Clinical Outcome of CF Patients with CF Related Diabetes: Do We Need to Change Our Policy?

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Abstract

Background: Many studies have shown that CFRD has a negative impact on CF prognosis. Current guidelines advise to screen for CFRD with an OGTT yearly from the age of 10 - 12. In our center we do not routinely screen for CFRD because the OGTT is cumbersome and not an ideal screening test. We therefore want to exclude unfavourable clinical evolution due to late diagnosis.

Methods: 23 CF patients with diagnosis of CFRD < 18 years old were matched to a control patient. Clinical evolution (BMI, lung function, and chronic infection treatment burden) was analyzed starting 2 years before until 2 years after diagnosis of CFRD. Results: In the 2 years before diagnosis of CFRD, BMI and LF were similar for both groups while need for IV AB treatment was higher in the CFRD group. In the 2 years following diagnosis and treatment, LF decline was worse in the CFRD despite more IV AB treatments. BMI was still comparable. We conclude that clinical status was comparable between cases and controls in the 2 years preceding the diagnosis of CFRD. However, the need for IV antibiotic treatment seems to precede the faster lung function decline after CFRD diagnosis.

Keywords

Cystic Fibrosis, Cystic Fibrosis Related Diabetes, Clinical Outcome

1. Introduction

Cystic fibrosis (CF) is a life-shortening, multi-organ disease, caused by mutations in the CF transmembrane conductance regulator (CFTR) gene. This gene encodes an ion channel highly expressed in the apical membrane of epithelial cells.

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of epithelial cells [1]. CFTR mutations resulting in dysfunction of the ion channel lead to disturbed epithelial water balance resulting in viscous secretions in exocrine organs like the airways and the pancreas. The main cause of death in CF is respiratory failure secondary to chronic lung infection. Chronic sinusitis, exo- and endocrine pancreatic dysfunction and male infertility are other CF disease manifestations.

CF related diabetes (CFRD) is one of the most common comorbidities of this disease [2] with about 50% of CF patients developing diabetes by the age of 30 years old. While it is rare in childhood, CFRD risk increases from adolescence on wards [3]. Many studies have shown that CFRD has a negative impact on CF prognosis, with worse nutritional status, more severe lung disease and higher mortality [4]-[12]. Even the prediabetic stage may lead to clinical decline [4] [9] [11] [13] [14]. In more recent reports the negative impact of CFRD were less pronounced most likely because of improved CF treatment [7] [15].

The pathophysiology of CFRD is complex. Thick viscous secretions cause obstruction of the exocrine pancreatic ducts with secondary pancreatic fibrosis and fatty infiltration [16]. This progressive pancreatic damage further leads to destruction of islet architecture and delayed and diminished insulin secretion [3]. Recent data suggest that impaired insulin secretion may also be a direct consequence of the mutated CTFR [17]. Insulin insufficiency is the primary defect but insulin resistance may be a contributing factor. Although CFRD thus shares features of both type 1 and type 2 diabetes, it is a separate entity based on pathophysiological and clinical differences [3]. At present insulin is the only recommended therapy for CFRD [2] [16], but this increases the overall CF treatment burden significantly.

Current guidelines [3] [16] [18]-[20] advise to screen on yearly basis for CFRD with an OGTT from the age of 10 - 12 years old. CFRD diagnosis is established if the glucose level is more than 200 mg/dl after two hours in an oral glucose tolerance test (OGTT) [16]. Although in the UK these guidelines are well followed [21], some do not support routine screening [22]. Recent insights suggest that glucose tolerance in CF ranges from normal glucose tolerance (NGT), over impaired glucose tolerance (IGT), to CFRD with(out) fasting hyperglycaemia [15] and the severity of the impaired glucose metabolism may fluctuate over time. Glucose tolerance will be abnormal long before the OGTT will reach the threshold of CFRD diagnosis. Therefore CFRD is not a clear-cut phenomenon that starts at a certain point in time. Moreover, the correlation between the OGTT and the glucose profile during an average day is very weak [23].

In our center, we do not perform yearly CFRD screening with OGTT but rather use this test as a low threshold for diagnostic purposes whenever a patient with CF between the age of 10 and 18 years old has an unstable evolution. In order to evaluate the impact of this practice on patient evolution, we decided to study the clinical evolution before and after diagnosis of CFRD in our pediatric cohort.

2. Methods
2.1. Study Design
This is a retrospective case-control study using the hospital patient registry from the pediatric CF database. Patients born between 1-1-1997 to 31-12-2012, diagnosed with CFRD and treated with insulin before the age of 18 years were included. Each patient diagnosed with CFRD patients was matched with a CF patient without CFRD based on gender, genotype, year of birth, age at CF diagnosis and chronic P. aeruginosa infection. Exclusion criteria were death within the follow up period, and lung transplantation before time zero.

2.2. Study Sample
Possible indications for OGTT apart from diabetic symptoms are: insufficient growth or weight gain increased respiratory symptoms or increased treatment need, vague complaints of fatigue or malaise. The pediatric CF cohort in our center counted 127 children (<18 years old) in 1997 and decreased to 118 children in 2012 (excluding transplanted CF patients).

2.3. Data Collection
We collected patient data two years before the start of insulin treatment (=time zero), until two years after. For the matched group, time zero was set at the same age as time zero of the index case. For CFRD patients receiving a lung transplant within the two year period after start of insulin, data after the transplantation were excluded.

The following parameters were used. For lung function, FEV1 was expressed as % predicted (FEV1%pred)
according to Wang et al. [24]. FEV1%pred decline for each year was calculated by the slope of the regression line through the best FEV1% predicted of each quartile.

Infection status was registered for *Pseudomonas aeruginosa* (PA), other Gram negative bacteria (for example *Achromobacter xylosoxidans*), *Methicillin Resistant Staphylococcus aureus* (MRSA) and *Aspergillus* spp in each year. Chronic Pseudomonas infection was defined according to the Leeds criteria [25]. The Leeds criteria groups ‘never’, ‘intermittent’, ‘free off’ were grouped as ‘non-chronic’. The same definition was applied for other Gram-negative bacteria. MRSA and *Aspergillus* spp infections were defined as ‘positive’ in case of one or more positive cultures were obtained.

Corticosteroid use was classified as “any” systemic steroids *versus* no systemic steroids over the year. Intravenous (IV) antibiotic use was counted as the number of days IV antibiotics per year, and the number of IV treatment courses per year.

Biometric data are given as BMI z-score. Best, worst and mean BMI z-score per year were included.

Diagnosis of CFRD was based on OGTT (glycaemia after 120 minutes > 200 mg/dl) or on a typical clinical presentation with polyuria, polydipsia, glycosuria, in the face of fasting hyperglycaemia.

For all patients the highest HbA1c value for each year was registered. For the OGTT fasting glycaemia and glycaemia after two hours were registered.

The Ethics Committee of the University Hospitals Leuven acknowledged that the study is carried out according to the prevailing ethical standards.

### 3. Results

#### 3.1. Baseline Characteristics

Data were analysed for 23 CFRD patients and the same number of matched non CFRD patients. All patients were pancreatic insufficient. Baseline characteristics are presented in Table 1. Baseline disease characteristics were similar in both groups apart from median HbA1C at time of diagnosis which was higher in the CFRD group (*p* < 0.001).

All control patients had at least one OGGT excluding CFRD in the study period (Year − 2 to Year + 2): 6/11 patients had at least 1 OGGT in the J-2 to time 0 period and 9/11 patients at least one test in the period time 0 to Year + 2 (median glycaemia at 2 hours 126 mg/dl IQR 106 - 160).

#### 3.2. Lung Function

Best FEV1 % predicted of each quartile of the four years’ timeline did not significantly differ between CFRD and control patients (see figure 1). Lung function declinetwo years before start of insulin treatment was not different: a median (IQR) of −0.85% (−1.44% - −0.16%) for the CFRD group and −0.33% (−1.40% - 0.13%) for the controls (*p* = 1.00). Despite start of insulin treatment, we notice a significantly faster lung function decline in the CFRD group compared to the control group (median (IQR) −0.67% (−1.62 - 0.11%)) *versus* 0.10% (−0.91 - 0.46%) over a period of 2 years.

#### 3.3. Infection Status

The incidence of chronic infection with *Pseudomonas aeruginosa* or with other Gram negative bacteria was similar for both groups because this was one of the matching criteria (Table 2). When we looked at all the gram negative bacteria together, the number of positive cultures per year tended to be higher in the CFRD group, in comparison with the controls (data not shown). The incidence of MRSA infections was 7% in the CFRD group versus 10% in the control group and did not significantly differ.
Table 1. Baseline characteristics. Continuous variables are expressed as median (IQR).

<table>
<thead>
<tr>
<th></th>
<th>CFRD</th>
<th>Matched controls</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 23</td>
<td>N = 23</td>
<td></td>
</tr>
<tr>
<td>Current age</td>
<td>21.2 years (16.7 - 23.6)</td>
<td>20.7 years (16.0 - 23.5)</td>
<td>1.00</td>
</tr>
<tr>
<td>Gender F/M</td>
<td>14/9</td>
<td>14/9</td>
<td>1.00</td>
</tr>
<tr>
<td>Age at CF diagnosis</td>
<td>0.1 years (0 - 0.5)</td>
<td>0.1 years (0 - 0.1)</td>
<td>0.167</td>
</tr>
<tr>
<td>Age at CFRD diagnosis</td>
<td>14.0 years (13.4 - 17.0)</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>FEV1 % predicted at time zero</td>
<td>71.6 (59.2 - 89.2)</td>
<td>82.3 (57.8 - 92.5)</td>
<td>0.095</td>
</tr>
<tr>
<td>BMI Z-score at diagnosis</td>
<td>−0.89 (−2.23 - 0.42)</td>
<td>−0.71 (−1.29 - 0.16)</td>
<td>0.628</td>
</tr>
<tr>
<td>HbA1c at diagnosis</td>
<td>6.30% (6.2% - 6.7%)</td>
<td>5.75% (5.5% - 6.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OGGT at time zero: fasting glycaemia</td>
<td>96 mg/dl (85 - 106)</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>OGGT at time zero: glycaemia at 120'</td>
<td>214 mg/dl (192 - 233)</td>
<td>/</td>
<td>/</td>
</tr>
</tbody>
</table>

Table 2. Overview of chronic versus non chronic infection status of P. aeruginosa and other gram negative bacteria, over the four years’ timeline.

<table>
<thead>
<tr>
<th></th>
<th>CFRD +</th>
<th>CFRD −</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non chronic</td>
<td>Chronic</td>
<td>Non chronic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y − 2</td>
<td>P. aeruginosa</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Other Gram-bacteria</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Y − 1</td>
<td>P. aeruginosa</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Other Gram-bacteria</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Y + 1</td>
<td>P. aeruginosa</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Other Gram-bacteria</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Y + 2</td>
<td>P. aeruginosa</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Other Gram-bacteria</td>
<td>11</td>
<td>12</td>
</tr>
</tbody>
</table>

3.4. Medication Use

The number of IV antibiotic days per year increased in both groups over the years but was always significantly higher in the CFRD group (Table 3).

The number of patients treated with oral steroids varied significantly from year to year in the CFRD group (between 4/23 or 17.4% to 6/23 or 26.1%), as well as in the control group (from 1/23 or 4.5% to 4/23 or 18.2%) in the control group. This was not different between groups. All years combined, 18/92 (19.6%) of CFRD group used steroids which is higher than the control group: 8/88 (9%) (p = 0.0458).

3.5. Nutritional Status

The median BMI z-score per year was comparable in both groups for each year (−0.77, −0.88, −0.89, −1.18 for the CFRD group, −0.94, −0.73, −0.72, −0.90 for the control group).

3.6. HbA1c

Median HbA1c rose in the CFRD group from 6.1% in year −2, to 6.4% in the fourth year. In the control group median HbA1 increased from 5.75% to 5.9%. The highest HbA1c per patient was significantly higher in the
Table 3. Overview of use of IV antibiotics per year, expressed as number of IV antibiotics days. Medians (range).

<table>
<thead>
<tr>
<th></th>
<th>CFRD+</th>
<th>CFRD-</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR) of IV antibiotic days</td>
<td>Y – 2</td>
<td>18 (12 - 43)</td>
<td>5 (0 - 16)</td>
</tr>
<tr>
<td></td>
<td>Y – 1</td>
<td>26 (13 - 58)</td>
<td>1.5 (0 - 15)</td>
</tr>
<tr>
<td></td>
<td>Y + 1</td>
<td>40 (15 - 58)</td>
<td>7 (0 - 18)</td>
</tr>
<tr>
<td></td>
<td>Y + 2</td>
<td>33 (15 - 64)</td>
<td>0 (0 - 36)</td>
</tr>
<tr>
<td></td>
<td>Y – 2 and Y – 1</td>
<td>45 (18 - 101)</td>
<td>7 (0 - 24)</td>
</tr>
<tr>
<td></td>
<td>Y + 1 and Y + 2</td>
<td>59 (44 - 122)</td>
<td>15 (0 - 59)</td>
</tr>
</tbody>
</table>

CFRD group compared to the control group for the first three years of the timeline: medians in year –2 were 6.1% vs. 5.75% (p = 0.03), in year –1 6.2% vs. 5.8% (p < 0.001), and in year +1 6.3% vs. 5.75% (p<0.001). Only in the fourth year—that is the second year after start of insulin treatment—this difference was no longer significantly different (medians 6.4% vs. 5.9%; p = 0.10).

3.7. Transplantation and Mortality

There was no significant difference in transplantation between cases and controls (4 out of 23 for the CFRD group, 3 out of 23 for the controls, p = 0.681). Concerning mortality: 3 out of 23 in the CFRD group died (at 4, 9 and 10 years after time zero), 1 out of 23 for the controls died 7 years after time zero (p = 0.295).

4. Discussion

Since we do not systematically screen for CFRD with OGTT, we decided to study the clinical evolution of CF patients diagnosed with CFRD before the age of 18 years in our CF clinic using a case control approach. FEV1 (expressed as best FEV % predicted per quartile) did not significantly differ between the two groups over a time period starting 2 years before up to the diagnosis of CFRD. Despite start of insulin treatment FEV1 decreased faster in the CFRD group in the 2 years after the diagnosis. In a large data set from the European Epidemiologic Registry of Cystic Fibrosis (ERCF) (7566 CF patients), mean FEV1 % was significantly lower in pediatric patients diagnosed with CFRD [5]. Other studies also documented this negative effect on lung function [9] [10] [12]. In an older study [4] also using a matched control design, lung function was already worse in the 4 years preceding the diagnosis of CFRD. Faster lung function decline has been reported before diagnosis in a retrospectively cohort of 457 CF patients [26]. A large part of CFRD patients in our series have a relatively preserved lung function with a median (IQR) FEV1% at start of 82% (66-93%) which may partially explain the difference with older studies.

Chronic infection with *P. aeruginosa* and other gram negative bacteria was overall rare in the CFRD group and control patients were matched for this. Isolation of MRSA and *Aspergillus* spp were rather infrequent and not significantly different. We did not find literature to compare these data with.

Biometric evolution did not differ between both groups and this is in agreement with other recent data [15] where BMI z-score did not differ between those with and without CFRD. As in other multidisciplinary CF teams, there is a strong emphasis on dietary measures with close and intensive dietary follow-up by the dietician aimed at maintaining hyper caloric intake after CFRD diagnosis.

Our study cohort was not appropriate to estimate mortality. An extensive retrospective multicentre cohort study of 4234 CF patients showed that diabetes is a clear determinant of mortality [6]. Patients included were aged 0 - 65 years old and data are based on UK registry data form 1996-2005. Also other data on mortality date back at least 10 years [7]-[9].

The only difference between patients and controls in the years preceding the CFRD diagnosis was burden of therapy which may be an indication of disease severity. Higher need for therapy is one of the clinical reasons to plan an OGTT in our clinic. However, higher need for IV antibiotic treatment persisted after start of insulin treatment. We did not find other data on need for antibiotic treatment in CFRD to compare our data with.

Prescription of oral steroids (which in our centre reflects mostly occurrence of allergic bronchopulmonary as-
pergillosis) was higher in the CFRD patients only when grouping all the years. Oral steroid use may increase insulin resistance and therefore worsen glucose intolerance.

European (2005) as well as American guidelines (2010) [18] [19] recommend annual CFRD screening with an OGTT, starting at the age of 10 - 12 years old. There is however controversy about annual screening using OGTT [22]. The prerequisites for screening are that the natural course of the disease is well known, an adequate screening test is available and earlier diagnosis and treatment improves prognosis. There is consensus that random glucose, HbA1c and fasting glucose have insufficient sensitivity and specificity to be used for CFRD screening [27]. The problem is that the OGTT hardly performs better. Concerning specificity, glucose tolerance in CF patients is variable over time and a diabetic OGTT at one time point may revert to ‘non diabetic’ in a large proportion of patients or vice versa [4] [28] Additionally, the test sensitivity is low because discordance has been documented between OGTT results and glucose profile during normal feeding (as can be measured by home glucose monitoring). Only the latter will tell the clinician if and how the patients should be treated [19] [20]. Continuous glucose monitoring would even be more informative [19] [29]. However, current data are insufficient to link GCM results to treatment needs and long term outcome. Most patients with CF have some degree of intermittent glucose elevation but it is not known whether they all need treatment [30]-[35].

The rationale to screen is that CFRD has a negative impact on disease course and increases mortality [4]-[12] while treatment may partially reverse these negative effects [4] [7] [13] [15] [36]. The rationale to use the OGTT is that there is no other easy and adequate screening test. Clinical harm may however already occur before the OGTT reaches the diabetic level (and thus before start of insulin treatment) [4] [9] [11] [13] [14]. Even modest increases in glycaemia may cause an increase in glucose concentration in the bronchial mucosae. This may facilitate the growth of respiratory pathogens and thus aggravate chronic endobronchial infection [37] because pathogens like S. aureus and P. aeruginosa utilise glucose as a growth substrate [38]. Furthermore, insulin insufficiency compromises nutritional status and loss in BMI has a negative impact on lung function [39].

There are little data on the benefit of treating the prediabetic status with insulin [40] [41] and doing so would add significant burden of therapy and risk for hypoglycaemia. Small uncontrolled studies suggest that treatment with insulin or oral antidiabetic drugs improves weight and clinical status in IGT CF adolescents [40]-[44].

So the arguments pro screening are the following: no early or specific symptoms and treatment improves prognosis. Arguments against screening are: OGTT is cumbersome and time consuming, OGTT is not a good screening test (OGGT fluctuates over time and normal OGTT does not rule out post prandial hyperglycaemia), respiratory decline may occur already before abnormal OGTT. Additionally, no firm data are available that earlier therapy based on screening (ideally with CGM) in otherwise stable CF patients improves prognosis. Finally, there is a cost issue: at the age of 12 years, CFRD prevalence is around 7%. Therefore in 93% of children this test is futile. The cost of this test in a day care setting in our center is 330 euros.

In our CF clinic, we do not screen annually and the OGTT is used as diagnostic instead of screening tool. We do realise that because diabetes symptoms are often mild and a specific, diagnosis may be made too late. A recent study form Brazil suggested that from 52 screened patients, 10 had CFRD based on the OGTT while only 8 had a diagnosis based on clinical suspicion [45]. Although we do not have similar data for our center, we believe that the percentage of missed patients in our center will be lower due to our very low level of suspicion. This is supported by the finding that we currently have a comparable CFRD prevalence in our pediatric CF centre, in comparison to prevalence of the Belgian CF Register (5% vs. 2.5%). In a retrospective US study on 872 CF patients followed at the University of Minnesota [15], there was a CFRD prevalence of 2% in the group of children less than 10 years old, and 19% in de adolescent group.

Limitations of our study are the small cohort, the retrospective design, and the fact that we did not always find a perfect match for each CFRD patient fulfilling all of the matching criteria. The strengths of our study are the homogenous treatment of the patients and the extensive documentation of clinical status including airway pathogens and therapy burden.

5. Conclusions

Based on the results presented here we have no indication that the diagnosis of CFRD is made too late since lung function and weight are comparable for cases and controls. However, the higher treatment burden with IV antibiotics in the CFRD group and faster decline of lung function at follow-up might be avoided by earlier diagnosis.
These data are presented as a plea for more studies into optimized screening tests together with more studies on when and how to treat (pre) CFRD. As soon as more data are available on how to use continuous glucose monitoring as a screening tool for CFRD diagnosis and treatment decision, we are keen to change or clinical practice in order to optimise the treatment of our CF patients [23] [27].

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