Diabetes: a major co-morbidity of cystic fibrosis

M Costa¹, S Potvin¹, Y Berthiaume², L Gauthier¹, A Jeanneret³, A Lavoie², R Levesque², JL Chiasson¹, R Rabasa-Lhoret¹,³

SUMMARY

Cystic fibrosis-related diabetes (CFRD) is a frequent complication of cystic fibrosis, its prevalence increases with age of patient and is close to 30% at the age of 30 years. As life expectancy greatly increases, the number of cystic fibrosis patients developing diabetes will increase too. CFRD shares some features with type 1 and type 2 diabetes, initial phase is characterised by postprandial hyperglycaemia followed by a progression toward insulin deficiency. Insulin deficiency is an essential factor in the development of diabetes with an additional contribution of insulin resistance. Systematic screening with an oral glucose tolerance test is recommended from the age of 14 years because clinical signs of CFRD are often confused with signs of pulmonary infection and CFRD occurrence is associated with weight and pulmonary function deterioration. In observational studies CFRD diagnosis is associated with a significant increase in mortality, while treatment allow correction of weight and lung deterioration suggesting that CFRD has a significant impact on CF evolution. Microvascular complications are recognised, although paucity of data does not permit a clear description of their natural history. Annual screening for microvascular complication is recommended. There is no evidence by now that CF patients develop macrovascular complications. The only recommended pharmacological treatment is insulin therapy.

Key-words: Cystic fibrosis · Diabetes · Insulin therapy.

Key-words: Fibrose kystique · Mucoviscidose · Diabète.

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Cystic fibrosis (CF) is the most common lethal autosomal disease affecting Caucasian individuals with an incidence of 1 per 3000 live births [1]. CF impacts upon several organ systems of the human body with a complex interaction between CF gene mutations, modifier genes and environmental factors that produces a wide spectrum of phenotypes and disease severity. Pulmonary disease and pancreatic insufficiency are the most important clinical manifestations. The involvement of the lungs causes chronic pulmonary infections leading to respiratory failure, which is the major cause of death in CF patients [2]. Approximately 90% of CF patients also have exocrine pancreatic insufficiency which leads to malabsorption and malnutrition [3]. A third of the patients have abnormal liver function secondary to fatty infiltration that can progress to cirrhosis [3]. Most men (> 95%) are sterile with azoospermia secondary to congenital absence of vas deferens. In women, infertility is much less frequent with a potential role of abnormal cervical mucus in some cases [3]. With improved survival, impaired glucose tolerance (IGT) and cystic fibrosis related diabetes mellitus (CFRD) are becoming more frequent secondary complications and may have an important impact on CF management [2, 4].

Cystic fibrosis is caused by mutations on the long arm of chromosome 7 encoding a chloride channel protein called cystic fibrosis transmembrane regulator (CFTR). CFTR is a cyclic Adenosine Monophosphate-dependent chloride channel of 1480 amino acids. Although the exact role of CFTR in the pathophysiology of cystic fibrosis has not been elucidated, it has been proposed that the absence or the dysfunction of CFTR is directly or indirectly, through the modulation of other ions channels, involved in the modulation of the ion and fluid composition of airway surface liquid as well as sweat content, intestinal and pancreatic secretion [1]. The absence of CFTR leads to thick and viscous secretions associated with progressive obstruction, scarring and destruction of the organs (Tab I) [2].

Since the first description of CF in 1936, survival rates of patients have increased overtime. Whereas in the 1940s, around 80% of the subjects died within the first years of life, median survival is currently over 30 years and a child born with CF in the year 2000 is expected to live at least 40 years [5, 6]. This improved longevity is related to improved medical management as well as improved nutritional status [3, 5] (Tab II). Since the prevalence of glucose intolerance increases with age, the improvement in survival explains the important increase in CFRD prevalence, which is now the major co-morbidity associated with CF [2, 7].

**Table I**

<table>
<thead>
<tr>
<th>Class of mutation</th>
<th>Effects of mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1</td>
<td>CFTR is not synthesised</td>
</tr>
<tr>
<td>Class 2</td>
<td>Defective intracellular trafficking</td>
</tr>
<tr>
<td>Class 3</td>
<td>Abnormal regulation</td>
</tr>
<tr>
<td>Class 4</td>
<td>Defective conductance</td>
</tr>
<tr>
<td>Class 5</td>
<td>Partly defective production or processing</td>
</tr>
<tr>
<td>Class 6</td>
<td>Defective regulation in other channels</td>
</tr>
</tbody>
</table>

**Definition and classification**

In various classifications proposed by European and North-American Associations, CFRD is placed in the category of “Other specific types of diabetes-diseases of the exocrine pancreas” [8-11]. Oral glucose tolerance test (OGTT) (1.75 g/kg, maximum 75 g) is used to classify glucose tolerance into 4 classes: normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and two categories of diabetes, with and without fasting hyperglycaemia (Tab III) [2, 11]. The distinction between diabetes with and without fasting hyperglycaemia is specific to CFRD because of its importance in the prognosis and/or treatment indications [2, 7, 11, 12]. It has also been suggested to include a fifth class of CFRD, CF associated with intermittent diabetes, defined as diabetes occurring during period of infections or steroid treatment followed by a reversion to normal glucose tolerance. However, the prevalence, prognostic value and frequency of reversion to normal glucose tolerance has not been well studied [2, 7, 11].

**Prevalence-Incidence**

The various estimates of CFRD prevalence vary between 5 to 50% with an additional 15 to 40% of the patients having impaired glucose tolerance [13-16]. These major differences reflect ethnic background as well as differences in age and screening methods [11].

**Table II**

<table>
<thead>
<tr>
<th>Respiratory treatment</th>
<th>Nutritional treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Å Antibiotic therapy</td>
<td>Å Hypercaloric diet with 40% of energy requirements from fats</td>
</tr>
<tr>
<td>Å Chest physical therapy</td>
<td>Å Pancreatic enzymes replacement and mucolytics</td>
</tr>
<tr>
<td>Å Anti-inflammatory treatment</td>
<td>Å Vitamins A, D, E, K supplement treatment</td>
</tr>
</tbody>
</table>

**Abbreviations:**

CF: cystic fibrosis
CFRD: cystic fibrosis related diabetes
CFTR: cystic fibrosis transmembrane regulator
IGT: impaired glucose tolerance
Diabetes: a major co-morbidity of cystic fibrosis

In 2000, the North American CF registry included approximately 21,000 adult patients, 16.2% (~3,400) of them with CFRD diagnosis making diabetes the primary comorbidity associated with CF [17]. When annual systematic screening is performed using OGTT, the prevalence has been reported to increase regularly with age with less than 10% of CFRD occurring before the age of 10 to more than 40% over 30 years of age [18, 19].

There is only one publication that has reported the incidence with a 5-year prospective study using annual oral glucose tolerance tests (OGTT) from the age of 2 years. The average annual incidence rate was 3.8% which increased with age. Patients over 10 and over 20 years having respectively a 5.0% and 9.3% incidence [16].

Median age at onset of CFRD is close to 20 years [1, 6, 16]. Beside the presence of exocrine pancreatic deficiency and increasing age, no clinical or biological parameters predicting the development of glucose intolerance or CFRD have been identified [12, 16, 20, 21].

Clinical presentation

The onset of CFRD is often insidious and some symptoms can be confused with those of CF [2, 14]. CFRD should be suspected if patients have clinical signs of diabetes (such as polyuria and polydipsia) as well as other non-specific symptoms including delayed puberty, poor weight gain or weight loss despite adequate nutritional intervention, poor growth velocity and unexplained decline in pulmonary function (Tab IV) [2]. CFRD shares features with both type 1 and type 2 diabetes but there are also several important differences (Tab V) [2]. Though initial presentation is frequently postprandial hyperglycaemia similar to type 2 diabetes, with time, the frequent paradigm is a progression to severe insulin deficiency necessitating multiple insulin injections similar to type 1 diabetes [2].

The genotype-phenotype relationship

CFTR mutations can be grouped into six classes (Tab I) [3]. Class 1 to 3 mutations produce very low or undetectable CFTR activity and are associated with exocrine pancreatic insufficiency, whereas class 4 to 6 mutations are not associated with pancreatic insufficiency [3]. The most common mutation, F508, (> 60% of the subjects) results in the loss of a phenylalanine at position 508 of CFTR caused by the deletion of three base pair and is classified as a class 2 mutation.

The relationship between genotype and CFRD is controversial. For some investigators, the development of diabetes in CF patients is related to pancreatic insufficiency which itself correlates to mutations on CFTR gene, especially for F508 mutation [12, 22, 23], however this relationship has not been confirmed by others [24, 25]. Moreover in the general population, heterozygoty for CF mutation is not a risk factor for type 2 diabetes [26, 27].

Table III
Classification of glucose tolerance in cystic fibrosis.

<table>
<thead>
<tr>
<th>Fasting blood glucose (mmol/l)</th>
<th>2-hour glucose (mmol/l)</th>
<th>Home glucose monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal glucose tolerance</td>
<td>&lt; 7.0</td>
<td>&lt; 7.8</td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td>&lt; 7.0</td>
<td>7.8-11.1</td>
</tr>
<tr>
<td>CFRD without fasting hyperglycaemia</td>
<td>&lt; 7.0</td>
<td>2 11.1</td>
</tr>
<tr>
<td>CFRD with fasting hyperglycaemia</td>
<td>2 7.0</td>
<td>Test</td>
</tr>
</tbody>
</table>

*Blood glucose after a standard oral glucose tolerance test.*

<table>
<thead>
<tr>
<th>5-9</th>
<th>10-19</th>
<th>20-29</th>
<th>+30</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>80%</td>
<td>60%</td>
<td>40%</td>
</tr>
<tr>
<td>Normal glucose tolerance</td>
<td>Impaired glucose tolerance</td>
<td>Diabetes without fasting hyperglycaemia</td>
<td>Diabetes with fasting hyperglycaemia</td>
</tr>
</tbody>
</table>

Figure 1
Glucose tolerance categories in patients with cystic fibrosis: prevalence within age groups (adapted from Moran et al. [4]).

Table IV
Symptoms suggestive of diabetes in CF patients.

- Polyuria-polydipsia
- Poor weight gain
- Poor growth velocity
- Delayed progression of puberty
- Unexplained chronic decline in pulmonary function.
Finally rare mutations have been related to an increase risk (N1303K or W1282X) or the absence of risk (A455E) for CFRD [14, 25]. Earlier studies suggested an association between CFRD and increased level of auto-antibodies usually present in type 1 diabetes [28] but more recent reports failed to confirm this association [29].

**Impact of CFRD on outcome**

A number of observations suggest that CFRD is not only a marker of the severity of the disease but have by itself a significant impact on CF prognosis [11].

Pathophysiological mechanisms that could explain the impact of CFRD on CF include defective proteolysis suppression secondary to insulin deficiency [30-32] whereas e hyperglycaemia could act indirectly through an increase in energy expenditure, more frequent infections, and vascular complications [7, 30, 33] and maybe directly, since reduced lung volumes and airflow have been related to chronic hyperglycaemia in both type 1 and type 2 diabetes [34-36].

Observational data indicates that diabetes has a significant impact on CF outcome. The observed survival of CFRD patients at the age of 30 years is below 25%, whereas it is over 60% in CF patients without diabetes [1]. This is consistent with the data from the American cystic fibrosis foundation patients registry. The presence of diabetes increases mortality by six-fold [37]. Moreover, in a 5-years survival predictive model in cystic fibrosis, diabetes is a power prognostic marker of early mortality. Studies have shown that CFRD is associated with a significantly worse pulmonary function and nutritional status [1, 20, 38-42]. The decline in pulmonary function as well as weight loss begins 2 to 4 years before the diagnosis of CFRD [42]. In prospective studies, the magnitude of abnormal glucose tolerance predicts the rate of decline in pulmonary function [41]. Treatment rapidly reverses weight loss and decreased pulmonary function associated with CFRD [18, 43, 44]. It is also associated with a reduced rate of subsequent infection with *Haemophilus influenzae* and *Streptococcus pneumoniae* [18].

**Specific complications of CFRD**

Beside its impact on CF natural history, CFRD exposes the patients to diabetes mellitus acute and chronic complications as well as associated metabolic abnormalities [11].

Ketoacidosis is rare and reported in less than 4% of Danish patients with CFRD [16]. Possible explanations include incomplete insulin and concomitant glucagon deficiency.

Hypoglycaemia is a common complication of intensive insulin therapy. Despite glucagon deficiency there is no report of an abnormal frequency of severe hypoglycaemia in CFRD patients [4].

Microvascular complications such as retinopathy, nephropathy and neuropathy exist in CFRD [14, 15, 45]. There are numerous reports of retinopathy for CFRD patients including neovascularization and blindness [46-49]. Yung et al. [47] reported a retinopathy prevalence of 16% 5 years after diagnosis and 23% at 10 years. Nephropathy with increased albumin excretion and renal insufficiency including histological confirmation of the diagnosis [50, 51], is reported, with a prevalence ranging between 3% to 16% [1, 49]. Peripheral neuropathy prevalence is estimated between 5% and 21% [1]. However toxic effect of some medications (*i.e.* antibiotics, anti-inflammatory medications) and vitamin deficiency may also contribute to eye, kidney and nerve abnormalities [49, 52, 53]. It remains to be determined whether the prevalence and the severity of microvascular complications is similar to that observed in

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Type 1 diabetes</th>
<th>Type 2 diabetes</th>
<th>CFRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most common age of onset (y)</td>
<td>&lt; 20</td>
<td>&gt; 40</td>
<td>~20</td>
</tr>
<tr>
<td>Body Mass index</td>
<td>Normal</td>
<td>Overweight- Obese</td>
<td>Thin</td>
</tr>
<tr>
<td>Insulin secretion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possible progression to</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoimmune aetiology</td>
<td>Yes</td>
<td>Rare</td>
<td>No</td>
</tr>
<tr>
<td>Islet amyloid</td>
<td>No</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Ketoacidosis</td>
<td>Yes</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Microvascular complications</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Macrovascular complications</td>
<td>Yes</td>
<td>Caloric restriction if overweight; Oral hypoglycaemic agents and/or insulin</td>
<td>High caloric intake; Insulin</td>
</tr>
<tr>
<td>Treatment</td>
<td>Insulin</td>
<td></td>
<td>The place of oral agents remain controversial</td>
</tr>
</tbody>
</table>

type 1 or type 2 diabetes mellitus and if the subtype of CFRD without fasting hyperglycaemia is associated with a different risk for microvascular complications.

The risk of macrovascular complications appears to be quite low. There is a single case report of a patient with long standing CFRD who had diffuse atherosclerosis noted on autopsy [54]. Possible explanations include a low frequency of dyslipidemia and hypertension as well as too short a life expectancy to develop such complication [2]. As patients live longer, macrovascular complications may well be more prevalent in the future.

Few studies have investigated the prevalence of dyslipidemia. The largest study indicates that more than 15% of CF patients have hypertriglyceridemia whereas cholesterol concentrations are generally low [55]. Hypertriglyceridemia may be related to chronic low-grade inflammation and/or to dietary macronutrient imbalance.

At the time of the diagnosis of CFRD (with and without fasting hyperglycaemia), it is recommended to begin annual screening for microvascular complications including eye and feet examination as well as blood pressure and urine albumin excretion measurement. There are no recommendations for macrovascular complication screening, but a baseline fasting lipid profile is recommended in CFRD patients [2].

Pathophysiology of CFRD

Insulin deficiency is believed to be the primary cause of CFRD, but insulin resistance is also present in CF patients [2, 11]. Deficient insulin secretion is caused by the association of a reduced β-cell mass of Langerhans islets combined with functional abnormalities. Some investigators report a significant reduction in surface area of insulin-staining cells in islets of CFRD patients compared to non-diabetic CF and controls patients [56, 57]. Though fibrosis is a major characteristic of CF there is also fatty infiltration and amyloid deposition in the islets similar to type 2 diabetes [56, 58-62]. These anatomic abnormalities translate into a reduced and delayed insulin secretion in response to intravenous [63, 64] or oral glucose [4, 63-66]. Until patients develop fasting hyperglycaemia, abnormalities are mostly altered kinetic in insulin secretion, but as the disease progresses absolute insulinopenia frequently occurs [17]. The importance of insulinopenia as a factor involved in CF clinical deterioration is supported by the fact that in non-diabetic CF patients with unexplained weight loss the initiation of insulin treatment is associated with rapid weight regain as well as improved lung function [67]. Thus glucose tolerance abnormality could be a marker of much more global effect of insulin deficiency which could precede the diagnosis of diabetes.

Significant abnormalities are also present in other islet cells. Though basal glucagon levels are normal, response to oral glucose challenge and insulin induced hypoglycaemia is reduced [4, 65]. Like in chronic pancreatitis, somatostatin response to arginine is increased [68] which could exert a paracrine inhibitory effect on both insulin and glucagon secretion. Finally pancreatic polypeptide secretion is severely impaired in most CF patients [64, 65].

Though insulinopenia play an important role in CFRD, three observations suggest that other mechanisms are involved:

1) The degree of fibrosis and fatty infiltration does not correlate with insulin deficiency [4, 59, 69].

2) Cuicinotta et al. [20, 22, 39] reviewed a group of CF patients over a 6 to 10 year period and described a mild yearly decline in insulin secretion. However this decline was similar across all glucose tolerance categories and was not predictive of those who developed CFRD and those who did not.

3) There is a weak correlation between the degree of insulinopenia and OGTT abnormalities [70] while glucose excursion is a better predictor of future CFRD occurrence than insulinopenia [22].

In cross sectional studies, using hyperinsulimenic euglycaemic glucose clamp, reduced peripheral [71] and hepatic [72, 73] insulin-sensitivity is documented in CFRD patients. The magnitude of insulin resistance is positively associated with worse clinical status [71]. Prospective studies however do not provide similar information. Using indices of insulin resistance derived from an OGTT with a mean follow up of 13 years, an Italian group recently reported a decrease in insulin resistance over time despite an increase in CFRD prevalence [20]. Results are also controversial for CF patients without diabetes or with IGT, where insulin sensitivity has been reported to be increased [73, 74], normal [75, 75-77], or decreased [66, 71, 72, 77, 78].

Differential biases could explain these conflicting results. These biases include small number of patients, various degree of illness severity, interference of puberty, associated problems (i.e. recent infection or steroid treatment), and differences in methods used to measure or estimate insulin resistance. Studies reporting increased insulin sensitivity in such patients are surprising if one considers the numerous reasons that could generate insulin resistance in CF patients such as low grade infection, cytokine hypersecretion (TNF-alpha, IL-1 or IL-6) as well as malnutrition which are frequent in CF patients [7].

The probable clinical paradigm is a progressive deterioration of insulin secretion in which beta-cell failure is aggravate by deterioration of insulin sensitivity (Fig 2) [2, 11, 13, 14]. However only a fraction of insulinopenic CF patients develop CFRD, thus additional yet unknown factors are also contributory.

Screening and diagnosis for CFRD

Because clinical presentation is often insidious and early treatment could prevent clinical deterioration associated with diabetes occurrence, systematic screening is recommen-
ded starting at age 14 years [2, 11]. Available tools include fasting and/or random plasma glucose, glycated haemoglobin (HbA1c) and oral glucose tolerance test (OGTT).

Fasting and/or random plasma glucose are easy to implement but since most CFRD patients do not have fasting hyperglycaemia at the onset of the disease this method has a poor sensitivity [79]. A recent study suggested that approximately 75% of patients with glucose tolerance abnormalities are not diagnosed with such a strategy [12]. Despite this very low sensitivity, fasting plasma glucose is the first screening step in the last US consensus report [2] (Fig 3).

HbA1c also has a low sensitivity for most [2, 80], but not all investigators [79]. Although elevated values indicate hyperglycaemia, HbA1c can be normal in 16 to 70% of patients with confirmed CFRD [7, 14, 16]. Despite this very low sensitivity, a North American survey indicated that HbA1c is the screening tool used by most physicians (- 50%) [81]. HbA1c remains useful to monitor patients with established CFRD, though values could be artificially lower in CF patients due to an accelerated red blood cells turnover caused by chronic inflammation and hypoxia or different glycation process [15, 80].

It has been proposed that the combination of an elevated random blood glucose (> 11.0 mmol/L), a high HbA1c (> 6.1% by ion capture assay), the presence of symptoms of hyperglycaemia and unexplained weight loss (> 5% in 3 months) can have a high (92%) sensitivity to identify CFRD patients [79].

OGTT is the only sensitive method to diagnose glucose tolerance abnormalities in patients without fasting hyperglycaemia and is thus the recommended tool by various investigators [12, 16, 45, 82]. This test should be performed in a stable patient at least one month apart from acute pulmonary infection or corticosteroid treatment. However, conventional values used to defined diabetes have been questioned for CF-patients. Despite normal fasting and 2 h blood glucose values non-diabetic CF patients have a significant increase of the glucose excursion during an OGTT confirmed continuous glucose monitoring system (CGMS) [80, 83]. Beside the choice of the best screening method, the main problem remains the low screening rate in various CF centres [17].

Pregnancy

CFRD is not by itself a contraindication for pregnancy [2, 11]. Women with CF are at high risk to develop gestational diabetes [2]. Patients who are considering pregnancy should undergo OGTT which should be repeated in the middle of the second and the third trimesters or earlier if maternal weight gain is inadequate [2, 6].

Women with established CFRD should be followed as for type 1 diabetic patients with an aggressive treatment to control blood glucose level before conception and throughout pregnancy as well as careful follow-up of potential microvascular complications [2].

Treatment

CFRD should be managed in a team setting, at least quarterly, ideally in a joint clinic with Endocrinologists and Pneumologists [17]. Glycaemic goals for CFRD patients are similar to those recommended for all individual with diabetes [2, 11]. Treatment indications are clearly established for patients with fasting hyperglycaemia, however a major chal-

Figure 3

a) Outpatient screening (age > 14 years old). Routine procedures for outpatient screening for the diagnosis of CFRD. Annual random plasma glucose should be done in > 14 years old patients when they are clinically stable. The oral glucose tolerance test (OGTT) should be performed to rule out the diabetes without fasting hyperglycaemia in patients with symptoms described in table 4.

b) Inpatient screening (age > 14 years old). Procedure for routine screening for CFRD in patients hospitalised for acute illness.
lenge will be to precise earlier treatment indications. Earlier
treatment could have a dual impact on CF evolution thou-
ght body weight maintenance as well as glycaemic control.

**Nutritional management**

Since the degree of malnutrition is related to the severity
of pulmonary dysfunction and survival rate, the main
objective is to normalise growth and weight [2, 11] (Tab II).

Because CF is characterised by fat maldigestion/malab-
sorption, protein catabolism and significant increase in
energy expenditure, a high fat (35-40% of energy), high
protein (15-20%) diet ensuring an intake of 120% of the
usual recommended daily intake is advocated [72, 84-86].
Calories should never be restricted in CF patients, with or
without CFRD. Increase in resting energy expenditure is
well documented in CF patients with FEV1 (Forced Expir-
atory Volume) below 60 to 85% and is ranging from
5 to 20% compared to control subjects [86]. Pancreatic
insufficiency, severe mutations and female sex are the main
contributing factors for elevated resting energy expenditure
in patients with CF [85]. Pancreatic insufficient patients
(80% of overall CF patients) are routinely supplemented
with fat-soluble vitamins and pancreatic enzyme prepara-
tions. There should be no restriction on salt intake and sup-
plementation is sometimes indicated [15]. The main goal is
to normalize body mass index (i.e. > 20 kg/m²) [17].

Thus dietary principles for CFRD substantially differs
from approach used in type 1 and type 2 diabetes and is lim-
ited by numerous associated factors (Tab VI), but a com-
mon goal is to maintain near normal blood glucose values [2]. To reach the glycaemic goal, emphasis should be
placed upon promoting the intake of complex carbohydrate
and the importance of spreading carbohydrate consump-
tion evenly throughout the day for all patients with glucose
intolerance [2, 7]. Energy requirement can significantly
increase during infection or if the disease progresses thus
requiring nutrition supplementation using nasogastric or
percutaneous gastrostomy or jejunostomy [14]. Since there
is an increased occurrence of diabetes when such supple-
mentation is initiated, a careful blood glucose monitoring is
justified [14]. Although aerobic exercise is recommended in
the management of CF to enhance pulmonary functional
capacity, its role in the management of CFRD has not been
investigated [87].

**Pharmacological treatment**

Insulin is the standard medical treatment of CFRD with
fasting hyperglycaemia [2, 11]. Because of pulmonary and
gastrointestinal problems associated with CF, dietary intake
can vary tremendously from day to day. Most patients with
CF will therefore require a flexible insulin regimen which
is best achieved with intensive insulin therapy using fast
acting insulin analogues before meals combined with car-
bohydrate counting [2, 17, 88]. For most CF patients, insu-
lin requirements before meals and large snacks are
important while basal insulin requirements are much lower
than in type 1 diabetes and sometimes not necessary [2, 17].
When basal insulin is indicated various insulin available
can be used (NPH, Ultralente or long acting insulin analog
glargin). In patients who receive night-time enteral feed-
ing an injection of NPH insulin combined with regular
insulin given 1 hour before the initiation of feeding is often
used [2, 7].

Additionally to usual preprandial and bedtime values,
postprandial excursion (1 to 2 hours) and night time capil-
lary blood glucose values should be monitored on a regular
basis to adjust insulin doses accordingly [2, 7]. Capillary
blood glucose should also be checked more carefully during
acute infection and/or corticosteroid treatment because such
stress can abruptly increase insulin requirements [2, 15].

The use of oral agents is controversial because most of
these drugs present contraindication or potential problems
in CF patients [2, 11]. Only a few studies are available, most
of them were done with small groups of patients and are
rarely randomised and placebo-controlled. However larger
trials are ongoing to precise the place of short acting insulin
secretagogues like repaglinide (see below) to control glu-
cose excursion and/or help to maintain body mass index.
Sulfonylureas enhance insulin secretion and thus
response to the primary defect involved in CFRD. One
study with tolbutamide demonstrated short-term improve-
ment but no sustained effect [7]. A retrospective European
study suggests that glibenclamide allows glucose control for
half of the patients with a mean efficacy duration of 2 to
3 years [89]. Patients who could be treated with glibencla-
mide over a longer period of time had a later onset of
CFRD. It is thus possible that patients responding well to
sulfonylurea treatment represent a subgroup of CFRD
patients with a better residual beta-cell function. Side
effects associated with sulfonylureas include hypoglycae-
ia, potential hepatic toxicity in patients with frequent
hepatic impairment and negative effect on CFTR's chloride
conductance because CFTR is believed to be a receptor for
sulfonylureas [89, 90].

Glinides, which also stimulates insulin secretion, specifi-
cally address postprandial hyperglycaemia and could be a

**Table VI**

Limitations for dietary management in CFRD.

- Pancreatic insufficiency: steatorrhoea despite enzymes
- Increased work for breathing
- Inflammation’s potential role in proteolysis and anorexia
- Liver disease
- Cases of ileal resection if patient have undergone a surgical
treatment of meconium ileus
good choice for CFRD patients without fasting hyperglycaemia. This hypothesis has been tested in an acute study comparing repaglinide (1 mg) and insulin lispro (0.1 U/kg). Repaglinide provided significant effects but insulin lispro was better to control postprandial glycemic excursion [91]. Ongoing trials will precise the place of this medication since its pharmacological profile (short half life and impact on postprandial plasma glucose) makes it theoretically suitable for CF patients.

Improving insulin resistance could be helpful in CF patients [92]. However available drugs are associated with a significant risk in CF. Metformin can increase gastrointestinal symptoms and is contraindicated in CF patients with respiratory insufficiency because of an increased risk of lactic acidosis. The thiazolidinediones, PPAR-γ agonists (Peroxisome Proliferator-Activated Receptor; ie, rosiglitazone and pioglitazone) also present potential problem because CF patients have frequent liver abnormalities [3]. However PPAR-γ expression is down regulated in CF and this is suspected to play a role in some complications (i.e.fatty acids abnormalities and abnormal modulation of the inflammatory response) [93, 94]. Thus a treatment with PPAR-γ agonist could be beneficial and is under investigation.

Alpha-glucosidase inhibitors (acarbose) reduces postprandial glycaemic excursion but are associated with significant gastrointestinal side effects [95], which represent a considerable limitation for CF patients who frequently have gastrointestinal symptoms. Acarbose have been used in a short (10 days) study in IGT patients where it reduced significantly glucose excursions compared to placebo; however, there was a significant increase in gastrointestinal side effects [96].

At the present time, there is no adequate data to support the use of oral agents in CF patients with CFRD [2].

TREATMENT INDICATIONS FOR SUBGROUPS OF PATIENTS

CFRD patients without fasting hyperglycaemia. Insulin therapy is not recommended for these patients, unless they present symptoms, unexplained decline in pulmonary function or weight [2, 11]. However, it is difficult to conceive that chronic postprandial hyperglycaemia does not have adverse effects at least for the risk of microvascular complications [97]. We thus give nutritional education to these patients and start insulin treatment if postprandial glucose excursion regularly exceeds 11.0 mmol/L. To detect the occurrence of fasting hyperglycaemia and evaluate the magnitude of postprandial hyperglycaemia it is suggested that these patients measure their blood glucose levels at home twice a week and more frequently during stress [17]. Such patients could be candidates for oral antidiabetic agents but this remains to be tested in ongoing randomised clinical trials.

CF patients with IGT and patients who have previously experienced intermittent CFRD should have an annual OGTT and check their blood glucose levels at least during infection or corticosteroid treatment [2].

PSYCHOLOGICAL PITFALLS

There is a lack of data in this field but clinical experience indicate that patients are poorly informed of the frequency of diabetes in CF such that many believe that the occurrence of CFRD means that death is imminent [2, 11, 15]. Many patients also have major difficulties to face the burden imposed by CFRD on top of the regular CF management [2, 15, 17]. Thus patients should be well informed on the frequency of CFRD, benefits of treatment, offered flexible treatment regimen with large educational and psychological support to enhance acceptance and compliance with diabetes treatment [2].

CONCLUSION AND FUTURE PERSPECTIVES

Cystic fibrosis-related diabetes is a common complication of cystic fibrosis, with an underestimated incidence. The improved longevity of patients with CF result both in an increasing prevalence of CFRD and an increased duration of diabetes exposure for each patient resulting in a greater clinical impact. After 20 years of age the majority of CF patients present glucose intolerance with approximately a third of them being diabetic. CFRD is mainly caused by insulin deficiency, but insulin resistance possibly plays a role in the development of diabetes. Annual screening with an OGTT is necessary to establish patient glucose tolerance and offer early treatment in case of diabetes. Treatment should aim at maintaining a normal weight, preventing lung function deterioration as well as diabetes related microvascular complications. There are few data on treatment indications and currently the only recommended pharmacological treatment for CFRD is insulin. Future studies are required to elucidate the pathophysiological mechanisms involved in the development of diabetes, to test different treatments and their indications, to test the impact of early treatment on pulmonary function, to evaluate feasibility of diabetes prevention and to define the role of the pancreas or islet graft when patients undergo lung transplantation. Since epidemiological data indicates that we are going to face a significant increase of CFRD in the near future, we need to be prepared!

REFERENCES


