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

## A technical review

Antoinette Moran, MD[1]
Dorothy Becker, MD[2]
Samuel J. Casella, MD[3]
Peter A. Gottlieb, MD[4]
M. Sue Kirkman, MD[5]

Bruce C. Marshall, MD[6]
Bonnie Slovis, MD[7]
THE CFRD CONSENSUS CONFERENCE COMMITTEE*

Cystic fibrosis–related diabetes (CFRD) is the most common co-morbidity 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).

## 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

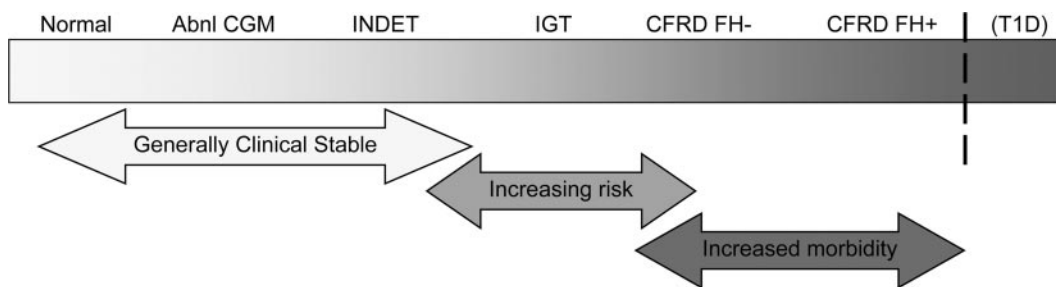**See accompanying articles, pp. 2660, 2697, 2716.**

**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 ele-

vated 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-

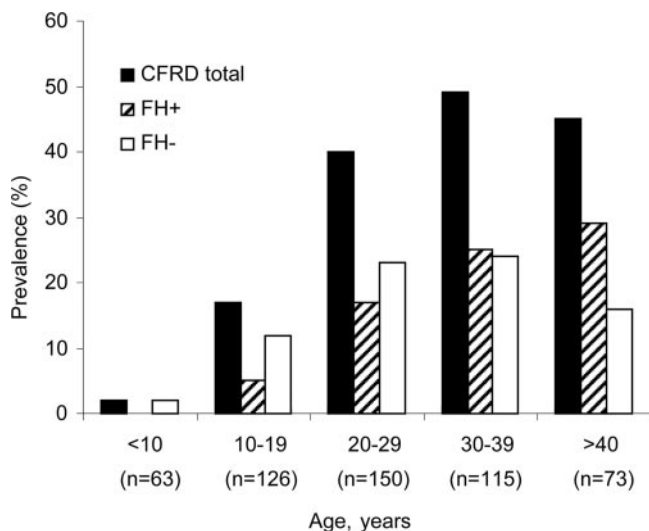

**Figure 2**—*Prevalence of CFRD based on 2005–2008 data for all patients within each age-group at the University of Minnesota. Data are presented for all patients with CFRD (CFRD total) and separately by fasting hyperglycemia status (ref. 7).*

**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.
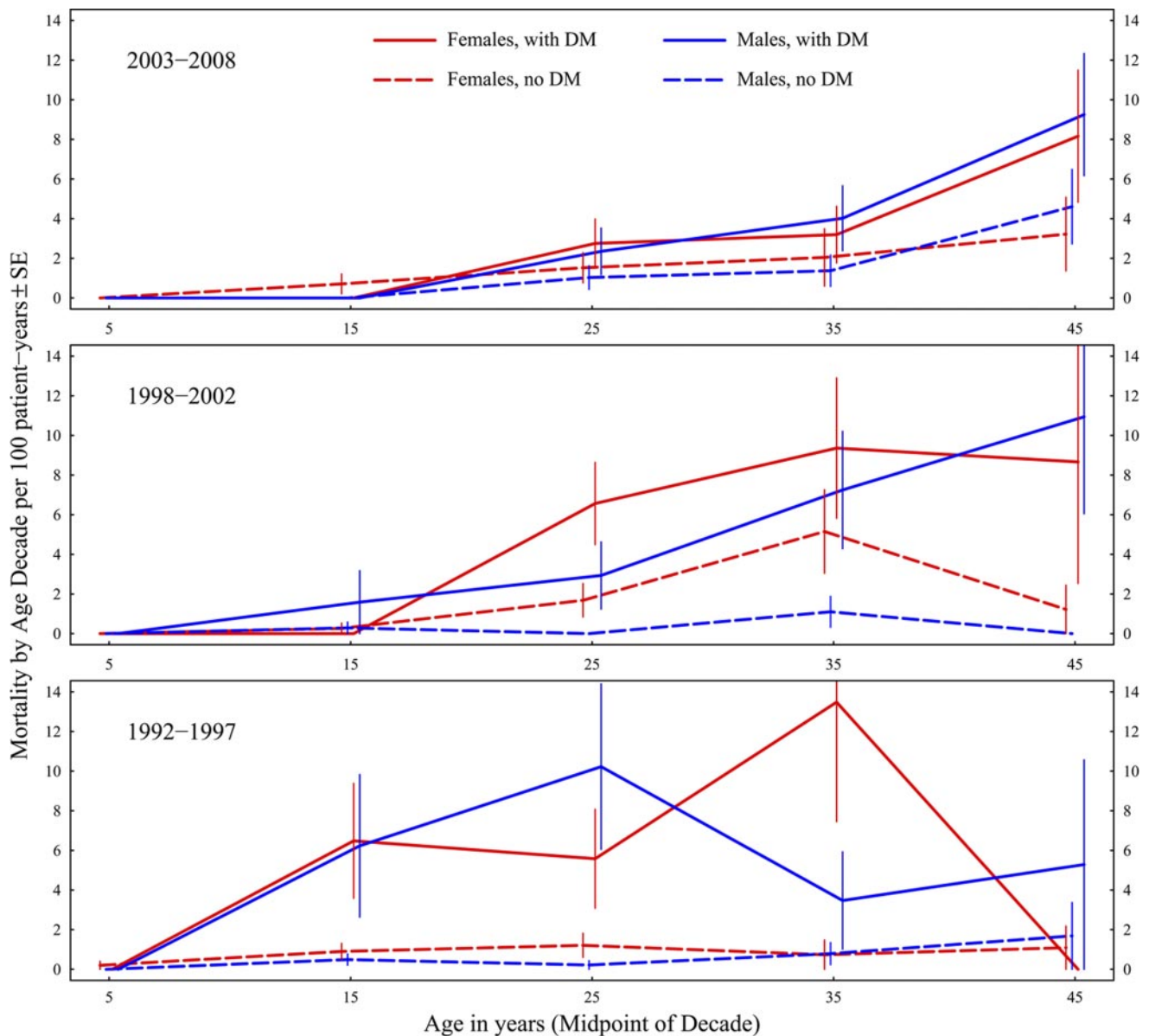
**Figure 3**—*CFRD mortality per 100 patient-years by sex and age decade over three time periods: 2003–2008, 1998–2002, and 1992–1997. Females are shown in red, and males are shown in blue. CF patients with diabetes are shown with solid lines, and CF patients without diabetes are shown with dashed lines. 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.

**APPENDIX** — The CFRD Consensus Committee: Paula Alexander, East Tennessee Children's Hospital, Knoxville, TN; Robert J. Beall, Cystic Fibrosis Foundation, Bethesda, MD; Dorothy Becker, Children's Hospital of Pittsburgh, Pittsburgh, PA; Carol Brunzell, University of Minnesota Medical Center, Fairview, Minneapolis, MN; Preston W. Campbell III, Cystic Fibrosis Foundation, Bethesda, MD; Samuel J. Casella, Children's Hospital at Dartmouth, Lebanon, NH; Melissa Chin, Cystic Fibrosis Foundation, Bethesda, MD; Richard C. Cohen, Kaiser Permanente, Portland, OR; Joan Finnegan Brooks, Patient-Focused Market Research, Boston, MA; Cynthia George, Cystic Fibrosis Foundation, Bethesda, MD; Peter A. Gottlieb, Barbara Davis Center, University of Colorado at Denver, Aurora, CO; Leslie Hazle, Cystic Fibrosis Foundation, Bethesda, MD; Marcia Katz, Baylor College of Medicine, Houston, TX; M. Sue Kirkman, American Diabetes Association, Alexandria, VA; Bruce C. Marshall, Cystic Fibrosis Foundation, Bethesda, MD; Catherine McKeon, National Institutes of Health, Bethesda, MD; Antoinette Moran, University of Minnesota, Minneapolis, MN; Gary Onady, Wright State University, Boonshoft Medical School, Dayton, OH; Karen A. Robinson, Johns Hopkins University, Baltimore, MD; Theresa Rodgers, University of Alabama, Birmingham, Irondale, AL; Kathryn A. Sabadosa, The Dartmouth Institute for Health, Lebanon, NH; Terri Schindler, Rainbow Babies and Children's Hospital, Cleveland, OH; Bonnie Slovis, Vanderbilt University Medical Center, Nashville, TN; Arlene Stecenko, Emory University School of Medicine, Atlanta, GA; Mary E. Wood, Dartmouth-Hitchcock Medical Center, Lebanon, NH; and David Young, Intermountain Cystic Fibrosis Adult Center, Salt Lake City, UT.

## References

1. Ode KL, Frohnert B, Laguna T, Phillips J, Holmes B, Regelmann W, Thomas W, Moran AM. Oral glucose tolerance testing in children with cystic fibrosis. Pediatr Diabetes 25 February 2010 [Epub ahead of print]
2. Sosenko JM, Palmer JP, Rafkin-Mervis L, Krischer JP, Cuthbertson D, Mahon J, Greenbaum CJ, Cowie CC, Skyler JS, Diabetes Prevention Trial-Type 1 Study Group. Incident dysglycemia and progression to type 1 diabetes among participants in the Diabetes Prevention Trial-Type 1. Diabetes Care 2009;32:1603–1607
3. Dobson L, Sheldon CD, Hattersley AT. Conventional measures underestimate glycaemia in cystic fibrosis patients. Diabet Med 2004;21:691–696
4. Moreau F, Weiller MA, Rosner V, Weiss L, Hasselmann M, Pinget M, Kessler R, Kessler L. Continuous glucose monitoring in cystic fibrosis patients according to the glucose tolerance. Horm Metab Res 2008;40:502–506
5. 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;151:653–658
6. Mueller-Brandes C, Holl RW, Nastoll M, Ballmann M. New criteria for impaired fasting glucose and screening for diabetes in cystic fibrosis. Eur Respir J 2005;25:715–717
7. 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;32:1626–1631
8. Casas L, Berry DR, Logan K, Copeland KC, Royall JA. Cystic fibrosis–related diabetes in an extremely young patient. J Cyst Fibros 2007;6:247–249
9. Gelfand IM, Eugster EA, Haddad NG. Infancy-onset cystic fibrosis–related diabetes. Diabetes Care 2005;28:2593–2594
10. Lombardi F, Raia V, Spagnuolo MI, Nugnes R, Valerio G, Ciccarelli G, Franzese A. Diabetes in an infant with cystic fibrosis. Pediatr Diabetes 2004;5:199–201
11. Siahanidou T, Mandyla H, Doudounakis S, Anagnostakis D. Hyperglycaemia and insulinopenia in a neonate with cystic fibrosis. Acta Paediatrica 2005;94:1837–1840
12. Adler AI, Shine BS, 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;31:1789–1794
13. Solomon MP, Wilson DC, Corey M, Kalnins D, Zielenski J, Tsui LC, Pencharz P, Durie P, Sweezey NB. Glucose intolerance in children with cystic fibrosis. J Pediatr 2003;142:128–132
14. Marshall BC, Butler SM, Stoddard M, Moran AM, Liou TG, Morgan WJ. Epidemiology of cystic fibrosis-related diabetes. J Pediatr 2005;146:681–687
15. Koch C, Rainisio M, Madessani U, Harms HK, Hodson ME, Mastella G, McKenzie SG, Navarro J, Strandvik B, Investigators of the European Epidemiologic Registry of Cystic Fibrosis. Presence of cystic fibrosis-related diabetes mellitus is tightly linked to poor lung function in patients with cystic fibrosis: data from the European Epidemiologic Registry of Cystic Fibrosis. Pediatr Pulmonol 2001;32:343–350
16. Couce M, O'Brien TD, Moran A, Roche PC, Butler PC. Diabetes mellitus in cystic fibrosis is characterized by islet amyloidosis. J Clin Endocrinol Metab 1996;81:1267–1272
17. Iannucci A, Mukai K, Johnson D, Burke B. Endocrine pancreas in cystic fibrosis: an immunohistochemical study. Hum Pathol 1984;15:278–284
18. Löhr M, Goertchem P, Nizze H, Gould NS, Gould VE, Oberholzer M, Heitz PU, Klöppel G. Cystic fibrosis associated islet changes may provide a basis for diabetes: an immunocytochemical and morphometrical study. Virchows Archiv A Pathol Anat Histopathol 1989;414:179–185
19. Cucinotta D, De Luca D, Arrigo T, De Benedetto A, Sferlazzas C, Gigante A,

Rigoli L, Magazzu G. First-phase insulin response to intravenous glucose in cystic fibrosis patients with different degrees of glucose tolerance. J Pediatr Endocrinol 1994;7:13–17

20. De Schepper J, Hachimi-Idrissi S, Smitz J, Dab I, Loeb H. First-phase insulin release in adult cystic fibrosis patients: correlation with clinical and biological parameters. Horm Res 1992;38:260–263

21. Lippe BM, Sperling MA, Dooley RR. Pancreatic alpha and beta cell functions in cystic fibrosis. J Pediatr 1977;90: 751–755

22. Arrigo T, Cucinotta D, Conti Nibali S, Di Cesare E, Di Benedetto A, Magazzù G, De Luca F. Longitudinal evaluation of glucose tolerance and insulin secretion in non-diabetic children and adolescents with cystic fibrosis: results of a two-year follow-up. Acta Paediatr 1993;82: 249–253

23. Lanng S, Thorsteinsson B, Røder ME, Orskov C, Holst JJ, Nerup J, Koch C. Pancreas and gut hormone responses to oral glucose and intravenous glucagon in cystic fibrosis patients with normal, impaired, and diabetic glucose tolerance. Acta Endocrinologica 1993;128:207–214

24. Moran A, Diem P, Klein DJ, Levitt MD, Robertson RP. Pancreatic endocrine function in cystic fibrosis. J Pediatr 1991;118: 715–723

25. Bismuth E, Laborde K, Taupin P, Velho G, Ribault V, Jennane F, Grasset E, Sermet I, de Blic J, Lenoir G, Robert JJ. Glucose tolerance and insulin secretion, morbidity, and death in patients with cystic fibrosis. J Pediatr 2008;152:540–545

26. Costa M, Potvin S, Hammana I, Malet A, Berthiaume Y, Jeanneret A, Lavoie A, Levesquie R, Perrier J, Karelis AD, Chiasson J-L, Rabasa-Lhoret R. Increased glucose excursion in cystic fibrosis and its association with a worse clinical status. J Cyst Fibros 2007;6:376–383

27. Cucinotta D, Conti Nibali S, Arrigo T, Di Benedetto A, Magazzù G, Di Cesare E, Costantino A, Pezzino V, De Luca F. Beta cell function, peripheral sensitivity to insulin and islet cell autoimmunity in cystic fibrosis patients with normal glucose tolerance. Horm Res 1990;34:33–38

28. Cucinotta D, Arrigo T, De Luca F, Di Benedetto A, Lombardo F, Scoglio R, Sferlazzas C, Magazzù G. Metabolic and clinical events preceding diabetes mellitus onset in cystic fibrosis. Eur J Endocrinol 1996;134:731–736

29. De Luca F, Arrigo T, Di Benedetto A, Tedeschi A, Sferlazzas C, Crisafulli G, Di Cesare E, Romano G, Magazzù G, Cucinotta D. Four-year follow-up of glucose tolerance and beta-cell function in nondiabetic cystic fibrosis patients. Horm Res 1995; 44:45–50

30. Holl RW, Wolf A, Thon A, Bernhard M, Buck C, Missel M, Heinze E, von der Hardt H, Teller WM. Insulin resistance with altered secretory kinetics and reduced proinsulin in cystic fibrosis patients. JPGN 1997;25:188–193

31. Lombardo F, De Luca F, Rosano M, Sferlazzas C, Lucanto C, Arrigo T, Messina MF, Crisafulli G, Wasniewska M, Valenzise M, Cucinotta D. Natural history of glucose tolerance, beta-cell function and peripheral insulin sensitivity in cystic fibrosis patients with fasting euglycemia. Eur J Endocrinol 2003;149:53–59

32. Miller RJ, Tildesley HD, Wilcox PG, Zhang H, Kreisman SH. Sex disparities in effects of cystic fibrosis–related diabetes on clinical outcomes: a matched study. Can Respir J 2008;15:291–294

33. Hammana I, Malet A, Costa M, Brochiero E, Berthiaume Y, Potvin S, Chiasson JL, Coderre L, Rabasa-Lhoret R. Normal adiponectin levels despite abnormal glucose tolerance (or diabetes) and inflammation in adult patients with cystic fibrosis. Diabete Metab 2007;33:213–219

34. Ahmad T, Nelson R, Taylor R. Insulin sensitivity and metabolic clearance rate of insulin in cystic fibrosis. Metabolism 1994; 43:163–167

35. Cucinotta D, De Luca F, Gigante A, Arrigo T, Di Benedetto A, Tedeschi A, Lombardo F, Romano G, Sferlazzas C. No changes of insulin sensitivity in cystic fibrosis patients with different degrees of glucose tolerance: an epidemiological and longitudinal study. Eur J Endocrinol 1994;130:253–258

36. Lanng S, Thorsteinsson B, Roder ME, Nerup J, Koch C. Insulin sensitivity and insulin clearance in cystic fibrosis patients with normal and diabetic glucose tolerance. Clin Endocrinol 1994;41:217–223

37. Moran A, Pyzdrowski KL, Weinreb J, Kahn BB, Smith SA, Adams KS, Seaquist ER. Insulin sensitivity in cystic fibrosis. Diabetes 1994;43:1020–1026

38. Hardin DS, LeBlanc A, Lukenbough S, Seilheimer DK. Insulin resistance is associated with decreased clinical status in cystic fibrosis. J Pediatr 1997;130:948–956

39. Hardin DS, LeBlanc A, Marshall G, Seilheimer DK. Mechanism of insulin resistance in cystic fibrosis. Am J Physiol 2001; 281:E1022–E1028

40. Kien CL, Horswill CA, Zipf SB, McCoy KS, O'Dorisio T. Elevated hepatic glucose production in children with cystic fibrosis. Pediatr Res 1995;37:600–605

41. Hardin DS, LeBlanc A, Para L, Seilheimer DK. Hepatic insulin resistance and defects in substrate utilization in cystic fibrosis. Diabetes 1999;48:1082–1087

42. Ali BR. Is cystic fibrosis-related diabetes an apoptotic consequence of ER stress in pancreatic cells? Med Hypotheses 2009; 72:55–57

43. Stalvey MS, Muller C, Schatz DA, Wasserfall CH, Campbell-Thompson ML, Theriaque DW, Flotte TR, Atkinson MA. Cystic fibrosis transmembrane conductance regulator deficiency exacerbates islet cell dysfunction after beta-cell injury. Diabetes 2006;55:1939–1945

44. Carrington M, Krueger LJ, Holsclaw DS Jr, Iannuzzi MC, Dean M, Mann D. Cystic fibrosis-related diabetes is associated with HLA DQB1 alleles encoding Asp-57- molecules. J Clin Immunol 1994;14:353–358

45. Minicucci L, Cotellessa M, Pittaluga L, Minuto N, d'Annunzio G, Azanzini MA, Lorini R. Beta-cell autoantibodies and diabetes mellitus family history in cystic fibrosis. J Pediatr Endocrinol Metab 2005; 18:755–760

46. Nousia-Arvanitakis S, Galli-Tsinopoulou A, Dracoulacos D, Karamouzis M, Demitriadou A. Islet autoantibodies and insulin dependent diabetes mellitus in cystic fibrosis. J Pediatr Endocirnol Metab 2000; 13:319–324

47. De Luca F, Arrigo T, Conti Nibali S, Sferlazzas C, Gigante A, Di Cesare E, Cucinotta D. Insulin secretion, glycosylated haemoglobin and islet cell antibodies in cystic fibrosis children and adolescents with different degrees of glucose tolerance. Horm Metab Res 1991;23:495–498

48. Geffner ME, Lippe BM, Maclaren NK, Riley WJ. Role of autoimmunity in insulinopenia and carbohydrate derangements associated with cystic fibrosis. J Pediatr 1988;112:419–421

49. Lanng S, Thorsteinsson B, Pociot F, Marshall MO, Madsen HO, Schwartz M, Nerup J, Koch C. Diabetes mellitus in cystic fibrosis: genetic and immunological markers. Acta Paediatr 1993;82:150–154

50. Rolon MA, Benali K, Munck A, Navarro J, Clement A, Tubiana-Rufi N, Czernichow P, Polak M. Cystic fibrosis–related diabetes mellitus: clinical impact of prediabetes and effects of insulin therapy. Acta Paediatr 2001;90:860–867

51. Atlas AB, Finegold DN, Becker D, Trucco M, Kurland G. Diabetic ketoacidosis in cystic fibrosis. AJDC 1992;146:1457–1458

52. Swartz LM, Laffel LM. A teenage girl with cystic fibrosis–related diabetes, diabetic ketoacidosis, and cerebral edema. Pediatr Diabetes 2008;9:426–430

53. Blackman SM, Hsu S, Ritter SE, Naughton KM, Wright FA, Drumm ML, Knowles MR, Cutting GR. A susceptibility gene for type 2 diabetes confers substantial risk for diabetes complicating cystic fibrosis. Diabetologia 2009;52:1858–1865

54. Blackman SM, Hsu S, Vanscoy LL, Collaco JM, Ritter SE, Naughton K, Cutting GR. Genetic modifiers play a substantial role in diabetes complicating cystic fibrosis. J Clin Endocrinol Metab 2009; 94:1302–1309

55. Derbel S, Doumaguet C, Hubert D, Mosnier-Pudar H, Gradbar S, Chelly J, Bienvenu T. Calpain 10 and development of

diabetes mellitus in cystic fibrosis. J Cyst Fibros 2006;5:47–51

56. Figueroa V, Milla C, Parks EJ, Schwarzenberg SJ, Moran A. Abnormal lipid concentrations in cystic fibrosis. Am J Clin Nutr 2002;75:1005–1011

57. Schwarzenberg SJ, Thomas W, Olsen TW, Grover T, Walk D, Milla C, Moran A. Microvascular complications in cystic fibrosis–related diabetes. Diabetes Care 2007;30:1056–1061

58. Andersen HU, Lanng S, Pressler T, Laugesen CS, Mathiesen ER. Cystic fibrosis–related diabetes: the presence of microvascular diabetes complications. Diabetes Care 2006;29:2660–2663

59. van den Berg JM, Morton AM, Kok SW, Pijl H, Conway SP, Heijerman HG. Microvascular complications in patients with cystic fibrosis–related diabetes (CFRD). J Cyst Fibros 2008;7:515–519

60. Yung B, Landers A, Mathalone B, Gyi KM, Hodson ME. Diabetic retinopathy in adult patients with cystic fibrosis–related diabetes. Respir Med 1998;92:871–872

61. Lanng S, Thorsteinsson B, Nerup J, Koch C. Influence of the development of diabetes mellitus on clinical status in patients with cystic fibrosis. Eur J Pediatr 1992;151:684–687

62. Finkelstein SM, Wielinski CL, Elliott GR, Warwick WJ, Barbosa J, Wu SC, Klein DJ. Diabetes mellitus associated with cystic fibrosis. J Pediatr 1988;112:373–377

63. Milla CE, Warwick WJ, Moran A. Trends in pulmonary function in patients with cystic fibrosis correlate with the degree of glucose intolerance at baseline. Am J Resp Crit Care Med 2001;162:891–895

64. Kien CL, Zipf WB, Horswill CA, Denne SC, McCoy KS, O'Dorisio TM. Effects of feeding on protein turnover in healthy children and in children with cystic fibrosis. Am J Clin Nutr 1996;64:608–614

65. Hardin DS, LeBlanc A, Lukenbaugh S, Para L, Seilheimer DK. Proteolysis associated with insulin resistance in cystic fibrosis. Pediatrics 1998;101:433–437

66. Moran A, Milla C, Ducret R, Nair KS. Protein metabolism in clinically stable adult cystic fibrosis patients with abnormal glucose tolerance. Diabetes 2001;50:1336–1343

67. Moran A, Basu R, Milla C, Jensen MD. Insulin regulation of free fatty acid kinetics in adult cystic fibrosis patients with impaired glucose tolerance. Metabolism 2004;53:1467–1472

68. Rafii M, Chapman K, Stewart C, Kelly E, Hanna A, Wilson DC, Tullis E, Pencharz PB. Changes in response to insulin and the effects of varying glucose tolerance on whole-body protein metabolism in patients with cystic fibrosis. Am J Clin Nutr 2005;81:421–426

69. Franzese A, Spagnuolo MI, Sepe A, Valerio G, Mozzillo E, Raia V. Can glargine reduce the number of lung infections in patients with cystic fibrosis–related diabetes? (Letter). Diabetes Care 2005;28:2333

70. Lanng S, Thorsteinsson B, Nerup J, Koch C. Diabetes mellitus in cystic fibrosis: effect of insulin therapy on lung function and infections. Acta Paediatrica 1994;83:849–853

71. Mohan K, Israel KL, Miller H, Grainger R, Ledson MJ, Walshaw MJ. Long-term effect of insulin treatment in cystic fibrosis-related diabetes. Respiration 2008;76:181–186

72. Mozzillo E, Franzese A, Valerio G, Sepe A, De Simone I, Mazzarella G, Ferri P, Raia V. One-year glargine treatment can improve the course of lung disease in children and adolescents with cystic fibrosis and early glucose derangements. Pediatr Diabetes 2009;10:162–167

73. Nousia-Arvanitakis S, Galli-Tsinopoulou A, Karamouzis M. Insulin improves clinical status of patients with cystic fibrosis-related diabetes mellitus. Acta Paediatr 2001;90:515–519

74. Moran A, Pekow P, Grover P, Zorn M, Slovis B, Pilewski J, Tullis E, Liou TG, Allen H, Cystic Fibrosis Related Diabetes Therapy Study Group. 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;32:1783–1788

75. Bizzarri C, Lucidi V, Ciampalini P, Bella S, Russo B, Cappa M. Clincial effects of early treatment with insulin glargine in patients with cystic fibrosis and impaired glucose tolerance. J Endocrinol Invest 2006;29:1–4

76. Brennan AL, Gyi KM, Wood DM, Johnson J, Holliman R, Baines DL, Philips BJ, Geddes DM, Hodson ME, Baker EH. Airway glucose concentrations and effect on growth of respiratory pathogens in cystic fibrosis. J Cyst Fibros 2007;6:101–109

77. Ntimbane T, Krishnamoorthy P, Huot C, Legault L, Jacob SV, Brunet S, Levy, E, Guéraud F, Lands LC, Comte B. Oxidative stress and cystic fibrosis-related diabetes: a pilot study in children. J Cyst Fibros 2008;7:373–384

78. Milla CE, Billings J, Moran A. Diabetes is associated with dramatically decreased survival in female but not male subjects with cystic fibrosis. Diabetes Care 2005;28:2141–2144

79. Sims EJ, Green MW, Mehta A. Decreased lung function in female but not male subjects with established cystic fibrosis–related diabetes. Diabetes Care 2005;28:1581–1587