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Advances in cystic fibrosis-related diabetes: Current status and future directions

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ABSTRACT

Aims: The aim of this review is to give an update of the recent advances in the pathophysiology, prognosis, diagnosis and treatments of cystic fibrosis-related diabetes (CFRD).

Methods: The literature survey focuses on original and review articles dealing with CFRD between 2006 and 2023, and in particular with: pathophysiology, risk and predictive factors, screening, chronic complications of CFRD, management and the effects of CFTR channel modulator therapies on glucose homeostasis, using PubMed®.

Results: The rising prevalence of CFRD is due to prolonged life survival among patients with cystic fibrosis (CF). Advances in the understanding of the pathophysiology highlight the singularity of CFRD. Adherence to diagnostic guidelines remains challenging. Besides the classical OGTT, alternative diagnostic tests are being considered: HbA1c measurement, continuous glucose monitoring (CGM), intermediate measurements of alternative glucose tolerance stages through OGTT and homeostatic model assessment (HOMA). Early treatment of (pre)diabetes in CF patients is mandatory. The advent of CFTR channel modulator therapies have created a paradigm shift in the management of CF: they seem to improve glucose homeostasis, but the mechanism remains unclear.

Conclusion: CFRD management is an ongoing concern. Optimal care has reduced the negative impact of CFRD on lung function, nutrition, and survival. Increasing prevalence of CFRD and prolonged lifespan lead to more microvascular complications. New screening tools (Hba1c, CGM, HOMA) show potential for better classification of patients. The effect of CFTR modulators on glucose metabolism warrants further research.

1. Introduction

Over the last decade, the expected lifespan of patients with cystic fibrosis (CF) increased by more than 10 years [1]. This has naturally led to a surge in the prevalence of cystic fibrosis-related diabetes (CFRD): in 2009, 40–50 % of adult with CF suffer from CFRD [2]. This adds a heavy burden to an already complex disease and requires diabetologists to take on a growing interest in this subject.

Moreover, CFRD diagnostic presents two major challenges. First, adherence to diagnostic guidelines is poor. Only 25%–50 % of CF patients are screened annually [3]. Second, current screening tools are imperfect. Alternative tests are being considered, such as the inclusion of HbA1c, CGM and HOMA in the diagnostic algorithm. For that reason, it is essential for practitioners to be up to date with ongoing research.

Finally, the advent of CFTR modulator therapies, aimed at correcting the root cause of CF, have changed the paradigm of CF. With it, their effect on glucose metabolism has been the subject of intensive research, which has challenged our understanding of CFRD. While the literature is large and recent, it still lacks consensus. This makes it particularly complex for diabetologists to sort through.

As a result, the aim of this review is to provide a global synthesis of CFRD for diabetologists, whose role is becoming increasingly important in the multidisciplinary approach required in the management of patients with CF. More specifically, this review provides an update on epidemiological, pathophysiological and clinical developments concerning the screening and management of CFRD and its complications.

2. Definition and epidemiology

CF is an autosomal recessive inherited disease, with the highest prevalence observed in Europe, North America and Australia and a worldwide estimated prevalence of 2025/100,000 people [4]. It is

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caused by mutations in the cystic fibrosis transmembrane regulator gene (CFTR) coding for a protein which physiologically functions in epithelial cells as a chloride and bicarbonate channel regulating fluid and electrolytes composition of secretions. These mutations are stratified into 6 classes according to the CFTR defect: (1) absence of mRNA, (2) absence of protein expression, (3) altered protein traffic to the plasma membrane of epithelial cells, (4) altered channel gating, (5) decreased protein conductance, (6) protein abundance or stability [5]. Classes 1–3 are associated with more severe disease [6].

CF results in progressive obstruction of the bronchial and the gastrointestinal tracts causing consecutively infections, chronic inflammation and organic dysfunction. Respiratory disorders remain the leading cause of mortality in CF patients. However, over the last few years, life expectancy in CF patients has increased due to earlier diagnosis and improvement in care. As a consequence, the prevalence of other chronic complications, such as CFRD, also sore.

CFRD is one of the most common non-respiratory comorbidities of CF patients [1]. It concerns 20 % of adolescents and 40–50 % of adults [2]. A recent review shows that its occurrence increases by 10 % each decade. According to European Register, the prevalence of CFRD is very heterogeneous among countries and age groups, probably because of different screening methods. Male and female are equally represented but female gender is reported to be a risk factor for acquisition of CFRD in younger age groups [7]. Dysglycaemia is frequently diagnosed before overt diabetes: prevalence of impaired fasting glycaemia (IFG) and impaired glucose tolerance (IGT) are respectively about 22–32 % (rising with age and OGTT category [2]) and 14–43 % [8–10].

As shown in Fig. 1, CFRD is part of a continuum of glucose tolerance abnormalities ranging from normal glucose tolerance (NGT) to conventional IFG or IGT as defined by ADA [11] to overt diabetes with or without fasting hyperglycaemia. Intermediate stages of abnormal glucose tolerance (AGT) have also been reported. AGT is defined as all glucose tolerance stages that are not NGT [12] including INDET (indeterminate glycaemia defined as a blood glucose level (BGL) after a 1 h oral glucose tolerance test (OGTT) > 200 mg/dl), AGT140 (defined as a BGL after a 1 h OGTT between 140 and 200 mg/dl) and AGT160 (defined as a BGL after a 1 h OGTT between 160 and 200 mg/dl). While distinction between CFRD with or without fasting hyperglycaemia was common, it is no longer considered determinant as there is no difference in lung function and nutritional status between CFRD FH- and CFRD FH + [1]. Diagnostic criteria for CFRD by itself in stable outpatients are the same as those recommended in the general population [11,12]. Early defects in glucose metabolism occur in most patients with CF. Yi et al. [13] show that 39 % of patients aged between 3 months and 5 years have AGT and those with NGT mostly present a diminished insulin response after stimulation. A recent study highlights that 20 % of CF children considered as having NGT during OGTT have INDET [14].

CFRD is a unique form of diabetes with its own clinical and pathophysiological characteristics. As shown in Table 1, CFRD differs from type 1 diabetes (T1D) in that there is no underlying autoimmune process and inaugural ketoacidosis is rare. Moreover, unlike type 2 diabetes (T2D), CFRD patients have no metabolic syndrome and macroangiopathy is uncommon [11].

CFRD is asymptomatic in the early stages. Polyuria and polydipsia are rare and keto-acidosis even more. It is associated with decreasing pulmonary function, precarious nutritional status and poorer prognosis. Thereby, despite efficient screening tools and improving management, mortality and morbidity are still higher than in CF patients without diabetes. Therefore, early diagnosis and efficient management are paramount in the challenge of improving nutritional and pulmonary status to reduce pulmonary exacerbations and overall survival.

3. Physiological pathways

3.1. Insulin deprivation

The pathophysiology of glucose abnormalities in CF is not fully understood. Its pathogenesis is multifactorial. Diabetes is mainly the consequence of a mixture of insulin deprivation and insulin resistance. However, the former seems to be the leading cause of CFRD.

The main mechanism of CFRD is the destruction of the pancreatic islets by contiguous inflammation from the exocrine tissue where CFTR

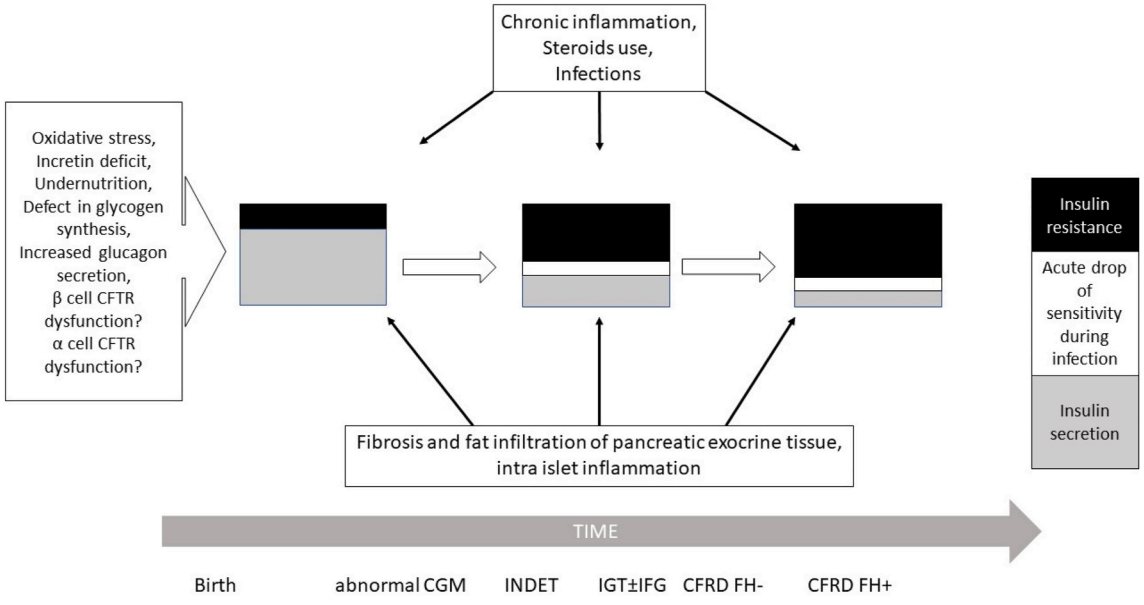

Fig. 1. Timeline of pathophysiological process in CFRD

Fig. 1. CFRD is part of a range of abnormalities in glucose tolerance, which spans from NGT to IFG or IGT. These abnormalities can progress to overt diabetes, with or without fasting hyperglycaemia, and may also include intermediate stages of AGT. AGT encompasses all glucose tolerance stages that do not fall under NGT, such as INDET (which is defined as a 1-h OGTT result exceeding 200 mg/dL). The diagram above is just an example. Each individual experiences a different rate of decline in glucose homeostasis.

Abbreviations: AGT, abnormal glucose tolerance; CFRD, cystic fibrosis-related diabetes; CGM, continuous glucose monitoring; FH, fasting hyperglycaemia; IGT, impaired glucose tolerance; INDET, glycaemia.

Table 1
Comparison between CFRD, T2D and T1D.

Features	CFRD	T2D	T1D
Worldwide total estimated number of adult people with diabetes in 2021 (estimated adult population 5 × 10^9) [66]	35 × 10^3 (7 × 10^{-6} %) [3,4,67]	483 × 10^6 (7 %) [66]	7 × 10^6 (0,1 %) [66]
Familial history of diabetes	14 % [68]	20 % (first degree relative) [69]	10 % (first degree relative) [70]
Age at diagnosis	25y [7]	>35y [11]	<35y [11]
Auto-immune mechanism	no	no	yes
Insulin deficiency	not complete, evolving over time	not complete, evolving over time	yes
Insulin resistance	mild (but severely increased during infection)	severe	mild
Keto-acidosis as initial presentation	no (yes if acute infection)	variable (yes if acute condition such as infection, or cardiovascular event)	yes
Treatment	oral drugs, insulin	diet, oral drugs, and insulin	insulin
Insulin requirement	yes, early	after several years of illness	yes, immediately
Microvascular complications	yes	yes	yes
Macrovascular complications	no	yes	yes
Comorbidities	pulmonary, pancreatic, hepatic	metabolic syndrome	auto-immune context
Cause of death	pulmonary	cardiovascular and increased risk of cancer	cardiovascular and renal
Dyslipidaemia and hypertension	Not uncommon [29,71]	common	rare

Abbreviations: CFRD, cystic fibrosis-related diabetes; T1D, type 1 diabetes; T2D, type 2 diabetes; y, years.

channel is abundant. CFTR channel defect leads to viscous secretions and obstruction of the small ducts with as consequence pancreas fibrosis and fat infiltration. Animal and human studies have shown that such a significant reduction in β-cell mass, starting early in life, leads to the development of CFRD. Because of a "crosstalk", pancreatic islets are damaged with a reduction of total mass of almost 50 % [15].

The study of Hart et al. [16] on mice directly supports this concept, by showing an intra islet inflammation related to the migration of inflammatory cells from the exocrine tissue to the endocrine tissue. Several studies suggest that the environment outside the islet plays a significant role in its dysfunction and that CFTR does not play a key role in insulin secretion [15–17]. This "environment" hypothesis is reinforced by the observations that CFTR channels are poorly expressed in β cells [16].

In view of these pathophysiological mechanisms, the first step in the genesis of hyperglycaemia is a delayed early phase insulin response to oral glucose ingestion, followed by a reduction in total insulin secretion. Later, a downfall in insulin secretion appears.

However, reports suggest that insulin secretion in CFRD could be altered without pancreatic exocrine insufficiency and loss of islet mass. This implies that other pathophysiological pathways could be involved: basic intrinsic CFTR defects in B-cell function, interference of genetic susceptibility loci conferring risk for T2D, and oxidative stress [15]. In addition, pancreatic islet amyloidosis is identified in CFRD patients but not in CF patients, suggesting a potential role of amyloid deposits (just like in T2D) [17]. It is also of interest to note that a loss of incretin effect in CFRD can occur despite adequate secretion of incretin hormones, which could also contribute to postprandial hyperglycaemia [18].

3.2. Insulin resistance

As shown in Fig. 1, CFRD is also characterized by insulin resistance in basal conditions provoked by a silent inflammatory state, sarcopenia, and eventually cirrhosis leading to elevated hepatic glucose output and impaired glycogen synthesis [19]. In addition, defective intracellular GLUT-4 transporters may also be the cause of impaired insulin response and altered glucose homeostasis [20]. Moreover, as far as other hormones are concerned, Huang et al. [21] demonstrate excessive glucagon secretion in CFTR mutant Fdel508 mice. Involvement of the incretin axis could also be partially responsible for increased glucagon levels. Finally, insulin resistance is exacerbated by episodic systemic infections and/or corticosteroid therapy [15].

4. Predictive and risk factors

IFG and IGT, as reported by Schmid et al. [10], are independent predictive factors for diabetes in CF patients. Clearly, patients with both IFG and IGT have the highest propensity for diabetes. Patients with INDET are also at higher risk. IGT and INDET combined show a higher possibility of developing diabetes than IGT only or INDET alone [22]. Finally, it has been shown that patients presenting BGL below 140 mg/dl (8 mmol/L) every 30 min during a OGTT have no risk to develop diabetes over a 15 years period [23]. The main studies exploring AGT as predictive factor for CFRD are presented in Table 2. Piona et al. [24] show that insulin parameters (secretion, clearance and sensitivity) are significantly different across all glucose tolerance stages. The results indicate that AGT140 could represent a distinctive stage of glucose tolerance. Therefore, it could be useful to reassess glucometabolic decline grades across glucose tolerance stages in CF. Recently, Hb1Ac >6 % was associated with a higher risk of CFRD and lower weight gain [25].

Adler et al. [26] show that CFTR genetic class is an important determinant of diabetes outcome. Patients with CFTR mutations from classes 1 and 2 are more at risk of diabetes. Within the CFTR Fdel508 mutation (class 1), homozygous patients are not more at risk than heterozygous ones [27]. Several independent risk factors are also identified: advanced age, corticoid use, decreasing FEV_1 (predicted%), undernutrition, liver and exocrine pancreatic dysfunction [26]. Furthermore, family history of T2D, night eating and organ transplantation were also linked to CFRD [28].

5. Screening tools for diabetes

Screening for CFRD requires an annual 2 h 75 g OGTT from the age of 10 [12]. In the absence of another criteria (polyuria-polydipsia, HbA1c ≥ 6.5 %), OGTT must be repeated once after a first positive test before confirming the diagnosis. CFRD diagnosed by OGTT correlates with lung function decline over the next four years, the risk of microvascular complications and premature death [29]. However, OGTT-based diagnostics present three main issues. First, OGTT results are imperfect as they present high variability over time. Second, perfect application of the test is not certain as the ingestion of 75 g of glucose is difficult for some patients. Finally, glycaemic thresholds were initially defined to prevent microvascular complications on T2D patients. As a result, they are not tailored to the specific health issues of CFRD patients, which are mainly nutritional and pulmonary status [30].

HbA1c is deemed as an unreliable biomarker for the diagnosis of CFRD [11] because it underestimates glycaemia in patients with CF (due to their increased renewing of red blood cells caused by chronic

Table 2
AGT as predictive factor for CFRD in literature.

Author	Study design	Baseline characteristics: Age, BMI, FEV_1	Risk of diabetes: NGT vs INDET and/or AGT	Conclusion in article
Ode et al., 2010 [14]	Retrospective match paired cohort study, 94 patients, NGT vs AGT, 5y FU	No statistical difference between groups	3 vs 42 % *p=0.0009* OR 11	AGT (IGT or INDET) predicts CFRD
Schmid et al., 2014 [10]	Longitudinal prospective study, 1093 patients, NGT vs IGT vs IFG vs INDET	No statistical difference between groups; no information about FEV_1	Subanalysis of 993 patients, NGT vs IGT[a], 3.6±2y FU: 10.4 vs 20 % *p < 0.001* *OR 2.37* [1.48–3.79]	IGT predicts CFRD
			Subanalysis of 385 patients, NGT vs INDET[a], 3.7 ±2y FU:7.1 vs 17.2 % *p=0.002* OR 2.81 [1.43–5.51]	INDET predicts CFRD
Sheikh et al., 2015 [72]	Retrospective cohort study, 80 patients, NGT vs AGT160, 5y FU	NA	Rates NA: risk of diabetes greater with AGT160 present at baseline, *p=0.04*OR 4.5 [1.7, 18.7]	AGT160 predicts CFRD
Nyirjesy et al., 2018 [73]	Cross sectional study of β-cell secretory capacity, 42 patients, NGT vs AGT155 vs IGT	No statistical differences between groups	–	AGT155 shows impaired β-cell secretory capacity with reduced early-phase insulin secretion
Piona et al., 2021 [24]	Cross sectional study, characterisation of different glucose tolerance stages through β-cell function, insulin sensitivity and clearance, 232 patients	No statistical differences between groups; no information about FEV_1	–	AGP140 is a distinct glucose tolerance stage since patients with AGT140 present a different pattern of glucose regulation determinants
Potter et al., 2021 [22]	Prospective observational study, INDET + IGT vs NGT	No statistical differences between groups	MCFC cohort: 198 patients,6.9 ± 3.8y FU; 17 vs 42 % *p=0.0109*	IGT + INDET predict CFRD
			DIAMUCO cohort: 105 patients,2.4 ± 1.2y FU; 17 vs 56 % *p=0.0105*	IGT + INDET predict CFRD

Results are expressed as mean ± SD and rates; p: statistical signification.
Abbreviations: AGT, abnormal glucose tolerance; BMI, body mass index; CFRD, cystic fibrosis-related diabetes; CI, confidence interval; FEV_1, first second of forced expiration in 1 s; FU, follow-up; INDET, indeterminate glycaemia; NA, not available; NGT, normal glucose tolerance; NS, not significative; OR, odds ratio; SD, standard deviation; vs, versus; y, year.
[a] Adjusted for age, BMI SD, gender, and time interval between first and last OGTT.

inflammation). This leads to poor sensitivity and specificity of the usual tests. To solve this issue, alternative HbA1c limits are being considered (see Table 3). Based on a retrospective study of 320 patients, Gilmour et al. [31] suggest <5.5 % as threshold to exclude CFRD diagnosis, with a sensitivity of 91.8 %. Since the specificity of this limit is poor, the authors wish to use HbA1c as a pre-screening test to reduce the need of performing an OGTT. At this lower level of 5.5 %, HbA1c could be an interesting indicator to rule out CFRD [31,32]. Patients with a HbA1c ≥5.5 % and <6.5 % would undergo an OGTT. At the moment, thresholds and validity of HbA1c for the diagnosis of CFRD are still the subject of intensive debate [33,34].

With regards to fasting BGL measurement, it is not recommended for screening CFRD as fasting hyperglycaemia occurs late in CFRD [12]. Two-thirds of patients with newly diagnosed diabetes do not have fasting hyperglycaemia [1].

More recently, the use of continuous glucose monitoring (CGM) offers hope in diagnosing diabetes in its early stages as it allows for detection of hyperglycaemia excursions even for patients with normal OGTT [35]. The intermittent post-prandial hyperglycaemia >200 mg/dl threshold has even been proven reliable by several studies [36]. Scully et al. [37] highlighted the relevance of the percentage of time exceeding a certain threshold by demonstrating that a BGL >140 mg/dl for more than 17.5 % of time or >180 mg/dl for more than 3.4 % of time are efficient in detecting CFRD. High CGM values are also correlated with HbA1c levels and with poor nutritional and pulmonary status. Thus, several CGM diagnostic criteria are under study (the % of time spent >140 mg/dl, the area under the curve >140 mg/dl, and the number of hyperglycemic excursions >200 mg/dl), especially as they correlate with clinical decline [36–38].

Finally, a few studies reported that the Homeostasis Model Assessment (HOMA) could be a valuable screening tool since a HOMA-B value > 100 % shows good sensitivity and good negative predictive value to exclude diagnosis of CFRD [39,40]. However, more data are required to validate HOMA as a diagnosis tool for CFRD. More specifically, there has yet to be a study that links HOMA levels to declining nutritional status and lung function.

As a conclusion, despite its limits, OGTT remains the gold standard. Alternative screening tools are considered but are not expected to replace OGTT in the short run. They might rather be used as pre-screening tools, reducing the need for OGTT [31]. This review presents an alternative algorithm for the screening of CFRD (see Fig. 2), useful to limit the need of OGTT (especially in situations where the test cannot be performed).

6. Complications and prognosis

6.1. *Lung function*

Pulmonary status is the main and most important life-threatening endpoint in CF patients. It has been postulated that hyperglycaemia participates in the process of chronic inflammation with a bad influence on the occurrence of pulmonary infections and an accelerated decline of pulmonary function [1]. Compared to CF patients without diabetes, CFRD subjects have worse lung function [1,41] and are more at risk for decline (FEV_1<40 %) as well as for *Pseudomonas aeruginosa* colonization [7]. As already mentioned, early impairment in insulin secretion and glucose intolerance are associated with lung function decline, increased hospitalization rate for lung complications, weight loss, lower survival and higher rates of lung transplantation [41]. Some studies show a

Table 3
HbA1c as biomarker for diagnosis of CFRD.

Author	Study design[a]	Threshold of HbA1c (%)	Sensitivity (%)	Specificity (%)	Conclusion in article
Burgess et al., 2016 [34]	Retrospective, 429 adult patients	5.8	93.8	53	reduction in OGTT requirement by 51 %
Boudreau et al., 2016 [74]	Retrospective, 207 adult patients	5.8	68.2	60.5	31.8 % of unidentified CFRD patients: HbA1c is not a suitable screening test
		5.5	95.5	31.4	4.5 % of unidentified CFRD and low OGTT saving rate (absolute number NA)
Gilmour et al., 2019 [31]	Retrospective, 295 adult patients	5.5	91.8	34.1	reduction in OGTT requirement by 36.7 %
Boudreau et al., 2019 [32]	Retrospective, 345 adult patients	5.5	90.9	29.7	reduction in OGTT requirement by 23.5 %
Racine et al., 2021 [33]	Retrospective, 256 children	5.8	90.9	60.7	reduction in OGTT requirement by 56 %

Abbreviations: Hb1Ac, glycated hemoglobin; NA, non-available; OGTT, oral glucose tolerance test.
[a] All studies listed compared HbA1c to OGTT (using WHO diabetes criteria as gold standard) for the diagnosis of CFRD.

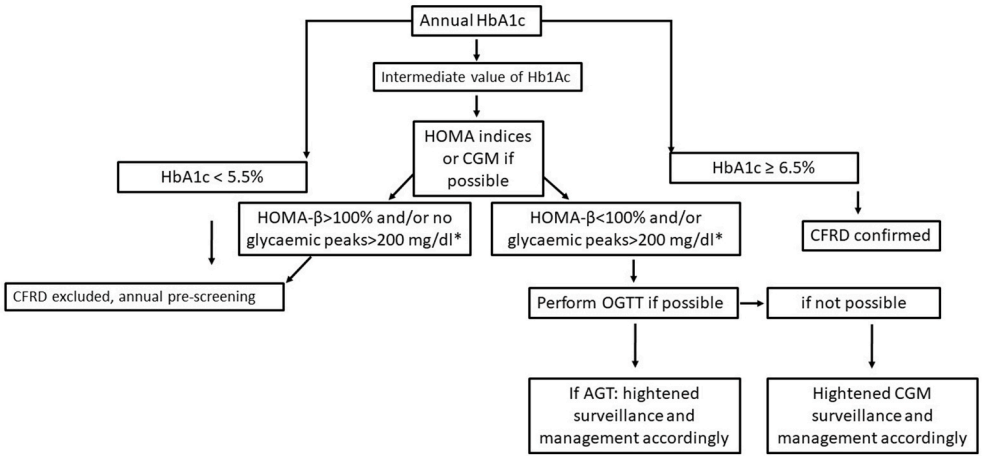

Fig. 2. Screening strategy model
Fig. 2. HbA1c should be checked annually. If the level is less than 5.5 % it is reasonable to exclude diabetes. If the level is equal or superior to 6.5 % the diagnosis of CFRD should be retained. In case of an intermediate value, it might be appropriate to perform a CGM or a HOMA test before prescribing an OGTT. *Other criteria as mean glucose level, % of time spent >140 mg/dl, AUC >140 mg/dl suffer from a lack of robustness and consensus in the diagnosis of CFRD
Abbreviations: AGT, abnormal glucose tolerance; AUC, air under the curve; CGM, continuous glucose monitoring; HbA1c, glycated hemoglobin; HOMA, Homeostasis Model Assessment; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test.

negative association between the 60-min OGTT BGL above 200 mg/dl and pulmonary function. 60-min OGTT insulin levels below 301.4 pmol/L are associated with lower pulmonary function [42]. Hameed et al. demonstrate that CGM levels above 140 mg/dl more than 4.5 % of time and peak BGL during OGTT above 148 mg/dl are linked with loss of weight and declining lung function in the preceding 12 months [43].

Data highlight the relation between high CGM values and upcoming altered lung function [37,43]. A French group explored CGM profiles in 38 patients aged 10 years or more with normal OGTT. They show occasional plasma glucose peaks above 200 mg/dl among some of these subjects. This condition is associated with a poorer lung function (FEV_1 68.2 % vs 87.3 %; *p=0.01*) and a higher rate of *Pseudomonas aeruginosa* colonization. Nutritional status is not different [35]. They conclude that CGM detects early abnormalities of glucose homeostasis.

6.2. Nutritional status

CFRD patients are more at risk for weight loss than CF patients without diabetes [7,41,44]. Insulin deprivation results in a protein catabolism and malnutrition leading to low body weight which is markedly associated with mortality [44]. It has been shown that 60-min OGTT insulin values during OGTT are positively associated with BMI [42].

6.3. Classical diabetes related complications

CFRD patients do not encounter the classical macrovascular complications described in T2D because they do not present classical cardiovascular risk factors to date [12,15]. Nonetheless, numerous recent publications report the onset of cardiovascular risk factors subsequent to the introduction of CFTR modulator therapies [12,45]. While scholars believed that CFRD provoked fewer microvascular complications than other diabetes, it has since been shown that, controlling for diabetes duration, the prevalence is similar. This was probably due to an under-representation of patients with longstanding CFRD. Microvascular complications are now more common as a result of prolonged life expectancy of patients with CF. In fact, numerous studies highlight a correlation between retinopathy and duration of CFRD [46,47]. Table 4 provides a summary of the research conducted in this field. As an example, a cross-sectional study including 401 CFRD patients, 32,409 T1D patients and 185,626 T2D patients adjusted for age, gender and diabetes duration, shows no difference in microvascular complications [48].

6.4. Hypoglycaemia

Hypoglycaemia is as common in CFRD as in every other type of

Table 4
Microvascular complications in CFRD.

Author	Study design	DR	microalbuminuria	Neuropathy	Nephropathy	Conclusion in article
Yung et al., 1998 [46]	32 patients with CFRD	DD = 5-10y: 16 % DD > 10y: 23 %	–	–	–	Despite previous reports, high prevalence of DR in patients with CFRD especially those with a DD > 10y
Andersen et al., 2006 [71]	Transversal observational study, 38 insulin-treated patients with CFRD (DD = 12y (0-31)) vs 38 T1D (DD = 9y (0-41))	27 vs 49 %	13 % vs 28 %[a]	NA	0 vs 0 %[b]	Significant prevalence of retinopathy among insulin-treated CFRD patients approaching the prevalence in T1D (adjusted for DD)
Schwarzenberg et al., 2007 [75]	Retrospective study, 775 patients with CFRD, DD > 10y	16 %	14 %	NA	NA	Microvascular complications are less frequent than in other forms of diabetes mellitus
Van den Berg et al., 2008 [76]	Match paired study, 79 patients with CFRD vs 79 patients with T1D	10 vs 24 % *p=0.044*	21 vs 4.1 % *p=0.003*[c]	2.9 vs *4.3 %* *p=0.640*	1.6 vs *1.6 %* *p=0.900*[d]	Prevalence of microvascular complications is similar in CFRD and T1D patients (adjusted for age)
Konrad et al., 2013 [48]	Transversal observational study, 401 patients with CFRD vs large cohort of patients with T1D and T2D	10.7 vs 10.4 vs 10.5 %; NS	NA	NA	25.2 vs 17.2 vs 24.7 % (T1D/T2D, *p < 0.01)*	No significant differences in microvascular damage compared with T1D and T2D (adjusted for age, sex, and DD)
Roberts et al., 2015 [47]	Prospective 43 insulin-treated patients with CFRD	42 %	–	–	–	Mean HbA1c, DD and duration on insulin were correlated with DR
Kempgowda et al., 2020 [77]	Retrospective cohort study, 189 patients with CFRD, 27-39y, DD = 9y	17.2 %	22.7 %	NA	7.2 %	Patients with CFRD are at risk of microvascular disease

Results are expressed as median (ranges) and rates; p: statistical signification.
Abbreviations: AGT, abnormal glucose tolerance; BMI, body mass index; CFRD, cystic fibrosis-related diabetes; CI, confidence interval; DD, duration of diabetes; DR, diabetic retinopathy; FEV_1, first second of forced; FU, follow-up; , INDET, indeterminate glycaemia; NA, not available; NGT, normal glucose tolerance; NS, not significative; OR, odds ratio; T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus; y, year.
[a] Microalbuminuria defined as ACR category 2 (30–300 mg/24 h).
[b] Nephropathy defined as ACR category 3 (>300 mg/24h).
[c] Microalbuminuria defined as ACR category 1 (<30 mg/g).
[d] Nephropathy defined as ACR categories 2 and 3 (>30 mg/g).

treated diabetes. It is however important to notice that hypoglycaemia can also occur in CF patients (without diabetes) during postprandial as well as fasting periods. This could be due to impaired glucagon secretion concurrently with a delayed insulin response [12].

6.5. Mortality

CFRD is associated with mortality which results from chronic lung disease and gastrointestinal complication such as cirrhosis and malnutrition. Mortality was higher among patient with CFRD in comparison to other CF patients [28]. In the nineties, there was an excess of female mortality around the age of 35 years old [1]. When comparing the time periods of 1992–1997 and 2003–2008, it was found that the mortality rate for females with diabetes in CF patients decreased by more than 50 %, from 6.9 to 3.2 deaths per 100 patient-years. Similarly, male mortality also decreased from 6.5 to 3.8 deaths per 100 patient-years [1]. There is no difference anymore in mortality according to gender [1], and difference in global mortality has been considerably reduced, again probably because of early screening and aggressive treatment.

7. Treatment and perspectives

Treatment aims to optimize glucose control (without provoking hypoglycaemias) to avoid long-term microvascular, pneumological and nutritional complications. Management in CFRD rests on a therapeutic tripod: nutritional adaptations, physical activity and insulin or other oral glycaemic lowering agents. The impact of CFTR channel modulators on glycaemic balance is also discussed. Treatment must be tailored to each individual and well balanced to avoid adding an extra burden to these patients.

7.1. Nutritional approach and physical exercise

Moran et al. [2] delivered several nutritional recommendations. Caloric and protein intake must respectively reach 1,2–1,5 and 1.5–2 times the daily recommended intake, and salt consumption must be increased. Dietary management in CFRD doesn't require carbohydrate restriction [12]. The main goal of these supportive measures is to avoid weight loss.

Moran et al. recommend 150 min of moderate aerobic activity one to three times a week. Resistance exercise training is encouraged since it has shown small but good results in insulin secretion.

7.2. Insulin and oral agents

At diagnosis, CFRD is commonly characterized by postprandial hyperglycaemia without fasting hyperglycaemia [2]. Postprandial glycaemia rapidly rises, and food intakes are often very variable across the day. This imposes the use of pre-prandial treatments like rapid acting premeal insulin therapy or hypoglycaemic agents. Insulin therapy is the recommended treatment [12,44]. It has been shown that premeal insulin therapy was effective and induced positive effects on nutritional and pulmonary status [1]. Indeed, several studies confirm that the use of insulin is effective in glycaemic control, slows down lung function deterioration, even improves FEV_1, diminishes pulmonary exacerbations and has a positive impact on BMI [12]. Long-acting insulin has also proven to be effective and can also be used in the absence of fasting hyperglycaemia with positive outcome in weight gain and lung function.

There is little data on the effectiveness of repaglinide compared to placebo and only a few studies compare insulin with oral agents [12]. Moran et al. [44] show in the Cystic Fibrosis-related Diabetes Therapy Trial (a 2009 randomized controlled trial, RCT), that insulin therapy with multiple premeal injections enhances fat intake and reduces weight loss compared to repaglinide and placebo in patients with IGT or CFRD without fasting hyperglycaemia. There is no significant difference regarding glucose control or lung function. Considering hypoglycaemias, repaglinide shows significantly more events than insulin therapy ($p < 0.04$). However, in another RCT, Ballman et al. [49] find

no difference regarding HbA1c, BMI and FEV_1 after 2 years of either multiple injections of insulin or repaglinide.

Efficiency of sitagliptin (DPP4 inhibitor) has been studied in 26 patients with AGT or diabetes in a RCT. After 6 months treatment, despite an improvement in meal-related GLP 1, and GIP concentrations and in early insulin response, no change in postprandial BGL and BMI were noticed [50]. GLP1 receptor agonists are not serious candidates in CFRD because of their considerable impact on weight.

Metformin does not present a convincing alternative. Risk of weight loss and gastrointestinal side effects remain a concern [12].

The advent of new insulin analogues, CGM, continuous subcutaneous infusion of insulin, closed loop systems etc., is expected to improve the management of diabetes.

CGM abnormalities occur in every CF patient whatever the OGTT values. Frost et al. show that CGM-guided insulin therapy in patients with CF and prediabetes improve FEV_1 and BMI at 3 months, reduce the use of intravenous antibiotic and slow the lung function decline at 12 months [51]. Other authors present better lung function and global health status when initiating insulin therapy during prediabetes period but no conclusive data exist [12]. Since more and more evidence shows that prediabetic status contributes to lung function decline and BMI loss, an upcoming recommended practice could be to start treating patients with AGT or with abnormal CGM levels before the onset of diabetes.

As a conclusion, insulin is currently the preferred treatment. Repaglinide could be a therapeutic alternative if the emphasis is on reducing treatment in burdensome situations or if the anabolic effect of insulin is not the priority [1].

7.3. CFTR modulator therapies

Cystic fibrosis transmembrane conductance regulator modulators are a new class of treatment used since 2012 to correct the basic defect in CF. Two types of modulators are currently considered, alone or in combination. They are small molecules, classified either as a potentiator that opens the channel (ivacaftor), or as a corrector that leads the channel to the cell membrane (lumacaftor, tezacaftor, or elexacaftor). The choice of modulator type (or combination) depends on the mutations.

Numerous clinical studies show that modulator therapies are both safe and effective to enhance lung function, reduce respiratory infection rates, improve weight gain and gastrointestinal issues, with benefits observed in the short-term and up to two years of follow-up [15]. Ivacaftor (IVA) alone, the first CFTR channel potentiator approved in 2012, and, later, a triple combination of IVA with two correctors of the CFTR channel, tezacaftor and elexacaftor (TEZA and ELE), approved in 2019 by the FDA, are considered as highly-effective CFTR modulator therapy (HEMT) [12]. The effectiveness of HEMT was set to a high standard by the significant enhancements seen in CFTR function (measured by a decrease in sweat chloride concentration) and pulmonary function (measured by an increase in FEV_1) resulting from IVA and later from triple therapy.

Improved lung function combined with lower inflammation could start a virtuous circle towards more physical activity, endurance, and muscle formation [52]. This could ultimately improve insulin sensitivity and result in better diabetes control and reduced insulin requirements. Reduced pancreatic inflammation might also improve insulin secretion.

Table 5 presents data concerning modulators in CFRD. The potential impact of CFTR modulator therapies on glucose balance depends on the CF causing mutation, and thus, the type of CFTR modulator and their possible association. Small pilot studies from a few years ago pointed out the improvement of glycaemic control with IVA [53,54]. In addition, the analyses of the US and the UK CF registries show favorable trends in glycaemic control in CFRD with IVA versus comparators, and even with lower prevalence of CFRD with time. This suggests that this treatment may slow down glycaemic unbalance [55]. However, these observations are limited to patients with the G551D mutation or another gating

Table 5
Effect on glucose metabolism of CFTR modulators.

Author	Study design	Mutation	Type of modulator	Outcomes
Bellin et al., 2013 [53]	Open label pilot study, 5 patients, 1 m FU	?/G551D	IVA	Improvement of OGTT (4/5)
Dagan et al., 2017 [54]	8 patients, 1y FU	?/S549R	IVA	Improvement of OGTT (5/8)
Thomassen et al., 2018 [58]	5 patients, 6-8w FU	Fdel508/ Fdel508	LUMA/IVA	Improvement of OGTT (3/5) and worsening of OGTT (2/5)
Li et al., 2018 [59]	9 patients, 29w FU	NA	LUMA/IVA	Worsening of HbA1c and no differences in OGTT CGM
Kelly et al., 2019 [78]	12 patients, NGT and AGT, 4 m FU	At least one gating mutation	IVA	Normalizing of glucose tolerance in one patient. Improvement in glucagon suppression and insulin secretion.
Volkova et al., 2020 [55]	Observational longitudinal study, USA register: 2509 patients. UK register: 2480 patients. Treated vs untreated. 5y FU	At least one gating mutation	IVA	Favorable trends in CFRD prevalence
Moheet et al., 2020 [79]	39 patients, 1y FU	Fdel508/ Fdel508	LUMA/IVA	No change in OGTT results during FU
Misgault et al., 2020 [57]	40 patients with AGT, 1y FU	Fdel50/ Fdel508	LUMA/IVA	Improvement of OGTT ($p < 0.0001$)
Colombo et al., 2021 [56]	Retrospective case control study, 13 patients without diabetes, 1y FU	Fdel508/ Fdel508	LUMA/IVA	No changes in OGTT, insulin secretion and sensitivity*
Gaines et al., 2021 [80]	Retrospective, 14 patients, only abstract available	NA	IVA or LUMA/IVA	One third of the patients get rid of insulin or almost.
Scully et al., 2022 [60]	Prospective observational study, 34 patients, with and without diabetes, 3–12 m FU	At least one Fdel508 mutation	ELE/ TEZA/IVA	Improvement of CGM data with treatment, time in target range increased
Piona et al., 2022 [61]	Prospective, 21 non-diabetic patients, 12–18 m FU	At least one Fdel508 mutation	LUMA/IVA or ELE/ TEZA/IVA	No improvement in insulin secretion and sensitivity*
Crow et al., 2022 [81]	Retrospective single center study, 11 CFRD patients, 6 m FU	At least one Fdel508 mutation	ELE/ TEZA/IVA	No improvement in CGM data and insulin requirements
Korten et al., 2022 [82]	Prospective, 12 patients, different glucose tolerance stages	At least one Fdel508 mutation	ELE/ TEZA/IVA	Improvement of OGTT ($p < 0.05$)
Chan et al., 2022 [63]	Prospective, 22 patients, different glucose tolerance stages	At least one Fdel508 mutation	ELE/ TEZA/IVA	No improvement of OGTT. Improving trends in CGM data. Improvement in insulin secretion but worsening in sensitivity*. Improvement in HbA1c.

(continued on next page)

Table 5 (*continued*)

Author	Study design	Mutation	Type of modulator	Outcomes
Granados et al., 2023 [64]	NA	NA	NA	Improvement in insulin secretion but worsening in sensitivity*
Steinack et al., 2023 [62]	Single center observational study, 33 patients, different glucose tolerance stages	At least one Fdel508 mutation	ELE/ TEZA/IVA	Improvement of OGTT and HbA1c. No improvement in insulin sensitivity, nor secretion*
Lurquin et al., 2023 [65]	Single center retrospective study, 15 patients with CFRD 17 patients without CFRD	At least one Fdel508 mutation	ELE/ TEZA/IVA or TEZA/ VA	Reduction in daily insulin dose. No improvement in insulin sensitivity, nor secretion* in patients without diabetes

p: statistical signification.
Abbreviations: AGT, abnormal glucose tolerance; CFRD, cystic fibrosis-related diabetes; CGM, continuous glucose monitoring ELE, elexacaftor; FU, follow-up; HbA1c, glycated hemoglobine; IVA, ivacaftor; LUMA, lumacaftor; m, month; NA, not available; OGTT, oral glucose tolerance test; TEZA, tezacaftor; UP, untreated patients; vs, versus; w, week; y, year. *Determined by a mathematical modeling.

mutation, which represents only 4–5 % of all CF cases [56] and the comparison group had more severe CFTR genotypes, thus more risk for CFRD [12].

Ivacaftor combined with lumacaftor (LUMA), a CFTR channel corrector, is the first dual therapy approved in the USA and in Europe in 2015. It includes more patients as it is approved for Fdel508 homozygous patients (the most frequent mutation). The observations seen with IVA are not confirmed in these patients. Only one study on 40 patients with CF highlights a better glucose tolerance after 1 year treatment with LUMA/IVA [57]. Inversely, a similarly designed study using OGTT shows no significant difference of glucose metabolism between non-diabetic CF patients treated with LUMA/IVA and others without [56]. Other small studies show no impact on diabetes control after initiation of LUMA/IVA [58,59].

More recently, a combination of IVA/TEZA has been commercialized and approved in Europe in 2018 for Fdel508 homozygous patients and later to some heterozygous Fdel508 mutation but no study has explored the impact of this dual therapy on glycaemic homeostasis.

IVA/TEZA/ELE has been approved in Europe in 2020 for patients with at least one copy of Fdel508 mutation and encouraging observations regarding glucose homeostasis have been noticed. Scully et al. [60] provides convincing data on glycaemic improvement with this triple combination in CFRD patients and also in CF patients.

HEMT seem to reduce insulin requirements, improve diabetes control, glucose tolerance during OGTT and general glucose homeostasis but the mechanism is not completely understood since glucose homeostasis determinants as insulin sensitivity and B-cell function do not change in patients without diabetes [56,61,62]. To date, it appears that 6 studies have employed mathematical modeling to examine the impact of CFTR channel modulators on glucose homeostasis. They opt for a comprehensive approach by simultaneously assessing B-cell function and insulin sensitivity through OGTT data. Their results show heterogeneous changes of glucose homeostasis determinants after CFTR modulator therapy in CF patients [56,61–65]. This could be due to small sample size, heterogeneity in the CFTR modulator type included and study design, and/or different on-treatment times in the above studies. Nevertheless, the positive effect of CFTR modulator therapies on glucose homeostasis in CFRD patients is more than likely and this positive effect is possibly due to an improvement in insulin sensitivity. However, more studies on a larger scale and with a longer follow up must be conducted.

8. Future directions

There is growing interest in CFRD, particularly in light of its escalating prevalence. Diabetologists are expected to encounter this form of diabetes with greater frequency in the future. Numerous initiatives are presently underway to address CFRD, and many more are still expected.

One of the main concerns is the screening and corresponding diagnostic tools. There is a pressing need for alternative diagnostic methods that are both reliable and less encumbering. Leveraging CGM data, investigating HOMA indices, and validating them on a larger scale through prospective studies are giving a new momentum to the diagnostic strategy. These methods, whether used individually, in combination, or through a sequential approach, hold the potential to diminish dependency on OGTT, as previously demonstrated with HbA1c. In the meantime, it remains crucial to continue to advocate for systematic screening for CFRD through OGTT, starting at the age of 10.

The extension of life expectancy for patients with CF and particularly those with CFRD, introduces a second set of challenges, no less significant than the first. Anticipated outcomes include an escalation in both microvascular and macrovascular complications due to prolonged exposure to hyperglycaemia, coupled with the emergence of classical cardiovascular risk factors such as arterial hypertension, dyslipidaemia, and obesity, within the population with CF since the introduction of CFTR modulator therapies. As a result, the proactive pursuit of microvascular and macrovascular complications must be integrated into the routine clinical practice of healthcare providers. However, the frequency of these screenings and the therapeutic targets for clinical and biological parameters remain uncertain.

Lastly, the advent of CFTR channel modulators has introduced an element of uncertainty into our understanding of CFRD pathophysiology. The precise mechanism by which HEMT impacts glycaemic homeostasis remains enigmatic. An analysis of the kinetics of residual β-cell function loss in the absence of modulator therapy, juxtaposed with prospective data collected under modulator usage, might shed light on whether or not there is a deceleration in β-cell function decline.

9. Conclusion

CFRD management is a work in progress and remains a significant health concern. A better understanding of pathophysiology is contributing to a more tailored approach to diabetes in CF. The possible impact of modulators on glucose balance challenges the direct role of CFTR channel in B-cells, which remains a controversial issue. While lung function, nutritional status, and life span of CFRD patients is known to be worse than CF patients without diabetes, these differences tend to diminish due to better care. The rising prevalence of diabetes, attributed to increased life expectancy, has led to a corresponding surge in exposure to chronic hyperglycaemia, resulting in a higher incidence of microvascular complications. Simultaneously, conventional cardiovascular risk factors are increasing. Screening tools are improving, but further studies are needed to establish evidence-based diagnostic cut-offs. HbA1c could eventually be useful in combination with CGM or HOMA indices for decreasing the use of OGTT. CGM technology clearly showed its capacity to detect patients at risk for clinical deterioration at an early stage and prevent the occurrence of complications, but its use for diagnosis is not validated at the moment. Recent data concerning CFTR modulator therapies on glucose control are encouraging. Optimized glucose control may be due to a possible physical capacity recovery with better insulin sensitivity. CF-specific recommendations and aggressive treatment implemented in the last 20 years explain the improvement in the management of CFRD. Future research is essential for a better understanding and optimal care of these patients.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Moran A, Dunitz J, Nathan B, Saeed A, Holme B, Thomas W. Cystic fibrosis-related diabetes: current trends in prevalence, incidence, and mortality. Diabetes Care 2009;32(9):1626–31. https://doi.org/10.2337/dc09-0586.
[2] Moran A, Becker D, Casella SJ, et al. Epidemiology, pathophysiology, and prognostic implications of cystic fibrosis-related diabetes: a technical review. Diabetes Care 2010;33(12):2677–83. https://doi.org/10.2337/dc10-1279.
[3] Cystic Fibrosis Foundation Patient Registry. Annual data report bethesda, Maryland ©2022 cystic fibrosis foundationle. 2021.
[4] Guo J, Garratt A, Hill A. Worldwide rates of diagnosis and effective treatment for cystic fibrosis. J Cyst Fibros 2022;21(3):456–62. https://doi.org/10.1016/j.jcf.2022.01.009.
[5] Marson FAL, Bertuzzo CS, Ribeiro JD. Classification of CFTR mutation classes. Lancet Respir Med 2016;4(8):e37–8. https://doi.org/10.1016/S2213-2600(16)30188-6.
[6] Lopes-Pacheco M. CFTR modulators: the changing face of cystic fibrosis in the era of precision medicine. Front Pharmacol 2019;10:1662. https://doi.org/10.3389/fphar.2019.01662.
[7] Olesen HV, Drevinek P, Gulmans VA, et al. Cystic fibrosis related diabetes in Europe: prevalence, risk factors and outcome; Olesen et al. J Cyst Fibros 2020;19(2):321–7. https://doi.org/10.1016/j.jcf.2019.10.009.
[8] Frohnert BI, Ode KL, Moran A, et al. Impaired fasting glucose in cystic fibrosis. Diabetes Care 2010;33(12):2660–4. https://doi.org/10.2337/dc10-0613.
[9] Elder DA, Wooldridge JL, Dolan LM, D'Alessio DA. Glucose tolerance, insulin secretion, and insulin sensitivity in children and adolescents with cystic fibrosis and No prior history of diabetes. J Pediatr 2007;151(6):653–8. https://doi.org/10.1016/j.jpeds.2007.05.012.
[10] Schmid K, Fink K, Holl RW, Hebestreit H, Ballmann M. Predictors for future cystic fibrosis-related diabetes by oral glucose tolerance test. J Cyst Fibros 2014;13(1):80–5. https://doi.org/10.1016/j.jcf.2013.06.001.
[11] ElSayed NA, Aleppo G, Aroda VR, et al. 2. Classification and diagnosis of diabetes: standards of care in diabetes—2023. Diabetes Care 2023;46(Supplement_1):S19–40. https://doi.org/10.2337/dc23-S002.
[12] Ode KL, Ballman M, Battezzati A, et al. <scp>ISPAD</scp> Clinical Practice Consensus Guidelines 2022: management of cystic fibrosis-related diabetes in children and adolescents. Pediatr Diabetes 2022;23(8):1212–28. https://doi.org/10.1111/pedi.13453.
[13] Yi Y, Norris AW, Wang K, et al. Abnormal glucose tolerance in infants and young children with cystic fibrosis. Am J Respir Crit Care Med 2016;194(8):974–80. https://doi.org/10.1164/rccm.201512-2518OC.
[14] Ode KL, Frohnert B, Laguna T, et al. Oral glucose tolerance testing in children with cystic fibrosis. Pediatr Diabetes 2010;11(7):487–92. https://doi.org/10.1111/j.1399-5448.2009.00632.x.
[15] Moheet A, Moran A. New concepts in the pathogenesis of cystic fibrosis–related diabetes. J Clin Endocrinol Metab 2022;107(6):1503–9. https://doi.org/10.1210/clinem/dgac020.
[16] Hart NJ, Aramandla R, Poffenberger G, et al. Cystic fibrosis-related diabetes is caused by islet loss and inflammation. JCI insight 2018;3(8). https://doi.org/10.1172/jci.insight.98240.
[17] Hull RL, Gibson RL, McNamara S, et al. Islet interleukin-1β immunoreactivity is an early feature of cystic fibrosis that may contribute to β-cell failure. Diabetes Care 2018;41(4):823–30. https://doi.org/10.2337/dc17-1387.
[18] Frost F, Jones GH, Dyce P, Jackson V, Nazareth D, Walshaw MJ. Loss of incretin effect contributes to postprandial hyperglycaemia in cystic fibrosis-related diabetes. Diabet Med 2019;36(11):1367–74. https://doi.org/10.1111/dme.14121.
[19] Hardin DS, Ahn C, Rice J, Rice M, Rosenblatt R. Elevated gluconeogenesis and lack of suppression by insulin contribute to cystic fibrosis-related diabetes. J Invest Med 2008;56(3):567–73. https://doi.org/10.2310/JIM.0b013e3181671788.
[20] Gu J, Zhang W, Wu L, Gu Y. CFTR deficiency affects glucose homeostasis via regulating GLUT4 plasma membrane transportation. Front Cell Dev Biol 2021;9. https://doi.org/10.3389/fcell.2021.630654.
[21] Huang WQ, Guo JH, Zhang XH, et al. Glucose-sensitive CFTR suppresses glucagon secretion by potentiating KATP channels in pancreatic islet α cells. Endocrinology 2017;158(10):3188–99. https://doi.org/10.1210/en.2017-00282.
[22] Potter KJ, Reynaud Q, Boudreau V, et al. Combined indeterminate and impaired glucose tolerance is a novel group at high risk of cystic fibrosis-related diabetes. J Clin Endocrinol Metab 2021;106(10):e3901–10. https://doi.org/10.1210/clinem/dgab384.
[23] Bonhoure A, Potter KJ, Colomba J, et al. Peak glucose during an oral glucose tolerance test is associated with future diabetes risk in adults with cystic fibrosis. Diabetologia 2021;64(6):1332–41. https://doi.org/10.1007/s00125-021-05423-5.
[24] Piona C, Volpi S, Zusi C, et al. Glucose tolerance stages in cystic fibrosis are identified by a unique pattern of defects of beta-cell function. J Clin Endocrinol Metab 2021;106(4):e1793–802. https://doi.org/10.1210/clinem/dgaa932.
[25] Potter KJ, Racine F, Bonhoure A, et al. A glycosylated hemoglobin A1c above 6% (42 mmol/mol) is associated with a high risk of developing Cystic Fibrosis-Related Diabetes and a lower probability of weight gain in both adults and children with Cystic Fibrosis. Diabetes Metab 2023;49(4):101455. https://doi.org/10.1016/j.diabet.2023.101455.
[26] Adler AI, Shine BSF, Chamnan P, Haworth CS, Bilton D. Genetic determinants and epidemiology of cystic fibrosis-related diabetes: results from a British cohort of children and adults. Diabetes Care 2008;31(9):1789–94. https://doi.org/10.2337/dc08-0466.
[27] Preumont V, Hermans MP, Lebecque P, Buysschaert M. Glucose homeostasis and genotype-phenotype interplay in cystic fibrosis patients with CFTR gene ΔF508 mutation. Diabetes Care 2007;30(5):1187–92. https://doi.org/10.2337/dc06-1915.
[28] Granados A, Chan CL, Ode KL, Moheet A, Moran A, Holl R. Cystic fibrosis related diabetes: pathophysiology, screening and diagnosis. J Cyst Fibros 2019;18(Suppl 2):S3–9. https://doi.org/10.1016/j.jcf.2019.08.016.
[29] Moran A, Brunzell C, Cohen RC, et al. Clinical care guidelines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. Diabetes Care 2010;33(12):2697–708. https://doi.org/10.2337/dc10-1768.
[30] Boudreau V, Reynaud Q, Dubois CL, et al. Screening for cystic fibrosis-related diabetes: matching pathophysiology and addressing current challenges. Can J Diabetes 2016;40(5):466–70. https://doi.org/10.1016/j.jcjd.2016.08.221.
[31] Gilmour JA, Sykes J, Etchells E, Tullis E. Cystic fibrosis-related diabetes screening in adults: a gap analysis and evaluation of accuracy of glycated hemoglobin levels. Can J Diabetes 2019;43(1):13–8. https://doi.org/10.1016/j.jcjd.2018.04.008.
[32] Boudreau V, Reynaud Q, Bonhoure A, Durieu I, Rabasa-Lhoret R. Validation of a stepwise approach using glycated hemoglobin levels to reduce the number of required oral glucose tolerance tests to screen for cystic fibrosis–related diabetes in adults. Can J Diabetes 2019;43(3):161–2. https://doi.org/10.1016/j.jcjd.2018.11.005.
[33] Racine F, Shohoudi A, Boudreau V, et al. Glycated hemoglobin as a first-line screening test for cystic fibrosis–related diabetes and impaired glucose tolerance in children with cystic fibrosis: a validation study. Can J Diabetes 2021;45(8):768–74. https://doi.org/10.1016/j.jcjd.2021.03.005.
[34] Burgess JC, Bridges N, Banya W, et al. HbA1c as a screening tool for cystic fibrosis related diabetes. J Cyst Fibros 2016;15(2):251–7. https://doi.org/10.1016/j.jcf.2015.03.013.
[35] Leclercq A, Gauthier B, Rosner V, et al. Early assessment of glucose abnormalities during continuous glucose monitoring associated with lung function impairment in cystic fibrosis patients. J Cyst Fibros 2014;13(4):478–84. https://doi.org/10.1016/j.jcf.2013.11.005.
[36] Weiss L, Reix P, Mosnier-Pudar H, et al. Dépistage des anomalies de la tolérance au glucose et du diabète de mucoviscidose. Position de la Société française de la mucoviscidose (SFM), de la Société francophone du diabète (SFD) et de la Société française d'endocrinologie et diabétologie pédiatriq. Médecine des Mal Métaboliques; 2023. https://doi.org/10.1016/j.mmm.2023.01.001. Published online January.
[37] Scully KJ, Sherwood JS, Martin K, et al. Continuous glucose monitoring and HbA1c in cystic fibrosis: clinical correlations and implications for CFRD diagnosis. J Clin Endocrinol Metab 2022;107(4):e1444–54. https://doi.org/10.1210/clinem/dgab857.
[38] Moreau F, Weiller M, Rosner V, et al. Continuous glucose monitoring in cystic fibrosis patients according to the glucose tolerance. Horm Metab Res 2008;40(7):502–6. https://doi.org/10.1055/s-2008-1062723.
[39] Toin T, Reynaud Q, Denis A, et al. HOMA indices as screening tests for cystic fibrosis-related diabetes. J Cyst Fibros 2022;21(1):123–8. https://doi.org/10.1016/j.jcf.2021.05.010.
[40] Mainguy C, Bellon G, Delaup V, et al. Sensitivity and specificity of different methods for cystic fibrosis-related diabetes screening: is the oral glucose tolerance test still the standard? J Pediatr Endocrinol Metab 2017;30(1):27–35. https://doi.org/10.1515/jpem-2016-0184.
[41] Bismuth E, Laborde K, Taupin P, et al. Glucose tolerance and insulin secretion, morbidity, and death in patients with cystic fibrosis. J Pediatr 2008;152(4):540–5. https://doi.org/10.1016/j.jpeds.2007.09.025. 545.e1.
[42] Coriati A, Ziai S, Lavoie A, Berthiaume Y, Rabasa-Lhoret R. The 1-h oral glucose tolerance test glucose and insulin values are associated with markers of clinical deterioration in cystic fibrosis. Acta Diabetol 2016;53(3):359–66. https://doi.org/10.1007/s00592-015-0791-3.
[43] Hameed S, Morton JR, Jaffé A, et al. Early glucose abnormalities in cystic fibrosis are preceded by poor weight gain. Diabetes Care 2010;33(2):221–6. https://doi.org/10.2337/dc09-1492.

[44] Moran A, Pekow P, Grover P, et al. Insulin therapy to improve BMI in cystic fibrosis-related diabetes without fasting hyperglycemia: results of the cystic fibrosis related diabetes therapy trial. Diabetes Care 2009;32(10):1783–8. https://doi.org/10.2337/dc09-0585.
[45] Petersen MC, Begnel L, Wallendorf M, Litvin M. Effect of elexacaftor-tezacaftor-ivacaftor on body weight and metabolic parameters in adults with cystic fibrosis. J Cyst Fibros 2022;21(2):265–71. https://doi.org/10.1016/j.jcf.2021.11.012.
[46] Yung B, Landers A, Mathalone B, Gyi KM, Hodson ME. Diabetic retinopathy in adult patients with cystic fibrosis-related diabetes. Respir Med 1998;92(6):871–2. https://doi.org/10.1016/s0954-6111(98)90390-0.
[47] Roberts R, Speight L, Lee J, et al. Retinal screening of patients with cystic fibrosis-related diabetes in Wales – a real eye opener. J Cyst Fibros 2015;14(2):282–4. https://doi.org/10.1016/j.jcf.2014.07.014.
[48] Konrad K, Scheuing N, Badenhoop K, et al. Cystic fibrosis-related diabetes compared with type 1 and type 2 diabetes in adults. Diabetes Metab Res Rev 2013;29(7):568–75. https://doi.org/10.1002/dmrr.2429.
[49] Ballmann M, Hubert D, Assael BM, et al. Repaglinide versus insulin for newly diagnosed diabetes in patients with cystic fibrosis: a multicentre, open-label, randomised trial. Lancet Diabetes Endocrinol 2018;6(2):114–21. https://doi.org/10.1016/S2213-8587(17)30400-X.
[50] Kelly A, Sheikh S, Stefanovski D, et al. Effect of sitagliptin on islet function in pancreatic insufficient cystic fibrosis with abnormal glucose tolerance. J Clin Endocrinol Metab 2021;106(9):2617–34. https://doi.org/10.1210/clinem/dgab365.
[51] Frost F, Dyce P, Nazareth D, Malone V, Walshaw MJ. Continuous glucose monitoring guided insulin therapy is associated with improved clinical outcomes in cystic fibrosis-related diabetes. J Cyst Fibros 2018;17(6):798–803. https://doi.org/10.1016/j.jcf.2018.05.005.
[52] Caterini JE, Ratjen F, Barker AR, et al. Exercise intolerance in cystic fibrosis-the role of CFTR modulator therapies. J Cyst Fibros 2022;21(2):282–92. https://doi.org/10.1016/j.jcf.2021.11.011.
[53] Bellin MD, Laguna T, Leschyshyn J, et al. Insulin secretion improves in cystic fibrosis following ivacaftor correction of CFTR: a small pilot study. Pediatr Diabetes 2013;14(6):417–21. https://doi.org/10.1111/pedi.12026.
[54] Dagan A, Cohen-Cymberknoh M, Shteinberg M, et al. Ivacaftor for the p.Ser549Arg (S549R) gating mutation - the Israeli experience. Respir Med 2017;131:225–8. https://doi.org/10.1016/j.rmed.2017.08.026.
[55] Volkova N, Moy K, Evans J, et al. Disease progression in patients with cystic fibrosis treated with ivacaftor: data from national US and UK registries. J Cyst Fibros 2020;19(1):68–79. https://doi.org/10.1016/j.jcf.2019.05.015.
[56] Colombo C, Foppiani A, Bisogno A, et al. Lumacaftor/ivacaftor in cystic fibrosis: effects on glucose metabolism and insulin secretion. J Endocrinol Invest 2021;44(10):2213–8. https://doi.org/10.1007/s40618-021-01525-4.
[57] Misgault B, Chatron E, Reynaud Q, et al. Effect of one-year lumacaftor–ivacaftor treatment on glucose tolerance abnormalities in cystic fibrosis patients. J Cyst Fibros 2020;19(5):712–6. https://doi.org/10.1016/j.jcf.2020.03.002.
[58] Thomassen JC, Mueller MI, Alejandre Alcazar MA, Rietschel E, van Koningsbruggen-Rietschel S. Effect of Lumacaftor/Ivacaftor on glucose metabolism and insulin secretion in Phe508del homozygous cystic fibrosis patients. J Cyst Fibros 2018;17(2):271–5. https://doi.org/10.1016/j.jcf.2017.11.016.
[59] Li A, Vigers T, Pyle L, et al. Continuous glucose monitoring in youth with cystic fibrosis treated with lumacaftor-ivacaftor. J Cyst Fibros 2019;18(1):144–9. https://doi.org/10.1016/j.jcf.2018.07.010.
[60] Scully KJ, Marchetti P, Sawicki GS, et al. The effect of elexacaftor/tezacaftor/ivacaftor (ETI) on glycemia in adults with cystic fibrosis. J Cyst Fibros 2022;21(2):258–63. https://doi.org/10.1016/j.jcf.2021.09.001.
[61] Piona C, Mozzillo E, Tosco A, et al. Impact of CFTR modulators on beta-cell function in children and young adults with cystic fibrosis. J Clin Med 2022;11(14). https://doi.org/10.3390/jcm11144149.
[62] Steinack C, Ernst M, Beuschlein F, et al. Improved glucose tolerance after initiation of Elexacaftor/Tezacaftor/Ivacaftor in adults with cystic fibrosis. J Cyst Fibros 2023. https://doi.org/10.1016/j.jcf.2023.01.004. Published online January 18.
[63] Chan CL, Granados A, Moheet A, et al. Glycemia and β-cell function before and after elexacaftor/tezacaftor/ivacaftor in youth and adults with cystic fibrosis. J Clin Transl Endocrinol 2022;30:100311. https://doi.org/10.1016/j.jcte.2022.100311.
[64] Granados A, Chan CL, Moheet A, Vigers T, Arbeláez AM, Larson Ode K. The impact of elexacaftor/tezacaftor/ivacaftor on body composition in a small cohort of youth with cystic fibrosis. Pediatr Pulmonol 2023. https://doi.org/10.1002/ppul.26388. Published online March 17.
[65] Lurquin F, Gohy S, Hermans MP, Preumont V. Combined CFTR modulator therapies are linked with anabolic benefits and insulin-sparing in cystic fibrosis-related diabetes. J Clin Transl Endocrinol 2023;33:100320. https://doi.org/10.1016/j.jcte.2023.100320.
[66] International Diabetes Federation. IDF diabetes atlas. tenth ed. Brussels, Belgium: International Diabetes Federation; 2021.
[67] ECFSPR annual report 2021, Zolin A, Orenti A, Jung A, van Rens J et al, 2023..
[68] Blackman SM, Hsu S, Ritter SE, et al. A susceptibility gene for type 2 diabetes confers substantial risk for diabetes complicating cystic fibrosis. Diabetologia 2009;52(9):1858–65. https://doi.org/10.1007/s00125-009-1436-2.
[69] Annis AM, Caulder MS, Cook ML, Duquette D. Family history, diabetes, and other demographic and risk factors among participants of the National Health and Nutrition Examination Survey 1999-2002. Prev Chronic Dis 2005;2(2):A19. http://www.ncbi.nlm.nih.gov/pubmed/15888230.
[70] Parkkola A, Härkönen T, Ryhänen SJ, Ilonen J, Knip M, Finnish Pediatric Diabetes Register. Extended family history of type 1 diabetes and phenotype and genotype of newly diagnosed children. Diabetes Care 2013;36(2):348–54. https://doi.org/10.2337/dc12-0445.
[71] Andersen HU, Lanng S, Pressler T, Laugesen CS, Mathiesen ER. Cystic fibrosis-related diabetes: the presence of microvascular diabetes complications. Diabetes Care 2006;29(12):2660–3. https://doi.org/10.2337/dc06-0654.
[72] Sheikh S, Putt ME, Forde KA, Rubenstein RC, Kelly A. Elevation of one hour plasma glucose during oral glucose tolerance testing. Pediatr Pulmonol 2015;50(10):963–9. https://doi.org/10.1002/ppul.23237.
[73] Nyirjesy SC, Sheikh S, Hadjiliadis D, et al. β-Cell secretory defects are present in pancreatic insufficient cystic fibrosis with 1-hour oral glucose tolerance test glucose ≥155 mg/dL. Pediatr Diabetes 2018;19(7):1173–82. https://doi.org/10.1111/pedi.12700.
[74] Boudreau V, Coriati A, Desjardins K, Rabasa-Lhoret R. Glycated hemoglobin cannot yet be proposed as a screening tool for cystic fibrosis related diabetes. J Cyst Fibros 2016;15(2):258–60. https://doi.org/10.1016/j.jcf.2016.02.005.
[75] Schwarzenberg SJ, Thomas W, Olsen TW, et al. Microvascular complications in cystic fibrosis-related diabetes. Diabetes Care 2007;30(5):1056–61. https://doi.org/10.2337/dc06-1576.
[76] van den Berg JMW, Morton AM, Kok SW, Pijl H, Conway SP, Heijerman HGM. Microvascular complications in patients with cystic fibrosis-related diabetes (CFRD). J Cyst Fibros 2008;7(6):515–9. https://doi.org/10.1016/j.jcf.2008.05.008.
[77] Kempegowda P, Sunsoa H, Chandan JS, et al. Retinopathy and microalbuminuria are common microvascular complications in cystic fibrosis-related diabetes. Ther Adv Endocrinol Metab 2020;11:2042018820966428. https://doi.org/10.1177/2042018820966428.
[78] Kelly A, De Leon DD, Sheikh S, et al. Islet hormone and incretin secretion in cystic fibrosis after four months of ivacaftor therapy. Am J Respir Crit Care Med 2019;199(3):342–51. https://doi.org/10.1164/rccm.201806-1018OC.
[79] Moheet A, Beisang D, Zhang L, et al. Lumacaftor/ivacaftor therapy fails to increase insulin secretion in F508del/F508del CF patients. J Cyst Fibros 2021;20(2):333–8. https://doi.org/10.1016/j.jcf.2020.09.001.
[80] Gaines H, Jones KR, Lim J, Medhi NF, Chen S, Scofield RH. Effect of CFTR modulator therapy on cystic fibrosis-related diabetes. J Diabet Complicat 2021;35(6):107845. https://doi.org/10.1016/j.jdiacomp.2020.107845.
[81] Crow H, Bengtson C, Shi X, Graves L, Anabtawi A. CGM patterns in adults with cystic fibrosis-related diabetes before and after elexacaftor-tezacaftor-ivacaftor therapy. J Clin Transl Endocrinol 2022;30:100307. https://doi.org/10.1016/j.jcte.2022.100307.
[82] Korten I, Kieninger E, Krueger L, et al. Short-term effects of elexacaftor/tezacaftor/ivacaftor combination on glucose tolerance in young people with cystic fibrosis-an observational pilot study. Front Pediatr 2022;10:852551. https://doi.org/10.3389/fped.2022.852551.