Diabetes Is Associated With Dramatically Decreased Survival in Female but Not Male Subjects With Cystic Fibrosis

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OBJECTIVE — Survival analysis was performed on a prospectively followed cohort of patients with cystic fibrosis (CF) to determine the impact of the development of diabetes on survival.

RESEARCH DESIGN AND METHODS — Clinical data were retrieved for patients diagnosed with CF-related diabetes (CFRD) at the Minnesota CF Center in 1987–2002. Kaplan-Meier survival analysis was performed to estimate median survival. Data were analyzed by Cox regression to evaluate the influence of clinical characteristics at the time of CFRD diagnosis on mortality.

RESULTS — Clinical information was reviewed from 1,081 CF patients. A total of 123 patients with CFRD with fasting hyperglycemia were identified (58 males). Median survival was 49.5 years for male subjects without diabetes, 47.4 years for male subjects with diabetes, 47.0 years for female subjects without diabetes, and 30.7 years for female subjects with diabetes. Only female sex and forced expiratory volume in 1 s at the time of CFRD diagnosis were significant predictors of the subsequent risk of death ($P < 0.001$). This strong association was not confounded by CFTR genotype, BMI, steroid use, respiratory pathogens, HbA_{1c}, or pregnancy.

CONCLUSIONS — Female subjects with CFRD have a remarkably poorer prognosis compared with all male subjects with CF and female subjects with CF but without diabetes. The etiology of this sex difference is not clear. We speculate it might involve the interaction of female hormones and diabetes on promotion of a proinflammatory state or that androgens might protect male subjects from the catabolic effects of insulin deficiency. Alternatively, the appearance of frank diabetes in female subjects with CF may simply be a marker for some other biological difference that is not immediately apparent.

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Cystic fibrosis (CF) patients experience scarring of the pancreas, leading to partial islet destruction and a spectrum of glucose tolerance abnormalities. CF-related diabetes (CFRD) with fasting hyperglycemia (FH) is found in 3% of patients aged 5–9 years, 11% of patients aged 10–19 years, and 15% of patients aged ≥20 years (1). A milder form of diabetes, CFRD without FH, is found in 6% of patients aged 5–9 years, 15% of patients aged 10–19 years, and 25% of patients aged ≥20 years. Impaired glucose tolerance is also common in CF, while impaired fasting glucose is rare. The primary pancreatic endocrine defect in CF is insulin deficiency (2). Even CF patients with normal or impaired glucose tolerance have low insulin levels, but these patients are able to maintain relatively normal glucose levels because they are sensitive to insulin (3).

In 1988, the University of Minnesota first reported that diabetes contributes significantly to morbidity and mortality in this population. Retrospective survival analysis of 448 living and deceased individuals with CF treated from 1960 to 1987 showed that while nearly 60% of CF patients without diabetes were alive at 30 years of age, <25% of those with diabetes reached this age (4). Based on these findings, aggressive screening and treatment of diabetes was instituted at the Minnesota CF Center in 1987. The following study, a retrospective survival analysis of living and deceased CF patients from 1987 through 2002, was undertaken to determine whether these changes had an impact on survival.

RESEARCH DESIGN AND METHODS

— Clinical data were retrieved from patients who were diagnosed with CFRD and treated at the Minnesota CF Center from 1 January 1987 to 31 December 2002. Only patients for whom complete follow-up information (either to the time of this study or the time of death) was available were included. CF patients are routinely seen at least at quarterly intervals, and patient data are recorded in the Minnesota CF Database (5). The information collected included demographics, pulmonary function tests, and clinical characteristics. Demographic information from the non-CFRD patient population was retrieved for survival comparisons. All patients followed at this center gave informed consent, permitting their records to be reviewed for research purposes.

CFRD diagnosis and management

Routine annual oral glucose tolerance tests (OGTTs) have been recommended

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Abbreviations: CF, cystic fibrosis; CFRD, CF-related diabetes; CRP, C-reactive protein; FEV_1, forced expiratory volume in 1 s; FH, fasting hyperglycemia; OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

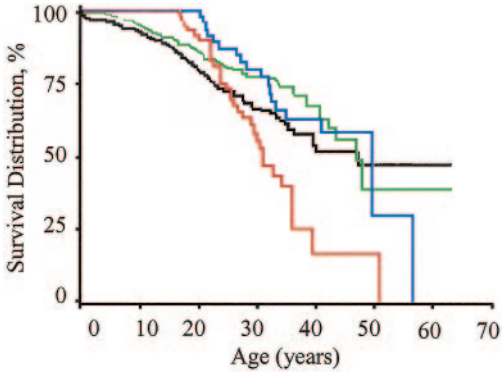

Figure 1—*Survival curves for male subjects with CF but without diabetes (green, median survival 49.5 years), male subjects with CF and diabetes (blue, median 47.4 years), female subjects with CF but without diabetes (black, median 47.0 years), and female subjects with CF and diabetes (red, median survival 30.7 years).*

since 1987 for patients aged ≥6 years (1.75 g/kg glucose, maximum 75 g). Hospitalized patients have preprandial and 2-h postprandial glucose levels measured during the first 48 h of hospitalization. Patients are diagnosed with CFRD with FH if the fasting glucose level is ≥126 mg/dl (7.0 mmol/l). CFRD without FH is diagnosed when the fasting glucose level is <126 mg/dl but the 2-h glucose level or at least two random glucose levels are ≥200 mg/dl (11.1 mmol/l). Diabetes management follows a uniform protocol that includes the involvement of an endocrinologist, a diabetes nurse educator, and a diabetes dietitian. Aggressive insulin treatment with near normalization of blood glucose levels is standard practice for patients with FH. The most common insulin regimen during the study period was a single injection of NPH insulin at bedtime and three to six injections of short- or rapid-acting insulin during the day. Patients who had diabetes without FH were not started on insulin therapy but were followed closely, and insulin therapy was started if FH developed.

Data analysis

Survival analysis was performed by the Kaplan-Meier method to estimate median survival. The date at which the patients were diagnosed with CFRD was defined as their entry date to create a life table for the group. If an individual had already died at the time of this study, his or her date of death was defined as the event date. The difference between this date and the entry date determined his or her survival time with CFRD. If an individual was alive at the time of this study, he or she was considered a date-censored observation, and his or her survival time was determined by the difference between the date of this study and his or her entry date. Similarly, those patients who had received a lung transplant before the date of the analysis were considered as date-censored observations. Further, the data were analyzed by Cox regression to evaluate for the influence of clinical characteristics at the time of CFRD diagnosis on risk for mortality after diagnosis.

RESULTS

Subjects

Clinical information was reviewed from a total of 1,081 CF patients followed at the Minnesota CF Center. Of this cohort, 123 (11.4%) patients with a diagnosis of CFRD with FH during the period of interest were identified (58 male and 65 female subjects). The mean age ±SD of the group at the time of CFRD diagnosis was 23 ± 9 years.

At the time of this study, 64 (52%) CFRD patients had died from complications of their pulmonary disease and 59 (48%) were still alive. The median survival age for patients with CFRD was 35.6 years (95% CI 31.9–45.4). This was significantly lower than the median survival age of 47.0 years observed in the non-CFRD patient population ($P = 0.001$).

Diminished survival in female subjects with CFRD

When the data were analyzed with stratification by sex, only female subjects with CFRD were at a higher risk of death compared with other patients (Fig. 1). Median survival was 49.5 years for male subjects without diabetes, 47.4 years for male subjects with diabetes, and 47.0 years for female subjects without diabetes ($P > 0.2$). In stark contrast, median survival was 30.7 years in female subjects with diabetes ($P < 0.001$ compared with all other groups). This effect of sex on CFRD survival was highly significant (Wald $\chi^2 = 11.1$, $P = 0.0008$) and accounted for a 54% increase in the risk of death.

In the nondiabetic CF population, there was the suggestion of an effect of sex on survival starting at about puberty, as male and female survival curves began to diverge. However, after ~40 years of age, these lines crossed in the opposite direction, and female subjects appeared to have a survival advantage. Thus, median survival over the lifetime of the sexes was similar.

Influence of clinical characteristics on survival

By Cox regression, of all the characteristics investigated, only female sex and forced expiratory volume in 1 s (FEV_1) at the time of CFRD diagnosis were significant predictors of the subsequent risk of death (Table 1, $P < 0.001$ for both param-

Table 1—*Clinical characteristics at CFRD diagnosis*

Characteristic	Female subjects	Male subjects	*P* value
n	65	58	
Age at CF diagnosis (years)	4.0 ± 0.8	5.0 ± 1.3	0.5
Age at CFRD diagnosis (years)	20.8 ± 1.0	25.5 ± 1.5	0.01
FVC (%-p)	80.9 ± 3.1	70.0 ± 3.3	0.02
FEV_1 (%-p)	56.8 ± 3.8	46.3 ± 3.8	0.06
Homozygous ΔF508	58.4	58.5	0.9
BMI (kg/m^2)	19.2 ± 0.3	19.6 ± 0.5	0.5
CRP	3.3 ± 0.5	4.1 ± 0.4	0.2
B. cepacia infection	15.2	15.5	0.9
Chronic systemic steroids	16.6	18.5	0.7

Data are means ± SE or percent, unless otherwise indicated. %-p, percent of the predicted normal; FVC, forced vital capacity.

eters). This strong association was not confounded by characteristics such as CFTR genotype, age at CF diagnosis, age of CFRD diagnosis, BMI, steroid use, or respiratory microbiology results. Lung function was already worse in female compared with male subjects at the time of diabetes diagnosis. Based on the predictive model generated, a female subject with an FEV_1 <50% predicted at CFRD diagnosis had a subsequent risk of death five times higher than a female subject with an FEV_1 >85% predicted. In contrast, the risk of death for a male subject with an FEV_1 <50% predicted at CFRD diagnosis was only two times higher than for a male subject with an FEV_1 >85% predicted.

Pregnancy during the study period did not influence survival differences between female subjects with and without diabetes. Twelve diabetic female subjects (18%) had 16 pregnancies during the study period; six of these female subjects subsequently died. Twenty-eight nondiabetic female subjects (12% of female subjects of child-bearing age) had 39 pregnancies; seven died. C-reactive protein (CRP) levels at the time of diabetes diagnosis (Table 1) and at each of 3 subsequent years (data not shown) did not differ between the sexes or from CF subjects without diabetes. Because CRP is routinely measured during acute illness, values were elevated in all groups. HbA_{1c} (A1C) levels in the 3 years after diagnosis did not differ between male and female subjects with CFRD (range of annual averages: male 7.0–7.6%, female 6.9–7.4%, P = NS), suggesting no difference in metabolic control.

CFRD without FH

During the study interval, 134 subjects (60 female) were diagnosed with diabetes without FH. Of these, 50 (22 female) subsequently developed FH and are included in the CFRD cohort. Thus, the risk of progression to FH was ~40%. The average time to development of FH was 1.5 ± 2.0 years after the first diabetic OGTT. Age at the time of the first diabetic OGTT was similar between those who progressed to FH (25 ± 11 years) and those who did not (23 ± 10 years). Twenty-six percent (five females, eight males) of progressors to FH died during the study period compared with 7% of nonprogressors (two females, four males). Death occurred 3.6 ± 2.8 years after the first diabetic OGTT. The survival curves of the 84 male and female subjects with CFRD without FH who had not yet developed FH at the time of this study followed the same trajectories as those of subjects without diabetes. However, since only six of these subjects died, it was not possible to calculate median survival. Although the average age at diagnosis of the population without FH (22.0 ± 1.0 years) was similar to that of the population with FH, these subjects were relatively young, with only five between the ages of 30 and 40 years and two subjects >40 years of age. It is therefore difficult to come to any conclusions about mortality in CFRD without FH.

CONCLUSIONS — Poorer female survival in CF has previously been reported in the U.S., Canada, Europe, New Zealand, and Australia (6–8). An analysis of 21,047 patients followed in the U.S. CF Foundation patient registry between 1988 and 1992 demonstrated that female subjects were 60% more likely to die than male subjects (7). Although nutritional status, pulmonary function, and airway microbiology were strong predictors of mortality in both sexes, these factors did not explain the sex difference. Cause of death was similar between the sexes, with ~80% of deaths due to pulmonary disease and the remainder due to transplant complications, liver disease, trauma, or other causes. In the current report, we found that diabetes had a strong adverse effect on female survival, since it accounted for a 48% increase in the risk of death over that explained by sex differences alone. The role of diabetes in sex mortality has not been explored in other series, perhaps because no other U.S. CF center has had as long or extensive a diabetes screening program as Minnesota.

Sex is known to influence pulmonary function in the general population. While the prevalence of asthma is similar in adult male and female subjects, female subjects have greater morbidity (9–11). A sex effect on pulmonary function does not explain the current findings, however, since mortality in female subjects with CF but without diabetes was not increased. Diabetes is also known to adversely influence lung function (12–16). In the current CF cohort, however, diabetes did not adversely influence male survival. Thus, rather than diabetes per se, it was the interaction of female sex and diabetes that determined increased mortality.

For reasons that are not well understood, diabetes erases the natural protection of premenopausal female subjects in the general population against cardiovascular disease, and risk of death is greater in diabetic female than in diabetic male subjects (17–20). CF patients are not at risk for cardiovascular disease: they are thin, their blood pressure is generally normal, they are insulin sensitive, they have low insulin (3) and cholesterol levels (21), and no CF patient has ever been reported to have died from an atherosclerotic cardiovascular event. Female subjects with CF and diabetes die from pulmonary rather than cardiovascular failure. However, inflammation may be a relevant common pathological factor linking these disease processes.

Inflammation is important in the pathophysiology of both atherosclerotic cardiovascular disease in the general population and lung disease in CF, and female sex and diabetes may have additive effects on inflammation in each of these conditions. In patients with chronic obstructive pulmonary disease, the additional diagnosis of diabetes is associated with a fourfold increase in cytokine levels (22). CRP levels are significantly more elevated in diabetic (median 1.62 mg/l) than in nondiabetic (0.85 mg/l) female subjects and diabetic (0.82 mg/l) or nondiabetic (0.81 mg/l) male subjects (23). While no sex- or diabetes-associated differences were noted in CRP levels in the current CF cohort, CRP elevation associated with acute pulmonary exacerbation may have obscured the subtle baseline changes in CRP reported to be associated with inflammation in cardiovascular disease.

We have previously shown a greater than expected decline in pulmonary function in CF patients with impaired glucose tolerance and diabetes without FH, directly related to the degree of insulin deficiency (24). We have hypothesized that this chronic decline in clinical status, which begins long before the appearance of overt diabetes, is related to excessive breakdown of protein and lipid stores (25,26). An alternative explanation is that the development of frank diabetes is a marker for some other biological difference that is not immediately apparent.

Sex-related differences in survival in the current cohort did not appear until after puberty, suggesting a hormonal influence. While a negative effect of estro-

gen and progesterone on lung function in CF patients with diabetes is possible, an alternative hypothesis is that higher testosterone levels may protect male subjects with CFRD. Muscle mass is often reduced in CF (27), and lung function is related to lean body mass (27). In the current study, BMI was similar between female subjects with CFRD and the other study groups, suggesting comparable nutritional status, but lean body mass was not specifically measured. Insulin is a potent anabolic hormone, and insulin deficiency may contribute to morbidity and mortality in CF by promoting an overall catabolic state (25). Androgens are effective anabolic agents that may help maintain muscle mass in male subjects with CF, even in the presence of insulin deficiency.

In summary, survival has dramatically improved for all male subjects with CF and for female subjects with CF but without diabetes. Female subjects with CFRD, however, have a remarkably poorer prognosis, despite early identification and aggressive treatment of diabetes. The etiology of this sex difference is not clear but might involve the combined influences of female hormones and diabetes on promotion of a proinflammatory state or might be related to a lack of sufficient androgens to counteract the catabolic effects of insulin deficiency. Diabetes may simply be a marker for an as yet unknown biologic difference. Studies are clearly needed to define a more effective clinical treatment approach for female patients with CF who develop diabetes.

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