

# Comparison of Cystic Fibrosis–Related Diabetes With Type 1 Diabetes Based on a German/Austrian Pediatric Diabetes Registry

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FOR THE GERMAN/AUSTRIAN DIABETES  
PROSPECTIVE DOCUMENTATION INITIATIVE

**OBJECTIVE**—The prevalence of cystic fibrosis–related diabetes (CFRD) has increased with improved life expectancy of patients. Clinical and care characteristics were compared with type 1 diabetes mellitus (T1DM) in a multicenter analysis of pediatric data.

**RESEARCH DESIGN AND METHODS**—Auxological and treatment data from 47,227 patients aged younger than 21 years with CFRD or T1DM in the German/Austrian Diabetes Prospective Documentation Initiative registry were analyzed by multivariable mixed regression modeling.

**RESULTS**—Diabetes onset (mean [interquartile range]) occurred later in individuals with CFRD (14.5 [11.8–16.3] years) than in individuals with T1DM (8.5 [4.9–11.8] years), with female preponderance in CFRD (59.1% vs. 47.5%;  $P < 0.01$ ). CFRD patients had lower BMI standard deviation scores ( $-0.85 [-1.59 \text{ to } -0.12]$  vs.  $+0.52 [-0.10 \text{ to } +1.16]$ ;  $P < 0.01$ ) and lower HbA<sub>1c</sub> (6.87% vs. 7.97%;  $P < 0.01$ ). Self-monitoring of blood glucose was more frequent in patients with T1DM (4.5 vs. 3.5;  $P < 0.01$ ); 72% of CFRD patients received insulin. In insulin-treated patients, insulin dosage adjusted for age, sex, and diabetes duration differed significantly (T1DM: 0.79 IE per kilogram of body weight; CFRD: 0.83 IE per kilogram of body weight). Use of short-acting and long-acting insulin analogs was significantly more frequent in T1DM (47% vs. 39% and 37% vs. 28%; both  $P < 0.05$ ). Metabolic control in CFRD patients without insulin was better compared with CFRD on insulin (HbA<sub>1c</sub>: 6.00 vs. 7.12;  $P < 0.01$ ), but duration of disease was significantly shorter (0.8 years [0.1–2.4] compared with 2.4 years [0.6–4.6]). There was no significant difference for BMI standard deviations scores between CFRD patients with or without insulin treatment.

**CONCLUSIONS**—Pediatric patients with CFRD show clear auxological and metabolic differences from those with T1DM, with different treatment choices.

*Diabetes Care* 36:879–886, 2013

With improvement of therapy and increasing life expectancy of cystic fibrosis (CF) patients, secondary diabetes is becoming more frequent (1) and is recognized as the most common comorbidity, occurring in approximately

2% of children, 19% of adolescents, and 40–50% of adults (2). The reported prevalence of CF-related diabetes (CFRD) varies depending on screening methods and diagnostic criteria (3). The true burden of the disease therefore may be

underestimated (4). Because CFRD is often asymptomatic, annual screening for CFRD in CF patients is recommended at 10 years of age and onward, using the oral glucose tolerance test (5). Other parameters, such as HbA<sub>1c</sub>, fructosamine, urine glucose, or random glucose levels, have low sensitivity in the CF population (6,7). Although positive results are highly suggestive of diabetes, the use of these tests alone will miss many cases of CFRD (4).

Early detection of CFRD is important, because weight loss, protein catabolism, lung function decline, and mortality are increased in CFRD (8,9). Because pediatric diabetes centers usually provide care for few patients with CFRD only, it is necessary to advance knowledge of the characteristics of this type of diabetes, which is a distinct clinical entity with unique features that has been described in a recent technical review (8).

The etiology of CFRD is complex, likely consisting of a combination of insulin deficiency and insulin resistance. Additional risk factors are a genetic predisposition toward the development of diabetes (2,10,11), exocrine pancreatic insufficiency, liver disease (1), chronic inflammation, exogenous glucocorticoids, female sex, and older age (1). It is well-known that insulin therapy stabilizes lung function and improves nutritional status in patients with CFRD (12,13). Patients with CFRD are insulin-insufficient and, based on available data, insulin is the recommended therapy for these patients (14). At the onset of CFRD, most patients only need a low dose of short-acting insulin before meals to control blood glucose. With disease progression and increasing insulin deficiency, intensification of insulin therapy is necessary.

Type 1 diabetes mellitus (T1DM) is the most frequent kind of diabetes in the pediatric population; therefore, its characteristics are well-described (15). In T1DM, autoimmunity leads to a destruction of  $\beta$  cells and finally to absolute insulin deficiency. To better define the

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Received 29 April 2012 and accepted 7 September 2012.

DOI: 10.2337/dc12-0807

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characteristics of CFRD, we compared CFRD to T1DM in pediatric patients who were followed up in a nationwide multicenter register.

## RESEARCH DESIGN AND METHODS

### Data collection

Data were collected during routine care from specialized diabetes centers in Germany and Austria by means of a computerized documentation called the Diabetes Prospective Documentation Initiative (*Diabetes Patienten Verlaufsdokumentation* [DPV]). The DPV register started in 1995 in Germany on a nationwide basis. For quality management, all centers use the same computer-based program for continuous documentation of treatment and outcome (16). Three-hundred thirty-five diabetes centers (including eight centers from Austria) contributed to this analysis. Participating centers transmit anonymous, standardized, prospective data from all their diabetic patients for central validation, benchmarking, and research twice per year to the central administrative unit in Ulm (Germany). To ensure optimal data plausibility, all inconsistent data are reported back to the respective centers for correction every 6 months (16). Sex, age, diabetes duration, type of diabetes, migration background, BMI, height, weight, insulin requirement, and number of severe hypoglycemia and HbA<sub>1c</sub> levels are documented. By March 2011, the total number of patient visits documented in the system was 2,008,389 from 242,153 diabetic patients. Total number of pediatric patient visits (younger than 20 years of age) was 870,531 from 51,307 patients; 48,368 (94%) of these patients had T1DM, 864 (2%) had type 2 diabetes mellitus (T2DM), and 1,930 (4%) had other types of diabetes mellitus. This group included 381 patients with CFRD (0.7% of total patient population).

### Patients

Analyses based on the last 12 months of care documented in each patient for 47,227 patients who fulfilled the inclusion criteria with complete data and a pediatric onset (younger than 20 years of age) of either CFRD ( $n = 381$ ) or T1DM ( $n = 46,846$ ) were performed. Only records from patients 21 years of age or younger at the time of the visits were included. Migration background was defined as at least one parent not born in

Germany or Austria. In addition, a subpopulation of patients with complete data was observed during the first (total:  $n = 8,805$ ; CFRD:  $n = 163$ ; T1DM:  $n = 8,642$ ) or fifth year (total:  $n = 6,335$ ; CFRD:  $n = 42$ ; T1DM:  $n = 6,293$ ) of diabetes.

### Anthropometry

Height and weight standard deviation scores (SDS) were calculated using contemporary, officially recommended national reference data for German children from Kromeyer-Hauschild (17). BMI values were adjusted for age and sex using BMI SDS. Definitions of underweight, overweight, and obesity in children and adolescents were based on BMI as follows: BMI values >90th percentile for age and sex were defined as overweight; BMI values >97th percentile were defined as obesity; and BMI values >99th percentile were defined as extreme obesity. BMI values <10th percentile for age and sex were considered underweight (18). Arterial hypertension was defined as blood pressure >95th percentile according to the American Heart Association's normal values (19).

### Metabolic control

HbA<sub>1c</sub> measurements from different centers were mathematically standardized to the Diabetes Control and Complications Trial reference range of 4.05–6.05% using the multiple of the mean method (20).

### Treatment modalities

Treatment regimen was categorized as insulin therapy alone, use of oral antidiabetic drugs (sulphonylureas, glinides with or without insulin), or nonpharmacological treatment with lifestyle modification only. Insulin therapy was documented as the number of daily injections or continuous subcutaneous insulin infusion (CSII), daily insulin dose per kilogram of body weight, and the use of long-acting or rapid-acting insulin analogs.

### Statistical analysis

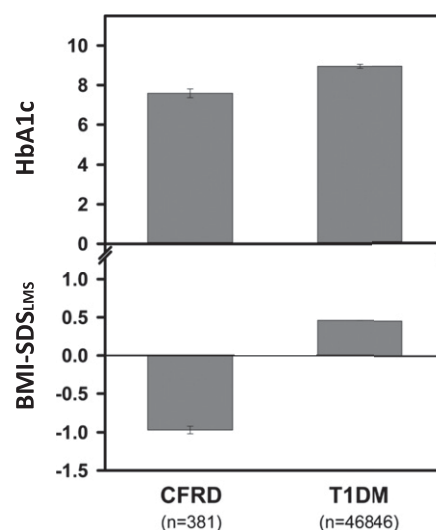
Data were analyzed using the SAS statistical software package (version 9.3; SAS Institute Inc., Cary, NC) and presented as median and interquartile range or percentage. For group comparison of continuous variables, Kruskal-Wallis test was used. Binary variables were compared by  $\chi^2$  test. Because multiple tests were performed,  $P$  values were adjusted using the Bonferroni step-down correction (method of Holm). To adjust for confounding effects

of age, sex, and diabetes duration, multivariable mixed regression analysis was applied including a random term for treatment center in the model with Cholesky covariance structure.  $P < 0.05$  was considered statistically significant. For graphical representation (Fig. 1), data of HbA<sub>1c</sub> and BMI were calculated for a typical patient with chronological age of 15 years and 2 years of diabetes, assuming equal sex distribution.

## RESULTS

### Clinical data

Anthropometric and clinical data of pediatric patients with CFRD or T1DM are given in Table 1. Diabetes diagnosis was 6 years later in CFRD patients, 14.5 years (quartile 1–quartile 3: 11.8–16.3) compared with T1DM, 8.5 years (quartile 1–quartile 3: 4.9–11.8) ( $P < 0.001$ ). A female preponderance was found for CFRD, 59.1% were female compared with 47.5% with T1DM ( $P < 0.001$ ). There was no significant difference between groups for migration background (T1DM, 15%; CFRD, 14%;  $P = 1.0$ ). CFRD patients were shorter (height SDS,  $-1.30$ ;  $-2.25$  to  $-0.43$ ) and had lower body weight (weight SDS,  $-1.51$ ;  $-2.49$  to  $-0.68$ ), resulting in a lower BMI (BMI SDS,  $-0.85$ ;  $-1.59$  to  $-0.12$ ) compared with T1DM patients (height SDS,  $-0.04$ ;  $-0.72$  to  $+0.63$ ; weight SDS:  $+0.43$ ;  $-0.23$  to  $+1.09$ ;



**Figure 1**—Data of HbA<sub>1c</sub> and BMI calculated for a typical patient with chronological age of 15 years and 2 years of diabetes, with equal sex distribution. Both  $P < 0.0001$ . BMI SDS: estimate  $\pm$  95% CI.

**Table 1—Demographic data and clinical characteristics for young T1DM and CFRD patients**

	T1DM	CFRD	Corrected <i>P</i>
All patients, <i>n</i> (%)	46,846 (99.2)	381 (0.8)	
Male/female, %	52/48	41/59	<0.001
Migration background, %	15.4	14.2	NS
Age, years	14.85 (11.10–17.40)	16.9 (15.10–18.50)	<0.001
Age at diagnosis, years	8.50 (4.90–11.80)	14.50 (11.80–16.30)	<0.001
Duration of diabetes, years	4.70 (2.00–8.10)	1.90 (0.45–4.05)	<0.001
Height SDS	−0.04 (−0.72 to +0.63)	−1.29 (−2.25 to −0.43)	<0.001
Weight SDS	+0.43 (−0.23 to +1.09)	−1.51 (−2.49 to −0.68)	<0.001
BMI SDS	+0.52 (−0.10 to +1.16)	−0.85 (−1.59 to −0.12)	<0.001
HbA <sub>1c</sub> , %	7.97 (7.11–9.15)	6.87 (5.96–8.28)	<0.001

Data are shown as median (lower–upper quartile) or percentage, if not otherwise indicated. NS, not significant.

BMI SDS, +0.52; −0.10 to +1.16; all *P* < 0.001). The rates of overweight and obesity were higher in T1DM, with 2% of patients being extremely obese, 6% obese, 13% overweight, and only 79% of patients with normal weight. In comparison, none of the CFRD patients was extremely obese or obese, and just 1.3% of CFRD patients were overweight. In contrast, the rate of underweight was significantly higher in the CF group (31.5% vs. 3% in T1DM).

Glycemic control, measured by HbA<sub>1c</sub>, was better in CFRD than in T1DM (6.87% [6.00–8.30%] vs. 7.97% [7.11–9.20%]; *P* < 0.001).

There were no significant differences between the two groups with regard to diabetes complications such as retinopathy (T1DM 1.7% vs. CFRD 3.0%; not significant) or nephropathy (T1DM 12.6% vs. CFRD 7.7%; not significant), but 26% of T1DM patients were hypertensive compared with only 9.7% in the CFRD group (*P* < 0.001).

Data on diabetic ketoacidosis (DKA) and initial blood glucose at diabetes onset also were analyzed. None of the CFRD patients presented with ketoacidosis (pH < 7.3), whereas 17% of patients with T1DM presented with DKA. Blood glucose levels at diabetes onset were documented for 35,395 patients with T1DM and 267 CFRD patients. We found significant differences with blood glucose levels of 249 mg/dL (180.0–331.0) in T1DM and 194.0 (126.0–272.0) in CFRD at diagnosis of diabetes (*P* < 0.001).

In addition, subpopulations of our patients were observed 1 year (*n* = 8,805) or 5 (*n* = 6,335) years after the diagnosis of diabetes. After 1 year of diabetes, CFRD

patients also had lower HbA<sub>1c</sub> (6.46% [5.84–7.43%] vs. 7.68% [6.70–9.30%]; *P* < 0.0001), were shorter (height SDS: −1.16 [−2.09 to −0.33]), and had lower body weight (weight SDS: −1.61 [−2.57 to −0.69]), resulting in a lower BMI (BMI SDS, −1.02 [−1.93 to −0.27]) compared with T1DM patients (height SDS, 0.11 [−0.53 to 0.77]; weight SDS, 0.26 [−0.42 to 0.95]; BMI SDS, 0.26 [−0.40 to 0.96]; all *P* < 0.0001). Differences in auxological parameters persist 5 years after the diagnosis of diabetes with height SDS of −1.60 (−2.84 to −0.69), weight SDS of −1.73 (−2.51 to −0.83), and BMI SDS of −0.92 (−1.63 to −0.40) in CFRD compared with T1DM (height SDS, −0.01 [−0.67 to −0.65]; weight SDS, 0.48 [−0.14 to −1.11]; BMI SDS, 0.57 [−0.01 to 1.17], all *P* = 0.0001). Glycemic control, measured by HbA<sub>1c</sub>, becomes similar in both groups after 5 years (CFRD 7.88% [6.67–9.40%] vs. T1DM 7.89% [7.10–8.93%]). However, after adjustment for age and sex, a difference in HbA<sub>1c</sub> was still present (CFRD 7.81 vs. T1DM 8.36; *P* < 0.05).

### Treatment

Treatment modalities differed between the two groups, as summarized in Table 2. All patients with T1DM received insulin therapy (99.4% insulin alone, 0.6% in combination with metformin), whereas in CFRD 72% of patients were treated with insulin (67% insulin alone, 5% in combination with OAD; *P* < 0.001). In insulin-treated patients with T1DM, 12% were treated with conventional therapy (one to three injections per day), 64% were treated with multiple injections (four to eight injections per day), and 23% were treated with CSII. In insulin-treated

patients with CFRD, 41% received conventional therapy, 54% received multiple injections of insulin, and only 5% were treated with CSII (*P* < 0.001). Fast-acting insulin analogs were used more frequently in T1DM patients (47% vs. 39%; *P* < 0.05). Similarly, the use of long-acting insulin analogs was significantly more frequent in T1DM than in CFRD (37% vs. 28%; *P* < 0.01).

Insulin dose per kilogram of body weight, analyzed without adjusting for confounding effects, did not differ significantly between the two groups (T1DM 0.82 [0.65–1.02] vs. CFRD 0.80 [0.40–1.14]; not significant). However, after adjustment for age, sex, and diabetes duration, a significant difference was present (T1DM 0.79 vs. CFRD 0.83; *P* < 0.05).

In the CFRD group, oral antidiabetic agents (sulfonylureas, glinides) alone were used by 8% of the patients; 20% of the CFRD patients were treated with nonpharmacological therapy only (lifestyle intervention). Corticosteroid use was documented in 18% of all CFRD patients, whereas 0.3% of 47,227 T1DM patients had received systemic steroids as a comedication during the course of their disease (*P* < 0.001).

Out of 46,846 patients with T1DM, 73% were treated in diabetes centers with >100 patients compared with 62% of 381 patients with CFRD (*P* < 0.001). After adjustment for sex, age, and diabetes duration, this difference was no longer present (T1DM 56.2% vs. CFRD 55.9%; not significant). In CFRD, 70% of all patients were treated at universities; however, for T1DM only 31% of all patients were treated at universities (*P* < 0.001).

Significant differences were also found for self-monitoring of blood glucose (SMBG) per day (T1DM, 4.6; CFRD, 3.7; *P* < 0.001) and number of visits per year (T1DM, 3.30; CFRD, 2.12; *P* < 0.001).

In addition, we investigated differences with regard to metabolic control and BMI in CFRD patients treated with or without insulin. Our results are demonstrated in Table 3. The corrected *P* values for HbA<sub>1c</sub> showed significant differences, with better metabolic control in patients without insulin therapy compared with CFRD patients with insulin treatment (HbA<sub>1c</sub>, 6.00% [5.56–6.76%] vs. 7.12% [6.14–8.67%]; *P* < 0.001). However, duration of disease was significant shorter in patients without insulin treatment: 0.8 years (0.1–2.4) compared with 2.4 years

**Table 2—Treatment modalities and control in CFRD compared with T1DM in pediatric patients**

	T1DM	CFRD	Corrected P
Patients, n (%)	46,846 (99.2)	381 (0.8)	
Treatment type			
Insulin alone, %	99.4	67.0	<0.001
OAD alone, %	0	8.0	<0.001
Insulin plus OAD, %	0.6	5.0	<0.001
Lifestyle modification only	0	20.0	<0.001
Insulin dose, IE/kg body weight	0.82 (0.65–1.02)	0.8 (0.40–1.14)	NS
CSII:MDI:CT, %	23.5:64.4:12.1	5.0:54.0:41.0	<0.001
Steroid therapy, %	0.3	18.4	<0.001

Data are shown as median (lower–upper quartile) and percentile. OAD, oral antidiabetics; NS, not significant; MDI, multiple daily injections (4–8 injections per day); CT, conventional treatment (1–3 injections per day).

(0.6–4.6;  $P < 0.001$ ). There was no significant difference for BMI SDS between patients without insulin (BMI SDS,  $-0.78$  [ $-1.58$  to  $-0.12$ ]) compared with insulin-treated patients with CFRD (BMI SDS,  $-0.85$  [ $-1.61$  to  $-0.12$ ]). If not otherwise stated, then all described differences could be confirmed after data were adjusted for confounding effects of age, sex, and diabetes duration.

All patients with T1DM received insulin 1 year and 5 years after diabetes diagnosis. In the CFRD group, only 59% of patients received insulin after 1 year. This percentage increased 5 years after diagnosis, when 88% of CFRD patients were treated with insulin.

Insulin dose per kilogram of body weight, adjusted for age and sex, did not differ significantly between the groups (1 year: CFRD 0.69 vs. T1DM 0.67; 5 years: CFRD 0.95 vs. T1DM 0.90; both not significant).

In both groups, insulin pump therapy and multiple daily injections were used more often 5 years after diagnosis compared with the first treatment year. In

insulin-treated patients with T1DM, 23.3% were treated with conventional therapy, 66% were treated with multiple daily injections, and 10.7% were treated with CSII 1 year after diabetes diagnosis. After 5 years of diabetes, only 9.6% of T1DM patients were treated with conventional therapy, 63.3% were treated with multiple daily injections, and 27.1% were treated with CSII. Similar changes are found in CFRD. One year after diabetes diagnosis, 59% of patients were treated with insulin, 25.2% of all patients were treated with conventional therapy, 33.1% were treated with multiple daily injections, and 6% were treated with CSII. Five years after diagnosis, 88.1% of CFRD patients were treated with insulin, 33.3% were treated with conventional therapy, 52.4% were treated with multiple daily injections, and 24% were treated with CSII. Similar to changes in insulin injections, use of short-acting and long-acting insulin analogs increased during the first 5 years of diabetes. In both T1DM and CFRD, insulin analogs were used more often 5 years after diagnosis

(short-acting: CFRD 45.9% vs. T1DM 52.5%; long-acting: CFRD 40.5% vs. T1DM 34.8; not significant) compared with the first year (short-acting: CFRD 40.1% vs. T1DM 35.1%; long-acting: CFRD 18.8% vs. T1DM 20.0%; not significant).

**CONCLUSIONS**—Our data show that patients with CFRD have clear demographic and metabolic differences compared with patients with T1DM. Previous data described female sex as a risk factor for development of CFRD (3). In our cohort, 59% of CFRD patients were female. In comparison, in T1DM, male-to-female ratio was close to 1. Hormonal differences and later onset of CFRD in adolescence or young adulthood are possible explanations. Estrogen and its receptors are especially important regulators of body weight and insulin sensitivity (21,22). In our analysis, diabetes diagnosis was later in CFRD than in T1DM. Our data show that patients with CFRD differ from patients with T1DM in auxological parameters. CF patients have a significant reduction in height and weight and a lower BMI. This is concordant with previous data. In a recent retrospective analysis, growth velocity was significantly lower in children with CFRD compared with controls matched for age, sex, and CF mutation (23). Reduced height and BMI are attributable to recurrent infections, exocrine pancreatic insufficiency, calorie loss because of malabsorption, and increased work of breathing. These differences in auxological parameters persist on follow-up, reflecting disease progression of CF.

In T1DM, DKA is a frequent acute complication at diabetes onset and remains a major cause of hospitalization and death in children and adolescents with diabetes (24,25). Previous data described that DKA also can occur at the time of initial presentation during the clinical course of CFRD, but DKA is rare in children with CFRD, most likely because of the persistence of endogenous insulin secretion or because glucagon secretion also is impaired (26). In our analysis, ketoacidosis at onset was not present in patients with CFRD, in contrast to T1DM.

For glycemic control after disease onset, we compared HbA<sub>1c</sub> levels. In contrast to T1DM, patients with CFRD present with recurrent infections and hemolysis that influences HbA<sub>1c</sub> levels, which are often falsely low in patients

**Table 3—Demographic data and clinical characteristics for young CFRD patients with and without insulin treatment**

	CFRD with insulin	CFRD without insulin	Corrected P
All patients, n, %	282 (74.02)	99 (25.98)	
Male/female, %	40/60	45/55	NS
Age, years	17.10 (15.40–18.60)	16.60 (12.95–18.40)	NS
Age at diagnosis, years	14.40 (11.80–16.10)	14.80 (11.60–16.80)	NS
Duration of diabetes, years	2.40 (0.60–4.60)	0.80 (0.10–2.40)	<0.001
BMI SDS	$-0.86$ ( $-1.61$ to $-0.12$ )	$-0.78$ ( $-1.58$ to $-0.12$ )	NS
HbA <sub>1c</sub> , %	7.12 (6.14–8.67)	6.00 (5.56–6.76)	<0.001

Data are shown as median (lower–upper quartile) or percentage. NS, not significant.

with CF (6,7). In our study, HbA<sub>1c</sub> in CFRD was lower than in T1DM. Further investigations are needed to establish whether therapeutic goals for HbA<sub>1c</sub> should be the same for CFRD and T1DM. Interestingly, HbA<sub>1c</sub> levels became similar in T1DM and CFRD in a subgroup of patients after 5 years of diabetes. Worsening in glycemic control in the CF group might be attributable to less follow-up visits and still less intense treatment compared with T1DM, systemic steroids, or recurrent exacerbations.

After the diagnosis of CFRD is made, the American Diabetes Association (ADA) recommends quarterly visits to a multidisciplinary team with expertise in diabetes and CF. Furthermore, similar to treatment of other patients with diabetes, HbA<sub>1c</sub> should be measured every 3 months (14). In our data, CFRD patients were followed-up less frequently in diabetes centers than T1DM patients. Patients with CFRD were seen twice per year compared with T1DM patients, who were seen three to four times. Fewer visits to diabetes centers for CF might be explained by additional visits to CF clinics or less intense treatment.

To safely achieve glucose goals, ADA recommends that all patients using insulin should perform SMBG at least three times daily (27). In our analysis, SMBG in CFRD was performed three to four times daily in accordance to ADA guidelines. In T1DM, SMBG was more frequent, on average four to five times daily.

Diabetes microvascular complications, such as retinopathy or nephropathy, have been described in case reports and small series of CFRD patients. In Denmark, 36% of patients with >10 years of duration of diabetes were reported to have retinopathy (28). In a larger series of 285 CFRD patients, none of the patients without fasting hyperglycemia had microvascular complications; in those with fasting hyperglycemia, complications were rare before 10 years of duration (29). Of the 39 patients who had CFRD with fasting hyperglycemia of >10 years duration, microalbuminuria was found in 14% and retinopathy was found in 16%. Other studies described similar risk for development of microvascular complications compared with T1DM (28,30). The risk is related to duration and progression of the primary disease and inversely to metabolic control of diabetes. In our cohort, disease duration was <10 years. This is the most likely explanation for us finding less

microvascular complications in our cohort. The prevalence of diabetes microvascular complications appears to be lower in CFRD, but it remains important to screen annually for these complications, starting 5 years after diagnosis (27). Macrovascular complications have not been described among the CFRD population (29). With regard to hypertension, we found a higher risk in pediatric patients with T1DM. Our results concur with previous data on the risk of hypertension and other cardiovascular risks in young patients with T1DM (15). In adult CF patients, hypertension also is not uncommon, particularly after transplantation (28) or with systemic steroids. In our pediatric cohort, hypertension in CFRD was less frequent compared with T1DM. Nevertheless, patients with CFRD should have their blood pressure measured at every routine diabetes visit, as recommended by the ADA guidelines (27).

Because the major cause of diabetes in CF seems to be severe insulin insufficiency, insulin therapy is recommended. Furthermore, acute illness, use of corticosteroids, and other therapeutic agents are associated with increased insulin resistance and altered insulin release (10,31), complicating therapy in CF patients. In our cohort, use of corticosteroids was documented in 18% of patients with CFRD.

To improve weight gain and lung function, and to avoid infections, current guidelines stated insulin therapy should be started as soon as the CFRD diagnosis is made to benefit from anabolic effects of insulin (12,13). Basis-bolus insulin regimen is recommended as first choice to avoid postprandial hyperglycemia (14).

Treatment regimen differed in both groups. Insulin pump therapy was especially less frequent in CFRD. Recent data demonstrated efficiency of insulin pump therapy. In a group of nine adults with CFRD, 6 months of insulin pump therapy was associated with improvements in body weight, lean muscle mass, glycemic control, and a decrease in protein catabolism and hepatic glucose output as compared with their baseline status using basal subcutaneous insulin injections (32). Pumps allow easy adjustment in basal rates during episodes of increased insulin resistance or variable carbohydrate intake, such as continuous tube feeding (33). To prove a long-time benefit of insulin pump therapy compared with other treatment regimen, further studies

over a longer period of time with larger patient numbers are necessary.

Our subgroup analysis at 1 year or 5 years of diabetes showed that insulin pump therapy was used more frequently with increasing diabetes duration in both patient groups. This reflects intensification of diabetes therapy in response to deteriorating metabolic control.

To describe differences within the CFRD patient group, we compared CFRD patients with and without insulin therapy. Patients with insulin therapy in our cohort had a longer duration of disease and their metabolic control was worse than in patients without insulin.

With regard to BMI SDS, no difference was found between insulin-treated or noninsulin-treated patients. We could not analyze longitudinal data once insulin therapy was started. According to published data, improvement in metabolic control and BMI should be expected (34).

In addition to recommendations for insulin treatment, the available data suggest that oral antidiabetic agents are not as effective as insulin to improve glycemic control, weight, protein anabolism, pulmonary function, and survival in CFRD (34–36). In small case or cohort studies of CFRD patients, oral sulfonylureas or glinides have shown limited benefit in improving insulin secretion and glycemic control. In our cohort, 8% of patients with CFRD in Germany and Austria are treated with oral antidiabetic agents alone, and 20% of the CF patients received nonpharmacological therapy. In T1DM, oral antidiabetic agents were used in addition to insulin for a very small number of patients. These patients received metformin to improve glycemic control in cases of insulin resistance during puberty (37). However, a recent systemic literature study concluded that additional benefit by adding metformin in T1DM remains unclear (38).

In insulin-treated patients, insulin dose per kilogram of body weight adjusted for age, sex, and diabetes duration differed significantly between patients with CFRD and T1DM. High caloric intake, including carbohydrates, insulin resistance, and use of corticosteroids in CFRD might be possible explanations for high insulin requirement in CFRD.

In conclusion, the results of our multicenter analysis of current DPV data show statistically significant demographic, clinical, and treatment differences between pediatric CFRD and T1DM patients. CFRD shares some features with

T1DM, but it is a special entity of diabetes with specific characteristics. With progression of CFRD, treatment modalities and glycemic control become more similar to T1DM, whereas differences in auxological parameters persist.

**Acknowledgments**—This analysis was funded by a grant from Mucoviszidose-EV Bonn, Germany.

The DPV initiative is funded by the Competence Network for Diabetes Mellitus (Kompetenznetz Diabetes mellitus), of the German Federal Ministry of Education and Research (FKZ 01GI1106), by the European Foundation for the Study of Diabetes (EFSD), and by Novo Nordisk. Study sponsors were not involved in data collection or analysis. No other potential conflicts of interest relevant to this article were reported.

K.K. wrote the manuscript. K.K., A.T., and M.F. edited the manuscript. A.T., M.F., E.F.-R., E.L., and R.W.H. contributed to discussion. A.T., M.F., S.A.W., and R.W.H. reviewed the manuscript. R.W.H. conceptualized the study and researched data. R.W.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The authors thank Prof. B.P. Hauffa, Department of Pediatrics II, University Children's Hospital Essen, Essen, Germany, for reviewing the manuscript. The authors also thank the following centers for participating in the DPV initiative and contributing their data to this study: Aachen-Uni-Kinderklinik RWTH, Aalen Kinderklinik, Ahlen St Franziskus Kinderklinik, Altötting Zentrum Inn-Salzach, Amsberg-Hüsten Karolinenhospital Kinderabteilung, Asbach Kamillus-Klinik Innere, Aue Helios Kinderklinik, Augsburg Innere, Augsburg Kinderklinik Zentralklinikum, Aurich Kinderklinik, Bad Aibling Internist. Praxis, Bad Driburg/ Bad Hermannsborn Innere, Bad Hersfeld Kinderklinik, Bad Kösen Kinder-Rehaklinik, Bad Lauterberg Diabeteszentrum Innere, Bad Mergentheim-Gemeinschaftspraxis Althausen, Bad Oeynhausen Diabetesfachklinik, Bad Waldsee Kinderarztpraxis, Bautzen Oberlausitz KK, Berchtesgaden CJD, Berchtesgaden MVZ Innere Med, Berlin DRK-Kliniken, Berlin Kinderklinik Lindenhof, Berlin Oskar Zieten Krankenhaus Innere, Berlin Schlosspark- Klinik Innere, Berlin St Josephskrankenhaus Innere, Berlin Virchow-Kinderklinik, Berlin Vivantes Hellersdorf Innere, Bielefeld Kinderklinik Gilead, Bocholt Kinderklinik, Bochum Universitätskinderklinik St Josef, Bonn Uni-Kinderklinik, Bottrop Knappschafts-Krankenhaus Innere, Bremen-Kinderklinik Nord, Bremen - Mitte Innere, Bremen Kinderklinik St Jürgenstrasse, Bremen-Epidemiologieprojekt, Bremerhaven Kinderklinik, Celle Kinderklinik, Chemnitz Kinderklinik, Chemnitz-Hartmannsdorf Innere

Medizin-DIAKOMED- Coesfeld Kinderklinik, Darmstadt Innere Medizin, Darmstadt Kinderklinik Prinz. Margareth, Datteln Vestische Kinderklinik, Deggendorf Kinderarztpraxis, Deggendorf Kinderklinik, Delmenhorst Kinderklinik, Detmold Kinderklinik, Dornbirn Kinderklinik, Dortmund Kinderklinik, Dortmund Knappschafts-Krankenhaus Innere, Dresden Neustadt Kinderklinik, Dresden Uni-Kinderklinik, Duisburg Malteser St Anna Innere, Düren-Birkendorf Kinderklinik, Düsseldorf Uni-Kinderklinik, Erfurt Kinderklinik, Erlangen Uni-Kinderklinik, Essen Diabetes-Schwerpunktpraxis, Essen Elisabeth Kinderklinik, Essen Uni-Kinderklinik, Esslingen, Städtische Kinderklinik, Eutin Kinderklinik, Eutin St Elisabeth Innere, Frankenthal Kinderarztpraxis, Frankfurt Uni-Kinderklinik, Frankfurt Uni-Klinik Innere, Freiburg Uni Innere, Freiburg Uni-Kinderklinik, Friedberg Innere Klinik, Friedrichshafen Kinderklinik, Fulda Innere Medizin, Fulda Kinderklinik, Fürth Kinderklinik, Gaissach Fachklinik der Deutschen Rentenversicherung Bayern Süd, Garmisch-Partenkirchen Kinderklinik, Geislingen Klinik Helfenstein Innere, Gelnhausen Kinderklinik, Gelsenkirchen Kinderklinik Marienhospital, Gera, Kinderklinik, Gießen Uni- Kinderklinik, Graz Universitäts-Kinderklinik, Göppingen Innere Medizin, Göppingen Kinderklinik am Eichert, Görlitz Städtische Kinderklinik, Göttingen Uni- Kinderklinik, Hachenburg Kinderpraxis, Hagen Kinderklinik, Halle Uni-Kinderklinik, Halle-Dörlau Städtische Kinderklinik, Hamburg Altonaer Kinderklinik, Hamburg Kinderklinik Wilhelmstift, Hamburg-Nord Kinderklinik Heidberg, Hameln Kinderklinik, Hamm Kinderklinik, Hanau Kinderklinik, Hanau St Vincenz - Innere, Hannover Kinderklinik MHH, Hannover Kinderklinik auf der Bult, Haren Kinderarztpraxis, Heide Kinderklinik, Heidelberg Uni-Kinderklinik, Heidelberg Uniklinik Innere, Heidenheim Kinderklinik, Heilbronn Innere Klinik, Heilbronn Kinderklinik, Herdecke Kinderklinik, Herford Kinderarztpraxis, Herford Klinikum Kinder & Jugendliche, Heringsdorf Inselklinik, Hermeskeil Kinderpraxis, Herten St Elisabeth Innere Medizin, Hildesheim Innere, Hildesheim Kinderarztpraxis, Hildesheim Kinderklinik, Hinrichs-Bruckmühl Diabetikerjugendhaus, Hof Kinderklinik, Homburg Uni-Kinderklinik Saarland, Idar Oberstein Innere, Ingolstadt Klinikum Innere, Innsbruck Universitätskinderklinik, Iserlohn Innere Medizin, Itzehoe Kinderklinik, Jena Uni-Kinderklinik, Kaiserslautern-Westpfalz-Klinikum Kinderklinik, Karlsburg Klinik für Diabetes & Stoffwechsel, Karlsruhe, Städtische Kinderklinik, Kassel Kinderklinik Park Schönfeld, Kassel Städtische Kinderklinik, Kaufbeuren Innere Medizin, Kempen Heilig Geist-Innere, Kiel Städtische Kinderklinik, Kiel Universitäts-Kinderklinik, Kirchen DRK Klinikum Westerwald, Kinderklinik, Kirchheim- Nürtingen Innere, Koblenz Kemperhof I. Med. Klinik, Koblenz

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Kinderklinik, Stuttgart Olgahospital Kinderklinik, Suhl Kinderklinik, Sylt Rehaklinik, Tettang Innere Medizin, Traunstein SPP Praxis, Trier Kinderklinik der Borromäerinnen, Tübingen Uni-Kinderklinik, Ulm Endokrinologikum, Ulm Schwerpunktpraxis Bahnhofplatz, Ulm Uni-Kinderklinik, Vechta Kinderklinik, Viersen Kinderklinik, Waiblingen Kinderklinik, Waldshut Kinderpraxis, Waldshut-Tiengen Kinderpraxis Biberbau, Weiden Kinderklinik, Weingarten Kinderarztpraxis, Wernberg-Köblitz SPP, Wetzlar/Braunfels Innere, Wien Uni-Kinderklinik, Wiesbaden Horst-Schmidt-Kinderkliniken, Wiesbaden Kinderklinik DKD, Wilhelmshaven Reinhard-Nieter-Kinderklinik, Wilhelmshaven, St Willehad Innere, Wolgast Kinderklinik, Worms Kinderklinik, Wuppertal Kinderklinik.

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