

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 a 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](#)). Though 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 evidence ([Kayani K. 2018](#)) shows that CFTR impairment itself has an important role in the release of insulin and glucagon and in the protection of β cells from oxidative stress and that intra-islet inflammation is another important cause of β cells damage ([Hart NJ. 2018](#)), ([Norris AW.2019](#)).

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) or glycated hemoglobin levels $>6.5\%$.

Oral glucose tolerance test (OGTT) is commonly used to screen an abnormal glucose metabolism and in CF patients with pancreatic insufficiency it has been speculated that a 1-hour OGTT glucose level $>155\text{mg/dL}$, already could manifest impaired β -cell secretory capacity with associated early-phase insulin secretion defects ([Nyiriesy SC.2018](#)). Continuous glucose monitoring could be a more useful tool for evaluating early abnormalities ([Taylor-Cousar JL. 2016](#)). HbA1c value does not possess the characteristics of a sensitive screening test for CFRD ([Boudreau V. 2016](#)), unless, perhaps, lower normal values are considered ([Gilmour JA. 2019](#)) It has been speculated that both serum fructosamine ([Lam GY. 2017](#)) and homeostasis model assessment index of β -cell function (HOMA-%B) ([Mainguy C. 2017](#)) may be effective.

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](#)).

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 2019 Cystic Fibrosis Foundation drug development pipeline no compounds for glycometabolic 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.

One Cochrane review ([Onady GM. 2016](#)) studied insulin and oral agents efficacy for managing CFRD and 22 studies have been considered. Four RCTs (200 participants) have been included in the analysis : one short-term single-center trial (n = 7) comparing insulin with oral repaglinide and no medication in people with cystic fibrosis-related diabetes and normal fasting glucose; one long-term multicenter trial (n = 100, 74 of whom had cystic fibrosis-related diabetes) comparing insulin with oral repaglinide and placebo; one long-term multicenter trial (n = 73) comparing insulin with oral repaglinide; and one 12-week single-center trial (n = 20) comparing the long-acting insulin glargine to short-term neutral protamine Hagedorn insulin. This review has not found any 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.

1 CDSR protocol is ongoing and it will include cross-sectional and prospective cohort studies. Continuous glucose monitoring system will be compared for accuracy against the reference standard method for CFRD diagnosis.

About the therapy in earlier stages of impaired 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.

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 sensitivity and specificity of different methods for cystic fibrosis-related diabetes screening ([NCT027239](#))

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 study is ongoing about the feasibility of methylated insulin DNA, as a a biomarker of beta cell death, in determining the development of diabetes. ([NCT03713437](#))

A study is ongoing to evaluate the glycemic improvement after nutritional orientation in patients with cystic fibrosis ([NCT0320590](#)) .

A study is ongoing to investigate the feasibility and the effectiveness of a viscous fiber supplement to reduce Post-Prandial Glycemic (PPG) excursions ([NCT02810691](#))

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 cystic fibrosis related diabetes (CFRD) management in the inpatient setting, with the aim of improving glycemic control. ([NCT03939065](#))

Keywords

Diabetes Mellitus; Glucose Intolerance; Hypoglycemic Agents; Insulin;