Cystic fibrosis-related diabetes compared with type 1 and type 2 diabetes in adults

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Abstract

Background With increasing life expectancy of patients with cystic fibrosis (CF), secondary diabetes becomes more prevalent. It appears to be the most common co-morbidity in persons with cystic fibrosis. Therefore, the objective of our study was to describe characteristics of cystic fibrosis-related diabetes compared with type 1 and 2 diabetes (T1DM/T2DM) in adults.

Methods Data from 218,436 patients >18 years with cystic fibrosis (n = 401), T1DM (n = 32,409) or T2DM (n = 185,626) in the multicenter Diabetes-Patienten-Verlaufsdokumentation or prospective documentation of diabetes patients registry were analysed.

Results Diabetes onset [median (interquartile range)] in cystic fibrosis [18.70 (15.50–25.30) years] was between T1DM [16.40 (10.50–31.80) years] and T2DM [58.50 (48.80–68.00) years], with female preponderance. Body mass index (BMI) and glycosylated haemoglobin (HbA1c) were lowest (19.6 [18.1–21.5] kg/m²) vs 50 mmol/mol (6.73%) versus T1DM (24.4 [22.1–27.4]) vs 62 mmol/mol (7.83%) vs T2DM (29.6 [26.1–33.9])/54 mmol/mol (7.06%); all p < 0.01. A total of 78.6% of cystic fibrosis patients with diabetes received insulin. Insulin dose (0.74 IE/kg bodyweight) was not significantly different from T1DM (0.73) and T2DM (0.76). Frequency of vascular complications, adjusted for confounding effects, across the groups was different: Hypertension (CFRD 16.1% vs T1DM 24.0% vs T2DM 32.2%; all p < 0.01), retinopathy (CFRD 10.7% vs T1DM 10.4% vs T2DM 10.5%, not significant), nephropathy (CFRD 25.2% vs T1DM 17.2% vs T2DM 24.7%; only T1DM/T2DM; p < 0.01).

Conclusion CFRD is a uniquely complex entity with clear differences from T1DM and T2DM in adults. Copyright © 2013 John Wiley & Sons, Ltd.

Keywords antihyperglycemic therapy; co-morbidities; metabolic control; steroid therapy; weight status; insulin

Background

With prolonged survival of patients with cystic fibrosis (CF), CF-related diabetes (CFRD) is becoming more frequent, occurring approximately in 40–50% of adults [1]. Early detection is important for treatment in order to achieve good metabolic control and prevent weight loss, protein catabolism, lung function decline and mortality [2,3].
A recent review [2] described CFRD as a unique clinical entity sharing features of type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). Its aetiology is multifactorial, consisting of a unique combination of insulin deficiency due to progressive destruction of the pancreas and insulin resistance in association, for example, with chronic inflammation, and additional risk factors [4,5]. The prevalence of diabetes autoantibodies appears to be no greater than in the general population [6]. On the basis of the available data, insulin is the only recommended therapy [7]. With disease progression, intensification of insulin therapy is often necessary. Acute illness and/or use of corticosteroids increase insulin resistance, and insulin therapy often needs to be started or adjusted during such episodes [8,9]. In other types of diabetes, the major goal of therapy is to achieve near normal blood glucose levels and prevent sustained hyperglycaemia while limiting hypoglycaemia to reduce the risk of microvascular and macrovascular complications. In CFRD, no cases of death from cardiovascular disease have been reported [2]. However, pulmonary function decline is directly related to insulin insufficiency [10]. Insulin substitution should be considered as an opportunity to deliver glucose (calories) to body tissues including the lung and in addition to prevent hyperglycaemia [11]. The main object of CFRD treatment is to restore nutritional status and lung function.

In T1DM, autoimmunity leads to destruction of beta-cells within the pancreas and to absolute insulin deficiency. T2DM results from peripheral and hepatic insulin resistance and inadequate insulin secretion, with obesity as a major risk factor.

We recently described differences of CFRD and T1DM in a paediatric cohort [12]. In order to better define characteristics of CFRD in adults, we compared CFRD with both T1DM and T2DM in adult patients from a large multicenter registry.

Patients and methods

Study population

Data were collected during routine care and retrieved from the ‘Diabetes-Patienten-Verlaufsdokumentation’ (DPV or prospective documentation of diabetes patients) database, a nationwide register for people with diabetes in Germany and Austria that started in 1995. For central analysis, anonymized, prospective data are transmitted twice a year from participating centres to Ulm, Germany. Inconsistent data are reported back for verification and correction. Data are used for quality assurance and clinical research.

To this analysis, 368 diabetes centres contributed data on sex, age, diabetes duration, type of diabetes, body mass index (BMI), height, weight, insulin requirement, number of severe hypoglycaemia and glycosylated haemoglobin (HbA1c). By September 2012, the total number of patient visits documented in DPV was 996 766 from 237 470 patients (>18 years of age). A total of 32 858 (13.84%) of these patients had T1DM, 1 856 626 (78.17%) had T2DM and 18 986 (7.99%) had other types of diabetes mellitus, including CFRD. Finally, 218 436 patients with either CFRD (n = 401), T1DM (n = 32 409) or T2DM (n = 185 626) fulfilled the inclusion criteria (complete data and >18 years of age) and were analysed on the basis of the last documented 12 months of care.

Anthropometry

Definitions of underweight, overweight and obesity were based on BMI, calculated as body weight in kilogrammes divided by the square of the height in metres (kg/m²). We defined BMI values from 25–30 kg/m² as overweight and >30 kg/m² as obese. BMI values below 19 kg/m² were stated as underweight.

According to official guidelines of the German hypertension league, arterial hypertension was defined as blood pressure above 140/90 mmHg [13].

Metabolic control

To adjust for differences among laboratories, HbA1c measurements from different centres were mathematically standardized to the Diabetes Control and Complication Trial reference range of 4.05–6.05% (21–43 mmol/mol) using the multiple of the mean method [14].

Anti-hyperglycaemic therapy

As described in our paediatric data [12], treatment regimen was categorized as insulin therapy alone or in combination with oral anti-diabetic drugs, use of oral anti-diabetic drugs (sulphonylureas, glinides) alone or non-pharmacological treatment with lifestyle modification only. Insulin therapy was documented as number of daily injections or continuous subcutaneous insulin infusion (CSII), daily insulin dose per kilogramme bodyweight and the use of insulin analogues.

Statistical analysis

The SAS statistical software package (version 9.3; SAS Institute Inc., Cary, NC, USA) was used for data analysis. For group comparison of continuous variables, non-parametric test (Kruskal–Wallis) was used. Binary variables
were compared by χ² test. As multiple tests were performed, p values were adjusted using the Bonferroni step down correction (method of Holm). Data were given as median and interquartile range or percentage. A multivariable mixed regression analysis, including a random term for treatment centre with Cholesky covariance structure, was applied to adjust data for confounding effects of age, sex and diabetes duration. Multiple comparisons were adjusted by Tukey–Kramer. A p-value < 0.05 was considered statistically significant.

Results

Clinical data

Table 1 shows anthropometric and clinical data of adult patients with CFRD, T1DM or T2DM. Age at diabetes diagnosis was highest in T2DM [58.5 years (Q1–Q3: 48.8–68.0)] compared with CFRD [18.7 years (15.5–25.3)] and T1DM [16.4 years (10.5–31.8)] (p < 0.001). Female preponderance was only found in CFRD: 55.9% were women compared with 46.3% in T1DM and 48.9% in T2DM (all p < 0.001).

The CFRD patients were shortest (women: 160.8 cm; men: 171.7 cm), with lowest BMI (women: 21.1 kg/m²; men: 21.3 kg/m²) compared with T1DM (height/BMI: women: 166.4 cm/25.3 kg/m²; men: 178.9 cm/24.7 kg/m²) and T2DM patients (height/BMI: women: 165.6 cm/34.7 kg/m²; men: 178.7 cm/31.7 kg/m²) (all p < 0.001). Rate of overweight and obesity was highest in T2DM with 47.3% of patients being obese, 34.9% overweight and 17% normal weight. In T1DM, 13.2% of patients were obese and 30.6% overweight and obesity was highest in T2DM with 47.3% of patients being obese, 34.9% overweight and 17% normal weight. In contrast, only 1.5% of CFRD patients were obese and just 2.7% were overweight. The rate of underweight was 39% and thereby highest in the CF group.

Glycaemic control, as measured by HbA1c, was better in CFRD than in T2DM and T1DM. CFRD: 50 (42–63) mmol/mol [6.7% (6.0–7.9)] versus T2DM: 54 (44–68) mmol/mol [7.1% (6.2–8.4)] versus T1DM: 62 (52–77) mmol/mol [7.8% (6.9–9.2)]; all p < 0.001.

The prevalence of vascular risk factors of diabetic complications, given in Figure 1, differed between the groups after adjustment for age, sex and diabetes duration. We found a significant difference with regard to hypertension for all patient groups: 16.1% of CFRD patients were hypertensive compared with 24.0% in T1DM and 32.2% in T2DM (all p < 0.01). The unadjusted prevalence of retinopathy was 3.4% in CFRD, 10.3% in T1DM and 9.3% in T2DM. However, after adjustment for age, sex and diabetes duration, a significant difference was no longer present (CFRD 10.7% vs. T1DM 10.4% vs. T2DM 10.5%). Nephropathy, defined by microalbuminuria, was found in

Figure 1. Frequency of co-morbidities in cystic fibrosis-related diabetes (CFRD), type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). Data are shown in percentage, adjusted for age, sex and diabetes duration.

Table 1. Demographic data and clinical characteristics for T1DM, T2DM and CFRD patients

<table>
<thead>
<tr>
<th></th>
<th>T1DM</th>
<th>T2DM</th>
<th>CFRD</th>
<th>corrected p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients, n (%)</td>
<td>32.409 (14.84)</td>
<td>185.626 (84.98)</td>
<td>401 (0.18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male/female (%)</td>
<td>54/46</td>
<td>51/49</td>
<td>44/56</td>
<td>n.s.</td>
</tr>
<tr>
<td>Migration background (%)</td>
<td>5.0</td>
<td>2.0</td>
<td>6.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>32.30 (19.40–51.20)</td>
<td>69.60 (60.20–77.10)</td>
<td>23.50 (19.70–30.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>16.40 (10.50–31.80)</td>
<td>58.50 (48.80–68.00)</td>
<td>18.70 (15.50–25.30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>11.45 (5.70–21.70)</td>
<td>8.05 (2.70–14.70)</td>
<td>3.8 (1.50–7.80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172.0 (165.0–179.8)</td>
<td>168 (162.0–175.0)</td>
<td>164.5 (159.4–171.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73.0 (64.3–83.3)</td>
<td>84.4 (73.0–95.0)</td>
<td>53.4 (47.8–59.7)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.4 (22.1–27.4)</td>
<td>29.6 (26.1–33.9)</td>
<td>16.6 (18.1–21.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>62 (52–77)</td>
<td>54 (45–68)</td>
<td>50 (42–62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.84 (6.90–9.16)</td>
<td>7.06 (6.24–8.39)</td>
<td>6.73 (6.03–7.86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Steroid therapy (%)</td>
<td>0.8</td>
<td>1.8</td>
<td>16.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BMI, body mass index; CFRD, cystic fibrosis-related diabetes; HbA1c, glycosylated haemoglobin; n.s., not significant; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Data are shown as median and interquartile range (IQR, lower–upper quartile) or percentage, if not otherwise indicated.
21.2% of CFRD patients compared with 24.0% in T1DM and 37.5% in T2DM. After adjustment for demographics, the prevalence of microalbuminuria in CFRD increased (25.2% vs. T1DM 17.2% vs. T2DM 24.7%). The difference between T1DM and T2DM was significant (p < 0.001), whereas the difference between CFRD did not reach statistical significance.

**Treatment**

As summarized in Figure 2a, treatment modalities differed between the groups. All patients with T1DM received insulin therapy [96.2% insulin alone, 3.8% in combination with oral antidiabetic (OAD)]. In CFRD, 78.6% of patients were treated with insulin (74.1% insulin alone, 4.5% in combination with OAD). A total of 52.6% of patients with T2DM received insulin therapy (32.3% insulin alone, 20.3% in combination with OAD) (all p < 0.001). In insulin-treated patients with T1DM, 14.8% were treated with conventional therapy (CT, 1–3 injections per day); 63.1% with intensified conventional therapy (ICT): multiple daily injections (4–8 injections per day) and 22.1% with insulin pumps (CSII). In insulin-treated patients with CFRD, 41% received CT, 54% ICT and only 5% were treated with CSII. A total of 53.8% of patients with T2DM received CT, ICT in 45.8% and CSII in 0.4% only (data shown in Figure 2b; all p < 0.001). Fast acting insulin analogues were used most frequently in T1DM patients (59.6% vs. CFRD 50.0% vs. T2DM 26.0%). After adjustment for age, sex and diabetes duration, a significant difference in the use of fast acting insulin analogues between CFRD and T2DM as well as T1DM and T2DM was found (both, p < 0.01). The difference between CFRD and T1DM was not significant (p = 0.84). Similarly, the use of long acting insulin analogues was most frequent in T1DM (43.7% vs. CFRD, 33% vs. T2DM, 29.4%). Again, the difference between CFRD and T2DM as well as T1DM and T2DM was statistically significant (p < 0.05, p < 0.01), but there was no significant difference in the use of long acting insulin analogues between CFRD and T1DM (p = 0.43).

Insulin dose per kilogramme bodyweight (Figure 2c), adjusted for confounding effects, did not differ significantly between CFRD and T1DM (0.74 vs. T1DM 0.73; n. s.) and CFRD and T2DM (0.74 vs. T2DM 0.76; n. s.). Insulin dose in T1DM and T2DM was significantly different (T1DM 0.73 vs. T2DM 0.76; p < 0.05).

In CFRD, OAD agents (sulfonylureas and glinides) alone were used by 6.7% of patients compared with 26.1% in T2DM and none of the T1DM patients. A total of 14.7% of CFRD patients were treated with non-pharmacological therapy only (lifestyle intervention) compared with 21.3% in T2DM. Corticosteroid use was documented in 16.5% of all CFRD patients, whereas only 0.8% of T1DM patients and 1.8% of T2DM patients had received systemic steroids as a co-medication during the course of their disease (p < 0.001).

We analysed data in CFRD with (n = 66) or without (n = 335) additional steroids. There were differences in the use of insulin (94% vs. 84%; p = 0.06) and insulin dose per kilogramme bodyweight (0.84 vs. 0.95; p = 0.18), but they were not significant. For demographics or glycemic control, differences between the two groups were not significant (data not shown).
Patients with CFRD were mostly treated in paediatric institutions (79.3%) and at universities (67.6%) as compared with patients with T1DM (34.4%/19.5%) and T2DM (1.1%/3.8%).

Self monitoring of blood glucose (SMBG) per day was most frequent in T1DM (4.0 vs. CFRD 3.7 vs. T2DM 2.8; all p < 0.05), with lowest number of visits per year (T1DM 2.0 vs. CFRD 2.3 vs. T2DM 2.8; all p < 0.05).

Conclusions

Our data on adult patients characterize CFRD as a unique and complex entity with specific differences to both T1DM and T2DM, and they demonstrate that differences in paediatric patients [12] persist into adulthood. In our cohort, 56% of adult CFRD patients were women. In comparison, in T1DM and T2DM, male to female ratio was close to one. Previous data described female sex as a risk factor for CFRD [15]. A possible explanation might be different changes in body weight and insulin sensitivity that are regulated by oestrogen and its receptors [16]. CF patients have, because of their primary disease and nutritional status, a significant reduction in height and weight and a lower BMI [17], which was confirmed by our analysis.

As a marker for glycaemic control, we compared HbA1c, which was lower in CFRD than in T1DM and T2DM. Older data described limitations of this parameter in CFRD, as recurrent infections and hemolysis influence HbA1c levels [18]. Another study found that HbA1c was strongly correlated with mean plasma glucose concentration. These results imply that HbA1c <7.0% (53 mmol/mol) predicts good blood glucose control in CFRD as in T1DM [19]. Nevertheless, further investigations are required to establish the relationship between HbA1c and diabetic complications in patients with CFRD compared with other types of diabetes and to define better target goals for HbA1c in CFRD.

After the diagnosis of CFRD, quarterly visits to a multidisciplinary team and HbA1c measurements every 3 months are recommended [7]. In our data, all patients were followed up less frequently in diabetes centres than recommended. More frequent visits were documented in T2DM, followed by CFRD and T1DM. Fewer visits for CFRD patients at diabetes centres might be explained by separate visits in CF clinics.

In contrast to other types of diabetes, a high percentage of CFRD patients was treated in paediatric institutions. A possible explanation is a lack of transition programmes for patients with CF [20].

The SMBG is recommended at least three times daily [21]. In our analysis, SMBG in CFRD was performed three to four times daily in accordance with current guidelines.

Case reports and small series of CFRD patients described diabetes associated microvascular complications. A recent retrospective study [22] analysed the prevalence of microalbuminuria. Transient microalbuminuria was not more common in CFRD than in the general population. Permanent microalbuminuria in CFRD was found in 6.1% of patients. Other studies showed similar risk for the development of microvascular complications compared with T1DM [23,24] but with a lower prevalence of retinopathy and a higher prevalence of microalbuminuria. The risk was related to duration and progression of the primary disease and inversely to metabolic control of diabetes [23]. Microvascular complications were rare before 10 years of diabetes duration [25]. Recent data comparing CFRD and T1DM in children could not find differences in diabetic complications in both groups as explained by its short disease duration [12]. A likely explanation for less microvascular complications in our adult cohort is the disease duration of CFRD that is below 10 years in our patients. After adjustment for confounding effects, the prevalence of retinopathy was the same for all patients. With regard to microalbuminuria, we found the highest prevalence in CFRD compared with other previous studies [23,24]. A possible explanation is exposure to nephrotoxic agents in CF. With disease progression, especially microalbuminuria in CFRD, it becomes more frequent, and it remains important to screen regularly for complications [21]. Macrovascular complications have not been described in CFRD [25]. With regard to hypertension, we found the highest risk in T2DM followed by T1DM and CFRD. The most possible explanation is that hypertension is part of the metabolic syndrome, and obesity is a manifestation factor. Nevertheless, in adult CF patients, hypertension is not uncommon, particularly after transplantation [24] or with systemic steroids. Patients with CFRD should have their blood pressure measured at every routine visit [21].

Even if the cause of CFRD seems to be multifactorial, the major cause seems to be insulin insufficiency. In addition, acute illness, use of corticosteroids and other therapeutic agents are associated with increased insulin resistance and altered insulin release [26]. In our cohort, use of corticosteroids was documented in 16.5% of patients with CFRD compared with only 0.8% in T1DM and 1.8% in T2DM.

To improve weight gain and lung function, current guidelines state insulin therapy should be started as soon as the CFRD diagnosis is made to benefit from anabolic effects of insulin [10,27]. Basis-bolus insulin regimen is recommended as first choice to avoid postprandial hyperglycaemia [7]. In clinical practise, multiple injection regimes are sometimes limited by compliance issues, as CFRD patients are already on onerous treatment regimes. Therefore, in some cases, insulin therapy needs to be individualized and deviated from current recommendations.
with respect to individual patient's needs and compliance issues in order to achieve acceptable glycemic control. And it is important to notice that – beside HbA1c values – nutritional status and lung function are other important parameters that reflect metabolic control in patients with CFRD.

Treatment regimen differed in all patient groups. Despite recent data demonstrating that CSII is safe and effective for treatment of CFRD and that there are metabolic benefits [28], insulin pump therapy was rarely used in CFRD.

Available data suggest that OAD agents are not as effective as insulin to improve glycemic control, weight status, protein anabolism, pulmonary function and survival in CFRD [29,30]. In small case or cohort studies of CFRD patients, oral sulfonylureas or glinides have shown benefit in improving insulin secretion and glycemic control. In our cohort, 6.7% of patients with CFRD were treated with OAD agents alone, whereas 14.7% of the CF patients received non-pharmacological therapy only. This is less than in a paediatric cohort that we recently described [12] and might be explained by intensification of therapy with disease progression into adulthood.

In insulin-treated patients, insulin dose per kilogramme body weight adjusted for confounding effects differed significantly only between patients with T1DM and T2DM, with CFRD patients in between.

In conclusion, our multicenter analysis of current real-life observational data show significant demographic, clinical and treatment differences between adult patients with CFRD, T1DM and T2DM. CFRD shares some features with other types of diabetes, but it is a special entity with specific characteristics.

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**Authors’ contributions**

K.K. wrote and edited the manuscript; N.S. contributed to the discussion, reviewed the manuscript and created the figures; K.B., M.B., B.G., J.S. and A.T. contributed to the discussion and reviewed the manuscript; C.S. reviewed the manuscript; R.H. conceptualized the study, researched the data, contributed to the discussion, reviewed the manuscript and is the principal investigator of the DPV initiative.

**Conflict of interest**

Study sponsors were not involved in data collection or analysis.

**References**


