Impaired Fasting Glucose in Cystic Fibrosis

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OBJECTIVE — While glucose tolerance abnormalities are common in cystic fibrosis (CF), impaired fasting glucose (IFG) has scarcely been explored. No studies have examined the relation between IFG and clinical status.

RESEARCH DESIGN AND METHODS — Data were retrieved from the University of Minnesota CF database on oral glucose tolerance tests (OGTTs) performed in 1996–2005. Subjects were identified as normal glucose tolerance (NGT), impaired glucose tolerance (IGT), or CF–related diabetes without fasting hyperglycemia (CFRD FH−). Patients with fasting hyperglycemia were excluded. The presence of IFG was assessed within each category. In a separate case-control cohort study, subjects with IFG were matched to CF control subjects by age, sex, and OGTT class to explore outcomes.

RESULTS — For the total population ($n = 310$), the prevalence of IFG was 22%, and by OGTT class was NGT 14%, IGT 31%, CFRD FH− 53%. Within the cohort study, mortality was significantly reduced in IFG (two vs. nine deaths, odds ratio [OR] = 0.2 [95% CI 0.04–0.9]). IFG did not confer increased risk of progression to diabetes (OR 0.66 [0.29–1.48]). Lung function was better in pediatric IFG subjects with IGT and not significantly worse in adults with IGT or adults and children with NGT and CFRD FH−. BMI was not significantly different in IFG subjects versus control subjects.

CONCLUSIONS — Contrary to expectations in patients with CF, IFG appeared to be associated with improved survival and was not associated with worse nutritional or pulmonary status or increased progression to fasting hyperglycemia.

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O ral glucose tolerance test (OGTT) categories were defined decades ago by the World Health Organization (WHO). In 1997, the American Diabetes Association (ADA) lowered the fasting glucose level used to define diabetes from 140 mg/dl (7.8 mmol/l) to 126 mg/dl (7.0 mmol/l) to better reflect risk of microvascular complications. The ADA also introduced the concept of impaired fasting glucose (IFG) because fasting glucose elevation in the range of 110–125 mg/dl (6.1–6.9 mmol/l) was shown to be a risk factor for the development of diabetes. In 2003, the ADA further lowered this prediabetes threshold to 100 mg/dl (5.6), again based on the future risk of developing diabetes. Using these newer

criteria, the prevalence of IFG in the general population may be as high as 30% among U.S. adults (1) and 11% among adolescents (2).

Oral glucose tolerance abnormalities are found in the majority of patients with cystic fibrosis (CF) (3), but IFG has been infrequently reported (4,5). No studies have reported current or future clinical outcomes in CF patients with IFG. Because impaired glucose tolerance (IGT) is associated with pulmonary function deterioration in CF (6) and risk of progression to diabetes (7), we hypothesized that IFG would also be associated with worse clinical status and the development of diabetes. Our aim was to determine the prevalence of IFG in the University of

Minnesota (UM) CF population and the consequences of that diagnosis over a period of at least 3.5 years' follow-up.

RESEARCH DESIGN AND METHODS

— CF patients at the UM CF Center are routinely seen at quarterly intervals, and their clinical and laboratory data are recorded in the CF database. Annual OGTT screening starts at 6 years of age for pancreatic-insufficient patients not already on insulin treatment for diabetes. Review of a prospectively collected database was performed to determine the prevalence of IFG. Clinical data were retrieved from patients who had an OGTT performed between January 1, 1996, and December 31, 2005, to identify individuals who had IFG as defined by fasting glucose 100–125 mg/dl (5.6–6.9 mmol/l). All patients and their parents gave informed consent, permitting their records to be reviewed for research purposes. This was approved by the institutional review board.

Population prevalence study
Subjects who had at least one OGTT performed during the study period were identified as having normal glucose tolerance (NGT), IGT, cystic fibrosis–related diabetes without fasting hyperglycemia (CFRD FH−) or CFRD with fasting hyperglycemia (CFRD FH+) by standard definitions (Table 1). Additionally, the presence of IFG was noted within each of the first three categories. As CF patients may have fluctuations in the OGTT category from year to year, baseline for subjects with IFG was considered the OGTT within the study period when they first demonstrated fasting glucose elevation. For all other subjects, baseline OGTT was their first OGTT in the study period.

Case-control cohort study
Following the initial population assessment of IFG prevalence, a case-control cohort study was performed. Subjects with IFG were matched by age, sex, and OGTT category to CF patients with normal fasting glucose (NFG) levels. Patients were evaluated for subsequent progression to CFRD FH+, changes in lung function and nutritional status, and death during the study period. Lung function was determined by change in forced expiratory volume in 1 s (FEV1) and forced

Table 1—*Classification of glucose tolerance abnormalities in CF*

	Fasting plasma glucose mg/dl (mmol/l)	2-h OGTT glucose mg/dl (mmol/l)	Number within category (%)
NGT	<100 (5.6)	<140 (7.8)	175 (86)
NGT + IFG	100–125 (5.6–6.9)	<140 (7.8)	29 (14)
IGT	<100 (5.6)	140–199 (7.8–11.1)	50 (69)
IGT+ IFG	100–125 (5.6–6.9)	140–199 (7.8–11.1)	22 (31)
CFRD FH−	<100 (5.6)	≥200 (11.1)	16 (47)
CFRD FH− + IFG	100–125 (5.6–6.9)	≥200 (11.1)	18 (53)
CFRD FH+	≥126 (7.0)	≥200 (11.1)	NA

Because OGTT results can vary from year to year, patients are categorized based on the first OGTT with IFG during the test period, or for those who never developed IFG, the first OGTT during the test period.

Table 2—*Case-control cohort study: demographic summary for pairs matched on age and sex*

	NFG	IFG
Number (% male)	68 (50)	68 (50)
Baseline age, years	25 ± 11	26 ± 12
Race		
White	65 (96)	66 (97)
Nonwhite	2 (3)	2 (3)
Unknown	1 (1)	0 (0)
Pancreatic insufficiency	63 (93)	67 (99)
Genotype		
Homozygous ΔF508	34 (50)	33 (49)
Heterozygous ΔF508	27 (40)	29 (43)
Other	7 (10)	6 (9)

Values are mean ± SD or n (%). There were no statistical differences between groups.

vital capacity (FVC). Nutritional status was determined by BMI.

Baseline characteristics

Subjects were determined to be pancreatic insufficient based on their need for enzyme replacement therapy. Subjects were screened for cystic fibrosis transmembrane regulator mutations. Only patients with diabetes with fasting hyperglycemia, and thus none of the patients included in the current analysis, were treated with insulin.

Clinical outcome measures

OGTTs occurred during yearly screening visits when patients were determined to be in a state of stable baseline health. Studies were postponed for at least 1 month after acute illness. Fasting status (≥8 h) was verified before testing. Glucose 1.75 g/kg (maximum 75 g) was orally administered. Blood was sampled through an indwelling catheter for glucose and insulin levels at time 0 and every 30 min for 2 h. Plasma insulin levels were measured in the UM Fairview Laboratory by radioimmunoassay using a double-antibody method.

Fasting weight was measured on the same calibrated clinic scale at each visit, and height was measured in triplicate on a wall-mounted stadiometer. BMI results for children and adolescents ≤18 years of age were reported as BMI percentile. Because a portion of the children were >18 years of age by the end of the study, pediatric BMI percentiles were reported for baseline values only. Adult values were reported at baseline and follow-up. Overall group values were reported for those >18 years of age only; therefore, data includes 96 individuals at baseline and 122 individuals at follow-up.

FEV1 and FVC were measured by standardized American Thoracic Society methods. For patients who died during the study period, final pulmonary function tests and weights included in the analyses were obtained at least 60 days before the time of death to exclude acute changes.

Data analysis

The effect of IFG within each glucose tolerance category was estimated in the paired case-control study using a mixed-effect linear model with a random effect for each pair to account for the correlation between patients in a pair. Odds ratio (OR) for death and progression to CFRD FH+ were estimated from conditional logistic regression stratified by pairs. χ^2 was used to compare IFG prevalence and the percentage of children between groups. All analyses were performed in SAS, version 9.2 (SAS Institute, Cary NC).

In the analysis of the clinical outcomes, similar patterns were found with and without inclusion of the patients who died, except that the paradoxical improvement in FEV1 in CFRD FH− became no change when deceased patients were excluded from baseline and follow-up (data not shown); therefore, the entire matched sample was used for statistical analyses.

RESULTS

Prevalence of IFG in the total study population

Of the 310 subjects in the total study population, IFG was found in 22% (Table 1). The prevalence of IFG increased with the severity of the OGTT glucose category, from 14% of those with NGT, 31% of IGT, and 53% of CFRD FH− ($P <$ 0.0001). When only patients with fasting glucose levels 110–125 mg/dl (6.1–6.9 mmol/l) were considered IFG (WHO criteria), the overall prevalence of IFG was 19% and by OGTT class was NGT 12.5%, IGT 25%, and CFRD FH− 46%.

Subject characteristics at baseline, cohort study

For the cohort study, subjects with IFG and their matched NFG control subjects showed no difference in sex, race, or baseline age (Table 2). Pancreatic insufficiency status was not significantly different (93% control subjects vs. 99% IFG case subjects, $P = 0.73$). CF mutations were similar between case subjects and control subjects with half of patients homozygous and 40% heterozygous for ΔF508. The year of study entry was earlier for IFG case subjects than for control subjects but when looked at by OGTT group, this was only significant for CFRD FH− (NGT = 9 months, $P = 0.25$; IGT = 15 months, $P = 0.10$; CFRD FH− = 24 months, $P = 0.02$). The frequency of OGTT evaluation was similar between groups (3.6 vs. 3.7 per patient, $P = 0.75$).

Table 3 shows the clinical characteristics of subjects and control subjects by glucose tolerance category for the total cohort and broken down by pediatric and adult age-groups. IFG subjects were matched for sex in all three categories and were matched as closely as possible for age to control subjects; however, adult IFG subjects in the IGT group were on average 2.4 years older than the control subjects ($P = 0.03$) (Table 3). The proportion of children ≤18 years of age was higher in NGT (38%) than in IGT (33%) and CFRD FH− (28%), but these differences were not significant.

At baseline, IFG case subjects within the IGT category had significantly better

Table 3—*Case-control cohort study: clinical characteristics of all patients with IFG and their matched NFG CF control subjects*

	NGT	NGT/IFG	IGT	IGT/IFG	CFRD FH−	CFRD FH−/IFG
Total cohort						
Number (% male)	29 (48)	29 (48)	21 (48)	21 (48)	18 (56)	18 (56)
Baseline age (years)	26.3 ± 2	26.6 ± 2	23.2 ± 3	*25.7 ± 3	24.8 ± 3	26.2 ± 3
Baseline fasting insulin	6.6 ± 1	9.5 ± 1	6.0 ± 1	9.5 ± 1	8.4 ± 2	4.7 ± 2
Follow-up duration (years)	6.5 ± 0.5	7.3 ± 0.5	6.3 ± 0.6	7.4 ± 0.6	5.6 ± 0.7	*8.2 ± 0.7
Deaths, number (%)	3 (10)	0	1 (5)	1 (5)	5 (28)	1 (6)
Progression to CFRD FH+	7 (24)	11 (38)	10 (48)	10 (48)	17 (94)	18 (100)
Baseline % predicted FEV_1	85 ± 5	76 ± 5	66 ± 6	*85 ± 6	70 ± 6	75 ± 6
Follow-up† % pred FEV_1	80 ± 5	70 ± 5	60 ± 5	*79 ± 6	78 ± 7	77 ± 6
Baseline % predicted FVC	92 ± 4	89 ± 4	84 ± 5	*95 ± 5	84 ± 5	90 ± 5
Follow-up† % predicted FVC	88 ± 4	85 ± 4	75 ± 5	*90 ± 5	95 ± 6	92 ± 5
Children ≤18 years						
Number (% male)	11 (45)	11 (45)	7 (29)	7 (29)	5 (20)	5 (20)
Baseline age (years)	12 ± 1	12 ± 1	14 ± 2	14 ± 2	16 ± 2	16 ± 2
Baseline fasting insulin	5.5 ± 2	10 ± 2	5.6 ± 2	7.4 ± 2	10 ± 3	5.7 ± 3
Follow-up duration (years)	7.2 ± 1	6.5 ± 1	5.9 ± 1	5.5 ± 1	6.7 ± 1	8.5 ± 1
Deaths, number (%)	1 (9)	0	0	0	1 (20)	0
Progression to CFRD FH+	3 (27)	4 (36)	1(14)	0	5 (100)	5 (100)
Baseline BMI percentile	53 ± 7	39 ± 7	34 ± 8	42 ± 8	62 ± 10	49 ± 10
Baseline % predicted FEV_1	97 ± 7	98 ± 7	83 ± 9	*108 ± 9	92 ± 10	82 ± 10
Follow-up† % predicted FEV_1	85 ± 7	84 ± 7	66 ± 8	*107 ± 8	95 ± 11	81 ± 10
Baseline % predicted FVC	101 ± 7	104 ± 7	97 ± 9	112 ± 9	100 ± 10	94 ± 10
Follow-up† % predicted FVC	93 ± 6	95 ± 6	79 ± 7	*115 ± 7	106 ± 9	96 ± 8
Adults						
Number (% male)	18 (56)	18 (56)	14 (64)	14 (64)	13 (54)	13 (54)
Baseline age (years)	35 ± 2	36 ± 2	28 ± 2	*31 ± 2	28 ± 2	30 ± 2
Baseline fasting insulin	7 ± 2	9 ± 2	6 ± 2	11 ± 2	8 ± 2	4 ± 2
Follow-up duration (years)	6.5 ± 0.7	7.4 ± 0.7	6.5 ± 0.8	8.3 ± 0.8	5.2 ± 0.7	*8.1 ± 0.8
Deaths, number (%)	2 (11)	0	1 (7)	1 (7)	4 (31)	1 (8)
Progression to CFRD FH+	4 (22)	7 (39)	9 (64)	10 (71)	12 (92)	13 (100)
Baseline BMI (kg/m^2)	25.2 ± 1	24.1 ± 1	21.9 ± 1	25.4 ± 1	21.5 ± 1	23.3 ± 1
Follow-up BMI (kg/m^2)	25.3 ± 1	23.6 ± 1	22.5 ± 1	25.1 ± 1	21.5 ± 1	23.9 ± 1
Baseline % predicted FEV_1	77 ± 5	62 ± 5	57 ± 6	73 ± 6	61 ± 6	73 ± 6
Follow-up† % predicted FEV_1	76 ± 6	61 ± 6	57 ± 6	65 ± 6	70 ± 8	76 ± 7
Baseline % predicted FVC	86 ± 4	80 ± 4	77 ± 5	86 ± 5	78 ± 5	89 ± 5
Follow-up† % predicted FVC	85 ± 5	78 ± 5	73 ± 5	76 ± 6	90 ± 7	91 ± 6

Values are n (%) or mean ± SE. *IFG significantly different from control subject within category ($P < 0.05$). †Follow-up % predicted FEV_1 and FVC measured >60 days before death.

measures of lung function compared with their control subjects with an ~20% higher FEV1 and a 10% higher FVC ($P = 0.005$ and 0.033, respectively). This was primarily related to better lung function in pediatric patients with IGT who had 30% higher FEV1 at baseline ($P = 0.008$). While adults with IFG had a 28% higher FEV1 at baseline than their NFG control subjects, it did not achieve statistical significance ($P = 0.081$). Lung function for both children and adults did not significantly differ between subjects with IFG and their NFG control subjects in the NGT or CFRD FH− categories.

Clinical status at follow-up
Overall there was a slightly longer duration of follow-up for the IFG subjects (7.6 vs. 6.2 years). Within glucose tolerance categories, this difference was significant only in the CFRD FH− group ($P = 0.003$) where it was related to the death rate of five deaths in subjects with NFG versus one death in an IFG subject.

Across all three glucose tolerance categories, the number of subjects who died among the IFG case subjects was less than or equal to the number of deaths in the control subjects for that group. Only two subjects with IFG died during the follow-up period, compared with nine in the NFG control group. The overall odds of death was eight times higher for control subjects than IFG case subjects (95% CI 1.001–64, $P = 0.0499$, based on nine informative pairs where paired participants had different outcomes).

At follow-up, analysis of lung function showed that within the IGT category, FEV1 continued to be about 20% higher and FVC about 15% higher in IFG than in control subjects with IGT and NFG ($P = 0.008$ and 0.023, respectively). When children and adults with IGT were evaluated separately, the difference in pulmonary function was only significant for children. Mean follow-up FEV1 and FVC in the IFG groups were lower in both the NGT and CFRD FH− categories. These differences did not reach significance. Thus, IFG was not associated with different pulmonary outcomes in the NGT and CFRD FH− categories, and it was associated with improved pulmonary status in the IGT category, especially in children.

Progression to CFRD with fasting hyperglycemia
In the IFG group, 57% of subjects progressed to CFRD FH+ compared with 50% of the control case subjects. This was consistent across NGT, IGT, and CFRD

FH− categories. Overall, the odds of progressing to CFRD FH+ was not significantly higher in IFG (OR 1.6 [95% CI 0.7–3.6], *P* = 0.301, based on 23 informative pairs where paired participants had different progression outcomes).

CONCLUSIONS — Few reports have described IFG in CF. A German review of 1,128 OGTTs performed on CF patients 10–64 years of age found 32% with IFG, but the data were not separated by OGTT category, and many subjects had diabetes (4). In an U.S. report of 73 children and adolescents with CF, 18% with NGT and 33% with IGT had IFG (5). In the present study of 310 children and adults, IFG was found in 14% of those with NGT, 31% of those with IGT, and 53% of those with CFRD FH−, with an overall prevalence of 22%.

Diabetes is associated with increased morbidity and mortality in CF. Nutritional status and pulmonary function begin to decline several years before the diagnosis of CFRD, in the pre-diabetic period (8,9), where clinical deterioration correlates with the degree of insulin insufficiency (10). Insulin insufficiency allows a catabolic state, negatively impacting nutrition and lung function (9,11). We hypothesized that IFG, as part of the spectrum of glucose tolerance abnormalities in CF, would be associated with worse outcomes. This was not the case. Mortality was significantly reduced in patients with IFG, and lung function was better in pediatric patients with IFG in the IGT group and not significantly worse in adults with IFG and IGT or in children and adults with IFG in the NGT and CFRD FH− groups.

An explanation for the unexpected association of IFG with improved or no worse clinical outcomes may lie in the etiology of IFG. In the general population, epidemiologic studies suggest that IFG and IGT are two distinct categories with only partial overlap (12–15). Both IFG and IGT identify individuals at risk for future diabetes, involve impairment of early (first-phase) insulin secretion, and are associated with insulin resistance (16). The site of insulin resistance differs, however. In IFG, it occurs primarily in the liver, which results in excessive hepatic glucose production (HGP) and fasting hyperglycemia despite normal fasting insulin levels. Fasting hyperglycemia may also be related to impaired glucose–mediated glucose uptake (glucose uptake not related to insulin, which predominates in
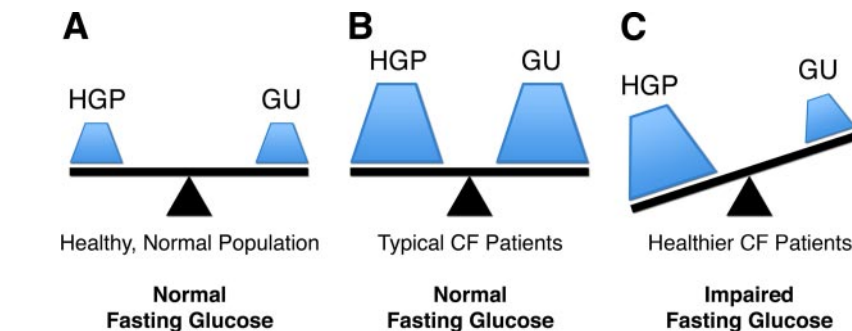

Figure 1—*Model for fasting blood glucose and IFG in CF. A: In the normal population, fasting HGP is balanced by total body glucose utilization (GU). B: Inflammation, undernutrition, and perhaps the CF gene defect increase GU in CF patients. HGP is elevated for reasons that are not understood very well, but fasting glucose levels are normal when HGP and GU are in balance. C: In healthier CF patients, HGP is similarly elevated but GU is reduced, leading to IFG.*

the fasting state) (14). Because peripheral muscle insulin sensitivity and late (second-phase) insulin secretion are normal in patients with IFG, glucose levels normalize after a glucose load. In contrast, insulin resistance in IGT occurs primarily in skeletal muscle; this, combined with defective second–phase insulin secretion, results in postload hyperglycemia (12,15).

In CF, euglycemic clamp studies demonstrate normal peripheral insulin sensitivity in nondiabetic CF patients and only mild peripheral insulin resistance in those with diabetes (17). For reasons that are unclear, in contrast to peripheral skeletal muscle, hepatic insulin resistance with increased HGP is found even in nondiabetic CF patients with completely NFG levels (17–20). Glucose-mediated glucose uptake is normal (17). Because elevated HGP correlates with resting energy expenditure (18), we and others (17,18) have hypothesized that NFG levels are seen in the face of increased HGP because of an adaptive physiologic balance between high glucose utilization and elevated glucose production. The current study supports this hypothesis since healthier, better nourished CF patients would be expected to have lower resting energy needs in the fasting state, thus less ability to metabolize extra glucose produced by the liver and leading to IFG (Fig. 1).

The relation between IFG and better pulmonary status was only seen in the patients with IGT. This relation was not seen in the NGT patients, who were healthier as a group. In the CFRD FH− group, the relation between IFG and clinical status may have been obscured by the greater degree of inflammation and peripheral insulin resistance that characterizes CF patients with diabetes. Nonetheless, the

greatest impact on survival was seen in the CFRD FH− group (the study group at the highest risk for imminent death). Within the IGT group, children with IFG and their control subjects were the same age, while adults with IFG were 2.4 years older than their control subjects. Although the difference in lung function compared with control subjects was only significant in children, the observation that adults with IGT and IFG were no worse than their younger control subjects may be clinically important since lung function declines with age in CF.

Unlike the general population where IFG is a pre-diabetic state, the current study demonstrates that IFG does not appear to be an independent risk factor for the progression to diabetes in CF, although there is a nonstatistically significant suggestion that it may confer increased risk in those with NGT. The extraordinarily high rate of progressive glucose tolerance abnormalities leading to diabetes in CF may overwhelm any relation between IFG and the future risk of diabetes.

While IGT is well known to be a risk factor for cardiovascular disease in the general population, it was initially reported that no such association existed for IFG (21). In the Framingham Heart Study, however, IFG was found to be associated with increased risk of coronary heart disease in women but not men (22). This is interesting given that a sex difference in mortality has also been reported in CFRD. The added diagnosis of diabetes has been associated with reduced survival in women but not men with CF, albeit from inflammatory lung rather than inflammatory cardiovascular disease (23,24). Recently gender differences in mortality have disappeared at UM, perhaps because of more aggressive diabe-

tes screening and treatment (25). No sex differences were apparent in the current study, but the sample size may have been too small for meaningful conclusions.

The major limitation of this study was the relatively small number of subjects. In addition, the length of follow-up was only about 5.5 years. Greater variability in lung function was seen in adults with NGT, and it cannot be ruled out that the sample was too small to detect clinically significant differences. Longitudinal assessment of this cohort will be important to determine whether current findings persist. IFG subjects and control subjects were matched by age at OGTT rather than year of entry so that the IFG case subjects were enrolled on average 16 months earlier than the NFG control subjects (significant only in the CFRD FH− group). At UM and elsewhere, the CF population has shown a trend toward improvement in outcomes over the years, implying later enrollment would confer improved clinical outcome. Thus, the earlier enrollment would be expected to result in a bias toward worse clinical outcomes, rather than the better results that were found in the IFG group.

In summary, IFG is relatively common in the CF population. It does not signify increased risk of progression to diabetes. In our study, it is associated with improved survival, and it appears to be associated with improved pulmonary status in pediatric patients with IGT. Larger studies are needed to confirm these observations.

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