Microvascular Complications in Cystic Fibrosis–Related Diabetes

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OBJECTIVE — The incidence of cystic fibrosis–related diabetes (CFRD) and the prevalence of diabetic 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-to-creatinine ratio ($U_{alb:Cr}$) screening and dilated retinal exams. In addition, 59 individuals underwent detailed retinopathy, nephropathy, neuropathy, and gastroenterpathy screening.

RESULTS — During 1990–2005, 775 patients aged ≥6 years were followed. CFRD was diagnosed by an oral glucose tolerance test or fasting hyperglycemia in 285 subjects (52% female), 64% of whom had fasting hyperglycemia. Most patients with CFRD without fasting hyperglycemia progressed to CFRD with fasting hyperglycemia over time. No subject with CFRD without fasting hyperglycemia had retinopathy or abnormal $U_{alb:Cr}$. In CFRD subjects with fasting hyperglycemia and diabetes for ≥10 years, 14% had microalbuminuria and 16% had retinopathy. Autonomic neuropathy and gastrointestinal symptoms each were seen in 52% and somatic abnormalities in 22% of patients with or without fasting hyperglycemia.

CONCLUSIONS — Diabetic 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 5 years in patients with CFRD with fasting hyperglycemia.

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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 diabetic microvascular complications in CFRD patients.

Diabetes is the most common comorbidity in patients with cystic fibrosis, occurring in ~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 to CFRD with fasting hyperglycemia. 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 cystic fibrosis 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 cystic fibrosis has dramatically increased. At the University of Minnesota, median survival is 47 years (7), which is greater than the U.S. median of 37 years (Cystic Fibrosis Foundation, personal communication). 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 41 CFRD patients had microvascular complications (14).

The University of Minnesota Cystic Fibrosis Center instituted annual oral glucose tolerance test screening in 1990. This well-characterized population allowed a more complete assessment of the prevalence of diabetic microvascular complications than has previously been possible. The following report characterizes 284 patients with CFRD followed after 1 January 1990, 192 of whom were living by 31 December 2005.

RESEARCH DESIGN AND METHODS

— The University of Minnesota Cystic Fibrosis Center has maintained a patient database for several decades and a specific diabetes database since 1990. Annual oral glucose tolerance test screening is recommended for all patients aged ≥6 years. 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 fasting hyperglycemia are treated with insulin, whereas insulin therapy only is rarely

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Abbreviations: CFRD, cystic fibrosis–related diabetes.

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

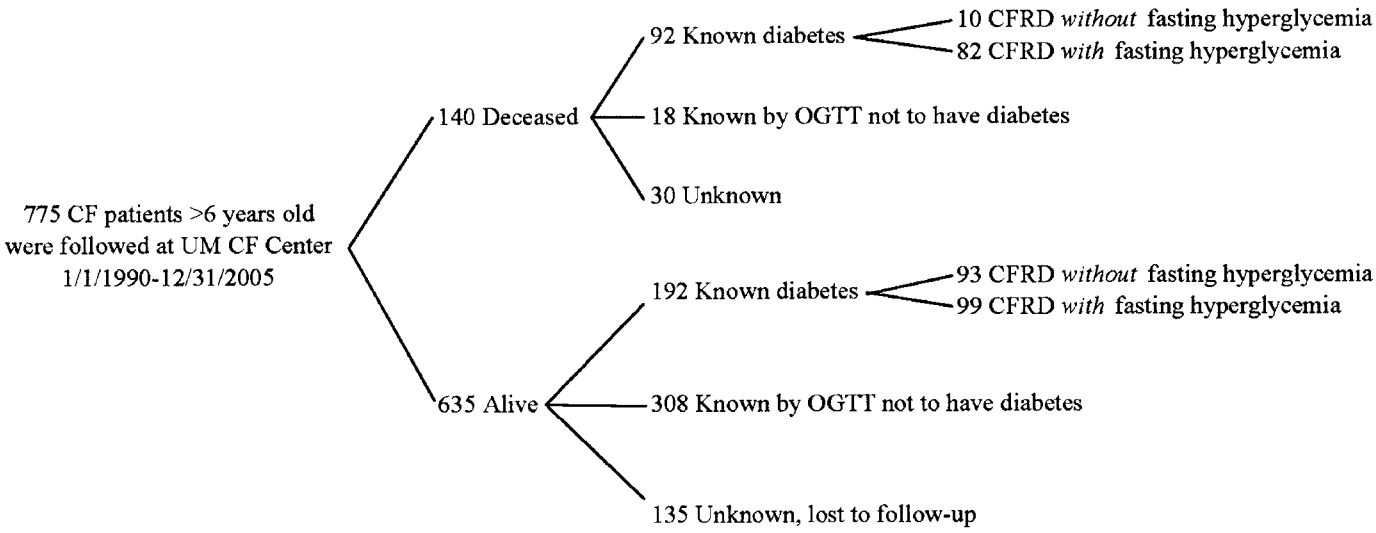

Figure 1—*Diabetes prevalence in patients aged ≥6 years followed at the University of Minnesota Cystic Fibrosis Center between 1 January 1990 and 31 December 2005. OGTT, oral glucose tolerance test.*

instituted in subjects without fasting hyperglycemia. Annual spot urine microalbumin-to-creatinine ratio ($U_{alb:cr}$) screening and dilated retinal exams are recommended for postpubertal patients. The urine test is done at the University of Minnesota in the morning before clinic. Insurance often dictates the location for annual eye exams, often at outside clinics. All patients followed at this center gave informed consent, permitting their records to be reviewed for research purposes.

Diabetes duration was calculated as the length of time from diagnosis to 31 December 2005 or, for deceased patients, to the date of death. For subjects with fasting hyperglycemia, the years they were known to have diabetes without fasting hyperglycemia were included in diabetes duration. Age also was calculated to 31 December 2005 or date of death. A1C values were averaged over 3 years.

Screening of the total CFRD population for microalbuminuria and retinopathy

$U_{alb:cr}$ was measured at the University of Minnesota Fairview Hospital Laboratory. Albumin was detected by nephelometry (Immage 800; Beckman Coulter). Microalbuminuria was defined as 30–299 μg/mg creatinine, whereas >299 μg/mg creatinine was considered gross proteinuria (15).

Records from ophthalmology clinics were available for subjects whose eye examination was performed at the University of Minnesota or whose ophthalmologist sent a visit letter. Remaining subjects (none of whom had diabetes >10 years) were contacted by telephone and asked to report if a dilated eye exam had been performed in the last 2 years. All subjects with reported eye changes were seen in follow-up by a retinal specialist at the University of Minnesota 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 who had diabetes for >10 years 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, and informed consent was obtained from all subjects.

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

- Examination of the ability to perceive light stroking of the skin with cotton, pinprick sensitivity, or 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 (heart rate changes with deep breathing) and heart rate variability during a Valsalva maneuver.

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

Statistical methods

Data are reported as means ± SD, with ranges given where appropriate. Rates were compared using χ^2 tests, and continuous variables were compared using ANOVA. All statistical tests were performed at the 0.05 level. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS

Subjects

During the period of 1 January 1990 to 31 December 2005, 775 patients aged ≥6 years were followed at the University of Minnesota Cystic Fibrosis Center. CFRD was diagnosed in 284 patients, of whom 192 were alive on 31 December 2005 (Fig. 1). Fifty-two percent of 284 patients were female, mean age was 30 ± 10 years (range 7–61), and 64% had diabetes with fasting hyperglycemia. Diabetes status

Table 1—*Characteristics of the University of Minnesota CFRD population by 5-year categories for diabetes duration*

	Duration of diabetes (years)			
	<5	5–10	>10	All
No fasting hyperglycemia				
n	44	27	22	93
Percent female	56	48	45	51
Age (years)	29 ± 10	29 ± 9	30 ± 7	29 ± 9
BMI (kg/m^2)	22.8 ± 3.9	23.3 ± 4.0	21.2 ± 1.9	22.5 ± 3.6
A1C (%)*	5.9 ± 0.5	5.9 ± 0.5	5.9 ± 0.4	5.9 ± 0.5
Percent with ↑ $U_{alb:cr}$ (*n* tested)	0 (36)	0 (23)	0 (20)	0 (79)
Percent with retinopathy (*n* tested)	0 (23)	0 (18)	0 (16)	0 (57)
With fasting hyperglycemia				
n	30	32	37	99
Percent female	38	55	51	49
Age (years)	28 ± 13	30 ± 10	37 ± 9	31 ± 11
BMI (kg/m^2)	23.7 ± 5.7	23.3 ± 3.5	23.4 ± 2.7	23.5 ± 4.2
A1C (%)	6.2 ± 0.8	7.0 ± 1.8†	7.2 ± 1.1†	6.8 ± 1.3†
Percent with ↑ $U_{alb:cr}$ (*n* tested)	0 (22)	4 (25)	14 (36)†	7 (83)†
Percent with retinopathy (*n* tested)	0 (20)	0 (28)	16 (37)†	7 (84)†

Data are means ± SD unless otherwise indicated. BMI (subjects aged ≥18 years), A1C, microalbuminuria (↑ $U_{alb:cr}$), and retinopathy results are given for CFRD patients alive 31 December 2005. Subjects with fasting hyperglycemia were compared to those without within each strata of diabetes duration and in total. *Mean A1C for duration of diabetes within last 3 years. †Significant differences between fasting hyperglycemia and no fasting hyperglycemia ($P < 0.05$).

was unknown in 165 subjects. A total of 140 subjects aged ≥6 years died, and, of these, 92 were known to have diabetes with an average duration of 4.7 ± 5 years (0.03–26). All but 10 subjects had fasting hyperglycemia.

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

Nephropathy and retinopathy screening in the CFRD cohort

$U_{alb:cr}$ was performed in 84% of all subjects with CFRD, including all but three with diabetes >10 years' duration (two without and one with fasting hyperglycemia). Five subjects with proteinuria not related to diabetes were excluded from analysis, including three 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 fasting hyperglycemia had an elevated $U_{alb:cr}$ (Table 1). In contrast, increased $U_{alb:cr}$ was found in six CFRD subjects with fasting hyperglycemia. In five cases, it was microalbuminuria; one subject with gross proteinuria was a 25-year-old woman with an 8-year history of diabetes, poor compliance, and an eating disorder. Of 37 subjects with CFRD with fasting hyperglycemia and ≥10 years' diabetes duration, 5 (14%) had an elevated $U_{alb:cr}$. All subjects with an abnormal $U_{alb:cr}$ 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 fasting hyperglycemia who had diabetes >10 years.

No subject with CFRD without fasting hyperglycemia had diabetic retinal changes (Table 1). Six of 37 subjects (16%) with fasting hyperglycemia and diabetes for >10 years had diabetic retinopathy, which was mild in 5 cases. A 27-year-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 fasting hyperglycemia progressed to CFRD with fasting hyperglycemia. In subjects with diabetes <2 years' duration, ~30% had fasting hyperglycemia. By 5 years, this number had increased to 45% and by 10 years to 60%. All subjects with diabetes >14 years had fasting hyperglycemia.

We examined associations between the presence of fasting hyperglycemia and several characteristics. There was no association between fasting hyperglycemia and BMI. Among those with fasting hyperglycemia, deaths were fourfold more prevalent (no sex difference) (Fig. 1). We believe the high prevalence of fasting hyperglycemia 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 A1C is spuriously low in CFRD, A1C levels in general were lower than one might expect in a diabetic population. However, A1C was significantly higher in subjects with fasting hyperglycemia. The highest individual average A1C in subjects with CFRD without fasting hyperglycemia was 7.9%, whereas A1C ranged from 3.7 to 10.9% in subjects with CFRD with fasting hyperglycemia.

Stratifying by duration of diabetes, those with fasting hyperglycemia showed

Table 2—*Prevalence of neurologic and gastrointestinal complications in 59 CFRD subjects intensively evaluated for diabetic microvascular complications*

	Duration of diabetes (years)					
	All	<5	5–10	10–15	≥15	*P* value
n	59	18	18	18	5	
Autonomic abnormalities (*n* = 20)*	34	11	33	50	60	0.05
Somatic abnormalities (*n* = 10)†	17	11	17	17	40	0.51
Gastrointestinal complications (*n* = 30)‡	51	56	44	44	80	0.48

Data are %. The *P* value represents the significance of the association with duration of diabetes. *Autonomic abnormalities: valsalva ratio <1.5 or heart rate variability during deep breathing R:R interval on EKG <18. †Somatic abnormalities: ↓ sensation, sural amplitude <8 μV, or nerve conduction velocity <38 m/s. ‡Gastrointestinal complications: gastroesophageal reflux, gastroparesis, constipation, or nocturnal diarrhea.

an association between longer duration and increased A1C and prevalence of retinopathy and abnormal $U_{alb:cr}$. In contrast, in patients without fasting hyperglycemia, A1C 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 of 11 subjects with retinopathy or albuminuria (one patient with both complications did not participate). Compared with the entire CFRD cohort, the intensively studied subset had a higher percentage of subjects with fasting hyperglycemia (71 vs. 52%), was slightly older (aged 34 vs. 30 years), and had slightly longer duration of diabetes (8.5 vs. 7.0 years). A1C was 6.5 ± 1.2%, BMI 22.9 ± 3.2 kg/m^2, fasting cholesterol 134 ± 29 mg/dl (range 77–205), triglycerides 119 ± 62 mg/dl (47–336), systolic blood pressure 118 ± 11 mmHg (97–144), and diastolic blood pressure 67 ± 14 mmHg (48–90). Retinal photographs confirmed previously reported abnormalities in five subjects and normal exams in the others. Similarly, $U_{alb:cr}$ confirmed previous findings in this cohort, with five subjects having elevated $U_{alb:cr}$ and normal values in the remaining subjects.

Forty-two percent of 59 subjects had at least one neurologic abnormality (Table 2). Autonomic neuropathy (reduced heart rate changes with deep breathing or an abnormal Valsalva ratio) was found in 34% of subjects. Six patients had undergone lung transplantation, all of whom, as expected, had abnormal heart rate changes with deep breathing; five of these patients 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 gastrointestinal complications in 51% of individuals. There was no association between somatic, autonomic, or gastrointestinal abnormalities.

There was a nonsignificant trend toward increased prevalence of autonomic neuropathy in subjects with CFRD with fasting hyperglycemia compared with CFRD without fasting hyperglycemia (40 vs. 18%, $P = 0.09$), whereas somatic neuropathy and gastrointestinal complications were not influenced by fasting hyperglycemia status. This is in contrast to retinal and renal changes, which only were found in subjects with fasting hyperglycemia. The highest rates of autonomic neurologic complications occurred in those with the longest duration of diabetes ($P = 0.05$). Somatic and gastrointestinal complications appeared to increase after 15 years' 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 gastrointestinal complications were related to diabetes control because they were more prevalent in subjects with A1C ≥7% versus those with lower A1C (autonomic: 63 vs. 23%, $P = 0.01$; gastrointestinal: 75 vs. 42%, $P = 0.02$).

CONCLUSIONS — This study represents the most comprehensive evaluation to date of the prevalence and severity of diabetic microvascular complications in CFRD. No patient with diabetes without fasting hyperglycemia was found to have any evidence of retinopathy or nephropathy. However, over time, the majority of these subjects experienced worsening β-cell function with progression to CFRD with fasting hyperglycemia. Of 37 patients with CFRD with fasting hyperglycemia who had diabetes for >10 years, 14% had increased $U_{alb:cr}$ 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 59 patients who underwent full neurologic testing, 42% had at least one neurologic abnormality, including 52% of those with diabetes >10 years' duration. Gastrointestinal symptoms were found in about half of subjects both with and without fasting hyperglycemia.

Mild neuropathy was the most common complication of CFRD and was similar in prevalence to published rates for type 1 or type 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, whereas these relations were not significant for somatic neuropathy. Although vitamin E deficiency also has been postulated as a cause of neurologic findings in cystic fibrosis (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 long-standing type 1 or type 2 diabetes have delayed gastric emptying, 20% have diarrhea, and ~60% have constipation (21). Cystic fibrosis per se also is associated with these gastrointestinal problems. Beacase the gastrointestinal survey was not administered to nondiabetic cystic fibrosis subjects, it is difficult to sort out the relative contributions of diabetes and cystic fibrosis. In the current study, however, gastrointestinal symptoms were more common in patients with

longer diabetes duration or worse control, suggesting that diabetes may aggravate underlying cystic fibrosis gastrointestinal dysfunction.

Diabetes is the most common cause of end-stage renal failure in the U.S. (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 type 2 diabetes (23). In the Wisconsin Epidemiologic Study of Diabetic Retinopathy, 4% of patients with type 1 diabetes were legally blind, and the prevalence of any retinopathy was 8% after 3 years, 25% after 5 years, 60% after 10 years, and 80% after 15 years (24). We may have underestimated the prevalence of retinopathy in subjects with <10 years' duration CFRD because we relied on patient reports in some of these cases. Ninety percent of subjects with diabetes duration ≥10 years, including 100% of those with fasting hyperglycemia, had a documented ophthalmologic exam. Not all of these, however, had retinal photographs. Although 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 with other forms of diabetes because hyperglycemia is less severe and because 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 cystic fibrosis patient. There appears to be a role for dyslipoproteinemia in the pathogenesis of diabetic retinopathy and nephropathy (25), but cholesterol levels are low in cystic fibrosis. Hypertension occurs but usually is 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, also may 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 $U_{alb:cr}$ was reported in cystic fibrosis patients without diabetes (26) because of 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 $U_{alb:cr}$ is spuriously elevated in cystic fibrosis and thus is a poor test of diabetic nephropathy. The present study did not confirm this finding because $U_{alb:cr}$ was normal in the majority of subjects.

In summary, although retinopathy and nephropathy are less common than in type 1 or type 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 American Diabetes Association guidelines for type 1 diabetes, it seems prudent to begin diabetic microvascular complication monitoring in patients who have CFRD with fasting hyperglycemia after 5 years diabetes duration. This only is 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.

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