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 childwood, 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). Furtheremore, among contributors to the development of CFRD, other genetic factors related or not related to type 2 diabetes are postulated (Iafusco F, 2021) Anyway, 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/liter (125 mg/deciliter) or OGTT value greater than 11.11 mmol/liter (200 mg/deciliter) at two hours or symptomatic diabetes with random glucose levels greater than 11.11 mmol/liter (200 mg/deciliter) and glycated hemoglobin levels >6.5%. However, in CF patients with pancreatic insufficiency it has been speculated that a 1-hour OGTT 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 value does not possess the characteristics of 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 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.

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 IG 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 tolence 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 (Kelly A, 2022) some corrections have been performed about the study.

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 partecipants.

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.

Unresolved questions

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

A study is ongoing about the feasibility of outpatient automated blood glucose control with the bionic pancreas (NCT03258853)

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

A pilot study is ongoing about the combination of continuous glucose monitor (CGM) and insulin pump therapy, also known as sensor augmented pump (SAP) therapy, for CFRD management in the inpatient setting, with the aim of improving glycemic control. (NCT03939065)

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

A study investigates the link between glucose abnormalities and elements critical to muscle function including mass, composition and energy metabolism. (NCT02776098)

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

Keywords

Diabetes Mellitus; Glucose Intolerance; Hypoglycemic Agents; Insulin;