Diabetes frequently complicates cystic fibrosis. Cystic fibrosis–related diabetes (CFRD) has an incidence in teenagers of up to 6% per year and a prevalence in adults of $>30\%$ (1,2). Diabetes further elevates the already high mortality rates in cystic fibrosis (3–5). In individuals without cystic fibrosis, diabetes increases the risk of death, and hyperglycemia itself increases the risk of death (6,7). In contrast, no study of CFRD using national data has investigated whether hyperglycemia, per se, increases the risk of death; likewise, no trial has tested whether controlling blood glucose prolongs survival. Proving an association between glycemia and mortality in cystic fibrosis would provide compelling observational evidence to inform clinical practice. Using the U.K. Cystic Fibrosis Registry, we performed longitudinal analyses to test the association between glycemia, as measured by HbA$_{1c}$, and mortality in individuals with CFRD.

**OBJECTIVE**—Diabetes is common in cystic fibrosis and increases the risk of death, yet the role of hyperglycemia remains unproven. An association between glycemia and mortality would provide compelling evidence to support glucose lowering in cystic fibrosis–related diabetes (CFRD).

**RESEARCH DESIGN AND METHODS**—Using the U.K. Cystic Fibrosis Registry, we analyzed longitudinal data from 2006 to 2009 in 520 individuals with diabetes. We tested the association between HbA$_{1c}$ and mortality.

**RESULTS**—During a median follow-up of 2 years, 36 patients died. The median value of HbA$_{1c}$ was higher in those who died (7.3%) than in those who did not (6.7%). An HbA$_{1c}$ value of $\geq 6.5\%$ was associated with a threefold increased risk of death (hazard ratio $3.3 [95\% \text{ CI} 1.4–7.3]; P = 0.005$) independent of potential confounders.

**CONCLUSIONS**—Hyperglycemia trebles the risk of death in patients with CFRD. These findings provide epidemiologic support for continued efforts to improve glycemic control.

An HbA$_{1c}$ value of 6.5% approximates the median value and reflects excellent glycemic control. Potential confounders, previously identified as plausibly related to both the incidence of diabetes and mortality (1,3) and measured at baseline, included age; sex; BMI z score; pulmonary function, as measured by percent predicted forced expiratory volume at 1 s (FEV$_1$); and use of corticosteroids (either oral or inhaled). The registry did not provide information on duration of diabetes. We measured time to event from registration to death or censoring modeling the data using proportional hazards regression with HbA$_{1c}$ as the main exposure variable in univariate and multivariate models. Death was the dependent variable.

**RESULTS**—The median age of patients was 25.0 years (range 0.4–67.8), and HbA$_{1c}$ was 6.7% (4.9–17.0). A total of 84% of patients received treatment to lower blood glucose. Patients with HbA$_{1c}$ values $\geq 6.5\%$, relative to those with values $<6.5\%$, did not differ significantly with respect to age, sex, BMI, pulmonary function, or use of corticosteroids. During a median follow-up of 2.01 years (0.02–3.53), 36 patients died. The median value of HbA$_{1c}$ was higher in those who died (7.3%) than in those who did not (6.7%) (Table 1). Table 1 contrasts the characteristics of the patients who died with those who did not. An HbA$_{1c}$ value of $\geq 6.5\%$ was associated with a threefold increased risk of death (hazard ratio 3.2 [95\% CI 1.4–7.3]; $P = 0.005$). The association did not change when controlling for risk factors for death conceivably related to hyperglycemia (age, sex, BMI z score, FEV$_1$, and use of corticosteroids). In multivariate analysis, HbA$_{1c}$ $\geq 6.5\%$ was associated with a hazard ratio of 3.3 (95\% CI 1.4–7.5; $P = 0.005$).

Respiratory disease was the number one cause of death. Among those who died, the proportion who died from respiratory disease did not differ between those with HbA$_{1c}$ values $\geq 6.5$ or $<6.5\%$, comprising 20 of 29 (69\%) deaths in individuals with HbA$_{1c}$ values at or above 6.5% and 4 of 7 (57\%) deaths in individuals with lower values.
CONCLUSIONS—This study shows that among individuals with cystic fibrosis and diabetes, those with HbA1c levels above the clinically defined target of 6.5% are more likely to die than those with lower values, an observation not accounted for by established risk factors for death. Whereas diabetes in cystic fibrosis is known to increase the risk of death, hyperglycemia in cystic fibrosis–related diabetes is not. We are not aware of another study that has shown an association between HbA1c, a validated measure of glycemia in cystic fibrosis (8), and death. In Minnesota, of adults with CFRD, more patients who developed fasting hyperglycemia died during the study period (26% [n = 8]) compared with 7% (n = 6) of patients who did not develop fasting hyperglycemia, suggesting a role for hyperglycemia (5).

In a few individuals, an elevated HbA1c value may have reflected their illness and impending death. There were too few individuals who died within months of measuring their HbA1c to test this possibility. In addition, other factors may have confounded the findings of this study. However, we do not have any change in the magnitude of the increase in risk associated with hyperglycemia when taking into account well-established markers of morbidity in cystic fibrosis. It also is possible, given the median value of HbA1c, that some included individuals did not have diabetes. Nonetheless, it is likely that they had dysglycemia, and, in any event, this misclassification would not have biased our findings.

Excluded from this study were a substantial proportion of individuals who had diabetes but who did not have available values of HbA1c and other clinical data. Of note, included individuals were not more likely to die than excluded individuals (data not shown). Our results, therefore, are likely generalizable.

This study shows that the increased mortality with hyperglycemia occurs for respiratory disease, which is not classically considered a complication of diabetes. The many potential mechanisms may include poorer nutrition, greater catabolism, and higher risks of infection. In cystic fibrosis, blood glucose values correlate with airway glucose concentrations, and these increase the probability of colonization with pathogens (9).

No randomized trial has yet addressed glucose lowering in cystic fibrosis with the a priori outcome of extending life. In the absence of trials, this report provides epidemiologic support for continued efforts to improve glycemic control in CFRD.

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Table 1—Characteristics of patients with CFRD by survival

| Characteristic | Alive | Dead | P  |
|---------------|-------|------|----|
| n             | 484   | 36   |    |
| Age (years)   | 26.6 ± 9.5 | 28.8 ± 9.6 | 0.18 |
| Female (%)    | 44.2  | 58.3 | 0.14|
| HbA1c (%)     | 6.6 (5.9–7.9) | 7.3 (6.6–8.3) | 0.009*|
| BMI z score   | −0.35 ± 1.18 | −1.14 ± 1.21 | <0.001|
| FEV1 (% predicted) | 54.3 ± 22.7 | 33.4 ± 19.5 | <0.001|
| Using prednisolone (%) | 19.0 | 27.8 | 0.29|

Data are means ± SD or median (interquartile range), unless otherwise indicated. *Tested using the Kruskal-Wallis one-way ANOVA.

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