Epidemiology, Pathophysiology, and Prognostic Implications of Cystic Fibrosis–Related Diabetes

A technical review

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Cystic fibrosis–related diabetes (CFRD) is the most common comorbidity in subjects with cystic fibrosis (CF). A consensus conference on CFRD was cosponsored by the Cystic Fibrosis Foundation (CFF), the American Diabetes Association (ADA), and the Pediatric Endocrine Society (PES) in September 2009. The committee's evidence-based recommendations for clinical management of CFRD are published in this issue of *Diabetes Care*. This review article describes the epidemiology, pathogenesis, and prognostic implications of CFRD.

Epidemiology

CFRD is part of a continuum of glucose tolerance abnormalities, ranging from normal glucose tolerance (NGT), to impaired glucose tolerance (IGT), to CFRD without fasting hyperglycemia (CFRD FH−), to CFRD with fasting hyperglycemia (CFRD FH+) (Fig. 1). Unlike patients with type 1 diabetes, those with CFRD do not develop complete absence of insulin secretion. At the other end of the spectrum, few CF patients have truly normal glucose metabolism. Approximately 20% of children who are categorized as having NGT based on their fasting and 2-h oral glucose tolerance test (OGTT) glucose levels have glucose elevation >200 mg/dl (11.1 mmol/l) mid-OGTT, which is termed indeterminate glycemia (INDET) (1). As in the general population where INDET is a risk factor for progression to diabetes (2), INDET in children with CF is associated with early development of CFRD (1). Home continuous glucose monitoring (CGM) has shown that intermittent, asymptomatic hyperglycemia is common even in CF patients whose OGTT is normal, but the prognostic significance of these early impairments in glucose metabolism is unknown (3,4). Impaired fasting glucose has also been described in CF (5,6).

CFRD is present in about 20% of adolescents and 40–50% of adults with CF (7) (Fig. 2). It is rare in childhood but has been described in children of all ages including infants (8–11). Beginning in the teenage years, the incidence is ~3%, with some but not all centers reporting an overall female predominance (7,12). In younger individuals CFRD FH− predominates, but the prevalence of fasting hyperglycemia rises with age (7). Diabetes is associated with more severe CF gene mutations, increasing age, worse pulmonary function, undernutrition, liver dysfunction, pancreatic insufficiency, and corticosteroid use (12–15).

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Pathophysiology

CFRD shares features of both type 1 and type 2 diabetes, but has enough pathophysiological and clinical differences to warrant separate diagnostic classification (Table 1). As in type 1 diabetes, individuals with CFRD are not obese, it often occurs in young people, insulin insufficiency is the primary defect, and metabolic syndrome features (hyperlipidemia, hypertension, visceral adiposity) are not usually present. Clinical management is similar to type 1 diabetes in the honeymoon phase. As in type 2 diabetes, this is not an autoimmune disease, insulin resistance is present (albeit usually mild), and ketosis is rare. Genetically, CFRD may be related to type 2 diabetes, as described below.

Insulin insufficiency. Reduced β-cell mass leading to insulin insufficiency is the hallmark of CFRD. The CF gene defect leads to abnormal or absent CF transmembrane conductance regulator (CFTR), a chloride channel that also influences sodium and water transport. Thick, viscous secretions cause inflammation, obstruction, and destruction of small ducts in the lungs, pancreas, liver, and reproductive organs. Autopsy findings include fibrosis and atrophy of the pancreas with ~50% reduction of the total islet mass (16–18).

Multiple studies have shown impaired first–phase insulin secretion in response to glucose, arginine, or glucagon, even in subjects with NGT (19–24). In response to oral glucose, the earliest defect is delayed insulin secretion, followed over time by a progressively diminished total insulin response (22–32). The β-cell destruction is not complete and residual endogenous insulin secretion is present, so these patients are not prone to ketosis. The lack of ketosis may also be related to low glucagon levels. While fasting glucagon levels are normal, CF patients are not able to appropriately increase glucagon secretion in response to arginine or hypoglycemia (21,24), consistent with reduced α-cell mass. Incretin levels (gastric

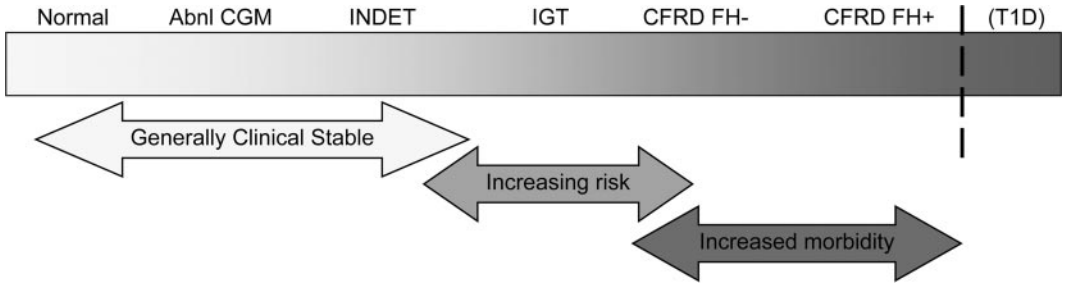

Figure 1—*The spectrum of glucose tolerance in CF. Unlike patients with type 1 diabetes, insulin secretion is never completely absent in CFRD. Clinical deterioration (pulmonary function, underweight) is associated with worse glucose tolerance status. Abnl CGM = abnormal home continuous glucose monitoring, T1D = type 1 diabetes, INDET = indeterminate glycemia.*

inhibitory peptide and glucagon-like peptide 1) are normal in CF (23), which may help to explain why glucose excursion is better in response to a mixed meal compared with oral glucose (33).

Insulin resistance. Euglycemic clamp studies generally demonstrate normal peripheral muscle insulin sensitivity in nondiabetic CF patients (34–37), although insulin resistance has also been described and may be related to greater severity of illness and inflammation (38,39). Modest peripheral insulin resistance occurs once diabetes develops (35–38).

The most surprising clamp finding is that liver insulin resistance with elevated hepatic glucose production (both in the fasting state and in response to insulin infusion) occurs not only in CF patients with diabetes, but also in those with completely normal fasting glucose levels (37,40,41). It has been hypothesized that the increased energy needs of CF patients create a physiologic balance between elevated hepatic glucose production and high glucose demand.

Genetic predisposition to diabetes. It is still not clear whether the underlying CF gene defect predisposes patients to diabetes. There has been speculation that β-cell failure is related to endoplasmic reticulum stress from retained abnormal CFTR protein, leading to apoptosis (42). It has not definitively been shown, however, that CFTR is even expressed in β-cells. In a mouse model of CF, $CFTR^{-}$ mice had greater impairment of insulin secretion than control mice after low-dose streptozotocin despite a similar loss of islets, perhaps suggesting an intrinsic involvement of CFTR in β-cell function (43).

What about genes predisposing to type 1 or type 2 diabetes? With a few exceptions (44–46), type 1 diabetes autoantibodies have not been found in patients with CFRD, and HLA DR3/4 associations have been similar to the general population (22,25,27,28,47–50). It is, however, possible for CF and autoimmune type 1 diabetes to occasionally coexist in the same individual (51,52).

There are interesting new data demonstrating genetic associations between type 2 diabetes and CFRD. The earliest suggestion that CFRD might be related to type 2 diabetes was a finding of islet amyloid deposition in individuals with CFRD, similar to type 2 but not type 1 diabetes or chronic pancreatitis (16). More recently, a family history of type 2 diabetes was found to increase the risk of CFRD (53). The concordance rate for diabetes was substantially higher in monozygous twins compared with dizygous twins or siblings with CF (54). Variation in a type 2 diabetes susceptibility gene, transcription factor 7-like 2 (TCF7L2), was shown to be associated with diabetes in CF and decreased the mean age of diabetes diagnosis by 7 years (53). An association was also found between CFRD and a genetic polymorphism in calpain-10, which has been reported in type 2 diabetes (55). Calpain-10 is involved in insulin secretion and inflammation, both of which may be relevant in CFRD. Thus, although more work needs to be done in this area, genetic variants conferring risk for type 2 diabetes in the general population appear to be modifiers of diabetes risk in CF.

Integrated hypothesis of CFRD pathophysiology. We hypothesize that all CF patients with pancreatic exocrine insufficiency have pancreatic endocrine insufficiency related to physical scarring and destruction of islets. Those patients who are pancreatic sufficient because of milder defects in CFTR experience less islet destruction, although chronic pancreatitis may damage and destroy islets over time. Despite significantly reduced β-cell mass, many people with CF have only mild glucose tolerance abnormalities because their peripheral insulin sensitivity is nor-

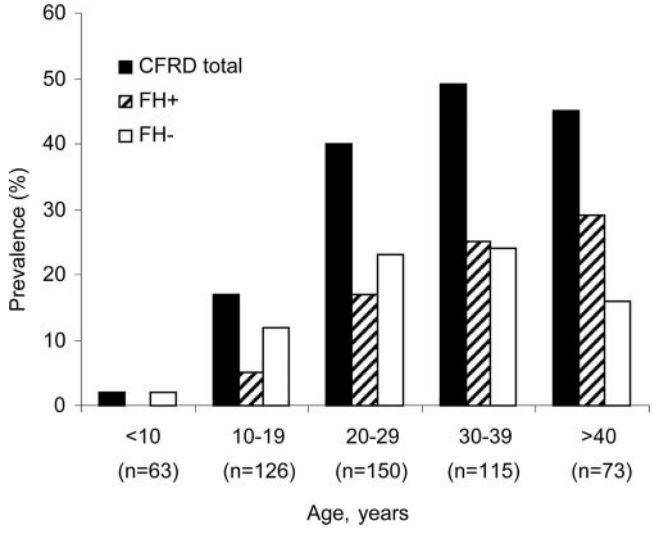

Figure 2—*Prevalence of CFRD based on 2005–2008 data for all patients within each age-group at the University of Minnesota. Data are presented for all patients with CFRD (CFRD total) and separately by fasting hyperglycemia status (ref. 7).*

Table 1—*CFRD compared with type 1 and type 2 diabetes*

	CFRD	Type 1 diabetes	Type 2 diabetes
Prevalence in population	35%	0.2%*	11%*
Peak age of onset	20–24 years	Childhood, adolescence	Mid to late adulthood
Usual body habitus	Normal to underweight	Normal	Obese
Insulin deficiency	Severe but not complete	Complete	Partial, variable
Insulin resistance	Usually modest, waxes and wanes with infection	Usually modest	Severe
Autoimmune etiology	No	Yes	No
Ketones	Rare	Yes	Rare
A1C	Unpredictable relation to mean blood glucose	Related to mean blood glucose	Related to mean blood glucose
Usual treatment	Insulin	Insulin	Oral agents, insulin
Microvascular complications	Yes	Yes	Yes
Macrovascular complications	No	Yes	Yes
Metabolic syndrome features	No	No	Yes
Cause of death	Lung disease	Cardiovascular	Cardiovascular

*Source: National Diabetes Information Clearinghouse, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health (http://diabetes.niddk.nih.gov/DM/PUBS/statistics/#allage).

mal and their remaining β-cells are competent enough to compensate. More severe glucose tolerance abnormalities develop in those who either have worse inflammation and thus greater insulin resistance, or who have intrinsic β-cell dysfunction related to type 2 diabetes–associated genetic variations.

Prognostic implications of diabetes in CF

Diabetes macrovascular and microvascular complications. Patients with type 1 and type 2 diabetes die from macrovascular disease. This is not the case in CFRD. Although many CF patients now live into their sixth and seventh decades, there has never yet been a CF patient reported to have died from atherosclerotic cardiovascular disease. This may be related to the fact that cholesterol levels are generally low despite a diet high in saturated fat (56). While low cholesterol levels have been attributed to fat malabsorption, there may also be some intrinsic connection to the basic CF gene defect since levels are low even in well-nourished patients.

Microvascular complications do occur in CFRD and, as in all individuals with diabetes, are related to the duration and metabolic control of diabetes (57–60). They typically do not become apparent until the diabetes has progressed to fasting hyperglycemia (57). Mild neuropathy is the most prevalent microvascular complication in CFRD (57). It is found in about half of the patients who have had diabetes for more than 10 years, similar to prevalence rates for other types of diabetes. The most common findings are reduced sural sensory nerve action potential amplitude and impaired cardiorespiratory reflexes, consistent with diabetic polyneuropathy. In contrast, retinopathy and nephropathy appear to be less frequent and less severe than in other diabetes populations. In CF patients with more than 10 years diabetes duration, 14% had microalbuminuria and 16% had retinopathy (57). The eyes and the kidneys may be somewhat protected in CFRD because of the presence of residual endogenous insulin secretion or because metabolic risk factors such as severe insulin resistance, hypertension, and hyperlipidemia are seldom present in this population. Delayed gastric emptying is found in about half of CFRD patients, but it is also common in CF patients who do not have diabetes; diabetes may exacerbate gastrointestinal motility problems intrinsic to CF.

The influence of diabetes on CF pulmonary function. The most important morbidity in subjects with CFRD may be the impact of diabetes on pulmonary function. Both insulin insufficiency and hyperglycemia negatively affect CF lung disease. Nutritional status and pulmonary function begin to decline in CF patients several years before the actual diagnosis of CFRD in the pre-diabetic period when minimal hyperglycemia is present (50,61,62). The rate of pulmonary function decline is directly related to the severity of insulin insufficiency; when followed for 4 years after a baseline OGTT, patients with IGT had a greater loss of lung function than those with NGT, and those with CFRD FH− had the greatest loss (63). The rate of pulmonary function decline was inversely related to the baseline OGTT area under the curve for insulin.

CF lung function is critically dependent on maintaining normal weight and lean body mass. Insulin insufficiency compromises nutritional status by creating a catabolic state with excessive protein and fat breakdown (64–68). There have been multiple reports demonstrating that insulin replacement therapy improves nutritional status and pulmonary function in patients with CFRD (50,69–73). Recently, a multicenter, randomized, placebo-controlled trial demonstrated that insulin therapy was able to reverse chronic weight loss in adult patients with CFRD FH− (74), ending the controversy about whether insulin should be prescribed for this "milder" form of diabetes. Whether patients with less severe glucose tolerance abnormalities such as IGT or indeterminate glycemia would benefit from insulin replacement remains to be determined, but small studies in adults and children suggest that this might be the case (72,75).

While it is often said that the nutritional consequences of insulin insufficiency are of greater concern than the metabolic effects of hyperglycemia in CF, high blood glucose levels may also play an important role in pulmonary function decline, even in patients with only intermittent postprandial glucose elevation.

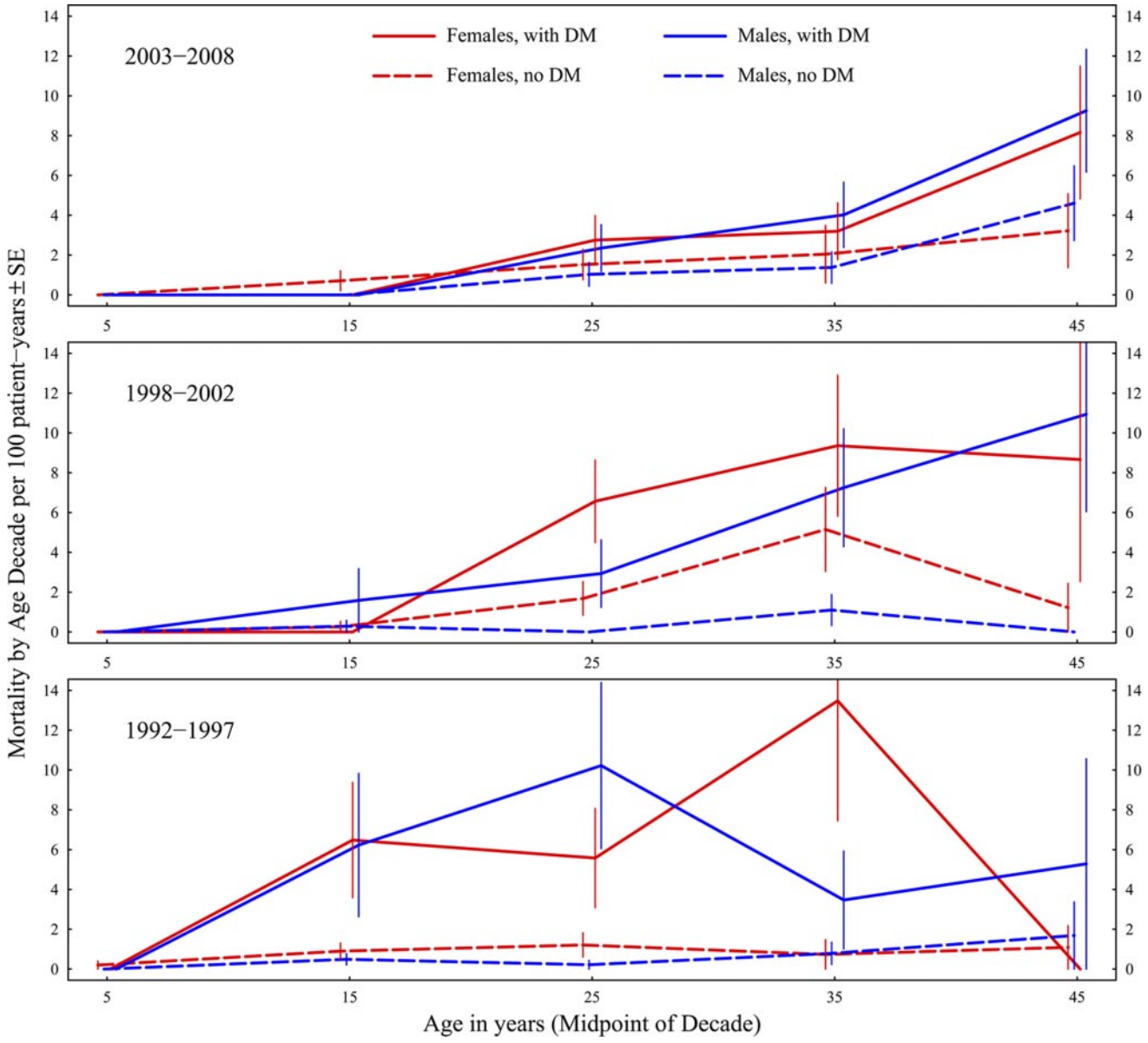

Figure 3—*CFRD mortality per 100 patient-years by sex and age decade over three time periods: 2003–2008, 1998–2002, and 1992–1997. Females are shown in red, and males are shown in blue. CF patients with diabetes are shown with solid lines, and CF patients without diabetes are shown with dashed lines. The gap in mortality between those with and without diabetes has diminished over these time periods, and the sex difference in mortality has disappeared in the most current analysis (ref. 7) DM, diabetes.*

When blood glucose levels are modestly elevated (>144 mg/dl, 8.0 mmol/l), airway glucose concentrations are also elevated in CF patients, and this environment has been shown to promote growth of respiratory pathogens (76). In addition, hyperglycemia has been noted to be associated with increased oxidative stress in CF (77). Thus, high blood glucose levels may contribute to CF lung disease by creating a proinflammatory, pro-bacteria environment in the airways. The presence of fasting hyperglycemia does not appear to be a critical determinant since lung function and nutritional status do not differ between CFRD FH− and CFRD FH+ (7).

Excessive mortality in CFRD. Unlike patients with type 1 and type 2 diabetes, patients with CFRD die from respiratory failure due to chronic lung inflammation and infection. The first inkling that diabetes might impact survival from pulmonary disease came in 1988 when it was reported that less than 25% of CF patients with diabetes reached the age of 30 years compared with about 60% of those without diabetes (62). Since then, multiple studies have shown that the additional diagnosis of diabetes in subjects with CF is associated with worse nutritional status, more severe lung disease, and greater mortality (14,15,78). For reasons that have never been well understood, females with CFRD have been noted to be particularly vulnerable (32,78,79).

On a positive note, longitudinal evaluation at one large CF center has demonstrated steady improvements over time in CFRD-associated mortality. Comparison of the periods between 1992–1997 and 2003–2008 revealed that female mortality dropped by >50% from 6.9 to 3.2 deaths per 100 patient-years, and male mortality dropped from 6.5 to 3.8 deaths

per 100 patient-years in CF patients with diabetes (7). Mortality is shown in Fig. 3 by diabetes status, sex, and age decade over three time intervals from 1992–2008. In 2008, lung function was still worse in CF patients with diabetes compared with those without diabetes, but the gap had narrowed and there was no longer a sex difference in mortality. This improvement was attributed to early detection of diabetes and aggressive management with insulin therapy.

Conclusions

Abnormal glucose tolerance, including diabetes, is present in the majority of individuals with CF and is related to insulin insufficiency and, to a lesser extent, to insulin resistance. While insulin insufficiency is directly related to reduced islet mass, the functional capacity of the remaining β-cells may be genetically determined. Insulin insufficiency creates a catabolic state and a nutritional compromise, which has a negative impact on pulmonary function and survival. Hyperglycemia also contributes to lung disease by promoting oxidative stress, inflammation, and infection. CFRD is associated with diabetes microvascular complications and with excessively high rates of death from CF lung disease, particularly in women. However, early detection combined with aggressive insulin therapy has been shown to reduce the mortality gap between CF patients with and without diabetes and to eliminate the sex disparity in survival.

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