.1 | 7.1 | 4.8 | 4.3 |
| **Moyenne** | 8.4 | 7.5 | 9.5 | 12.8 | 8.6 | 10.0 | 8.6 | 9.6 |
| **Écart type** | 1.1 | 2.1 | 2.9 | 2.8 | 2.3 | 2.2 | 2.5 | 2.9 |
| **% d'Écart Moyen Absolu** | 11.0 | N/A | 0.2 | 57.8 | 10.1 | 23.0 | 11.3 | 19.3 |
| **Corrélation** | N/A | N/A | N/A | N/A | 0.92 | -0.09 | N/A | 0.72 |
| **Nb calibrations valides** | 3 | 0 | 1 | 2 | 3 | 5 | 3 | 17 |
| **Désignation** | | C | X | X | | X | | |

X: Faites appel à votre appréciation clinique S: Aucune donnée du capteur C: Aucune glycémie de calibration

c)



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| **Supérieur à 7.8** | 0:45 | 7% | 3:10 | 13% | 0:00 | 0% | 0:00 | 0% | 3:15 | 14% | 3:05 | 13% | 0:25 | 2% | 10:40 | 7% |
| **Entre 3.9 - 7.8** | 10:05 | 93% | 18:05 | 76% | 24:00 | 100% | 24:00 | 100% | 20:45 | 86% | 20:55 | 87% | 23:35 | 98% | 141:25 | 91% |
| **Inférieur à 3.9** | 0:00 | 0% | 2:45 | 11% | 0:00 | 0% | 0:00 | 0% | 0:00 | 0% | 0:00 | 0% | 0:00 | 0% | 2:45 | 2% |