Cystic Fibrosis Related Diabetes: Current Trends in Prevalence, Incidence and Mortality

Running Title: CFRD prevalence, incidence and mortality

Antoinette Moran MD, Jordan Dunitz MD, Brandon Nathan MD, Asad Saeed MD, Bonnie Holme, William Thomas PhD

From the Departments of Pediatrics (AM, BN, BH), Medicine (JD, AS) and Division of Biostatistics, School of Public Health (WT), University of Minnesota

Address Correspondence To:
Antoinette Moran MD
Email: moran001@umn.edu

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**Objective:** CFRD diagnosis and management have changed considerably since diabetes was first shown to be associated with a poor prognosis in CF. Current trends in CFRD prevalence, incidence and mortality were determined from a comprehensive clinical database.

**Research Design and Methods:** Data were reviewed from 872 CF patients followed at the University of Minnesota during three consecutive intervals: 1992-1997, 1998-2002, and 2003-2008.

**Results:** CFRD is currently present in 2% of children, 19% of adolescents, and 40-50% of adults. Incidence and prevalence are higher in females age 30-39, but otherwise there is no gender difference. In younger individuals, CFRD without fasting hyperglycemia (FH-) predominates, but fasting hyperglycemia (FH+) prevalence rises with age. CFRD mortality has significantly decreased over time. From 1992–1997 to 2003–2008, female mortality dropped by >50% from 6.9 to 3.2 deaths per 100-patient-years, and in males from 6.5 to 3.8 deaths per 100-patient-years. There is no longer a gender difference in mortality. Earlier, diabetes was diagnosed as a peri-mortem event in nearly 20% of patients, but of 61 patients diagnosed with diabetes during 2003–2008, only 2 died. Lung function but not nutritional status is still worse in CF patients with diabetes compared to those without. Nutritional and pulmonary status are similar between FH- and FH+.

**Conclusions:** Previously noted gender differences in mortality have disappeared, and the gap in mortality between CF patients with and without diabetes has narrowed considerably. We believe that early diagnosis and aggressive treatment have played a major role in improving survival in these patients.
Diabetes is the most common co-morbidity in persons with cystic fibrosis (CF). It is particularly concerning that the additional diagnosis of diabetes has been associated with significantly greater mortality, particularly in women. In 1988, we reported that fewer than 25% of individuals with diabetes survived until age 30 years, compared to more than 60% of the non-diabetic CF population (1). We subsequently published data examining mortality at the University of Minnesota (UM) CF Center in the fifteen year period between 1987-2002, and came to the startling conclusion that diabetes reduced survival in women by more than 16 years (2). Unlike the general population, patients with CFRD are not at risk for atherosclerotic cardiovascular disease (3); as in other persons with CF, death occurs from chronic inflammatory lung disease. Pulmonary function and nutritional status have been shown in several studies to be intimately linked and to be worse in patients with CFRD compared to CF patients without diabetes (4-8). It has been postulated that this is a consequence of the protein catabolic effects of insulin deficiency combined with the pro-inflammatory effects of hyperglycemia.

Since 1987, experimental studies and careful clinical data collection have progressively increased our understanding of CFRD, and it is managed much differently today than even 5 years ago. With routine annual OGTT outpatient screening and careful inpatient glucose monitoring, patients are not likely to experience long periods of undiagnosed diabetes. We are much better able to accurately report prevalence and incidence of CFRD, particularly in the older age groups since CF patients are living longer. Early institution of intensive basal-bolus insulin therapy has become routine in the last five years. Thus, patients are diagnosed earlier and treated more aggressively than ever before. The current database review was undertaken to determine whether modern diabetes screening and management have influenced prevalence, incidence and mortality figures.

**RESEARCH DESIGN AND METHODS**

**Subjects:** Clinical information was reviewed from a total of 872 patients followed at the University of Minnesota CF Center from January 1, 1992 through September 15, 2008. CF patients are routinely seen at quarterly intervals, and patient data are record in the Minnesota CF Database. The information collected includes demographics, anthropometric data, pulmonary function tests, other laboratory tests, medications, and clinical characteristics. All patients followed at this center gave informed consent permitting their records to be reviewed for research purposes.

**CFRD diagnosis and management:** CFRD is diagnosed by standard criteria including 1) persistent random glucose levels >200 mg/dl (11.1 mmol/L), 2) persistent fasting glucose levels >126 mg/dl (7.0 mmol/L), or 3) by OGTT. Routine annual OGTT screening has been recommended at UM since the early 1990’s for patients aged ≥6 years (1.75g/kg glucose, maximum 75g). OGTTs are performed when patients are in their usual baseline state of health. Subjects are classified based on standards adopted by the 1998 CFRD consensus guidelines (9). Patients with a fasting glucose >126 mg/dl (7.0 mmol/L) have CFRD with fasting hyperglycemia (FH+), while those with a fasting glucose <126 mg/dl (7.0 mmol/L) and a 2h glucose >200 mg/dl (11.1 mmol/L) have CFRD without fasting hyperglycemia (FH-).

Diabetes management follows a uniform protocol that includes the involvement of an endocrinologist, a diabetes nurse educator, and a dietitian. Prior to 2003, the most common insulin regimen for patients with fasting hyperglycemia was a single injection of NPH insulin at bedtime and 3-4
injections of regular insulin (before 2000) or 4-6 injections of rapid-acting insulin (after 2000) with meals. Patients without fasting hyperglycemia were seldom treated with insulin. Since 2003, basal-bolus insulin therapy has been standard for CFRD FH+, using either an insulin pump or multiple daily injections including basal insulin. Patients with FH- have been encouraged to use pre-meal rapid-acting insulin. Hospitalized patients are now routinely treated with insulin if they are hyperglycemic; the need for persistent insulin is then re-evaluated once they are clinically well.

**Database Review:** In order to examine temporal changes, the data were examined for three consecutive intervals: 1/1/1992 through 12/31/1997, 1/1/1998 through 12/31/2002, and 1/1/2003 through 9/15/2008. All patients seen in clinic during an interval were included in calculations for that interval. Date of diabetes diagnosis was the earlier date for either starting insulin based on clinical criteria or an OGTT result diagnostic of diabetes. Percent predicted FEV1 was the last recorded value before 9/15/2008.

**Analytic Methods:** Prevalence percents and counts were compared between groups with logistic regression. Incidence and mortality rates were calculated as \(d/m\), where \(d\) is the total number of events during a time interval and \(m\) is the total time at risk of the event during the interval from all individuals. Under a Poisson model, the standard error of the rate is \(\sqrt{d/m}\). Incidence and mortality rates were compared between groups with Poisson regression. All analyses were performed with SAS Version 9.2 (SAS Institute, 2008, Cary NC).

**RESULTS**

**CFRD Prevalence:** In September 2008, there were 526 pediatric and adult patients actively followed at the UM Cystic Fibrosis Center. Of these, 33% had diabetes, similar to the 30% at the end of 2002 but a significant increase from the 20% of patients known to have diabetes at the end of 1997 (Table 1). In all three periods, the prevalence of diabetes rose steadily with age through the 30–39 age decade, and after age 40 remained at 45-50% (Figure 1A). In younger individuals, CFRD FH- predominated, but the prevalence of fasting hyperglycemia rose steadily with age so that the percentage of CFRD patients with and without FH was approximately equal for individuals in their 30’s, and after the age of 40 years CFRD FH+ predominated. In 2008, females had significantly higher diabetes prevalence in the 30–39 age decade than males, but otherwise no gender difference in prevalence was present (Figure 1B).

**CFRD Incidence:** While diabetes prevalence rose, incidence fell significantly: from 4 cases per 100-patient-years during the interval 1998–2002 to 2.7 cases per 100-patient-years during 2003–2008, representing a 40% decrease in the number of diabetes diagnoses (Table 1). The decrease in incidence occurred for both males and females, with a larger decrease in females. During the 1990’s, annual OGTT surveillance was just being established as the standard, so many of those receiving a new diagnosis of diabetes at their first screening may have had the disease for some time, inflating incidence. Currently, a peak in incidence is noted in women aged 30–39 (Figure 1).

**CFRD Mortality:** The increase in diabetes prevalence with a decrease in diabetes incidence resulted from a significant decrease in mortality in patients with diabetes. From 1992–1997 to 2003–2008, mortality for females with diabetes dropped by more than 50%, from 6.9 to 3.2 deaths per 100-patient-years, and the decrease for males was nearly as large, from 6.5 to 3.8 deaths per 100-patient-years (Table 1). During the earlier two time periods, diabetes was frequently diagnosed as a peri-morbid event. Of 108 patients diagnosed with diabetes during
1992–1997, 18 died during that same interval, and results were nearly identical during 1998–2002. During 2003–2008, 61 patients were diagnosed with diabetes, of whom only 2 died during the interval.

Mortality is shown in Figure 3 by diabetes status, gender, and age decade over the three time intervals. Over time there has been a steady decrease in mortality in CF patients with diabetes. In the most recent time period, overall mortality still remained significantly higher in those with CFRD compared to those without diabetes, but the gap has narrowed considerably compared to the earlier time periods. Importantly, during 2003–2008, gender differences in mortality by diabetes status appear to have disappeared.

Clinical Characteristics of the 2008 CFRD Patient Cohort: In September 2008, only 2 out of 92 children <11 years of age had diabetes, a boy and a girl, both FH-. Of 75 adolescents age 11-17, 19% had diabetes (6 girls and 8 boys---4 of the girls and 1 of the boys with FH+). There was a trend towards lower percent predicted FEV1 in those with diabetes, but this did not achieve statistical significance in this age group (83±29 vs 95±17, p=0.055). CF adolescents were generally normally nourished, and there was no significant difference in BMI percentile (47±27 vs 51±25, p=0.65) or BMI z-score (-0.1±0.9 vs 0.0±0.8, p=0.6) between those with and without CFRD. Among the 14 adolescents with CFRD, there were no significant differences in pulmonary or nutritional endpoints between those with and without FH.

Mortality has previously been shown to be greater in adult CF patients with diabetes, and thus the adult data are shown in Table 2. Of subjects age 18 and older, 155 of 360 (43%) had diabetes, half with and half without FH. There was no difference in age or nutritional status between subjects with and without diabetes. Lung function, however, was significantly worse in subjects with diabetes: (% predicted FEV1 65±24 vs 71±24, p<0.05). Surprisingly, this mean difference was almost entirely due to worse lung function in males. Among diabetic subjects, those with FH tended to be older with longer duration of diabetes, but with similar nutritional status and FEV1 compared to those without FH.

CONCLUSIONS

The 527 patients currently followed at the UM CF Center are well characterized with regards to diabetes prevalence, incidence and mortality. CFRD is present in 2% of children, 19% of adolescents, 40% of individuals in their 20’s, and 45-50% of those age 30 years and older. In the 30-39 age group, women with CFRD outnumber men, but otherwise we do not observe a gender difference in prevalence. Incidence is 2.7 cases per 100-patient years, with the exception of women in their 30’s, in whom it more than doubles. While mortality is still greater in CF patients who develop diabetes, over the last 15 years this difference has steadily and markedly diminished, and the previously noted gender difference in mortality appears to have completely disappeared.

Since 1988, several reports have documented worse clinical status in CF patients who developed diabetes. Both a 2005 North American review of 8247 CF patients (8) and a 2001 European study of 7500 patients (6) found that CFRD was associated with more severe pulmonary disease and worse nutritional status, and this was also documented in multiple smaller studies (1; 4; 5; 7). This has been postulated to be related to both insulin deficiency (with resultant protein catabolism and malnutrition) and to the influence of hyperglycemia on inflammation and infection. The current assessment demonstrates that while we still find worse lung function in patients with CFRD, the mortality associated with this condition has steadily and substantially decreased over
time. We speculate that this is related to both earlier detection of diabetes and to more aggressive treatment. CFRD is generally clinically silent and only detected by screening. Earlier, diabetes was often diagnosed in patients with existing but previously undetected (and untreated) disease, often in the peri-morbid period. Routine screening now ensures that diabetes is detected early in its course.

CFRD treatment is also much more aggressive today than in the past. The goals of treatment are to achieve near-normalization of blood glucose levels and to deliver as much insulin as possible without producing hypoglycemia in order to maximize the anabolic effects of insulin. At the time of the last CFRD consensus conference in 1998, it was not clear whether CFRD FH- was a milder form of diabetes requiring less intensive treatment. The current assessment suggests that pulmonary and nutritional parameters do not differ by fasting glucose status and that patients without fasting hyperglycemia are not “less sick” than those with fasting hyperglycemia. The standard of care at UM is now insulin therapy for CFRD patients with and without FH.

When UM CF mortality data from 1987-2002 were previously analyzed (2), women with CF and diabetes had dramatically worse survival. This could not be explained by age, age of diagnosis of CF or diabetes, HbA1c, BMI, pregnancy, glucocorticoid use, microorganism colonization, or genotype. A gender difference was also found in a multi-center British study which reported worse lung function in women with CF and diabetes (10). We speculated that diabetes might exacerbate CF-related pulmonary inflammation and protein catabolism, and that the presence of anabolic steroids might offer men natural protection from the catabolic effects of these two diseases. With modern intensive diabetes treatment, the gender difference in mortality appears to have disappeared.

In summary, diabetes is an expected complication as individuals with CF grow older. It is encouraging to note that previous gender differences in mortality have disappeared, and the gap in mortality between CF patients with and without diabetes has narrowed considerably. While many factors have changed in the management of individuals with CF over the last decade, we believe that early diagnosis and aggressive treatment of CFRD have played a major role in improving survival in these patients.
REFERENCES
Table 1: Mortality rates, CFRD prevalence and incidence for consecutive time intervals. During each interval, for all rates there was no significant difference between males and females.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Patients seen in clinic during interval</td>
<td>752</td>
<td>702</td>
<td>647</td>
</tr>
<tr>
<td>Females</td>
<td>53%</td>
<td>53%</td>
<td>53%</td>
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<tr>
<td>CFRD prevalence (%) at end of interval (± standard error)</td>
<td>20 $a \pm 2%$</td>
<td>30 $b \pm 2%$</td>
<td>33 $b \pm 2%$</td>
</tr>
<tr>
<td>CFRD incidence per 100 person-years (± standard error)</td>
<td>3.0 $a \pm 0.3$</td>
<td>4.0 $b \pm 0.4$</td>
<td>2.7 $a \pm 0.3$</td>
</tr>
<tr>
<td>CFRD mortality rate per 100 person-years (± standard error)</td>
<td>6.7 $a \pm 1.3$</td>
<td>5.4 $a \pm 0.9$</td>
<td>3.5 $b \pm 0.6$</td>
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<td>Patients diagnosed with CFRD during interval / number of those who were both diagnosed and died within same interval</td>
<td>108 / 18 $a$</td>
<td>102 / 12 $a$</td>
<td>61 / 2 $b$</td>
</tr>
<tr>
<td>Total population mortality rate per 100 person-years (± standard error)</td>
<td>1.2 $\pm 0.2$</td>
<td>1.6 $\pm 0.2$</td>
<td>1.8 $\pm 0.2$</td>
</tr>
<tr>
<td>Non-CFRD mortality rate per 100 person-years (± standard error)</td>
<td>0.5 $a \pm 0.1$</td>
<td>0.6 $ab \pm 0.2$</td>
<td>1.0 $b \pm 0.2$</td>
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$a$, $b$ Comparisons are between time intervals within each row. Rates that do not share a letter are significantly different ($p < 0.05$); rates that share a letter are not significantly different. Rows with no letters have no significant differences.
Table 2: Characteristics of the 2008 adult UM CF population, age 18 and older (n = 359). Data are not shown for 167 children and adolescents, in whom there was no significant difference in pulmonary function or BMI between those with and without diabetes (see text for details). Values are expressed as mean ± standard deviation

<table>
<thead>
<tr>
<th></th>
<th>Total Population</th>
<th>Females</th>
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<tr>
<td></td>
<td>CFRD</td>
<td>No CFRD</td>
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<tr>
<td>N</td>
<td>155</td>
<td>204</td>
</tr>
<tr>
<td>Age</td>
<td>33±10</td>
<td>32±10</td>
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<tr>
<td>Duration DM</td>
<td>10±5</td>
<td>−</td>
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<tr>
<td>BMI</td>
<td>22.6±4</td>
<td>23.3±4</td>
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<tr>
<td>% pred FEV1</td>
<td>65*±24</td>
<td>71*±24</td>
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</table>

*Significant differences (p<0.05) between CFRD and no CFRD
†Significant difference (p<0.05) in duration of diabetes between FH+ and FH− females
** Significant differences (p<0.05) between males and females within a diagnostic subgroup (FH+, FH−, or No CFRD)
Figure 1: Current prevalence of CFRD in the 527 patients actively followed at the University of Minnesota, Sept 15, 2008. A. CFRD total, CFRD FH+ and CFRD FH- by decade of age. B. CFRD total men versus women by decade of age. The number of total subjects (with and without diabetes) in each age group is noted. *p=0.02 men vs. women

Figure 2: UM CFRD incidence per 100 patient-years by gender and age decade 2003-2008. Females-red, males-blue. Sample sizes for the incidence rates are shown below the figure.

Figure 3: UM CFRD and CF mortality per 100 patient-years by gender and age decade over 3 time periods: 2003-2008, 1998-2002, and 1992-1997. Females-red, males-blue. CF patients with diabetes are shown with solid lines while CF patients without diabetes are shown as dashed lines. Zero rates estimated from fewer than 10 patients are not shown. The gap in mortality between those with and without diabetes has diminished over these time periods, and the gender difference in mortality has disappeared in the most current analysis.
CFRD prevalence, incidence and mortality

**Diabetes Mellitus Incidence per 100 patient-years ± SE**

**Age in years (Midpoint of Decade)**

2003–2008

- **Males**
- **Females**

**Number of patients at risk by decade**

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<th></th>
<th>5</th>
<th>15</th>
<th>25</th>
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<tbody>
<tr>
<td><strong>Females</strong></td>
<td>80</td>
<td>96</td>
<td>79</td>
<td>38</td>
<td>23</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td>80</td>
<td>102</td>
<td>88</td>
<td>59</td>
<td>35</td>
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