Cystic Fibrosis–Related Diabetes

The presence of microvascular diabetes complications

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OBJECTIVE — Cystic fibrosis (CF)-related diabetes has been regarded as a mild form of diabetes with a low risk of severe diabetes complications. The prevalence of CF-related diabetes increases with age, resulting in a 50% prevalence of diabetes at age 30 years. We sought to investigate whether microvascular complications in CF-related diabetes appear with a relevant frequency.

RESEARCH DESIGN AND METHODS — Thirty-eight patients aged 30 (range 18–55) years with CF-related diabetes for 20 (0–31) years were screened for diabetes complications. Because of chronic pulmonary infections, the majority of patients were regularly treated with aminoglycoside and cyclosporine given frequently.

RESULTS — Since the pharmacological treatment of lung transplant patients could influence metabolical regulation and renal function, the results are given separately for nontransplanted (n = 29) and transplanted (n = 9) CF patients. Nine patients (27%) had retinopathy, two of which had proliferative retinopathy and needed laser treatment. Lung transplantation did not affect the prevalence of retinopathy. In nontransplanted patients, nine had hypertension, three microalbuminuria, and one elevated creatinine. None had macroalbuminuria. In transplanted patients, eight of nine had hypertension, two had microalbuminuria, and none had macroalbuminuria. Seven of nine lung transplant patients had elevated plasma creatinine, and severely reduced glomerular filtration rate was significantly more frequent.

CONCLUSIONS — A high frequency of diabetic retinopathy was found in patients with insulin-treated CF-related diabetes, stressing the need for a regular screening program as in type 1 diabetes. Severely impaired kidney function was common in lung transplant patients, probably secondary to cyclosporine treatment.

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Cystic fibrosis (CF) is the most frequent autosomal recessive inheritable disease in the Caucasian population in Denmark, affecting 1 in 4,700 children. The disease is characterized by recurring lung infections, reduced function of the exocrine pancreas, intestinal obstruction, and liver diseases. Median life expectancy is increasing, presently ~30 years. Diabetes occurs with increasing frequency as the patient grows older; ~50% have developed diabetes at age 30 years. The pathogenesis of CF-related diabetes is unknown.

Previously, treatment of patients with CF-related diabetes did not aim for strict metabolic control due to the short life expectancy. However, ~20 cases of retinopathy, nephropathy, and neuropathy in CF patients with diabetes have been reported worldwide (1–6). Background and proliferative retinopathy in CF patients with diabetes was first reported in 1986 (1,2). Since then, at least four cases of proliferative retinopathy have been reported, with two cases leading to blindness (3). All cases had a poor metabolic control and associated nephropathy (1–3).

Patients with CF are at risk of developing secondary renal disease as a result of nephrotoxic medications, primarily aminoglycosides and cyclosporine. Aminoglycoside antibiotics have an important role in the treatment of *Pseudomonas aeruginosa* infections, a common cause of chronic pulmonary infection in CF. Macroangiopathy has not been reported, presumably due to decreased lipid absorption. However, the magnitude of the clinical problem of severe late diabetes complications in CF patients with diabetes is poorly described.

At the diabetes clinic, State University Hospital, Copenhagen, we are following a large group of patients with CF-related diabetes, previously well characterized by Lanng (7). The purpose of this study was to investigate the prevalence of serious late diabetes complications, specifically proliferative retinopathy, and kidney involvement in insulin-treated CF patients with diabetes.

RESEARCH DESIGN AND METHODS

— All patients aged >10 years in our tertiary referral center for CF are carefully screened annually for diabetes with an oral glucose tolerance test and insulin treatment initiated when appropriate. All CF patients aged >18 years with insulin-treated diabetes attending the diabetes clinic, State University Hospital, Copenhagen, were asked to participate in the study. One patient was excluded due to nonrelated serious illness (Hodgkin's disease), and one patient chose not to participate. A total of 38 patients (18 men and 20 women) were included in the study. As control subjects, 38 randomly selected type 1 diabetic patients (22 men and 16 women, aged 18–45 years) attending the same diabetes clinic, State University Hospital, Copenhagen, were also included. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee.

From the medical records the following data from August 2003 to July 2004

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Abbreviations: CF, cystic fibrosis.

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

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was recorded: age, sex, duration of diabetes, HbA_{1c} (A1C), BMI, sense of vibration at the index toe, pulsation in dorsalis pedis artery, blood pressure, use of antihypertensives, 24-h urinary albumine excretion, serum creatinine, and cholesterols, as described previously (4). When measurement of diurnal excretion of albumin was not possible, albumin-to-creatinine excretion ratio was measured ($n = 6$). Microalbuminuria was defined as the median urinary albumin excretion between 30 and 300 mg/24 h (30–300 albumin-to-creatinine excretion ratio) based on at least two measurements. Diabetic nephropathy was defined as 24-h urine albumin excretion >300 mg/24 h. ^{51}Cr-EDTA clearance was performed as described previously (8). A patient was defined as having hypertension when treated with antihypertensives or when the blood pressure was >140/90 mmHg. The following normal limits were used: blood pressure, <140/90 mmHg; serum creatinine, <110 μmol/l; total cholesterol, <5 mmol/l; HDL cholesterol, >1 mmol/l; LDL cholesterol, <3 mmol/l; triglycerides, <2 mmol/l; and threshold of vibration <20.

Ophthalmic examination

Best-corrected visual acuity was measured (Snellen). Fundus photography was performed with a digital camera (Zeiss FF450 plus IR) with a spatial solubility of 2,256 × 2,023, matching around 5,000,000 pixels. In general, we work with a 50° field matching 11 times enlargement.

As a minimum, three fundus pictures were taken of each eye: one central, one nasally, and one temporally situated. If more than mild diabetic retinopathy changes were present, the amount of pictures was increased to seven, according to the Airlie House classification study (9).

The obtained pictures were handled and saved in a picture database evolved by Zeiss named Visupac. The photographs were evaluated by one experienced ophthalmologist (C.S.L.), using modifications of the Airlie House classification (9), the Early Treatment Diabetic Retinopathy Study's retinopathy severity scheme (10), and the proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales (11).

Diabetic retinopathy

Patients with mild diabetic retinopathy had <10 intraretinal hemorrhages and/or microaneurisms. Those with moderate diabetic retinopathy had >10 punctiform intraretinal hemorrhages and/or microaneurisms and/or varying numbers of hard exudates and/or 1–10 soft exudates. No alterations present fulfilled criterions for preproliferative and proliferative retinopathy. Patients with preproliferative diabetic retinopathy had >10 soft exudates and/or intraretinal microvascular abnormalities and/or venous beading without proliferations present. In patients with proliferative diabetic retinopathy, there were new formations of blood vessels on the papilla disc and/or in the periphery with or without larger preretinal hemorrhages or bleedings in the corpus vitreum or proliferations on the iris and/or in the angle of the chamber. No patients with diabetic maculopathy defined as macular odema or hard exudates within the macula were found. Pulmonary function was evaluated as described elsewhere (12).

From onset of CF, presence of chronic pulmonary infection, bacteriological status, lung transplantation, and previous treatment with potential kidney-damaging drugs (as in aminoglycosides and cyclosporine) were registered in the medical records. All nine lung transplant patients had developed diabetes before transplantation. The patients received immunosuppressive treatment, including cyclosporine and azathoprine, adjusted according to renal function, leukocytes, and platelets. Methylprednisolone was administered at a daily dose of 0.1 mg/kg (13). Two nontransplanted patients were treated with prednisolone and cyclosporine due to allergic broncho-pulmonary aspergillosis. In addition, two nontransplanted patients were treated with prednisolone to suppress severe inflammations in the lungs. Infected patients were treated with antibiotics according to the resistance pattern of the microorganisms colonizing in the patients as described previously (14).

Statistical analysis

Student's *t*-test was used to evaluate any difference between variables in the two groups of CF patients. A P value <0.05 was considered significant. Data are expressed as median and observed range or numbers with percentages in parenthesis.

RESULTS — Since the pharmacological treatment of lung transplant patients could influence the metabolical regulation and renal function, the results are shown separately for the 29 nontransplanted and 9 transplanted patients.

The majority of the CF patients had acceptable A1C values on a relatively low dose of insulin (Table 1) compared with the control patients with type 1 diabetes with median age 32 years (range 20–45), duration of diabetes 9 years (0–41), insulin 44 IU/day (21–98), and A1C 7.8% (5.8–13.4). No significant differences were found between the transplanted and the nontransplanted patients regarding age, sex, dose of insulin, BMI, duration of diabetes, and A1C (Table 1).

Seven patients (18%) had a BMI <18.5 kg/m^2 with a median A1C of 6.5% (range 5.4–11.2). Six patients (16%) had a BMI >25 kg/m^2; one patient was obese. A1C in the prednisolone-treated patients was comparable with patients not treated with prednisolone (7.4 [5.4–8.3] vs. 6.7% [5.7–11.2]; P = NS).

Diabetic retinopathy

Retinopathy did occur in 9 of 25 patients with at least 10 years of diabetes duration (36%), but not in patients with a shorter duration of diabetes. Six of these patients (18%) had mild diabetic retinopathy, one patient had moderate diabetic retinopathy, and two patients (6%) had proliferative retinopathy. Lung transplantation did not affect the prevalence of retinopathy (Table 1). In the control group of type 1 diabetic patients, 51% had normal eye status, 38% had mild or moderate retinopathy, and 11% had proliferative retinopathy.

The two CF patients with the most severe eye disease were both 29-year-old men. The first patient has had diabetes for 10 years. Proliferative retinopathy occurred after 8 years of diabetes when A1C was 11.6%. The second patient has had diabetes for 22 years, and proliferative retinopathy occurred after 21 years of diabetes when A1C was 12.3%. Both have been treated with laser and are stable with normal vision.

Diabetic nephropathy

In nontransplanted CF patients, nine had hypertension, three had microalbuminuria, and one had elevated creatinine (Table 1). None had macroalbuminuria. The patient with elevated serum creatinine was one of two nontransplanted patients treated with cyclosporine due to an allergic pulmonary reaction. The duration of diabetes in the patients with microalbuminuria was 1, 10, and 22 years. One patient had proliferative retinopathy; the remaining two had normal eye status.

In transplanted CF patients, eight of

Table 1—*Clinical data for 38 insulin-treated patients with CF-related diabetes with or without lung transplantation*

	Nontransplant patients	Transplant patients
n	29	9
Sex (male/female)	14/15	4/5
Age (years)	29 (18–55)	37 (25–48)
BMI (kg/m^2)	20.6 (17–32.9)	20.7 (17.6–24.2)
Prednisolone treatment	6	9
FEV	61 (28–111)	84 (35–119)
FVC	86 (59–126)	101 (56–125)
Duration of diabetes (years)	12 (0–31)	13 (3–22)
Insulin (IU/day)	26 (4–96)	24 (16–57)
A1C (%)	6.9 (5.7–11.2)	7.1 (5.4–8.3)
Mild and moderate retinopathy	5 (21)	2 (22)
Proliferative retinopathy	1 (4)	1 (11)
Hypertension	9 (31)	8 (89)
Microalbuminuria (30–300 mg/24 h)	3 (13)	2 (22)
Macroalbuminuria (>300 mg/24 h)	0	0
Serum creatinine > 110 μmol/l	1 (4)	7 (78)
GFR (ml/min per 1.73 m^2)	102 (64–152)	35 (20–73)*
Total cholesterol	3.7 (2.3–4.8)	4.6 (4.2–6.1)
Pulsation of dorsalis pedis artery	28 (100)	8 (100)
Threshold of vibration at the index toe >20	0 (0)	3 (33)

Data are median (range) or *n* (%). Eye data was available from all 9 of the transplant patients and in 24 of 29 nontransplant patients (diabetes duration 0–17 years). Data on pulsation of dorsalis pedis artery was available in 8 transplant and 28 nontransplant patients. *$P < 0.0005$, $n = 24$ (nontransplant) and $n = 8$ (transplant). FEV, forced expiratory volume; FVC, forced vital capacity; GFR, glomerular filtration rate.

nine (89%; Table 1) had hypertension. No patients with macroalbuminuria were found, and only two patients currently had microalbuminuria. Both patients had relatively long duration of diabetes (10 and 14 years) and hypertension, but normal eye status, making the cause for microalbuminuria uncertain. Seven of nine lung transplant patients had elevated plasma creatinine, and severely reduced glomerular filtration rate was frequent (Table 1). One patient is receiving regular dialysis. In the control group of type 1 diabetic patients, 28% had microalbuminuria and none had macroalbuminuria or kidney failure.

Other complications

As expected, cholesterol levels were normal in most cases. None of the patients were treated with cholesterol-lowering drugs. Only two patients, both transplant recipients, had slightly elevated total cholesterol levels (Table 1), while four patients, all nontransplant patients, had decreased levels of HDL cholesterol, whereas none had an LDL cholesterol level >3 mmol/l (data not shown).

None of the patients had arterial insufficiency of the lower extremities as judged by normal pulsation in dorsalis pedis artery (Table 1) and no history of foot ulcers. Three patients (8%), all transplant patients and with a duration of diabetes between 12 and 14 years, had an increased threshold of vibration (Table 1).

No differences in forced vital capacity and forced expiratory volume were found between the two groups (Table 1). All patients with at least 10 years of diabetes duration had a chronic pulmonary infection, while only 75% with a shorter duration of diabetes was chronically infected. Eighty percent of the chronic pulmonary infections were caused by *P. aeroginosa*.

CONCLUSIONS

— In the current study, we found that 27% of patients with CF-related diabetes had retinopathy approaching the prevalence level in patients with type 1 diabetes of similar duration of diabetes. This prevalence is higher than previously described (3–6), partly due to a longer observation period with diabetes and partly because only insulin-treated CF patients were selected for this study. In a previous study, 5 of 31 patients (16%) were found to have diabetic retinopathy (5). One patient with a duration of diabetes of 23 years had proliferative retinopathy (5). In a study of the impact of diabetes on pulmonary function and clinical outcome of CF patients, 3 and 2 of 28 patients had retinopathy and nephropathy, respectively (6).

To our knowledge the present study is the largest evaluation of the prevalence of diabetes complications in insulin-treated patients with CF. Still, one may need some caution in interpreting the data because of the small number of patients. In general, the retinal changes were mild, but 6% had proliferative retinopathy. Retinal changes were mainly seen in CF patients with >10 years duration of diabetes. In addition, the metabolic regulation of the two patients with proliferative retinopathy was poor at onset of proliferative retinopathy, suggesting that duration of diabetes and poor metabolic regulation is playing a role in the development of retinopathy, as in other forms of diabetes. Indeed, breakdown of the blood-retinal barrier, one of the earliest detectable functional abnormalities that may be associated with the microangiopathy of diabetes, was found to occur with equal frequency in CF-related diabetes and type 1 diabetes (15).

Lung transplantation is currently the only treatment available for end-stage respiratory insufficiency, and today, CF patients are the second largest group of lung transplant recipients in Europe (13). In a recent study of lung transplant CF patients from our center, ^{51}Cr-EDTA clearance declined from normal levels of ~100–32 ml/min 6 months after transplantation and decreased further after 6 years (13). Three (11%) of 29 patients received end-stage renal replacement

treatment with dialysis or kidney transplantation (13). Cyclosporine treatment might be the main reason for the drop in kidney function. Evidently, nephrotoxic medications could act as confounding factors when evaluating whether diabetic nephropathy is present. Reduced kidney function was only demonstrated in patients receiving cyclosporine; persistent proteinuria was not present, and diabetic retinopathy was not more prevalent among these patients. Therefore, most likely the reduced kidney function is secondary to cyclosporine treatment and not due to diabetic nephropathy.

Recently, microalbuminuria as a screening tool in CF-related diabetes was questioned; CF patients, even without diabetes, were found to have increased urinary albumin excretion due to chronic infection and reduced urinary creatinine excretion due to low muscle mass (16). This could result in patients meeting the conventional criteria for microalbuminuria but not in developing diabetic nephropathy (16). In the present study, microalbuminuria was primarily evaluated as a measurement of diurnal excretion of albumin, and a possible low urinary excretion of creatinine in CF patients does not influence our results.

Severe proteinuria and decreased creatinine clearance has been reported previously in poorly regulated nontransplant CF-related diabetic patients (1–3). In our study, none of the patients developed persistent proteinuria despite many patients with long duration of diabetes. Microalbuminuria was often associated with hypertension and treated with ACE inhibitors when diagnosed. Therefore, it is difficult to elucidate whether microalbuminuria predicts the development of diabetic nephropathy in patients with CF-related diabetes if they are left untreated.

In accordance with previous reports (7), no sign of peripheral macroangiopathy was found as judged by normal pulsation of dorsalis pedis artery in all CF patients without a history of foot ulcers. In addition, the CF patients had a favorable cholesterol profile, which was probably related to the malabsorption prevalent in these patients. None of the patients have had an episode of acute myocardial infarction or stroke, but electrocardiogram and echocardiography were not performed to further elucidate the presence of macroangiopathy. A low frequency of mild neuropathy was found (7).

Until the 1980s, patients with CF had short life expectancies and few survived long enough to determine whether they would develop late diabetes complications. Due to better treatment of pulmonary complications, life expectancy of CF patients has increased dramatically in the last 20 years. In this study, a high frequency of diabetic retinopathy was found in patients with insulin-treated CF-related diabetes, approaching the prevalence found in patients with type 1 diabetes of similar duration of diabetes, which stresses the need for regular screening. Hypertension and microalbuminuria, but not diabetic nephropathy, were also prevalent. Severely impaired kidney function was common in lung transplant patients, probably secondary to cyclosporine treatment. Based on these results, we recommend that patients with CF follow the same screening program for retinopathy, hypertension, and microalbuminuria as patients with type 1 diabetes.

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