Abnormal glucose metabolism -CFRD- IGT therapy-

Abnormal glucose metabolism therapy

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Background

Cystic Fibrosis-related diabetes (CFRD) is the most frequent complication of Cystic Fibrosis (Kayani K, 2018). It is age-dependent (Kelly A, 2014), even if glucose metabolism abnormalities may begin also very early (Haliloglu B,2016) and deficiency in beta-cell number, already during childhood, has been speculated (Bogdani M,2017). (Banavath TN, 2018).

It is a uniquely complex entity with clear differences from T1DM and T2DM (Konrad K, 2013). Thought pancreatic insufficiency is a major CFRD risk (Soave D, 2014), it has been affirmed (Wooldridge JL, 2015) that CFRD screening guidelines should be followed also by patients with pancreatic sufficiency.

Emerging evidences (Kayani K, 2018), (Coderre L, 2021) show that CFTR impairment itself has an important role in the release of insulin and glucagon and in the protection of ? cells from oxidative stress and that intra-islet inflammation is another important cause of ? cells demage.(Hart NJ, 2018), (Norris AW,2019). Furthermore, among contributors to the development of CFRD, other genetic factors related or not related to type 2 diabetes are postulated (Iafusco F, 2021) Nonetheless, reduced insulin secretion is the key factor to explain high prevalence of glucose intolerance in patients with cystic fibrosis, even if, variations of insulin sensitivity are also associated (Boudreau V, 2016) (Colomba J, 2019)

According to CF Foundation, criteria for CFRD diagnosis are based on elevated fasting blood glucose level greater than 6.94 mmol/L (125 mg/dL) or serum glucose value greater than 11.11 mmol/L (200 mg/dL) at two hours or symptomatic diabetes with random glucose levels greater than 11.11 mmol/L (200 mg/dL) and glycated hemoglobin levels >6.5%. However, in CF patients with pancreatic insufficiency it has been speculated that a 1-hour serum glucose level ?155?mg/dL, already could manifest impaired ?-cell secretory capacity with associated early-phase insulin secretion defects (Tommerdahl K, 2021). Continuous glucose monitoring could be a more useful tool for evaluating early abnormalities (Taylor-Cousar JL, 2016), (Chan CL, 2022). HbA1c is not considered a sensitive screening test for CFRD (Bouddreau V, 2016). It has been speculated that both serum fructosamine (Lam GY, 2017) and homeostasis model assessment index of ?-cell function (HOMA-%B), may be more effective (Mainguy C, 2017)

The relationship between abnormal glucose metabolism and increased morbidity and mortality in CF patients, mostly in females, is well known (Kerem E, 2013), (Lewis C, 2015), (Bilodeau C, 2016) and also earlier stages of glucose metabolism impairment have been recognized, far back (Rolon MA, 2001), as relevant risk factors in the long-term prognosis (Lavie M, 2015). (Terliesner N, 2017). (Sandouk Z, 2021)

Diabetic microvascular complications may occur in CFRD (Schwarzenberg SJ, 2007) and, although the prevalence of retinopathy and nephropathy appears to be lower than that found in other forms of diabetes, annual complication screening should be performed at 5 years from diagnosis of CFRD with fasting hyperglycemia.

Even if the use of oral agents may prove beneficial in treating CFRD, insulin remains the mainstay of treatment (Brennan AL, 2015) (Moheet A, 2018) and, probably, it has to be started already in the first stages of glucose abnormal condition (Pu MZ,2016). It has been postulated (Hayes D Jr, 2014) that Ivacaftor, the CFTR modulator for patients with gating mutations, might be not only a mean to potentially delay or prevent the development of CFRD, but also a mean to correct well established CFRD. On the contrary, Lumacaftor/Ivacaftor, CFTR modulator for patients with two F508del mutations, did not demonstrate a consistent impact on glucose tolerance and insulin secretion (Thomassen JC, 2018).

In CFRD patients, a free diet is recommended, but it has been postulated that a low glycemic index diet may improve glucose tolerance status (Balzer B, 2012) (Birch L, 2018)

In the last years, regarding glucose abnormal metabolism in CF, hypoglycaemia, in the absence of diabetes or glucose lowering therapies, is receiving growing attention in the literature (Armaghanian N, 2016) (Kayani K,2018)

In the 2022 Cystic Fibrosis Foundation drug development pipeline no compounds for glicometabolic condition are considered.

Issues

Modalities of glucose tolerance screening.

Timing and protocols of treatment of abnormal glucose metabolism.

Role of oral hypoglycemic agents.

Role of insulin pump.

Optimal glycemic control to reduce the impact of CFRD on long-term prognosis.

What is known

In 2012, a Systematic Review by Health Technology Assessment (Waugh N,2012) reviewed the methods for CFRD screening and suggested that continuous glucose monitoring is the best screening test and that blood glucose level excursions > 8 mmol/l (= 144 mg/l) must be considered potentially harmful to the lung by promoting colonisation and infection.

A Cochrane review (Onady GM, 2020) studied insulin and oral agents efficacy for managing CFRD**.** Twenty nine studies studies have been considered. Four RCTs (200 participants) have been included in the analysis : one short-term single-center trial (7 adults) comparing insulin with oral repaglinide and no medication in people with cystic fibrosis-related diabetes and normal fasting glucose; one long-term multicenter trial (61 adults) comparing insulin with oral repaglinide and placebo; one long-term multicenter trial (67 adults) comparing insulin with oral repaglinide; and one 12-week single-center cross-over trial (20 adults) comparing the long-acting insulin glargine to short-term neutral protamine Hagedorn insulin. Two ongoing trials of newly approved incretin mimics have been noted for possible future inclusion.This review has not found any conclusive evidence that any agent has a distinct advantage over another in controlling hyperglycemia or the clinical outcomes associated with CFRD. However, given the treatment burden already experienced by people with cystic fibrosis, oral therapy may be a viable treatment option.

In 2021 (Toner A, 2021) a Cochrane review studied the impact of insulin therapy guided by continuous glucose monitoring system (CGMS) on the lives of people with CFRD and stated that there is currently insufficient evidence to determine benefit or potential adverse events linked to CGMS, if compared with other forms of glucose data collection.

A systematic review (Pietrzykowska A, 2025) studied cystic fibrosis-related diabetes in the era of modern treatment using CFTR modulators in pediatric patients. 5 studies met inclusion criteria - 1 clinical trial, 2 observational studies and 2 case reports. Evidence suggests CFTRm may improve glucose tolerance and insulin secretion in some pediatric patients, particularly in those with preserved ?-cell function or early-stage CFRD. However, results varied across studies with some showing no significant improvements in glycemic control. While early findings suggest CFTR modulators may offer metabolic benefits and potentially delay or reduce the need for insulin therapy in children CFRD, current evidence is limited. Larger, pediatric-focused clinical trials with standardized glycemic outcomes are essential to determine the long-term efficacy and safety of CFTRm in managing or preventing CFRD.

About the therapy in earlier stages of impared glucose tolerance (IGT), one RCT (Moran A, 2009) showed that insulin therapy safely reversed chronic weight loss in patients with CFRD without fasting hyperglycemia and another RCT (Minicucci L, 2012) showed that glargine treatment, in patients with glucose intolerance, was well accepted and tolerated, even if its efficacy in improving clinical and glycometabolic conditions was not demonstrated.

In a RCT (Beaudoin N, 2016) combined exercise training has proven to be effective to improve glycemic control in CF patients and, perhaps, to offer a possibility that could delay the onset of CFRD.

One multicentric european RCT (Ballmann M, 2018) compared efficacy and safety of a 24 months treatment with insulin (n=41) and repaglinide (n=34) in CFRD patients aged 10 years and older. The primary outcome was HbA1c. Boths treatments resulted equally efficacious and safe.

In 2019 a RCT (Geyer MC, 2019) has speculated that exanetide (a glucagon-like peptide-1 receptor agonist, used to treat diabetes mellitus type 2, given by injection under the skin, that works by increasing insulin release from the pancreas and decreases excessive glucagon release) could correct post-prandial hyperglicemia in young people with CF and impaired glucose tolerance (IGT) and that could be a candidate treatment in CFRD.

In 2021 (Colombo C, 2021) a retrospective case–control study on 13 patients homozygous for Phe508del CFTR mutation, who received LUMA/IVA for one year and on 13 patients with identical genotype who did not receive this treatment, did not find any evidence of improvements in glucose tolerance associated with LUMA/IVA treatment.

These results have been confirmed by the PROSPECT study conclusions published in the same year (Moheet A, 2021)

In 2021 (Kelly A, 2021) a RCT about 26 adult with abnormal glucose tolerance showed that sitagliptin intervention augmented meal-related incretin responses with improved early insulin secretion and glucagon suppression, even if no improvements in glucose tolerance or ?-cell sensitivity to glucose, including for second-phase insulin response, were found. In 2022 the same statudy (Kelly A, 2022) was corrected in Table 2.

In 2022 (Rakotoarizoa L, 2022) a multicenter, prospective, phase 1-2 trial showed that combined pancreatic islet-lung transplantation from a single donor restored metabolic control and pulmonary function , without increasing the morbidity of lung transplantation, in 7 out of 10 participants.

In 2022 (Nyirjesy S, 2022) a study, about 32 CF adult patients, postulated that GLP-1(glucagon -like peptide-1) agonists can enhance pancreatic islet function.

In 2022 (Granger E, 2022), using national UK registry data about 1616 patients diagnosed with CFRD, no evidence was found of long term insulin treatment on lung function and nutritional condition.

A study (Bass RM, 2022) examined diet quality in a population of young adults with CF using the Healthy Eating Index, a measure of diet quality in accordance with the U.S. Dietary Guidelines for Americans and evaluated and described how subcomponents of the HEI might apply to individuals with CF Methods: 3-day dietary recalls from healthy adolescents and young adults with CF were obtained and scored based on the Healthy Eating Index. Dietary recalls from 26 (14M/12F) adolescents and young adults with CF (ages 16–23), were obtained. Individuals with CF had significantly lower HEI scores than the general population and lower individual component scores for total vegetables, greens and beans, total fruits, whole fruits, total protein, seafood and plant protein and sodium (p values < 0.01 for all). In conclusion, Dietary quality was poor in these healthy adolescents and young adults with CF. Given the increased prevalence of overweight and obesity in CF, updated dietary guidance is urgently needed for this population. The Healthy Eating Index may be a valuable tool for evaluating dietary quality in CF.

One non-randomized clinical trial (Grancini V, 2023) investigated the effects of insulin therapy optimization with sensor augmented pumps on glycemic control and body composition in people with cystic fibrosis-related diabetes. 46 adults with CF-related diabetes

(CFRD) resulting from partial-to-complete insulin deficiency were enrolled. After 24 months changes in HbA1c were: -1.1% (-12.1 mmol/mol) (95% CI: -1.5; -0.8) and -0.1% (-1 mmol/mol) (95% CI: -0.5; 0.3) in the sensor augmented pump (SAP) and multiple daily injection (MDI) therapy group, respectively, with a between-group difference of -1.0 (-10 mmol/mol) (-1.5; -0.5). Sensor augmented pump (SAP) therapy was also associated with a decrease in mean glucose (between group difference: -32 mg/dL; 95% CI: -44; -20) and an increase in time in range (TIR) (between group difference: 19.3%; 95% CI 13.9; 24.7) and in fat-free mass (between group difference: +5.5 Kg, 95% CI: 3.2; 7.8). In conclusion therapy optimization with SAP led to a significant improvement in glycemic control, which was associated with an increase in fat-free mass.

One single-center, open-label, random-order, crossover trial (Sherwood JS, 2023) involved 20 adults with cystic fibrosis-related diabetes (CFRD) and investigated automated insulin delivery with the iLet bionic pancreas (BP). Participants were assigned in random order to 14 days each on the BP or their usual care (UC). No restrictions were placed on diet or activity. Time in range (TIR) was significantly higher in the BP arm than the UC arm (75 ± 11% vs. 62 ± 22%, P = 0.001). Mean CGM glucose was lower in the BP arm than in the UC arm (150 ± 19 vs. 171 ± 45 mg/dL, P = 0.007). There was no significant difference in percent time with sensor-measured glucose <54 mg/dL (0.27% vs. 0.36%, P = 1.0), although self-reported symptomatic hypoglycemia episodes were higher during the BP arm than the UC arm (0.7 vs. 0.4 median episodes per day, P = 0.01). No episodes of diabetic ketoacidosis or severe hypoglycemia occurred in either arm. Adults with CFRD had improved glucose control without an increase in CGM-measured hypoglycemia with the BP compared with their UC, suggesting that this may be an important therapeutic option for this patient population

A rerospective study (Cohen A, 2024) investigated the long-term therapy with CFTR modulators on glucose metabolism in adolescents and adults with cystic fibrosis (N=15; age range: 13-37 years). The 120-min OGTT value decreased from 159.7 mg/dL to 130.4 mg/dL post-CFTRm (p = 0.047). The average time elapsed between the two OGTTs was 49.87 months (ranging 9-157 months, median 38 months). Glycemic status improved in six pwCF (two CFRD to normal (NGT)/indeterminate (INDET) glucose tolerance; two impaired glucose tolerance (IGT) to INDET; two INDET to NGT) and worsened in one (IGT to CFRD). Six pwCF and NGT remained stable with no changes in glycemic status throughout the follow-up period. In conclusion, CFTRm therapy may decelerate the glycemic control deterioration in pwCF over an extended period. These findings indicate the need for periodic OGTTs following the initiation of CFTRm therapy to appropriately adjust insulin requirements and prevent hypoglycemia. Further larger cohorts are required to authenticate and substantiate these findings.

An observational study (Alexandre-Heymann L, 2025) investigated Cystic Fibrosis Related Diabetes Screening results in adult people with cystic fibrosis from 2004 onward in Montreal CF centre. Over the years, the authors observed a shift towards overweight and obesity among cystic fibrosis patients, along with improved lung function. This could be due to improved cystic fibrosis care and to the introduction of cystic fibrosis transmembrane conductance regulator modulators. The authors were also able to validate new, simplified screening modalities and management strategies (e.g. physical activity) for cystic fibrosis-related diabetes. Future research will focus on how cystic fibrosis transmembrane conductance regulator modulators influence glycaemic control and cardiometabolic health in people with cystic fibrosis.

An RCT (Hameed S, 2025) conducted in five children's hospitals in Australia and one in the USA investigated insulin for early glycaemic abnormality in children with cystic fibrosis without cystic fibrosis-related diabetes (CF-IDEA). Eligible participants were children with cystic fibrosis aged 5-18 years without cystic fibrosis-related diabetes and with peak glucose concentration on a five-point OGTT of 8·2-11·0 mmol/L (cystic fibrosis insulin deficiency stage 1) or ?11·1 mmol/L (cystic fibrosis insulin deficiency stage 2). Between Dec 6, 2010, and Feb 25, 2022, 109 participants. Participants were randomly assigned (1:1) to insulin or observation. Randomisation was done using the biased coin method, followed by minimisation when the study groups became imbalanced by chance. Randomisation was stratified by glycaemic category (cystic fibrosis insulin deficiency stage 1 or 2), weight Z score (more than or equal to -0·61 or less than -0·61), and study centre. Participants in the insulin group received once-daily, long-acting insulin detemir by subcutaneous injection before breakfast, commencing at 0·1 units per kg per day, adjusted in 0·5-unit increments to achieve all fingerstick blood glucose concentrations between 4 mmol/L and 8 mmol/L. Five participants withdrew after the baseline visit, and the analysis therefore included 104 participants (53 observation and 51 insulin); 95 participants completed the 12-month protocol and nine completed only 6 months. Baseline characteristics were similar between the groups; however, the observation group included 30 (57%) boys and 23 (43%) girls, whereas the insulin group included 23 (45%) boys and 28 (55%) girls. The median daily insulin dose at 12 months was 0·12 units per kg per day (range 0·05-0·41). There were no statistically or clinically significant differences between the observation and insulin groups in change in weight Z score (difference insulin minus observation 0·07 [95% CI -0·04 to 0·18]; p=0·20), change in ppFEV(1) (1·2 [-2·2 to 4·7]; p=0·48), or change in ppFVC (0·6 [-2·6 to 3·8]; p=0·72). Similarly, there were no significant differences in subgroup analyses by cystic fibrosis insulin deficiency stages 1 and 2. There were no episodes of severe hypoglycaemia or insulin-related adverse events, and we found no evidence of difference between the observation and insulin groups in CGM percentage time less than 3·9 mmol/L. Insulin treatment did not improve weight or lung function when given to children and adolescents with cystic fibrosis and early glycaemic abnormalities. Insulin treatment should not be given to those who do not meet OGTT criteria for cystic fibrosis-related diabetes.

Prospective cohort study (Grancini V, 2026) compared in 21 adults with Cystic fibrosis-related diabetes (CFRD) automated insulin delivery (AID) in place of multiple daily injections (MDI) or sensor-augmented pump (SAP). The Diabetes Treatment Satisfaction Questionnaire (DTSQ) and Audit of Diabetes-Dependent Quality of Life (ADDQoL) were administered at baseline and after 3 months. Primary outcomes were changes in DTSQ and ADDQoL scores; secondary outcomes included continuous glucose monitoring (CGM) metrics. After 3 months of AID use, DTSQ scores improved from 22 (IQR: 19-23) to 33 (IQR: 31-35), P < 0.001. ADDQoL scores increased from -2.1 (IQR: -2.7 to -1.2) to -0.9 (IQR: -1.7 to 0.5), P < 0.001. CGM metrics also improved significantly. In conclusion these findings provide preliminary evidence suggesting that AID may be a useful tool in the management of CFRD.

A multicenter randomized multicentre crossover trial (Rakotoarisoa L, 2026) compared postprandial ultra-fast insulin (PP-UFI) vs standard mealtime fast-acting insulin (MT-FI) in adults with cystic fibrosis-related diabetes (n=38; mean age: 33?±?11?years; 56% receiving CFTR modulators). The primary endpoint was time in range (TIR: 70-180?mg/dL). Baseline TIR was 74% [68-83], time below range (<70?mg/dL) was 4.1% [1.9-6.7], and ppFEV1 was 71?±?25%. The estimated difference between MT-FI and PP-UFI was?+?1.1 percentage points (95% CI: -1.1 to?+?3.3; p?=?0.316), with no statistically significant difference observed. Formal equivalence was not demonstrated. Other CGM metrics, HbA1c, and insulin doses were comparable between treatments. These findings support the potential of postprandial ultra-fast-acting insulin as a flexible treatment option for adults with CFRD

Unresolved questions

- Timing and protocols of treatment of abnormal glucose metabolism
- Role of oral hypoglycemic agents
- Role of insulin pump

A research is ongoing to find the genes and other factors that are responsible for the development of CFRD (NCT01113216)

A study is ongoing about the prevalence of Genome implicated with T2DM alleles, across the spectrum of glucose abnormalities in CF (NCT01852448)

An international multicenter observational study evaluates the predictive value of CGM

(continuous glucose monitoring) NCT05099939

A study investigates clinical and metabolic outcome, associated with linoleic acid assumption. NCT04531410

A Phase 2|Phase 3 study investigates (NCT06149793) is recruiting CFRD adult patients. It will investigate the effect of SGLT2 Inhibitor Therapy and will be focused on feasibility, safety, tolerability

A multi-center RCT (NCT06449677) will compare efficacy and safety endpoints using the insulin-only configuration of the iLet Bionic Pancreas System (BP) versus a control group using their usual care insulin delivery method and continuous glucose monitoring (CGM) during a 13-week study period in individuals ?14 years old with cystic fibrosis-related diabetes (CFRD). After 13 weeks, participants will continue in a 13-week Extension Phase in which the BP group will continue to use the BP system and the Usual Care group will initiate use of the BP system

Keywords

Diabetes Mellitus; Glucose Intolerance; Hypoglycemic Agents; Insulin;