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Cystic Fibrosis-Related Diabetes (CFRD)

Manfred Ballmann

Abstract

Cystic fibrosis-related diabetes (CFRD) is the most frequent comorbidity in CF. The prevalence is age-dependent and abnormalities in/of glucose homeostasis start early in life. As CFRD has an impact on pulmonary function and life expectancy, early diagnosis and treatment is mandatory. Screening is needed because initially, most patients with CFRD do not show any typical symptoms of diabetes. The question of which screening method gets the best results is still under discussion. For treatment insulin is recommended but a relevant percentage of patients do not use it, and even if insulin is used, there is no consensus on what the best insulin regime in the case of CFRD is. Recently, oral antidiabetic drugs were shown to be as effective and safe as insulin in the initial treatment of CFRD. This treatment might reduce the additional treatment burden for patients with CFRD. The best way to monitor CFRD is also under discussion (HbA1c and/or continuous glucose monitoring; CGM). The threshold of HbA1c might be lower than for other types of diabetes. As patients with CF become older, the duration of CFRD will also increase and typical diabetes complications will occur. So far, these are mainly microvascular complications. The new CFTR modulators might influence not only pulmonary function but potentially also glucose homeostasis.

Keywords: CFRD, epidemiology, diagnosis, screening, treatment, CFTR modulators

1. Introduction

CF is a multi-organ disease that also affects the exocrine and endocrine pancreas [1]. CFRD is a discrete entity of type 3 Diabetes mellitus, displaying aspects from both type 1 Diabetes mellitus and type 2 Diabetes mellitus. It is the most frequent comorbidity in CF involving around 31% of CF patients older than 18 years [2] and up to more than 40% in those older than 30 years [3]. It results from involvement of the endocrine pancreatic function and is the end stage of early onset impaired glucose homeostasis [4]. Today, additional CFRD is still a risk factor for decreased pulmonary function but no longer for increased mortality [3]. In the past, an increased mortality, in part depending on sex and severe CFTR mutation, was observed [5]. Several aspects of the disease's pathophysiology are not yet completely understood [6], but some new insights might help to understand the process [7]. Clinically, there is a need for screening since earlier prospective studies regarding CFRD showed that most CF patients exhibited no clinical signs of hyperglycemia at the time they were diagnosed with CFRD by oral glucose tolerance tests (OGTTs) [8]. The advantages and disadvantages of different screening approaches will be discussed. Even after diagnosis, there is some discussion on how to treat patients

with CFRD diagnosed by screening. Guidelines recommended insulin treatment [9] but registry data from the US [2] and Europe [10] showed that a relevant proportion of CF patients with CFRD are not treated with daily insulin. Alternative treatment options might be needed, and a recent study demonstrated that oral antidiabetic drugs are not inferior to insulin regarding HbA1c over 2 years after CFRD was diagnosed by annual OGTT screening [11]. Upcoming CFTR modulator treatment is an interesting area regarding glucose homeostasis and CFRD. The results of two small case studies [12, 13] on CF patients treated with ivacaftor imply that there is a possibility that CFTR modulation might also influence insulin secretion. Additionally, a registry study showed a trend to a reduced prevalence of CFRD in those treated with ivacaftor for a longer time [14]. In another case study with five patients (F508 del homozygous) treated with lumacaftor/ivacaftor, no consistent effect on glucose tolerance or insulin secretion was observed [15]. Overall, there are a number of important aspects of CFRD, from its pathophysiology to screening, diagnosis, treatment, best methods of follow-up, and new perspectives with CFTR modulator treatment options.

2. CFRD and epidemiology

2.1 Prevalence and incidence and risk factors

In 1994, a first study reporting the prevalence of CFRD was published [16]. Prevalence was 14.7% in all Danish CF patients. More recent data from the CFF patient registry showed an age-dependent prevalence from around 2% in those younger than 10 years up to around 40–50% in adults [2]. The prevalence is in the same range as reported from Germany (**Table 1**) [17] as a European country. The prevalence varies between different European countries based on a recent report of the ECFS patient registry [18]. While diabetes prevalence has risen, incidence has fallen significantly: from 4 cases per 100 patient-years during the 1998–2002 interval to 2.7 cases per 100 patient-years between 2003 and 2008, representing a 40% decrease in the number of diabetes diagnoses in the US [3]. In a longitudinal study from the UK, the incidence was 3.5% (observation period 1996–2005) [19].

Severe genotype, pancreatic insufficiency, and female gender remain considerable intrinsic risk factors for early acquisition of CFRD [18]. In a large prospective study with 1093 patients, impaired fasting glucose, impaired glucose tolerance, and indeterminate glucose tolerance were all predictors of future CFRD [20].

2.2 Sex differences and mortality

An increased mortality used to be described mainly for female CF patients with CFRD [21]. Mortality rate decreased from 1992–1997 to 2003–2008 in females from

Diabetes in CF	0–5 years	6–11 years	12–17 years	18–29 years	30–39 years	>40 years
Diabetes	0.1	1.2	11.1	21.6	32.0	46.6
Of these CFRD	0.0	100	86.7	96.5	94.5	94.3
Of these not CFRD	0.1	0.0	13.3	3.6	5.5	5.7

Adapted from table 17 and table 18 [17].

Table 1.
Frequency in % of CF patients with diabetes in 2018.

6.9 to 3.2 deaths per 100 patient-years and in male subjects from 6.5 to 3.8 deaths per 100 patient-years. There was no longer a sex difference in mortality [3]. A follow-up study (2008–2012) from the same CF center reported that there still was a sex difference in adults, but only in severe genotypes with higher prevalence of CFRD, resulting in an increased mortality in females [22]. Consequently, there is still a discussion about the gender influence on CFRD and survival.

2.3 Genetics

Since the CF gene was detected, there has been the question of a CFTR mutation/mutation class-related risk for CFRD or whether there are other mutations outside of the CFTR gene that may modify the risk of developing CFRD.

In a longitudinal study from the UK, CFTR mutation classes I and II were shown to increase the risk of CFRD independently of other known risk factors [19]. A more recent study reported the risk for CFRD and mortality in adults studied in the years 2008–2012 [22]. CFRD was associated with increased mortality independently of mutation category (mild or severe) [22].

A study looking for CFRD frequency in different age groups and the influence of mutation classes of the CFTR gene found that the prevalence of CFRD increased with age from 2.6% in patients <18 years to 22.1% in patients 18 years or older in those homozygous for group II (including del phen 508, the most frequent CFTR mutation) mutations. It was only 1.5% in patients 18 years or older in group IV/any CFTR mutations [23]. In general, group IV mutations are less severe than class II mutations and this results also in a low risk for CFRD. If CFRD as a complication of CF has developed, there is still an increased mortality risk even in mild mutation classes (e.g., CFTR mutation class IV), but the risk for developing CFRD is higher in severe CFTR mutation classes (e.g., CFTR mutation class I or II).

2.3.1 Genetic modifiers

The frequency of HLA types related to type 1 or type 2 diabetes were in the same range in CF patients with or without diabetes. There was also no difference in frequency compared to normal population [23]. As for other comorbidities, there are also modifiers for CFRD. Susceptibility to CFRD is at least in part determined by variants at SLC26A9 and at four loci associated with type 2 diabetes in the general population [24]. In a very recent study, a wide overlap with genetic modifiers of type 2 diabetes was described [25]. This might allow for a stratification of CFRD screening. Those with less risk depending on CFTR mutation classes and modifier genes might be screened starting at an older age and less frequently than those with a high risk for CFRD.

3. CFRD and pathophysiology

The mechanism of how diabetes develops in CF is not yet completely understood. Difficult access to animal models and human pancreatic tissue may contribute to this situation. Two recent reviews focused on the pathogenesis of CFRD [26, 27]. Insulin secretion is reduced even with normal OGTT and this is observed even in kids [28]. Insulin sensitivity is not or only minimally impaired apart from severe infections or systemic glucocorticoid treatment [29]. An often-discussed question concerned the possible existence of a direct influence of CFTR on α or β -cells. In an elegant study, murine models of β -cell CFTR deletion and human pancreas and islets from controls and CF patients were used [7]. There were some

important results: (1) In the murine cell model, CFTR did not affect β -cell function. (2) In human islets, nearly no expression of CFTR mRNA was detected. (3) Additionally, there was no CFTR protein or electrical activity. (4) The secretion of islet hormones (insulin and glucagon) was in the normal range and only minimal changes in important islet-regulatory transcripts were detected. (5) As a consequence of inflammation, only 35% of β -cell area was conserved and the other part of the islet was compounded by immune infiltration. Overall, CFRD seems to be a consequence of beta-cell loss, accompanied by inflammation of the islets. There is no reason to think that CFTR mutations directly cause islet dysfunction [7].

4. CFRD and diagnosis

4.1 Screening, initial symptoms, and outcome

As there are usually no typical diabetes-related symptoms [8], there is a need to screen for CFRD. Guidelines recommended a regular oral glucose tolerance test (OGTT) for screening [9]. Annual screening should start at the age of 10 years, as recommended in the US and by the ECFS, or at 12 years, as recommended in the UK. Because OGTT is time-consuming for patients and CF center staff, there is some interest in more comfortable alternative methods. The screening rate with OGTT in CF is nowhere near the recommendations in guidelines. In median, only 61.3% of CF patients aged 10–17 years and only 32.8% of adults were screened by OGTT in the US [2]. Nevertheless, it is possible to increase the rate of screening by OGTT, as shown from a program in a pediatric CF center that increased its annual screening rate for outpatients from 45% to 71% [30].

In a registry study, it has recently been reported that CF centers that screen more frequently for CFRD detected CFRD earlier and that those that screened less often had a faster decrease in pulmonary function [31]. This supports the view that screening for CFRD is an important tool to optimize CF care.

4.1.1 HbA1c for screening

HbA1c is quickly collected and simple to measure, which makes it a comfortable test for both patients and CF center staff. To reduce the need for OGTT, the question was whether HbA1c was able to identify those patients at risk for CFRD. However, because of low sensitivity to detect CFRD, HbA1c has not been recommended as a screening tool for CFRD [32] for many years. This has recently become controversial. If a low HbA1c (<5.5%) as threshold was used to identify CF patients with CFRD, the sensitivity covered a wide range from 93% [33] to only 78% [34]. As of now, there is not enough evidence that HbA1c is a reliable tool to screen for CFRD.

4.1.2 Different OGTT methods

To make OGTT more comfortable for patients and staff, different modifications of the OGTT procedure were investigated. A shorter sample time (1 h) [35, 36] was discussed, as well as a lower glucose load (50 g) [37]. Both approaches need evaluation in a larger cohort. So far, standard (WHO) OGTT is still recommended.

4.1.3 Continuous glucose monitoring (CGM)

Another way to uncover impaired glucose homeostasis and CFRD even earlier than using OGTT is CGM. OGTTs were compared with 6 days of CGM in detecting

glucose disturbance in 30 CF patients (age: 10–18 years). CGM identified glucose changes that had been missed by OGTT. This might help to initiate treatment of glucose disturbance before CFRD is diagnosed [38]. However, since even OGTT is only rarely used in many CF centers there is no reason to expect that the more sophisticated CGM will be used more frequently.

4.1.4 OGTT performance and diagnostic criteria

- OGTT: Glucose 1.75 g/kg body weight in 250–300 ml water max 75 g glucose drinking in 5 min
- Performed after >8 h of fasting in the morning.
- No physical activity during the test.
- Often the OGTT is done during the annual assessment. No other investigations during the OGTT (such as an ultrasound) are allowed.
- Blood glucose is measured before (0 min) and 60 min and 120 min after drinking the glucose load.

5. CFRD and treatment

5.1 Treatment

Disturbance of glucose homeostasis starts early in life, CFRD being the end stage [4]. This opens the discussion on the best time to start treatment even before CFRD is diagnosed by OGTT. Insulin is the only recommended treatment. This should be accompanied by an education program and dietary advice. Despite recommendations, insulin is used only in around 75% of all CFRD patients all over the world [2, 17, 40].

5.1.1 Insulin

Insulin is the recommended treatment for CFRD. There are two problems with this recommendation. (1) A relevant percentage of CFRD patients do not use insulin (see **Table 2**). This is the case in the US [2], the UK [41], and Germany [17] at least, as the national registers documented. All these are registries sponsored by CF organizations. Data from a German/Austrian general diabetes registry [42] that collects data from both CFRD patients and type 1 and 2 diabetes patients have shown that only 77% of CFRD patients were on insulin [40]. There might be several reasons for this. First of all, most patients do not realize symptoms of hyperglycemia early in the course of CFRD [8]. Secondly, CF treatment is an enormous burden for adult CF patients and families [43] as well as for children with CF. They spent 74 min a day with treatment, compared to type 1 diabetes with 56 min and asthma with 6 min [44]. Perhaps they like to avoid this additional burden of insulin treatment. (2) The optimal insulin regime is not defined and different regimes are in use. This includes long-term once-daily insulin, intensified insulin treatment several times a day, or an insulin pump with continuous insulin and pushes with meals. The more intensive insulin treatment with a pump is less in use, at least in adolescents and young adults, compared to type 1 diabetes patients in the same age range [45]. In adult CFRD patients treated with insulin, the mean daily dose was not different to matched type 1 or type 2 diabetes patients [46].

	Blood glucose mmol/l (mg/dl)		
	Start	60 min	120 min
Normal glucose tolerance (NGT)	<5.6 (100)	<11.1 (200)	<7.8 (140)
Fasting hyperglycemia (FH)	>5.6 (100) and <7.0 (126)	<11.1 (200)	<7.8 (140)
Impaired glucose tolerance (IGT)	<7.0 (126)	<11.1 (200)	>7.8 (140) <11.1 (200)
Indeterminate glycemia (INDET)	<7.0 (126)	>11.1 (200)	<7.8 (140)
Diabetes (CFRD) without FH	<7.0 (126)	–	>11.1 (200)
CFRD with FH	≥7.0 (126)	–	>11.1 (200)
<i>Adapted from [39].</i>			

Table 2.
Classification of glucose tolerance.

One single optimal insulin regime for all CFRD patients does not exist, since individual adjustment to medical needs and patients’ options is required. The treatment of CFRD is a team approach including dietitians, diabetologists, psychologists, and the CF physician.

5.1.2 Oral antidiabetic drugs

Oral antidiabetic drugs have been used in CFRD for many years [47]. The group of sulfonylurea (glibenclamide) had some disadvantages. They showed inhibitions of CFTR Cl channels in vitro [48–50]. The non-sulfonylurea hypoglycemic agent repaglinide showed only a weak inhibition of CFTR Cl channels [51]. In 2001, a study was published that showed postprandial effects of premeal insulin lispro and premeal repaglinide on postprandial glucose levels in humans. Glucose decreased (peak, 2 h and 5 h AUC) with insulin lispro, and glucose decreased with repaglinide only 5 h AUC. Insulin secretion (5 h AUC) increased only with insulin lispro [52]. In the latest Cochrane review regarding the use of oral antidiabetic drugs in CFRD, published in 2016, it was concluded that controlled prospective studies are needed [53]. There are two prospective randomized controlled trials comparing the effects of insulin versus repaglinide in patients with newly diagnosed CFRD [11, 54]. In a 12-month trial, there was a significant increase in BMI only in the insulin group. Comparing the insulin to the repaglinide group, there was no significant difference in BMI, HbA1c, or pulmonary function changes over the study period [54]. In the other study over 24 months, there was no difference between the groups (insulin and repaglinide) regarding HbA1c, BMI, and pulmonary function. It was concluded from that study that at least a subgroup of patients with newly diagnosed CFRD can be treated initially with oral antidiabetic drugs [11]. This might be an option for those who refuse insulin due to the additional treatment burden (Table 3).

Indication therapy in case of CFRD	0–5 years	6–11 yeas	12–17 years	18–29 years	30–39 years	>40 years
Insulin	100	72.7	64.0	67.6	76.9	75.7
Oral antidiabetics	0	9.1	11.0	9.3	9.3	8.8
Dietary measures	0	27.3	39.0	21	25	23.3

Adapted from table 22 and table 23 [17].

Table 3.
Frequency in % of CF patients with indication therapies related to diabetes in 2018.

5.1.3 Diet

The well-known diet restrictions and advice for type 1 or type 2 diabetes are not transferable to CFRD. In CFRD, the patients need a high-caloric nutrition, in contrast to what is recommended in other types of diabetes. Therefore, a dietician trained in CFRD is needed to support the patient with detailed information regarding nutrition in the special situation of CFRD [55].

5.2 Treatment monitoring

5.2.1 HbA1c

HbA1c is not recommended to diagnose CFRD (see Section 4.1.1.). The situation is different for monitoring CFRD. HbA1c is used to monitor glycemic control in CFRD. In CFRD, the target value for HbA1c should be lower than in type 1 diabetes, because in CFRD mean plasma glucose does not correlate with HbA1c [56]. This is, for example, incorporated in the Australian Standards of Care for CFRD [57]. Adults with CFRD have a significantly lower HbA1c value compared to type 1 diabetes adults (6.8% vs. 7.9%) [58]. How low HbA1c values should be to prevent long-term diabetic comorbidities like microangiopathies (see also Section 6.1) is unknown.

5.2.2 CGM

A more strict control of glucose homeostasis with insulin treatment is achievable with CGM and is accompanied by an improved clinical outcome [59]. This requires the cooperation of the entire CFRD team and particularly the support by a diabetologist.

In general, adherence to diabetes care guidelines (ADA/CFF) is suboptimal [40] and improvement is urgently needed.

6. CFRD and complications

6.1 Microvascular complications

With decreased mortality, CF patients spend more years living with CFRD. Today, CF patients tend to develop microvascular complications, much like patients with type 1 or type 2 diabetes [60]. In long-standing CFRD (>10 years) with fasting hyperglycemia, 14% of patients had microalbuminuria and 16% had retinopathy [61]. The percentage of patients with hypertension was lower in adult CFRD patients while the percentage of patients suffering from nephropathy was higher compared to type 1 and 2 diabetes [58]. These data underline the need for routine screening for CFRD complications.

6.1.1 Retinal complications

More sophisticated eye investigations demonstrated changes at the retina level. Screening for this kind of complication should be also mandatory [62]. Percentage of patients with retinopathy did not differ between adults with CFRD and type 1 or type 2 diabetes [58].

6.1.2 Macrovascular complications

Macrovascular complications have not been described so far. However, with increasing duration of CFRD in older CF patients, this kind of complication has

to be expected. Even microvascular complications develop later in CFRD than in other types of diabetes.

6.2 Risk for hyperglycemia

The risk for acute severe hyperglycemia exists but the condition is very rare [63]. Most CFRD patients do not develop a ketoacidosis. This might be related to residual insulin secretion and glucagon counter regulation. Hyperglycemia measured by HbA1c is a risk factor for mortality. In a prospective observational study, a HbA1c $\geq 6.5\%$ was associated with a threefold increased risk of death [64]. Measuring HbA1c is mandatory and it should be kept in mind that the target value is lower than in type 1 or type 2 diabetes (see also Section 5.2.1).

6.3 Risk for hypoglycemia

The detected frequency of hypoglycemia is higher with CGM than with OGTT [65]. There is no prognostic relevance of hypoglycemia during OGT for later development of CFRD [66]. In general, it seems that the risk of hypoglycemia is not different from other types of diabetes and instruction on how to handle CFRD in daily life should address this risk.

7. CFRD and special situations

7.1 Pregnancy

With improved clinical course of CF and improved life expectancy, more female CF patients want to become pregnant. According to the UK guidelines [55], there are four groups.

- CFRD and IGT: optimized diabetes control and needs to be referred to a specialized diabetes team.
- NGT (tested in the last 3 months): OGT in first trimester and the next between week 24 and week 28.
- Unknown glycemic status: OGT before becoming pregnant, if possible.

7.2 Physical activity

With better clinical conditions, physical activities in all age groups of CF patients increased. Patients with CFRD should exercise and be educated about the risk of hypoglycemia, like other diabetic patients. CFRD is no reason to stop physical activities.

8. CFRD and cystic fibrosis transmembrane regulator (CFTR) modulators

Since 2012, there is a new class of medication for CF patients on the market. These drugs are called “CFTR modulators.” They are CFTR mutation specific and are administered orally. This offers the chance that these drugs might affect

different organs that are reached by the bloodstream. The regulation of glucose homeostasis is a complex process and CFTR modulators might interfere at different steps.

8.1 CFRD and ivacaftor

Ivacaftor is a CFTR potentiator and acts with gating mutations (e.g., G551D). It increases pulmonary function, weight, and quality of life (QoL) and decreases sweat chloride concentration [67].

In two siblings, insulin secretion and glucose AUC were measured during an OGTT before and 16 weeks after initiation of ivacaftor [12]. This paper described the beneficial effect of 4-month ivacaftor treatment on the pathologic OGTT of two patients with CF carrying the S549R gating mutation. This beneficial effect may be partially due to the increased earlier insulin secretion capacity [12]. Two other studies also reported an increase in insulin secretion after ivacaftor was initiated in CF patients with a gating mutation [68, 69]. As of now, reports have included only small numbers of patients and/or are uncontrolled studies. Sufficiently powered studies are still missing. In a registry study using data from the US and the UK with a follow-up of more than 5 years, a trend to a reduced prevalence of CFRD in ivacaftor-treated patients [14] was reported. If this observation will be corroborated in future studies, many CF patients would benefit from a postponed CFRD treatment burden.

8.2 CFRD and Ivacaftor/lumacaftor combination therapy

The combination therapy with ivacaftor/lumacaftor was administered to patients with the del F508 mutation [70]. The overall clinical effect regarding pulmonary function, weight, and QoL was low compared to ivacaftor in patients with a gating mutation [67]. Using CGM and OGTT to control glucose homeostasis in five patients after initiation of ivacaftor/lumacaftor treatment, glycemic abnormalities persisted [71]. A consistent impact of the combination of ivacaftor/lumacaftor on insulin secretion or glucose tolerance was not detected in five patients [15]. In a very recent article from France [72], the change of OGTT categories after 1 year of lumacaftor/ivacaftor treatment was described in an uncontrolled study design. The reported improvement, for example, from CFRD to IGT is within the range of the well-known high variability of OGTT results in CF patients [73]. It is not surprising that the combination treatment, which had less of an effect on clinical outcome in gating mutations compared to ivacaftor, has so far no proven effect on CFRD, even if only a small number of CF patients were investigated.

8.3 CFRD and outlook

The recently published results with a triple combination CFTR modulator therapy in patients with a del phen 508 allele are impressive regarding pulmonary function increase, sweat chloride decrease, and other outcomes [74]. With a highly clinically effective CFTR modulator treatment and a sufficient number of patients, the demonstration of a positive influence on glucose homeostasis in a prospective study seems realistic.

However, there is currently no evidence-based information that CFTR modulators have a relevant influence on the complex pathophysiology regarding glucose homeostasis.

9. Conclusions

CFRD is still a highly relevant comorbidity in CF. Nevertheless, there are many questions regarding its optimal handling from both patients' and physicians' point of view. CFRD is a team approach, which includes the CF team but also the diabetes team.

Adherence to all aspects of CFRD diagnosis and treatment is low and needs urgent efforts to increase.

As long as no better screening procedure is established, 2h of OGTT should be used annually as screening for CFRD.

Education regarding CFRD should include patients, families, physicians, and the entire team.

Treatment as recommended by guidelines prefers only insulin. The recently published controlled prospective trials may endorse the use of oral antidiabetic drugs, at least in a subgroup of patients.

Monitoring must include all the measurements that are recommended for other types of diabetes. HbA1c target value for treatment should be lower than in type 1 or 2 diabetes.

Typical microvascular complications are reported and patients should be regularly checked for these.

In future, the new and effective CFTR modulator therapies might also influence the prevalence of CFRD. In a perfect world, they might also improve glucose homeostasis in patients with CFRD and postpone CFRD entirely.

Conflict of interest

The authors declare no conflict of interest.

Author details

Manfred Ballmann
University Medicine Rostock, Rostock, Germany

*Address all correspondence to: manfred.ballmann@med.uni-rostock.de

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