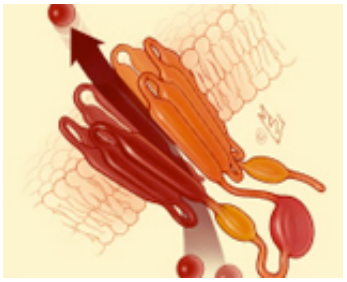
JOHNS HOPKINS MEDICINE
eLITERATURE REVIEW
eCysticFibrosis Review

Presented by
The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing

Supported by Educational Grants from Genentech, Inc., Eurand Pharmaceuticals, Inc., Vertex Pharmaceuticals, Incorporated, Axcan Pharma, Inc. and Gilead Sciences, Inc.



Welcome to Volume 2 of eCysticFibrosis Review

With the launch of this issue, we want to welcome back our returning subscribers, say hello to our newly registered clinicians, and thank the more than 1730 of you receiving this issue for your involvement in this program. In Volume 2, we'll continue to provide you with current, clinically relevant data on topics important to helping you improve outcomes in your patients. The topics will be delivered bi-monthly: 6 bi-monthly newsletters and 6 case-based podcasts. Topics will include: Nutritional Challenges and Complications, Novel Inhalational Therapies, Allergic Bronchopulmonary Aspergillosis (ABPA), Vitamin D and Bone Health.

The Program Directors, Author, and Editors of eCysticFibrosis Review.

December 2009: VOLUME 2, NUMBER 1

Cystic Fibrosis–Related Diabetes

In this Issue...

Diabetes, the most common comorbidity in persons with cystic fibrosis (CF), is associated with increased morbidity and mortality. The single most important question in this field today is whether less severe glucose tolerance abnormalities are also clinically relevant and thus warrant diabetes therapy.

In this issue, we review new studies that explore the genetic links to diabetes in individuals with CF, demonstrate the frequency of hyperglycemia in the nondiabetic CF population under free-living conditions, determine a threshold glucose level at which blood glucose crosses into airway secretions, and present the results of aggressive diabetes treatment on patient outcomes, both in clinical practice and in a multicenter, randomized, placebo-controlled trial.

LEARNING OBJECTIVES

At the conclusion of this activity, participants should be able to:

- Describe the ways in which hyperglycemia may impact lung function in patients with cystic fibrosis
- Identify current trends in morbidity and mortality associated with cystic fibrosis–related diabetes (CFRD)
- Evaluate the results of the Cystic Fibrosis–Related Diabetes Therapy (CFRDT) trial

IMPORTANT CME/CE INFORMATION ▼ Program Begins Below

ACCREDITATION STATEMENTS
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of The Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing . The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

LEARNING OBJECTIVES
At the conclusion of this activity, participants should be able to:

Newsletter

- Describe the ways in which hyperglycemia may impact lung function in patients with cystic fibrosis
- Identify current trends in morbidity and mortality associated with cystic fibrosis–related diabetes (CFRD)

Program Information
CME/CE Info
Accreditation
Credit Designations
Intended Audience
Learning Objectives
Internet CME/CE Policy
Faculty Disclosures
Disclaimer Statement

Length of Activity
Physicians
1 hour
Nurses
1 contact hour
Dieticians
1 contact hour
Physical Therapists
1 contact hour

Release Date
December 8, 2009

Expiration Date
December 7, 2011

Podcast Release
January 8, 2009

Next Newsletter Issue
February 9, 2010

TO COMPLETE THE POST-TEST

Step 1.
Please read the newsletter.

Step 2.
See the Post-test link at the end of the newsletter.

Step 3.
Follow the instructions to access the post-test.

The Institute for Johns Hopkins Nursing is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

CREDIT DESIGNATIONS

Physicians

Newsletter: The Johns Hopkins University School of Medicine designates this educational activity for a maximum of 1.0 *AMA PRA Category 1 Credit(s)*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Podcasts: The Johns Hopkins University School of Medicine designates this educational activity for a maximum of 0.75 *AMA PRA Category 1 Credit(s)*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Nurses

Newsletter: This 1 contact hour Educational Activity is provided by The Institute for Johns Hopkins Nursing. Each Newsletter carries a maximum of 1 contact hours or a total of 6 contact hours for the six newsletters in this program.

To obtain contact hours, you must complete this Education Activity and post-test before December 7, 2011.

Podcasts: These paired 0.75 contact hour Educational Activities are provided by The Institute for Johns Hopkins Nursing. Each podcast carries a maximum of 0.75 contact hours or a total of 4.5 contact hours for the three podcasts in this program.

To obtain contact hours, you must complete this Education Activity and post-test before January 7, 2011.

Dieticians

Newsletter: The Johns Hopkins University has approved this activity for 1.0 contact hours for non-physicians.

Podcasts: The Johns Hopkins University has approved this activity for 0.75 contact hours for non-physicians.

Physical Therapists

Newsletter: The Johns Hopkins University has approved this activity for 1.0 contact hours for non-physicians.

Podcasts: The Johns Hopkins University has approved this activity for 0.75 contact hours for non-physicians.

Respiratory Therapists

For United States: Visit this page to confirm that your state will accept the CE Credits gained through this program.

For Canada: Visit this page to confirm that your province will accept the CE Credits gained through this program.

INTENDED AUDIENCE

This activity has been developed for Pulmonologists, Pediatric Pulmonologists, Gastroenterologists, Pediatricians, Infectious disease specialists, Respiratory therapists, Dieticians, Nutritionists, Nurses, and Physical therapists.

LAUNCH DATE

This program launched on December 8, 2009, and is published monthly; activities expire two years from the date of publication, ending in December 7, 2011.

- Evaluate the results of the Cystic Fibrosis–Related Diabetes Therapy (CFRDT) trial

POST-TEST

To take the post-test for eCysticFibrosis Review you will need to visit The Johns Hopkins University School of Medicine's CME website and The Institute for Johns Hopkins Nursing . If you have already registered for other Hopkins CE programs at these sites, simply enter the requested information when prompted. Otherwise, complete the registration form to begin the testing process. A passing grade of 83% or higher on the post-test/evaluation is required to receive CE credit.

STATEMENT OF RESPONSIBILITY

The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing take responsibility for the content, quality and scientific integrity of this CME/CE activity.

INTERNET CME/CE POLICY

The Office of Continuing Medical Education (CME) at The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing are committed to protect the privacy of its members and customers. The Johns Hopkins University maintains its Internet site as an information resource and service for physicians, other health professionals and the public.

Continuing Medical Education at The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing will keep your personal and credit information confidential when you participate in a CE Internet-based program. Your information will never be given to anyone outside The Johns Hopkins University program. CE collects only the information necessary to provide you with the service you request.

FACULTY DISCLOSURE

As a provider accredited by the Accreditation Council for Continuing Medical Education (ACCME), it is the policy of Johns Hopkins University School of Medicine to require the disclosure of the existence of any relevant financial interest or any other relationship a faculty member or a provider has with the manufacturer(s) of any commercial product(s) discussed in an educational presentation. The presenting faculty reported the following:

- **Michael P. Boyle, MD, FCCP** discloses that he has received grant/research support Vertex Pharmaceuticals, Inc.
- **Peter J. Mogayzel, Jr, MD, PhD** discloses that he has no financial relationship with commercial supporters.
- **Meghan Ramsay, MS, CRNP** discloses that she has no financial relationship with commercial supporters.
- **Donna W. Peeler, RN** discloses that she has no financial relationship with commercial supporters.

Guest Author's Disclosures

DISCLAIMER STATEMENT

The opinions and recommendations expressed by faculty and other experts whose input is included in this program are their own. This enduring material is produced for educational purposes only. Use of Johns Hopkins University name implies review of educational format design and approach. Please review the complete prescribing information of specific drugs or combination of drugs, including indications, contraindications, warnings and adverse effects before administering pharmacologic therapy to patients.

HARDWARE & SOFTWARE REQUIREMENTS

Pentium 800 processor or greater, Windows 98/NT/2000/XP or Mac OS 9/X, Microsoft Internet Explorer 5.5 or later, 56K Modem or better, Windows Media Player 9.0 or later, 128 MB of RAM Monitor settings: High color at 800 x 600 pixels, Sound card and speakers, Adobe Acrobat Reader.

IN THIS ISSUE

GUEST AUTHOR OF THE MONTH

Commentary & Reviews:

Antoinette Moran, MD
Professor and Division Chief
Pediatric Endocrinology and Diabetes
University of Minnesota
Minneapolis, Minnesota

Guest Faculty Disclosures

Dr. Moran discloses that she has no financial relationship with commercial supporters.

Unlabeled/Unapproved Uses

The author has indicated that there will be no reference to unlabeled or unapproved uses of drugs or products in the presentation.

Program Directors' Disclosures

JANUARY PODCAST

***eCysticFibrosis Review* is happy to offer our accredited PODCASTS, to be sent to you in January.**

The *eCysticFibrosis Review* podcast complements the topic presented in this issue by applying the information to patient scenarios. Our November author, Antoinette Moran, MD and Robert Busker, *eCysticFibrosis Review's* Managing Editor discuss the topic: Cystic Fibrosis–Related Diabetes.

Participants can now receive 0.75 credits per podcast after completing an online post-test via the links provided on this page.

To learn more about podcasting and how to access this exciting new feature of *eCysticFibrosis Review*, please visit this page..

back to top

COMMENTARY

Cystic fibrosis–related diabetes (CFRD) is part of a spectrum of progressively worsening glucose tolerance abnormalities. As defined by the oral glucose tolerance test (OGTT), approximately 60% of children, 30% of adults age 20-40 years and 20% of adults older than 40 years have normal glucose tolerance (NGT). Glucose tolerance abnormalities become more prevalent with age and include impaired glucose tolerance (IGT), CFRD without fasting hyperglycemia (CFRD FH-), and CFRD with fasting hyperglycemia (CFRD FH+). Diabetes is associated with increased morbidity and mortality in patients with CF. In the general population, individuals with both type 1 diabetes (T1D) and type 2 diabetes (T2D) frequently die of atherosclerotic cardiovascular disease; in contrast, CF patients with and without diabetes typically die of pulmonary disease. Nutritional status and lung function begin to decline several years before the actual diagnosis of CFRD—that is, in the prediabetic period. Nutrition is intimately linked to pulmonary function, and insulin is an important anabolic hormone involved in the conservation of weight and lean body mass. The degree of insulin insufficiency is related to the rate of pulmonary function decline; when followed for 4 years after a baseline OGTT, patients with IGT had more rapid loss of lung function than did those with NGT, and those with CFRD FH- had the greatest loss.[1] The rate of decline in pulmonary function was inversely related to the OGTT area-under-the-curve for insulin.

The first suggestion that diabetes might negatively impact survival in persons with CF occurred in 1988, when it was reported that <25% of CF patients with diabetes reached the age of 30 years, compared with ~60% of those without diabetes.[2] Since that time, multiple studies have demonstrated that CFRD is associated with worse nutritional status, more severe lung disease, and increased mortality. For reasons that are not well understood, females with CFRD are particularly vulnerable to excess morbidity and mortality. In one study, women with CFRD died a full 16 years earlier than did women without diabetes or men with CF.[3] Careful investigation did not reveal an explanation for the excess female risk, but it was hypothesized that insulin insufficiency and diabetes each created a catabolic state that men were better able to counterbalance because of endogenous anabolic steroids.

Several important questions remain to be answered in patients with CFRD, but recent studies, including those presented in this review, are moving this field forward. Among these questions are:

Why is it that all patients with CF do not eventually develop diabetes?
Approximately 50% of the islet mass is destroyed by atrophy and fibrosis in essentially all pancreatic-insufficient CF patients, yet only about half of them actually develop diabetes. Blackman and associates have published 2 studies linking CFRD to a family history of T2D and to a gene known to be involved in the etiology of T2D. Their findings support a hypothesis linking both fibrosis-associated reduced islet mass and genetic defects in beta-cell function to CFRD:

> *Physical destruction of pancreatic islets leads to insulin insufficiency in the majority of patients with CF. Glucose tolerance is relatively normal in many of these patients because their remaining beta cells are sufficiently competent to compensate for reduced beta-cell numbers. Others go on to develop CFRD because their beta cells are relatively dysfunctional due to the same genetic defects that are associated with T2D.*

The genetics of T2D are complicated and there are many candidate genes; future identification of those genes specifically associated with CFRD may shed light on the pathophysiology of this disorder and help to inform treatment options, as well as identify at-risk individuals.

Is hyperglycemia an important contributor to the morbidity and mortality associated with CF?
We have long believed that the nutritional consequences of insulin deficiency in patients with CF are of greater consequence than the metabolic effects of hyperglycemia, with much research over the last decade having focused on this aspect of diabetes. The impact of hyperglycemia per se has been largely ignored. In the articles reviewed in this issue, Dobson and coworkers used home continuous glucose monitoring technology to

demonstrate that even patients with NGT experience intermittent glucose levels in the diabetic range under free-living conditions. Should these individuals receive diabetes treatment? Brennan and colleagues demonstrated that when blood glucose levels are elevated above a modest threshold of 144 mg/dL, airway glucose concentrations are also elevated, thus creating an environment that encourages bacterial growth. These studies suggest that even relatively low levels of hyperglycemia may be harmful in patients with CF.

Is increased mortality inevitable in patients with CFRD, especially women? Encouraging new data from the University of Minnesota, reviewed in this issue, suggest that early detection and aggressive insulin therapy have narrowed the gap in mortality between CF patients with and without diabetes, and have eliminated the gender disparity in mortality. In a separate investigation, also described in this issue, a multicenter, placebo-controlled trial demonstrated that insulin therapy not only stopped but also reversed chronic weight loss in men and women with "mild" diabetes (CFRD FH-). These reports provide evidence of the benefits of aggressive insulin therapy in patients with CFRD and offer hope for those with this diagnosis.

Taken together, the findings discussed in this issue suggest that hyperglycemia is common in the majority of patients with CF, that even modest hyperglycemia may have negative consequences, and that aggressive treatment at the more severe end of the glucose tolerance spectrum improves patient outcomes. As with all good clinical research, these studies have created as many new questions as they have answered. Additional research is needed to further explore genetic predisposition to CFRD, to understand the consequences of intermittent hyperglycemia in patients with CF who have otherwise relatively normal glucose metabolism, and to define glucose tolerance threshold levels for instituting diabetes therapy in individuals with CF.

Commentary References

1. 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 Respir Crit Care Med.* 2001;162(3 pt 1):891-895.
2. Finkelstein SM, Wielinski CL, Elliott GR, et al. Diabetes mellitus associated with cystic fibrosis. *J. Pediatr.* 1988;112(3):373-377.
3. 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(9):2141-2144.

STUDIES LINKING CFRD TO TYPE 2 DIABETES

Blackman SM, Hsu S, Vanscoy LL, Collaco JM, et al. **Genetic modifiers play a substantial role in diabetes complicating cystic fibrosis.** *Clin Endocrinol Metab.* 2009;94(4):1302-1309.

(For non-journal subscribers, an additional fee may apply for full text articles.)

View journal abstract View full article

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):1858-1865.

(For non-journal subscribers, an additional fee may apply for full text articles.)

View journal abstract View full article

For many years, speculation has existed that the genetic risk for CFRD might be related to genes associated with T2D. Blackman and associates, of the Johns Hopkins University School of Medicine, have recently published 2 reports that support this notion. In the first study, entitled "Genetic Modifiers Play a Substantial Role in Diabetes Complicating Cystic Fibrosis," the authors used data from an ongoing twin and sibling study to estimate the

relative contributions of genetic and nongenetic modifiers to the development of diabetes in persons with CF. They gathered clinical and biochemical data on 1366 individuals from 109 centers, including 68 monozygous twin pairs, 23 dizygous twin pairs, and 588 sibling pairs, all with CF. In a second report, entitled "A Susceptibility Gene for Type 2 Diabetes Confers Substantial Risk for Diabetes Complicating Cystic Fibrosis," this same patient cohort was used to question whether a family history of T2D affects diabetes risk. In addition, 988 patients from the family-based study plus 802 unrelated patients with CF were assessed in a case-control study to evaluate a gene known to be associated with T2D susceptibility (transcription factor 7-like 2, or TCF7L2).

The concordance rate for diabetes was significantly higher in monozygous twins compared with dizygous twins or sibling pairs with CF (*P*=.002), suggesting an important role for genetic modifiers in the development of CFRD. Family history of T2D significantly increased the risk for diabetes in patients with CF (odds ratio [OR], 3.1; *P*=.0009). A TCF7L2 variant known to be associated with T2D was also commonly found in patients with CFRD (*P*=.0002), decreasing the mean age at which diabetes was diagnosed by 7 years.

Thick, viscous pancreatic secretions lead to inflammation, obstruction, and obliteration of small ducts in the pancreas, with associated pancreatic fibrosis and scarring. Both exocrine and endocrine tissues are destroyed. Originally, it was believed that diabetes was related strictly to mechanical factors—that is, the more islets that were destroyed, the more likely it was that a patient with CF would develop diabetes. Autopsy studies did not support this theory, however, since the reduction in islet mass was about 50% in both patients with and those without diabetes, suggesting that additional factors were involved in the pathogenesis of CFRD.[1] The earliest speculation that CFRD might be related to T2D followed the discovery that pancreatic islet amyloid deposition occurred in CFRD, similar to that observed in T2D, but not in T1D or chronic pancreatitis.[1] The 2 recent studies by Blackman and coworkers are the first to demonstrate a clear genetic link between CFRD and T2D. This does not mean that CFRD is T2D, though, since the 2 forms of diabetes have very different clinical manifestations. However, it does explain why beta cells work better in some patients with CF compared with others. Additional studies are warranted in this area to help better explain how these genetic modifiers interact with the pathophysiology of CF to give rise to early diabetes in this patient population, which, in turn, might influence medication options. In addition, early identification of those individuals most likely to develop diabetes would be a valuable clinical and research tool. Studies could be instituted to determine if early prediabetes therapy might have a positive impact on clinical course, and diabetes prevention strategies could then be developed accordingly.

References

1. 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(3): 1267-1272.

back to top

HYPERGLYCEMIA IS DETECTED EVEN AMONG PATIENTS WITH CF WHO HAVE NORMAL GLUCOSE TOLERANCE

Dobson L, Sheldon CD, Hattersley AT. **Conventional measures underestimate glycaemia in cystic fibrosis patients.** *Diabet Med.* 2004;21(7):691-696.

(For non-journal subscribers, an additional fee may apply for full text articles.)

View journal abstract View full article

Glucose tolerance in CF is traditionally defined by the results of a standard OGTT. However, it has frequently been noted that few patients with CF have truly normal glucose tolerance, since the OGTT glucose area-under-the-curve is higher in those with CF and NGT compared with normal control subjects, even though fasting and 2-hour glucose

levels are the same. Dobson and colleagues used the technology of continuous interstitial glucose monitoring (CGM) to evaluate glucose levels in nondiabetic patients with CF, and age- and body mass index (BMI)–matched non-CF controls, under free-living conditions at home. The authors had previously validated the use of CGM in persons with CF.[1] After the sensor was attached, subjects underwent an OGTT and then continued to wear the sensor for 72 hours at home during their usual daily activities.

Of the 21 patients with CF, 5 (25%) had impaired glucose tolerance and were excluded from the final analysis, compared with 2 of the 21 controls (5%). The remaining subjects all had NGT by OGTT fasting and 2-hour glucose criteria. Among those with NGT, fasting glucose, 2-hour glucose, and hemoglobin (Hb)A1c were normal and did not differ in patients with CF compared with controls. However, as has been previously described, mid-OGTT (at 30, 60, or 90 minutes) glucose levels and OGTT glucose area-under-the-curve were greater in those with CF. During the 72 hours of sensor assessment, the mean CGM glucose levels were significantly higher in NGT patients with CF compared with normal controls (106 vs 92 mg/dL, respectively; *P*=.004). Under these free-living conditions, 33% of subjects with CF had ≥1 continuous glucose monitoring system (CGMS) glucose value >200 mg/dL, compared with 5% of control subjects (*P* =.00001). The investigators concluded that both HbA1c and OGTT underestimate glucose abnormalities in individuals with CF.

This study confirmed previous reports that mid-OGTT levels tend to be higher than normal even in CF patients with NGT, expanding those observations to include abnormal glucose elevation under free-living conditions. Patients with CF consume high-calorie diets, and it is not surprising that glucose levels might be higher when carbohydrate intake is substantially greater than the 75 grams that has been standardized for the OGTT. The clinical relevance of these findings is unclear, however. American Diabetes Association criteria for the diagnosis of diabetes include any of the following: (1) fasting hyperglycemia; (2) hyperglycemia at the end of a standard 2-hour OGTT; and (3) casual (random) glucose levels >200 mg/dL in the presence of symptoms. These criteria were developed based on the risk for microvascular complications in the general diabetes population. Microvascular complications do occur in patients with CFRD, but tend to be less common and less severe than in those with T1D or T2D. Notably, such complications have not been described in patients with CF who do not have fasting hyperglycemia,[2] thus the patients in the Dobson et al study are not likely to be at risk for eye or kidney disease associated with diabetes. Of greater concern in patients with CF are the potential negative consequences of insulin insufficiency or hyperglycemia on nutritional status and pulmonary function. This has been described in patients with CFRD and IGT, but not in those with NGT.[3]

So what are the clinical implications of intermittent casual glucose level elevation under free-living conditions in asymptomatic patients with CF who have otherwise normal glucose tolerance? Additional studies are needed linking CGM results to outcomes before this question can be answered.

References

1. Dobson L, Sheldon CD, Hattersley AT. Validation of interstitial fluid in continuous glucose monitoring in cystic fibrosis (letter). *Diabetes Care.* 2003;26(6):1940-1941.
2. Schwarzenberg SJ, Thomas W, Olsen TW, Grover T, Walk D, Milla CE, Moran A. Microvascular complications in cystic fibrosis-related diabetes. *Diabetes Care.* 30(5):1056-1061.
3. 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 Respir Crit Care Med.* 2001;162(3 pt 1):891-895.

back to top

BLOOD GLUCOSE ELEVATION LEADS TO AIRWAY GLUCOSE ELEVATION IN PATIENTS WITH CF

Brennan AL, Gyi KM, Wood DM, et al. **Airway glucose concentrations and effect on growth of respiratory pathogens in cystic fibrosis.** *J Cyst Fibros.* 2007;6(2):101-109.

(For non-journal subscribers, an additional fee may apply for full text articles.)

View journal abstract View full article

Multiple studies have demonstrated that insulin insufficiency has a negative impact on CF morbidity and mortality by creating a catabolic state, and compromising body weight and lean body mass. What about the accompanying hyperglycemia? Does it have a direct effect on CF lung function? As a first step in answering these questions, Brennan and coworkers conducted a study to determine whether blood glucose (BG) elevation resulted in airway glucose (AG) elevation. A total of 40 patients with CF with a range of blood glucose levels underwent paired BG and AG measurements to determine the relationship between the 2 measurements. This team had previously validated the technique of using nasal secretion glucose levels as a surrogate for airway glucose levels. In a follow-up study, 10 CF patients with CFRD, 10 CF patients with NGT, and 10 normal control subjects were assessed for 48 hours at home by CGM, to determine the proportion of time each day patients with CF spent with blood glucose levels elevated above the airway glucose threshold. Finally, an *in vitro* study was conducted at glucose airway threshold levels to determine the effect of hyperglycemia on bacterial growth.

The authors determined that BG was significantly correlated with nasal glucose concentrations. Although glucose is not normally detected in airway secretions, individuals with CF who had BG levels >144 mg/dL had glucose in their nasal secretions more often and at higher concentrations than did those with BG levels less than this threshold. The CMG study showed that patients with CFRD spent about half of their time during the 48-hour monitoring period with glucose levels above this threshold, compared with 6% of the time in those with NGT CF and 1% in healthy volunteers. *Staphylococcus aureus* and *Pseudomonas aeruginosa* growth increased *in vitro* when cultured at these elevated glucose levels.

Concerns over morbidity and mortality in patients with CF have been focused largely on the catabolic effects of insulin insufficiency. This report shifts the focus to the deleterious effects of hyperglycemia *per se*. The authors offer insight into how blood glucose elevation might impact pulmonary disease in individuals with CF, by pathologically increasing airway glucose concentrations and creating an environment conducive to bacterial growth. The investigators speculate on additional mechanisms via which hyperglycemia might have an effect on CF lung function, including impairment of host immune function, structural changes in the lung from increased levels of advanced glycation end products, and upregulation of the inflammatory process. Along these lines, increased oxidative stress was recently noted to be associated with hyperglycemia in patients with CF.[1] This study suggests that tight control of blood glucose levels in individuals with CFRD might be important not just for the well-known benefit of reducing the risk for microvascular complications, but also to reduce airway compromise. Because patients with CF die of inflammatory lung disease, this is particularly relevant and warrants additional study.

References

1. Ntimbane T, Krishnamoorthy P, Huot C, et al. Oxidative stress and cystic fibrosis-related diabetes: a pilot study in children. *J Cyst Fibrosis.* 2008;7(5):373-384.

back to top

UPDATED CFRD PREVALENCE, INCIDENCE, AND MORTALITY DATA

Moran A, Billings J, Dunitz J, et al. **Cystic fibrosis–related diabetes: modern trends in prevalence, incidence and mortality.** *Diabetes Care.* In press.

The University of Minnesota (UM) CF Center has been conducting OGTT screening since the 1990s and recording the results in a CF database, along with clinical and other laboratory data. Previously published prevalence and incidence figures were collected at a time when routine screening had not been fully implemented. Survival statistics demonstrating significantly greater mortality in women with CFRD included data going back to the 1990s.[1] Because screening is now more efficient and the treatment of diabetes has changed considerably since these earlier reports, a new database review was performed to gather more recent information and to document trends over time with respect to prevalence, incidence, and mortality associated with CFRD. Data were reviewed from 872 patients with CF followed at the UM during 3 consecutive intervals: 1992 to 1997, 1998 to 2002, and 2003 to 2008.

As of September 2008, CFRD was present in 2% of children, 19% of adolescents, and 40% to 50% of adults with CF. Beginning in the teenage years, the incidence was ~3%. The only time there was a gender difference in incidence and prevalence was in the fourth decade of life, when there were more females. Diabetes included both CFRD FH- and CFRD FH+. In younger individuals, CFRD FH- predominated, but the prevalence of fasting hyperglycemia rose with age, with CFRD FH+ being more common among older individuals. Lung function and nutritional status did not differ between patients with CFRD FH- and those with CFRD FH+. From the earliest to the latest interval (1992 to 1997; 2003 to 2008), female mortality decreased by 51%, from 6.9 to 3.2 deaths per 100 patient-years, and male mortality decreased by 42% from 6.5 to 3.8 deaths per 100 patient-years. In the earlier time periods (before screening had become routine), diabetes was often first diagnosed in the perimorbid period, with about 20% of patients dying during the same interval as diagnosis. During 2003 to 2008, however, only 3% of subjects diagnosed in that period died. During this most recent period, while lung function (but not nutritional status) was still worse in CF patients with diabetes compared with those without the disorder, the gap had narrowed compared with the previous time intervals and the gender difference in mortality had completely disappeared. This improvement was attributed to early detection of diabetes and aggressive management with insulin therapy.

This report provided updated information on CFRD prevalence and incidence, and because patients with CF are living longer, these observations were extended into older age-groups. The most important finding was the improvement over the last 5 years in morbidity and mortality in CFRD patients in general, particularly among women. During the 1990s, many of the patients who received a new diagnosis of diabetes likely had had undetected and untreated disease for some time. Many of them were very ill patients who were more likely than the general CF population to be screened for diabetes because they were receiving extra medical attention related to severe illness. This resulted in a high association between CFRD and mortality. Currently, with more efficient routine screening, diabetes is generally detected early in the disease course. Over the last several years, treatment of CFRD FH+ has been similar to that of T1D, with basal bolus insulin therapy by insulin pump or multiple daily injections. Premeal insulin has been recommended for patients with CFRD FH-. The goal has been to treat patients with as much insulin as is safely possible, in order to maximize the anabolic effects. This database review suggests that this aggressive approach to screening and treatment has had a positive impact on morbidity and mortality in patients with CFRD.

Reference

1. 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(9):2141-2144.

back to top

RESULTS OF THE CFRDT TRIAL

Moran A, Pekow P, Grover P, et al; the CFRDT Study Group. **Insulin therapy to improve BMI in cystic fibrosis related diabetes without fasting hyperglycemia: results of the CFRDT trial.** *Diabetes Care.* In press.

(For non-journal subscribers, an additional fee may apply for full text articles.)

View journal abstract View full article

CFRD occurs both with and without fasting hyperglycemia. In the general population, these 2 forms of diabetes are not differentiated, because the risks for microvascular and macrovascular complications are the same. The CF population is different, however, with CFRD FH+, but not CFRD FH-, associated with microvascular complications in these patients.[1] Macrovascular complications do not appear to occur in any patients with CF. This has led to debate over whether those with CFRD FH- require diabetes treatment. At the time of the 1998 CFRD consensus conference report[10], this was identified as the most pressing research question. The CFRDT trial was undertaken in order to determine whether diabetes treatment would improve clinical status in this population. A 3-arm, multicenter, placebo-controlled trial was conducted to compare premeal rapid-acting insulin aspart, the oral insulin secretagogue repaglinide, and oral placebo. The primary study endpoint was comparison of the change in BMI the year prior to initiating therapy vs the change in BMI after 1 year of treatment.

A total of 100 patients were enrolled. In all, 81 completed the study, including 61 with CFRD FH- and 20 with severe IGT (glucose >200 mg/dL mid-OGTT and between 180 and 200 mg/dL at 2 hours). During the year prior to starting study medication, BMI declined in all groups. After 1 year of premeal insulin, the trajectory of BMI loss reversed in patients with CFRD FH-. Instead of losing 0.30 BMI units, these patients gained 0.39 BMI units (P=.02). This corresponded to ~2.5 pounds in women and 3 pounds in men being gained instead of lost. There was no significant change in the rate of BMI loss in placebo-treated patients (P=.45). The third arm of the study was premeal repaglinide. Although CFRD FH- patients initially gained weight with this oral agent, the effect was not sustained, and after 6 months the rate of BMI loss was similar to pretreatment; over the total 1-year study period, there was no significant improvement in the rate of BMI loss. No significant changes were observed in response to either treatment in those with severe IGT, but there was greater variability in this group and more subjects would have been needed to determine statistical significance.

CFRD FH- can only be diagnosed with an OGTT. During the 1998 consensus conference, controversy over whether these patients should receive diabetes treatment was the primary stumbling block to recommending OGTT as the screening test of choice in CF—why perform a test if it will not influence treatment decisions? Multiple reports have suggested that insulin therapy might improve nutritional status and/or pulmonary function in patients with CFRD,[2-7] but these generally involved small cohorts with no control group, which contained mixed populations of CFRD with and without fasting hyperglycemia. The results of the CFRDT trial demonstrated that a chronic, insidious loss of weight is present in patients with CFRD FH-, which insulin therapy is able to reverse. At first, the oral insulin secretagogue repaglinide also resulted in weight gain, but this effect was short-lived, likely because the reduced beta-cell mass simply could not maintain this level of stimulated insulin secretion. There was no change in pulmonary function over the study year, but in previous studies at UM, a 4-year time period was needed to document significant changes in lung function related to glucose tolerance status.[8] This study has shown that patients with CFRD FH- should be treated with insulin therapy. Because the OGTT is the only way to diagnose this form of diabetes, it is now the screening test of choice in patients with CF. Controversy still exists regarding whether diabetes therapy should be prescribed for patients with less severe glucose tolerance abnormalities, such as IGT,[5,9] with additional studies warranted in these populations.

References

1. Schwarzenberg SJ, Thomas W, Olsen TW, et al. Microvascular complications in cystic fibrosis-related diabetes. *Diabetes Care.* 2007;30(5):1056-1061.
2. 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? *Diabetes Care.* 2005;28(9):2333.
3. Lanng S, Thorsteinsson B, Nerup J, Koch C: Diabetes mellitus in cystic fibrosis: effect of insulin therapy on lung function and infections. *Acta Paediatr.* 1994;83(8):849-853.
4. 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(2):181-186.
5. Mozzillo E, Franzese A, Valerio G, et al. 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(3):162-167.
6. Nousia-Arvanitakis S, Galli-Tsinopoulou A, Karamouzis M. Insulin improves clinical status of patients with cystic-fibrosis-related diabetes mellitus. *Acta Paediatr.* 2001;90(5):515-519, 2001
7. Rolon MA, Benali K, Munck A, et al. Cystic-fibrosis-related diabetes mellitus: clinical impact of prediabetes and effects of insulin therapy. *Acta Paediatr.* 2001;90(8):860-867.
8. 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 Respir Crit Care Med.* 2001;162(3 pt 1):891-895.
9. Bizzarri C, Lucidi V, Ciampalini P, Bella S, Russo B, Cappa M. Clinical effects of early treatment with insulin glargine in patients with cystic fibrosis and impaired glucose tolerance. *J Endocrinol Invest.* 2006;29(3):RC1-RC4.
10. Manuscript expected in *Diabetes Care* in 2010.

back to top

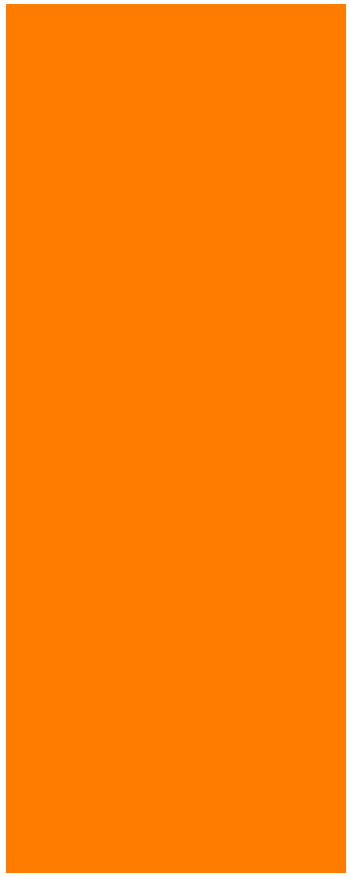


Illustration © Michael Linkinhoker