Microvascular Complications in Cystic Fibrosis Related Diabetes

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ABBREVIATIONS
BMI: body mass index
CF: cystic fibrosis
CFRD: cystic fibrosis related diabetes
FH: fasting hyperglycemia
GI: gastrointestinal
HRDB: heart rate changes with deep breathing
HbA1c: hemoglobin A1c
OGTT: oral glucose tolerance test
Ualb:cr: urine albumin to creatinine ratio
UM: University of Minnesota
OBJECTIVE

The incidence of cystic fibrosis related diabetes (CFRD) and the prevalence of diabetes microvascular complications were determined at the University of Minnesota.

RESEARCH DESIGN AND METHODS

Cystic fibrosis patients have undergone annual oral glucose tolerance testing since 1990. Database review was performed to determine diabetes duration and the results of annual urine albumin: creatinine ratio (U_{alb:Cr}) screening and dilated retinal exams. In addition, 59 individuals underwent detailed retinopathy, nephropathy, neuropathy, and gastroenteropathy screening.

RESULTS

During 1990-2005, 775 patients age ≥6y were followed. CFRD was diagnosed by oral glucose tolerance test or fasting hyperglycemia (FH) in 285 subjects (52% female), 64% of who had fasting hyperglycemia (FH). Most patients with CFRD without FH progressed to CFRD with FH over time. No subject with CFRD without FH had retinopathy or abnormal U_{alb:Cr}. In CFRD subjects with FH with diabetes ≥10yrs duration, 14% had microalbuminuria and 16% had retinopathy. Autonomic neuropathy and GI symptoms were each seen in 52% and somatic abnormalities in 22% of patients with or without FH.

CONCLUSIONS

Diabetes microvascular complications occur in CFRD, although the prevalence of retinopathy and nephropathy appears to be less than that found in other forms of diabetes. Annual complication screening should occur after known diabetes duration of 5yrs in patients with CFRD with FH.
Microvascular complications are common in individuals with type 1 and type 2 diabetes, and represent a significant source of morbidity and mortality. They have been anecdotally reported in cystic fibrosis related diabetes (CFRD). The goal of the current study was to determine the prevalence of diabetes microvascular complications in CFRD patients.

Diabetes is the most common comorbidity in patients with CF, occurring in approximately 40% of adults, 25% of adolescents and 9% of children (1). CFRD shares features of both type 1 and type 2 diabetes, but is a distinct clinical entity requiring a unique management approach (2). Over time, fibrotic disruption of the pancreatic architecture leads to partial loss of islets and increasingly severe insulin deficiency. A progressive spectrum of glucose tolerance abnormalities is seen, ranging from impaired glucose tolerance, to CFRD without fasting hyperglycemia (FH), to CFRD with FH. Ketoacidosis is rare. Insulin sensitivity is relatively well preserved unless patients are acutely ill or have severe chronic inflammation (3; 4).

Blood cholesterol levels are low in CFRD (5), and atherosclerotic cardiovascular disease has never been reported. Despite the apparent absence of macrovascular complications, diabetes has a negative impact on CF morbidity and mortality. It is associated with a rapid decline in lung function (6) and increased risk of death from respiratory failure, particularly in women (7). The mechanism for this clinical decline is postulated to be related to increased protein catabolism due to insulin deficiency.

Longevity in CF has dramatically increased. At the University of Minnesota (UM), median survival is 47yrs (7), which is greater than the US median of 37yrs (personal communication, CF Foundation, April 2006). As patients with CFRD live longer, it becomes increasingly likely that some will develop microvascular complications. The literature consists primarily of case reports (8-10) and small series (11-13). A Danish study found that 10% of their 41 CFRD patients had microvascular complications (14).

The UM CF Center instituted annual oral glucose tolerance test (OGTT) screening in 1990. This well-characterized population allowed a more complete assessment of the prevalence of diabetes microvascular complications than has previously been possible. The following report characterizes 284 patients with CFRD followed after 1/1/1990, 192 of whom were living by 12/31/2005.

RESEARCH DESIGN AND METHODS

Subjects

The UM CF Center has maintained a patient database for several decades and a specific diabetes database since 1990. Annual OGTT screening is recommended for all patients ≥6y. Diabetes is diagnosed by standard criteria (15). Fasting hyperglycemia is defined as glucose ≥126 mg/dl (7.0 mmol/L) on more than one occasion. All patients with FH are treated with insulin, while insulin therapy is only rarely instituted in subjects without FH. Annual spot urine microalbumin: creatinine ratio (U alb:crea) screening and dilated retinal exams are recommended for post-pubertal patients. The urine test is done at UM in the morning before clinic. Insurance often dictates the location for annual eye exams, often at outside clinics. All patients followed at this center give informed consent permitting their records to be reviewed for research purposes.

Diabetes duration was calculated as the length of time from diagnosis to 12/31/2005 or, for deceased patients, to the date of death. For subjects with FH, the years they were known to have diabetes
without FH were included in diabetes duration. Age was also calculated to 12/31/2005 or date of death. Hemoglobin A1c values were averaged over 3yrs.

**Screening of the Total CFRD Population for Microalbuminuria and Retinopathy**

$U_{\text{alb:cr}}$ was measured at the UM Fairview Hospital Laboratory. Albumin was detected by nephelometry (Immage 800, Beckman Coulter). Microalbuminuria was defined as 30-299 µg/mg creatinine, while >299 µg/mg creatinine was considered gross proteinuria (15).

Records from ophthalmology clinic were available for subjects whose eye examination was performed at UM or whose ophthalmologist sent a visit letter. Remaining subjects (none of whom had >10yr duration diabetes) were contacted by telephone and asked to report if a dilated eye exam had been performed in the last 2yrs. All subjects with reported eye changes were seen in follow-up by a retinal specialist at UM Department of Ophthalmology.

**Detailed Complication Screening of a Subset of Patients**

A letter was sent to all 192 CFRD patients inviting them to participate in more intensive screening. Subjects with >10yrs duration diabetes and those with a history of retinopathy or albuminuria were actively recruited. Approval was obtained from the Committee for the Use of Human Subjects in Research; informed consent was obtained from all subjects.

$U_{\text{alb:cr}}$ was measured as described above. Standard 7-field color stereoscopic fundus photographs were obtained to evaluate diabetic retinopathy. The photographs were reviewed by an ophthalmologist (TWO) and categorized according to the modified Airlie-House classification system (16). Neurological history and physical examination were performed by a neurologist with extensive experience with diabetic neuropathy (DW). Neurological examination for diabetes changes consisted of the following:

- Examination of the ability to perceive light stroking of the skin with cotton, pinprick sensitivity, vibration sensitivity using a 128 Hz tuning fork, and joint position sense,
- Nerve conduction studies of the left sural sensory, peroneal motor and tibial motor nerves,
- Cardiorespiratory reflex testing, consisting of evaluation of heart rate variability during deep breathing (HRDB) and heart rate variability during a Valsalva maneuver.

A validated questionnaire was used to detect diabetic gastroenteropathy (17; 18). Abnormal findings potentially related to diabetes in patients with CF included gastroesophageal reflux, gastroparesis, constipation, and nocturnal diarrhea.

**Statistical Methods**

Data are reported as mean ± standard deviation, with ranges given where appropriate. Rates were compared using chi-square tests, and continuous variables were compared using analysis of variance. All statistical tests were performed at the 0.05 level. All analyses were performed using SAS Version 9.1 (SAS Institute, 2003, Cary NC).

**RESULTS**

**Subjects**

During the period of 1/1/1990-12/31/2005, 775 patients >6yrs of age were followed at the UM CF Center. CFRD was diagnosed in 284, of whom 192 were alive on 12/31/2005 (Figure 1). Fifty-two percent of the 284 were female, mean age was 30±10yrs (range 7-61), and 64% had diabetes with FH. Diabetes status was unknown in 165 subjects. 140 subjects age
≥6yrs old died and, of these, 92 were known to have diabetes with an average duration of 4.7±5yrs (0.03-26yrs). All but 10 had FH.

Mean body mass index (BMI) in subjects with CFRD was 23.1±4.0kg/m$^2$ for those ≥18yrs; mean weight for height was 101±8% for subjects <18yrs. Nineteen percent of adults were underweight (BMI<20kg/m$^2$), 62% were normally nourished (BMI 20-25kg/m$^2$), and 19% were overweight (BMI > 25kg/m$^2$). Similarly, percent weight for height for patients <18yrs ranged from 87-127%, with 18% underweight (<95%wt:ht), 70% normally nourished (95-110% wt:ht) and 12% overweight (>110% wt:ht).

Nephropathy and Retinopathy Screening in the CFRD Cohort

U$_{\text{alb:cr}}$ was performed in 84% of all subjects with CFRD, including all but three with diabetes >10yrs duration (2 without and 1 with FH). Five subjects with proteinuria not related to diabetes were excluded from analysis, including 3 adults with renal failure clearly secondary to calcineurin inhibitor toxicity following lung transplantation, a child with IgA nephropathy, and a child with Henoch-Schonlein purpura. No subject with CFRD without FH had an elevated U$_{\text{alb:cr}}$ (Table 1). In contrast, increased U$_{\text{alb:cr}}$ was found in 6 CFRD subjects with FH. In 5 cases it was microalbuminuria; the 1 subject with gross proteinuria was a 25yr old woman with an 8yr history of diabetes, poor compliance, and an eating disorder. Of the 37 subjects with CFRD with FH ≥10yrs duration, 5 (14%) had an elevated U$_{\text{alb:cr}}$. All subjects with an abnormal U$_{\text{alb:cr}}$ had mild hypertension.

Retinal findings followed a similar pattern. Seventy-three percent of all CFRD subjects had ophthalmology exams documented by written or verbal report (with approximately half of these including retinal photographs), and written documentation of a dilated retinal exam with retinal photographs was available for 100% of subjects with FH who had >10yrs duration diabetes.

No subject with CFRD without FH had diabetic retinal changes (Table 1). Six of the 37 subjects (16%) with FH and diabetes duration >10yrs had diabetic retinopathy, which was mild in five cases. A 27yr old man with proliferative retinopathy and macular edema requiring panretinal laser photocoagulation and pars plana vitrectomy was suspected to have type 1 diabetes because he was pancreatic sufficient (which carries significantly less risk of CFRD) and had multiple episodes of ketoacidosis.

Comparison of CFRD subjects with and without fasting hyperglycemia

Over time, the majority of subjects with CFRD without FH progressed to CFRD with FH. In subjects with diabetes <2yrs duration, approximately 30% had FH. By 5yrs this number had increased to 45%, and by 10yrs to 60%. All subjects with diabetes >14yrs had FH. We examined associations between the presence of FH and several characteristics. There was no association between FH and BMI. Among those with FH, deaths were 4-fold more prevalent (no gender difference) (Figure 1). We believe the high prevalence of FH in CFRD patients at the time of death is at least partially related to the development of severe insulin resistance during critical illness. Similar to previous observations that hemoglobin A1c (HbA1c) is spuriously low in CFRD, HbA1c levels in general were lower than one might expect in a diabetes population. However, HbA1c was significantly higher in subjects with FH. The highest individual average HbA1c in CFRD without FH was 7.9%,
while HbA1c ranged from 3.7-10.9% in CFRD with FH.

Stratifying by duration of diabetes, those with FH showed an association between longer duration and increased HbA1c and prevalence of retinopathy and abnormal \( U_{\text{alb:cr}} \). In contrast, in patients without FH, HbA1c was persistently low and was not related to duration of diabetes.

**Detailed Microvascular Complications Subset Screening**

A subset of 59 CFRD subjects consented to more detailed screening, including 10/11 subjects with retinopathy or albuminuria (the single patient with both complications did not participate). Compared to the entire CFRD cohort, the intensively studied subset had a higher percentage of subjects with FH (71 vs 52%), was slightly older (34 vs 30yrs) and had slightly longer duration of diabetes (8.5 vs 7.0yrs). Hemoglobin A1c was 6.5±1.2%, BMI 22.9±3.2 kg/m\(^2\), fasting cholesterol 134±29mg/dl (range 77-205), triglycerides 119 ±62mg/dl (47-336), systolic blood pressure 118±11mm Hg (97-144), diastolic blood pressure 67±14mm Hg (48-90).

Retinal photographs confirmed previously reported abnormalities in five subjects and normal exams in the others. Similarly, \( U_{\text{alb:cr}} \) ratios confirmed previous findings in this cohort, with five subjects having elevated \( U_{\text{alb:cr}} \), and normal values in the remaining subjects.

Forty-two percent of the 59 subjects had at least one neurologic abnormality (Table 2). Autonomic neuropathy (reduced HRDB or an abnormal valsalva ratio) was found in 34%. Six patients had undergone lung transplantation, all of whom, as expected, had abnormal HRDB; five of these also had other evidence of neuropathy not expected to be associated with transplantation. Somatic abnormalities (reduced sural conduction velocity or lower limb sensory deficits) were found in 17%, and GI complications were found in 51% of individuals. There was no association between somatic, autonomic or GI abnormalities.

There was a non-significant trend towards increased prevalence of autonomic neuropathy in CFRD with FH compared to CFRD without FH (40% vs 18%, \( P=0.09 \)), while somatic neuropathy and GI complications were not influenced by FH status. This is in contrast to retinal and renal changes, which were only found in subjects with FH. The highest rates of autonomic neurologic complications occurred in those with the longest duration of diabetes (\( P=0.5 \)). Somatic and GI complications appeared to increase after 15 yrs duration of diabetes (40% and 80% of subjects, respectively), but the number of patients in this category was too small to achieve statistical significance. Autonomic and GI complications were related to diabetes control since they were more prevalent in subjects with HbA1c ≥7% versus those with lower HbA1c (autonomic: 63% vs 23%, \( P=0.01 \); GI: 75% vs 42%, \( P=0.02 \)).

**CONCLUSIONS**

This study represents the most comprehensive evaluation to date of the prevalence and severity of diabetes microvascular complications in CFRD. No patient with diabetes without FH was found to have any evidence of retinopathy or nephropathy. However, over time, the majority of these subjects experienced worsening \( \beta \)-cell function with progression to CFRD with FH. Of 37 patients with CFRD with FH who had diabetes for >10yrs, 14% had increased \( U_{\text{alb:cr}} \) and 16% had retinopathy. Retinopathy was only severe in one subject, who was suspected to have type 1 diabetes, and only one subject had gross proteinuria. Of the 59 patients who underwent full neurologic testing, 42%
had at least one neurologic abnormality, including 52% of those with diabetes >10yrs duration. Gastrointestinal symptoms were found in about half of subjects both with and without FH.

Mild neuropathy was the most common complication of CFRD, and was similar in prevalence to published rates for type 1 or 2 diabetes (19). The most common neurologic abnormalities consisted of reduced sural sensory nerve action potential amplitude and impaired cardiorespiratory reflexes. This is consistent with diabetic polyneuropathy, which is a length-dependent, sensory-predominant disorder, commonly occurring together with autonomic dysfunction. Autonomic neuropathy was more likely in patients with longer duration and poorer control of diabetes, while these relations were not significant for somatic neuropathy. Although vitamin E deficiency has also been postulated as a cause of neurologic findings in CF (20), careful attention to nutrition in general and vitamin supplementation in particular is universal in our clinic, making a clinically significant vitamin E deficiency unlikely.

Gastrointestinal complications of diabetes are a common manifestation of autonomic neuropathy. About 50% of patients with longstanding type 1 or 2 diabetes have delayed gastric emptying, 20% have diarrhea and about 60% have constipation (21). CF per se is also associated with these GI problems. Since the GI survey was not administered to non-diabetic CF subjects, it is difficult to sort out the relative contributions of diabetes and CF. In the current study, however, GI symptoms were more common in patients with longer diabetes duration or worse control, suggesting that diabetes may aggravate underlying CF GI dysfunction.

Diabetes is the most common cause of end-stage renal failure in the United States (22), with nephropathy developing in 20-30% of patients. Microalbuminuria was less common than expected in CFRD subjects with long-standing diabetes, and in the last 19 years we have known of only two patients with renal failure secondary to diabetes.

Similarly, retinopathy was less common in CFRD than in type 1 or 2 diabetes (23). In the Wisconsin Epidemiologic Study of Diabetic Retinopathy, 4% of patients with T1DM were legally blind, and the prevalence of any retinopathy was 8% after 3y, 25% after 5yrs, 60% after 10yrs and 80% after 15yrs (24). We may have underestimated the prevalence of retinopathy in subjects with <10yrs duration CFRD, since we relied on patient reports in some of these cases. Ninety percent of subjects with diabetes ≥10yrs duration, including 100% of those with FH, had a documented ophthalmologic exam. Not all of these, however, had retinal photographs. While it is reassuring that our total group data were similar to data obtained by retinal photographs in the intensively studied subset, we may be underreporting mild retinopathy in some of these cases.

The prevalence and severity of retinopathy and nephropathy may be lower in CFRD compared to other forms of diabetes because hyperglycemia is less severe, since patients with CFRD have variable degrees of persistent endogenous insulin secretion. This explanation does not explain why neuropathy rates are similar, however. The discrepancy may be related to a protective metabolic milieu in the CF patient. There appears to be a role for dyslipoproteinemia in the pathogenesis of diabetic retinopathy and nephropathy (25), but cholesterol levels are low in CF. Hypertension occurs but is usually mild, and insulin resistance tends to be minimal unless patients are acutely ill. Thus, the absence of...
metabolic risk factors, which clearly shields
the CFRD patient from macrovascular
disease, may also be partially protective
with regards to retinopathy and nephropathy.
Alternatively, the persistence of endogenous
insulin secretion may have protective effects
on cell survival.

Recently, elevated $U_{\text{alb:cr}}$ was
reported in CF patients without diabetes
(26), due to a combination of increased urine
albumin (hypothesized to be related to
infection) and decreased urine creatinine
(felt to reflect poor muscle mass). It was
concluded that $U_{\text{alb:cr}}$ is spuriously elevated
in CF and thus is a poor test of diabetic
nephropathy. The present study did not
confirm this finding, since $U_{\text{alb:cr}}$ was normal
in the majority of subjects.

In summary, while retinopathy and
nephropathy are less common than in type 1
or 2 diabetes, they do occur in CFRD and
appear to be related to duration of diabetes
and level of glycemic control. Neuropathy
and gastropathy occur as commonly in
patients with CFRD as in other forms of
diabetes. Similar to ADA guidelines for type
1 diabetes, it seems prudent to begin
diabetes microvascular complication
monitoring in patients who have CFRD with
FH after 5y diabetes duration. This is only
relevant if subjects have previously been
screened for diabetes so that true duration is
known. In the absence of systematic
screening, all new-onset CFRD patients
should have a dilated retinal exam and urine
albumin measurement.

Acknowledgments
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(GCRC) and R01-DK58356.
References
15. American Diabetes Association Clinical Practice Recommendations. *Diabetes Care* Supplement 1, 2004


Table 1. Characteristics of the University of Minnesota CFRD population by 5-year categories for diabetes duration. BMI (subjects ≥18y), HbA1c, microalbuminuria (↑Ualb:cr) and retinopathy results are given for CFRD patients alive Dec 31, 2005. Values are mean ± SD, or number. Subjects with FH were compared to those without FH within each strata of diabetes duration and in total. Significant differences between FH and no FH are indicated by an asterisk (P<0.05).

<table>
<thead>
<tr>
<th>Duration of Diabetes (years)</th>
<th>No Fasting Hyperglycemia</th>
<th>Less than 5</th>
<th>5 to 10</th>
<th>&gt;10</th>
<th>All</th>
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<td>% female</td>
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<td>Age (years)</td>
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<td>Hemoglobin A1c (%)</td>
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<td>% with Retinopathy (#tested)</td>
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<td>With Fasting Hyperglycemia</td>
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<td>Hemoglobin A1c (%)</td>
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<td>% with ↑Ualb:cr (#tested)</td>
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<tr>
<td>% with Retinopathy (#tested)</td>
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*Mean hemoglobin A1c for duration of diabetes within last 3 years.
Table 2. Prevalence of neurologic and gastrointestinal complications in 59 CFRD subjects intensively evaluated for diabetic microvascular complications. The $P$-value represents the significance of the association with duration of diabetes.

<table>
<thead>
<tr>
<th>Duration of Diabetes (years)</th>
<th>All (n=59)</th>
<th>&lt; 5 (n=18)</th>
<th>5 to 10 (n=18)</th>
<th>10 to 15 (n=18)</th>
<th>≥ 15 (n=5)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autonomic abnormalities</td>
<td>34% (n=20)</td>
<td>11%</td>
<td>33%</td>
<td>50%</td>
<td>60%</td>
<td>.05</td>
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<tr>
<td>Somatic abnormalities</td>
<td>17% (n=10)</td>
<td>11%</td>
<td>17%</td>
<td>17%</td>
<td>40%</td>
<td>.51</td>
</tr>
<tr>
<td>GI complications</td>
<td>51% (n=30)</td>
<td>56%</td>
<td>44%</td>
<td>44%</td>
<td>80%</td>
<td>.48</td>
</tr>
</tbody>
</table>

*a Autonomic abnormalities: valsala ratio <1.5 or heart rate variability during deep breathing R:R interval <18

*b Somatic abnormalities: ↓ sensation, sural amplitude <8 µV, or nerve conduction velocity <38 m/sec

*c GI complications: gastroesophageal reflux, gastroparesis, constipation, or nocturnal diarrhea
Figure 1. Diabetes prevalence in patients age 6 years and older followed at the UM CF Center between 1/1/1990 and 12/31/2005.

775 CF patients >6 years old were followed at UM CF Center 1/1/1990-12/31/2005

- 92 Known diabetes
  - 10 CFRD without fasting hyperglycemia
  - 82 CFRD with fasting hyperglycemia
- 140 Deceased
  - 18 Known by OGTT not to have diabetes
  - 30 Unknown
- 192 Known diabetes
  - 93 CFRD without fasting hyperglycemia
  - 99 CFRD with fasting hyperglycemia
- 635 Alive
  - 308 Known by OGTT not to have diabetes
  - 135 Unknown, lost to follow-up