



# Does $\beta$ -Cell Autoimmunity Play a Role in Cystic Fibrosis–Related Diabetes? Analysis Based on the German/Austrian Diabetes Patienten Verlaufsdocumentation Registry

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## OBJECTIVE

Research on  $\beta$ -cell autoimmunity in cystic fibrosis (CF)–related diabetes (CFRD) is still rare. We aimed to analyze the frequency of  $\beta$ -cell autoimmunity and the influence on age at diabetes onset, insulin requirement, type of insulin therapy, and hypoglycemic or ketoacidotic events in patients with CFRD compared with antibody-negative patients with CFRD in the Diabetes Patienten Verlaufsdocumentation (DPV) registry.

## RESEARCH DESIGN AND METHODS

We analyzed data of 837 patients with CFRD in the German/Austrian DPV database by multivariable mixed-regression modeling.

## RESULTS

In our cohort, 8.5% of patients with CFRD ( $n = 72$ ) were found to be  $\beta$ -cell antibody positive. There was a female preponderance in this patient group: 65.3 vs. 57.6%. Diabetes onset (median [interquartile range]) was earlier (14.00 [10.15–15.90] vs. 16.10 [13.50–21.20] years;  $P < 0.005$ ), and insulin dose/kg body weight was higher (0.95 [0.61–1.15] vs. 0.67 [0.33–1.04] IU/kg;  $P < 0.05$ ). There were also differences in the type of insulin treatment. Insulin pump therapy was used significantly more often in patients with CFRD with  $\beta$ -cell autoimmunity (18.2 vs. 6.4%;  $P < 0.05$ ). The differences for multiple daily injections (ICT) and conventional therapy (CT) were not significant (ICT: 67.7 vs. 79.0%; CT: 15.2 vs. 14.6). Oral antidiabetic agents were rarely used in both groups. Rate of severe hypoglycemia with coma and rate of ketoacidosis were higher in antibody-positive patients (hypoglycemia with coma: 8.0 vs. 1.4,  $P < 0.05$ ; ketoacidosis: 9.3 vs. 0.9,  $P < 0.05$ ).

## CONCLUSIONS

Presence of  $\beta$ -cell autoantibodies in our cohort of patients with CFRD (8.5%) appeared to be greater than in the general population and was associated with female sex, earlier onset of diabetes, and higher insulin requirement. Insulin pump therapy was used significantly more often in patients with  $\beta$ -cell antibodies. Severe hypoglycemia and ketoacidosis were significantly more frequent in CFRD with  $\beta$ -cell autoimmunity compared with  $\beta$ -cell antibody-negative patients with CFRD.

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With improved therapy and better life expectancy of patients with cystic fibrosis (CF), comorbidities become more frequent. The prevalence of CF-related diabetes (CFRD) increased significantly over the years and was recently well described (1–4). Several publications report that CFRD became the most common endocrine comorbidity in patients with CF (5). The CFRD Guidelines Committee defined the onset of CFRD as the first time a person with CF meets diagnostic criteria for diabetes, even if glucose tolerance subsequently appears to improve (6). Pathophysiology of the disease seems to be complex, sharing aspects of insulin deficiency, comparable to type 1 diabetes mellitus (T1DM), and insulin resistance, as known with type 2 diabetes (2,3). The etiology is thereby still poorly understood and most probably multifactorial. The primary defect seems to be insulin deficiency caused by pancreatic fibrosis and fatty infiltration, which results in destruction of islet cell mass with loss of endocrine  $\beta$ - and  $\alpha$ -cells (7,8). Contrary to T1DM, insulin secretion is never totally absent in CFRD because destruction of  $\beta$ -cells is incomplete. Additional risk factors for CFRD are a genetic predisposition toward the development of diabetes (9–11), exocrine pancreatic insufficiency, liver disease, chronic inflammation, and use of exogenous glucocorticoids (4). Other factors, including autoimmunity, may play an important role in the degree of islet destruction, but research on  $\beta$ -cell autoimmunity in CFRD is still rare, and data concerning the potential impact of autoimmunity are conflicting (12).

There are different data on  $\beta$ -cell autoimmunity in individuals without diabetes. Yu et al. (13) described that in the general population, ~2% of individuals are positive for proteintyrosinase phosphatase (IA-2), glutamic acid decarboxylase (GADA), zinc transporter 8 (ZnT8), or insulin autoantibodies (IAA). In contrast, 55–98% of patients with T1DM are positive for at least one of these autoantibodies (14). Results from the Nord-Trøndelag Health Study (HUNT) showed similar results with a frequency of anti-GAD positivity of 1.7% in adults without diabetes (15). Another analysis comparing  $\beta$ -cell autoimmunity between Russian Karelia and Finland showed a slightly higher frequency in schoolchildren without diabetes with 4.5%  $\beta$ -cell autoimmunity in Russia

and 3.9% in Finland (16). In 2011, Libman et al. (17) studied  $\beta$ -cell autoimmunity in young, overweight patients without diabetes. They found that ~1.9% of overweight and 4.4% of control subjects (normal weight children) had evidence of  $\beta$ -cell autoimmunity, with GAD65 autoantibodies detected in all subjects, but none with IA-2 (17).

In 2012, Gottlieb et al. (12) described the presence of diabetes-specific antibodies and HLA haplotype in a small cohort of patients with CFRD ( $n = 76$ ). The authors found that the frequency of  $\beta$ -cell autoantibodies and HLA types associated with T1DM was similar to that of the general population and concluded that  $\beta$ -cell destruction in CF is not related to an autoimmune disease (12). In another recent analysis by Bizzarri et al. (18), 90 subjects with CF were tested for glucose tolerance and IAA, GADA, IA-2, and ZnT8. In this study, four subjects were found positive for both IAA and GADA (4.4%), one subject (1.1%) for both IA-2 and GADA, and one subject (1.1%) for isolated GADA. Three subjects (3.3%) showed isolated ZnT8 positivity, which was not associated with other autoantibodies. The authors concluded that ZnT8 positivity is not a specific indicator for a primary autoimmune  $\beta$ -cell destruction (18).

Overall, research on  $\beta$ -cell autoimmunity in CFRD is still rare, and the impact of  $\beta$ -cell autoimmunity on diabetes progression, treatment, and the risk for diabetes complications is unclear. Current international guidelines do not recommend screening for  $\beta$ -cell autoimmunity in patients with CF developing diabetes (19). We aimed to analyze the frequency of  $\beta$ -cell autoimmunity and its influence on age at diabetes onset, insulin requirement, type of insulin therapy, and hypoglycemic or ketoacidotic events in patients with CFRD compared with antibody-negative patients with CFRD in a large cohort of patients documented in the Diabetes Patienten Verlaufsdokumentation (DPV) database. We also aimed to increase awareness for possible autoimmunity in patients with CFRD.

## RESEARCH DESIGN AND METHODS

### Data Collection

All data were collected during routine care and retrieved from the DPV (or prospective documentation of patients with diabetes) database, a German/Austrian

register for people with diabetes. DPV data are used for quality control/benchmarking and clinical research. Anonymized documented data are transmitted twice a year from participating health care facilities, using the DPV software, to Ulm, Germany, for central analysis. Implausible and inconsistent data are reported back to the centers for verification and correction. A total of 140 diabetes centers, including 7 centers from Austria and 1 center from Luxembourg, contributed data from in- and outpatient care for this analysis. Sex, age, diabetes duration, type of diabetes, migration background, BMI, height, weight, insulin requirement, number of severe hypoglycemia events, and HbA<sub>1c</sub> levels are documented. Migration background was defined as at least one parent not born in Germany or Austria.

### Patients

We included 837 patients with diabetes with complete data and CFRD in our analysis. Patient medical data were documented between January 1995 and March 2015. Individual data of the most recent year of follow-up were aggregated to set up the final dataset. Our study sample included 72 patients with CFRD with documented  $\beta$ -cell autoimmunity.

### $\beta$ -Cell Autoimmunity

$\beta$ -Cell autoimmunity was present if one or more of the following antibodies were documented in the database: IAA, GADA, IA-2, and islet cell antibodies. Antibodies against insulin were just included if measured before insulin treatment was initiated. We did not include ZnT8 antibodies, as these are not measured routinely at diabetes onset in all centers. Determination of  $\beta$ -cell antibodies was provided by local laboratories participating in the  $\beta$ -cell antibody-standardization program.

### CFRD

In line with current guidelines (World Health Organization classification), any patient in the DPV registry fulfilling criteria of diabetes, including elevated fasting glucose  $>126$  mg/dL (7 mmol/L) and HbA<sub>1c</sub>  $>6.5\%$  (47.54 mmol/mol), at one point of the disease, was classified as CFRD.

### Anthropometry

BMI values were adjusted for age and sex using BMI SD scores (BMI-SDS) and calculated by the LMS method of Cole.

National reference data from Kromeyer-Hauschild (20) were also used for height and weight SD scores.

### Metabolic Control

Glycemic control was evaluated by HbA<sub>1c</sub>. In order to adjust for differences among centers, HbA<sub>1c</sub> data were mathematically standardized to the Diabetes Control and Complication Trial reference range of 4.05–6.05% (20.77–42.62 mmol/mol) using the multiple of the mean method (21).

### Residual Insulin Secretion

If available, residual insulin secretion is given as C-peptide. Depending on laboratory methods, fasting values of 0.81–3.85  $\mu$ g/L are considered as normal. Values <0.2  $\mu$ g/L indicate severe insulin deficiency.

### Acute Diabetes Complications

Diabetic ketoacidosis (DKA) was defined as blood pH value <7.3. Severe hypoglycemic episodes were defined as unconsciousness, convulsion, or being unable to take glucose without help from others (22).

### Treatment Modalities

Treatment was predominantly insulin therapy and treatment regimen was documented as the number of daily injection time points or insulin pump therapy (continuous subcutaneous insulin infusion [CSII]) and daily insulin dose per kilogram body weight. We distinguished between multiple daily injections and conventional therapy with one to three daily injections, with fixed doses without dose adjustment.

### Statistical Analysis

Statistical analysis was performed using the SAS statistical software package (version 9.4; SAS Institute Inc., Cary, NC) and presented as median with interquartile range or percentage. A *P* value <0.05 was considered statistically significant. For group comparison of continuous variables, Kruskal-Wallis test was used. Binary variables were compared by  $\chi^2$  test. In order to adjust for confounding effects, a multivariable mixed regression analysis was applied including a random term for treatment center.

## RESULTS

We analyzed data of 837 patients with CFRD in the database and found 72

patients with CFRD with additional  $\beta$ -cell autoimmunity in this group (8.5%). We only included patients with diagnosis of diabetes in our analysis. Further details on  $\beta$ -cell autoimmunity are given in Table 1.

### Clinical Data

Anthropometric and clinical data of patients with CFRD with or without  $\beta$ -cell autoimmunity are given in Table 2. Patients with CFRD with autoimmunity were shorter (height-SDS: median  $-1.28$ ; quartile [Q]1–Q3  $-2.13$  to  $-0.32$ ), with lower body weight (weight-SDS:  $-0.92$ ;  $-2.11$  to  $-0.12$ ), resulting in a lower BMI (BMI-SDS:  $-0.46$ ;  $-1.29$  to  $-0.05$ ) compared with antibody-negative patients with CFRD (height-SDS:  $-1.18$ ;  $-1.98$  to  $-0.40$ ; weight-SDS:  $-1.31$ ;  $-2.26$  to  $-0.43$ ; BMI-SDS:  $-0.78$ ;  $-1.55$  to  $-0.01$ ). However, these differences were not significant.

Diabetes diagnosis was 2.1 years earlier in patients with CFRD and  $\beta$ -cell autoimmunity: median 14.0 years (Q1–Q3: 10.2–15.9) compared with 16.1 years (13.5–21.2) for patients with CFRD without  $\beta$ -cell autoimmunity; *P* < 0.05. Diabetes duration was  $\sim 2.5$  years longer in patients with  $\beta$ -cell autoimmunity.

A female preponderance was found in  $\beta$ -cell-positive patients: 65.3% were female compared with 57.6% in antibody-negative patients; *P* < 0.05.

Residual insulin secretion, measured by C-peptide, was only available in a small number of patients in the database. The reason is that this parameter is not part of routine diagnostics and therefore not measured regularly. Data were available for 33 patients (4.31%) without autoimmunity and 5 patients (6.94%) with  $\beta$ -cell antibodies (C-peptide: median 1.34  $\mu$ g/L [Q1–Q3 0.37–1.25] vs. 0.70  $\mu$ g/L [0.6–0.7]; not significant). Proper statistical evaluation is difficult because of small patient numbers, but C-peptide was lower in patients with CFRD and  $\beta$ -cell autoimmunity, indicating

more severe insulin insufficiency in these patients.

HLA-DR3/-4 was also only available in a small percentage of our patients. HLA status was documented in 15 (1.96%) antibody-negative patients and in 5 (6.94%) patients with  $\beta$ -cell autoimmunity. In patients with available data, HLA-DR3/-4 was positive in 60% of antibody-negative patients versus 80% of patients with  $\beta$ -cell autoimmunity (not significant). Interpretation of these data are difficult because of small patient numbers with available data.

Thyroid autoimmunity was significantly more common in patients with  $\beta$ -cell autoimmunity: 20.3 vs. 8.5%; *P* < 0.05.

Proportion of patients with migration background was not significantly different between the groups (CFRD and  $\beta$ -cell autoimmunity compared with CFRD without  $\beta$ -cell autoimmunity: 5.6 vs. 7.8%).

Glycemic control, measured by HbA<sub>1c</sub>, was significantly better in patients without  $\beta$ -cell autoimmunity (median 6.7%; Q1–Q3 5.9–7.9 [50 mmol/mol; 41–63] vs. 7.1%; 6.1–8.8 [54 mmol/mol; 43–73]; *P* < 0.05).

There were significant differences between the two groups with regard to acute diabetes complications such as severe hypoglycemia with coma ( $\beta$ -cell antibody-positive patients: 8.0 vs. 1.4%; *P* < 0.05) and ketoacidosis (9.3 vs. 0.9%, *P* < 0.05). Episodes of DKA and severe hypoglycemia with coma are given for every patient experiencing these complications at least once.

CF health status as measured by percentage of forced expiratory volume for 1 s was only available for a small number of patients in our database. Data were given for 35 of 765 patients (4.6%) without  $\beta$ -cell autoimmunity and 3 of 72 patients (4.2%) with  $\beta$ -cell autoimmunity (percentage of forced expiratory volume for 1 s: median 56.78% [Q1–Q3 35.58–78.25]

**Table 1—Frequency of diabetes antibodies in our cohort of 72  $\beta$ -cell-positive patients with CFRD in the DPV database**

	Patient number (n)	Percent of total
IA-2	46	63.9
ICA	55	76.4
GADA	52	72.2
IAA (before insulin treatment)	60	83.3
ICA, islet cell antibodies.		

**Table 2—Demographic data and clinical characteristics of patients with CFRD with or without  $\beta$ -cell autoimmunity documented in the DPV system**

	CFRD with $\beta$ -cell autoimmunity	CFRD without $\beta$ -cell autoimmunity	Nonadjusted <i>P</i> value
All patients, <i>n</i> (%)	72 (8.6)	765 (91.4)	
Male/female (%)	34.7/65.3	42.4/57.6	NS
Migration background (%)	5.6	7.8	NS
Age (years)	17.80 (15.73–20.80)	19.30 (16.50–25.95)	NS
Age at diagnosis (years)	14.00 (10.15–15.90)	16.10 (13.50–21.20)	<0.05
Duration of diabetes (years)	5.1 (2.3–9.2)	2.7 (0.4–6.0)	<0.05
Height-SDS	−1.3 (−2.1 to −0.3)	−1.2 (−2.0 to −0.4)	NS
Weight-SDS	−0.9 (−2.1 to −0.1)	−1.3 (−2.3 to −0.4)	NS
BMI-SDS	−0.5 (−1.3 to −0.1)	−0.8 (−1.6 to 0.0)	NS
HbA <sub>1c</sub> (%)	7.1 (6.1–8.8)	6.7 (5.9–7.9)	<0.05
HbA <sub>1c</sub> (mmol/mol)	54.10 (43.17–72.68)	49.73 (42.98–62.84)	<0.05
Insulin dose (IU/kg body weight)	0.95 (0.61–1.15)	0.67 (0.33–1.04)	<0.05
One to three fixed daily injections (%)	13.6	13.8	NS
Multiple daily injections (%)	68.2	79.8	NS
Insulin pump therapy (%)	18.2	6.4	<0.05
Severe hypoglycemia with coma (%)	8.0	1.4	<0.05
Ketoacidosis (%)	9.3	0.9	<0.05

Data are shown as median (lower–upper quartile) or percentage unless otherwise indicated. As patient numbers are low, *P* values were not adjusted for confounders.

vs. 71.22% [14.40–107.54]; not significant). Number of patients with available data are too low for proper evaluation.

### Treatment

Treatment modalities differed between the two groups. Insulin therapy was used in 91.7% of patients with CFRD with  $\beta$ -cell autoimmunity and in 75.9% of antibody-negative patients. Insulin pump therapy was thereby used more frequently in patients with  $\beta$ -cell autoimmunity, comparable to T1DM: 18.2 vs. 6.4%; *P* < 0.05. In addition, dose of insulin was different for the groups. Insulin dose per kilogram body weight in patients with autoimmunity was 0.95 (0.61–1.15) compared with 0.67 (0.33–1.04) in antibody-negative patients. This difference was significant and persisted after adjustment for confounders as age and sex. More detailed results of insulin doses are shown in Table 3. Oral antidiabetic drugs were used in both groups ( $\beta$ -cell–positive patients: 5.6 vs. 11.8%) without significant difference, but patient

numbers with oral antidiabetic drugs were very low in both groups.

If not otherwise stated, all described differences could be confirmed after data were adjusted for confounding effects of age and sex. Data were not adjusted for diabetes duration, as diabetes diagnosis in CFRD might sometimes be delayed by absence of obvious diabetes symptoms at diagnosis.

### CONCLUSIONS

This is the first report on patients with CFRD with additional  $\beta$ -cell autoimmunity compared with antibody-negative patients with CFRD based on a large diabetes registry. The aim of our analysis was to describe the prevalence and the effects of  $\beta$ -cell autoimmunity in patients with CFRD documented in the DPV database.

We identified a total of 837 patients with CFRD in the DPV database. According to the estimated size of the CF population in Germany, current frequency of

CFRD is at least 10.5%. The estimated CF population size is based on the German quality report on CF (Berichtsband Qualitätssicherung Mukoviszidose 2012). A total of 80 CF centers in Germany include their patients in this database. In 2012, a total number of 5,111 patients was listed. The database covers ~65% of all patients with CF in Germany, which brings the estimated total size of CF population in Germany to 8,000.

The prevalence of diabetes-specific autoantibodies in our cohort of patients with CFRD was higher than in the general population, previously described by up to 4.5% (16), and higher than reported earlier for patients with CFRD (12). However, individuals have occasionally been found to have both T1DM and CF (6,23). Only a prospective protocol with yearly determination of diabetes antibodies from diagnosis on would resolve the question of progress and trends of autoimmunity in CFRD. In the DPV database, such data are currently not available

**Table 3—Insulin dose in patients with or without  $\beta$ -cell autoimmunity as documented in the DPV system**

	CFRD with $\beta$ -cell autoimmunity	CFRD without $\beta$ -cell autoimmunity	Nonadjusted <i>P</i> value
Insulin dose (IU/kg body weight)	0.95 (0.61–1.15)	0.67 (0.33–1.04)	<0.05
Total daily insulin dose (IU)	45.10 (32.00–63.50)	31.00 (16.00–54.00)	<0.05
Prandial dose (IU)	29.50 (18.50–40.75)	20.65 (12.00–34.50)	<0.05
Basal dose (IU)	16.75 (11.00–22.85)	15.00 (9.00–23.10)	<0.05

Data are shown as median (lower–upper quartile). As patient numbers are low, *P* values were not adjusted for confounders.

on a regular basis, as it is not addressed in routine care and part of current guidelines. It is possible that long-term disease has impact on the progression of autoimmunity. Further research is necessary to address this question. In our cohort, diagnosis of CFRD was significantly earlier in patients with CFRD with additional autoimmunity, and therefore, diabetes duration was longer. This hints to the assumption that autoimmunity leads to a more rapid progression of CFRD. The classification of glucose metabolism disorders is principally derived from etiology and includes staging of pathophysiology based on the degree of deficiency of insulin action. These disorders are currently classified into four groups: T1DM, type 2 diabetes, diabetes due to other specific mechanisms or diseases, and gestational diabetes mellitus. As CFRD is a multifactorial disease, influenced by comedication, especially steroids, acute inflammation, and illness, current classification is challenging.

In current guidelines, determination of HLA is not recommended as standard routine care in patients with autoimmune diabetes. Therefore, data on HLA types associated with T1DM are not routinely collected and documented in the DPV system.

Autoimmune thyroid disease is frequently associated with T1DM. Recently, Riquetto et al. evaluated 233 children and adolescents with T1DM and analyzed the prevalence of autoimmune thyroid disease in these patients, which was found in 23% (24). Data on thyroid autoimmunity in patients with CF is rare. We identified thyroid autoimmunity in 20.3% of patients with CF and  $\beta$ -cell autoimmunity, which is comparable to T1DM (25). In contrast, only 8.5% of patients without  $\beta$ -cell autoimmunity were positive for thyroid autoantibodies.

In general, patients with CFRD with  $\beta$ -cell positivity in our cohort were comparable to patients with T1DM. Diabetes onset was earlier, and acute complications, especially severe hypoglycemia with coma, were more frequent. One possible explanation might be the influence of autoimmunity on severe diabetes progression with rapid loss of endogenous insulin secretion and therefore need for an earlier start of insulin therapy and more intense insulin therapy, with the risk of imperfect insulin replacement.

Hypoglycemia is common in patients with CF, with or without diabetes, and

up to 15% of patients with CF develop hypoglycemia during an oral glucose tolerance test (26). This is presumed to be related to delayed insulin secretion. Reactive hypoglycemia was recently considered as an early stage of CFRD. In T1DM, hypoglycemia is the most common acute complication and a common side effect of insulin therapy. The incidence of severe hypoglycemia varies with different surveys, but careful prospective studies suggest a rate of 5 to 20/100 patient-years (27).

DKA is common in patients with T1DM and a major problem with increased morbidity and mortality (28). Rates of DKA in youth with T1DM vary widely from 15 to 70% at diagnosis (29) to 1 to 15% per established patient per year (30,31). Data on ketoacidosis in CFRD is rare, with only a few case reports (32,33). It seems that DKA is an extremely rare event in CFRD (2). In our cohort of patients, DKA was 10 times higher in patients with  $\beta$ -cell positivity compared with antibody-negative patients.

Diabetes control, measured by HbA<sub>1c</sub>, was significantly different in patients with or without  $\beta$ -cell autoimmunity, with higher HbA<sub>1c</sub> in patients with  $\beta$ -cell autoimmunity. Recurrent ketoacidosis and hyperglycemic state in this patient group might be a possible explanation. Recent data compared glycemic control in CFRD with T1DM (2). HbA<sub>1c</sub> values in both groups of our patients with CFRD were lower than recently described in T1DM. One possible reason might be that HbA<sub>1c</sub> is not a good marker for metabolic control in patients with CF, as recurrent infections and hemolysis influence HbA<sub>1c</sub> levels, which are often falsely low in these patients (34). Some data suggest that there is no relationship between mean plasma glucose and glycated hemoglobin in patients with CFRD (35). However, data on the value of HbA<sub>1c</sub> are conflicting with recent data suggesting an HbA<sub>1c</sub>  $\geq$ 5.8% as an effective tool for CFRD screening (36). Another possible explanation might be the persistence of endogenous insulin secretion, especially in the baseline state.

Besides differences in the frequency of acute diabetic complications in patients with CFRD with or without  $\beta$ -cell autoimmunity, we also found significant differences in insulin therapy. In contrast to current guidelines for the

treatment of CFRD, a small number of patients in both groups was not treated with insulin. Possible reasons for non-adherence to current guidelines were discussed previously by our group (37). In insulin-treated patients, insulin dose per kilogram body weight and total daily dose were both higher in the group of patients with  $\beta$ -cell autoimmunity, suggesting that autoimmunity leads to more progressive destruction of  $\beta$ -cell mass and results in severe insulin deficiency with lower endogenous insulin secretion. Both prandial and basal insulin needs were higher in the presence of  $\beta$ -cell autoantibodies, indicating that more intense insulin treatment is needed for this patient group. Similar results were found with regard to the use of insulin pumps.

In T1DM, the use of CSII/insulin pump therapy has increased steadily in recent years (38). Previous studies established CSII as a safe and effective alternative to conventional insulin injection regimes in pediatric patients with T1DM (39,40). Despite these data, insulin pump therapy is rarely used in adolescents and young adults with CF, as recently described (41). In our cohort of patients with CFRD, use of insulin pump therapy was more frequent, if  $\beta$ -cell autoimmunity was present. Reasons for this difference remain unclear, but more severe diabetes progression with higher insulin doses comparable to T1DM and a greater risk of acute diabetes complications, (e.g., hypoglycemia) might be possible explanations for this adjustment of treatment modalities. Another possible explanation might be that patients with CFRD with autoimmunity are treated in specialized diabetes centers, as there they receive more intense and complex therapy compared with antibody-negative patients. Other caregivers might be less familiar with CSII compared with diabetologists. Overall, there is a lack of large controlled studies on the effect and safety of insulin pump therapy in CFRD and a lack of diabetes information for this patient group.

In summary,  $\beta$ -cell autoimmunity seems to play a role in a small percentage of patients with CFRD. Our data show that  $\beta$ -cell autoimmunity exists in patients with CF classified as patients with CFRD, but so far, screening for autoimmunity is not generally recommended. Patients with CFRD and

autoimmunity are younger at diabetes onset, present with more acute diabetes complications, and their insulin requirement is higher. There is a need to discuss diabetes classifications, as by the World Health Organization guidelines, where diabetes in patients with CF is classified as CFRD (type 3 diabetes), irrespective of  $\beta$ -cell antibody positivity. The overlap with T1DM is difficult to recognize, but those few patients with autoimmunity and CFRD are more similar to subjects with T1DM. As autoimmunity influences diabetes therapy and the risk of acute diabetic complications, it seems to be advisable to test patients with CFRD, at least those with a diagnosis early in life, high insulin requirement, and unusual diabetes presentation, at onset of diabetes for  $\beta$ -cell autoimmunity preferable before insulin treatment is started, as the result has an impact on diabetes progress, care, and treatment. Once insulin treatment is started, interpretation of  $\beta$ -cell autoimmunity (IAA) is difficult, as exogenous insulin influences the results. As patients with  $\beta$ -cell autoimmunity suffer significantly more often from severe hypoglycemia with coma and from ketoacidosis, diabetes education in this patient group should focus more intensely on acute diabetic complications.

Furthermore, once  $\beta$ -cell autoimmunity is established in patients with CFRD, screening for other autoimmune diseases, especially thyroid autoimmunity, seems to be advisable. This is not recommended in current CFRD guidelines, as autoimmunity is not the major focus or primary cause of diabetes in most patients with CFRD.

Further research on autoimmunity and the role of HLA types in CFRD in larger patient groups is necessary to better define its influence on diabetes progression and outcome.

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