CYSTIC FIBROSIS-RELATED DIABETES

Dana-Teodora Anton-Paduraru[1], Carmen Oltean[2], Maria-Liliana Iliescu[3], Ginel Baciu[4], Laura Mihaela Trandafir[1]

[1]3rd Clinic of Pediatrics, "Gr. T. Popa" University of Medicine and Pharmacy, Iasi
[2]Children's Emergency Hospital "Sf. Maria", Iasi
[3]Department of Public Healthcare and Medical Management
[4]Faculty of Medicine – 1st Clinic of Pediatrics,"Dunărea de Jos" University, Galati

ABSTRACT

Cystic fibrosis-related diabetes is an entity distinct from diabetes mellitus type 1 and 2, but with symptoms characteristic to them. Along with the extension of the life expectancy, the prevalence of diabetes increased in association with a more severe decline of the lung function and a poorer nutritional status in comparison to that of people with cystic fibrosis but without diabetes. The authors present current data regarding the prevalence and physiopathology of the disease, the clinical picture, and the useful examinations in establishing the diagnosis, the therapeutic possibilities and disease prognostic. We conclude that the early diagnosis and appropriate therapeutic interventions may diminish the negative impact of diabetes on the lung function and the nutritional status in cystic fibrosis.

Keywords: cystic fibrosis, diabetes mellitus, child

Patients with cystic fibrosis (CF) have only one type of diabetes, called *cystic fibrosis related diabetes* (CFRD), being described for the first time in 1955 (1,2).

CFRD prevalence increased in time (from 1% in 1962 to 31% in 2007) and an increase has been noticed also with age: 9% between 5-9 years, 26% between 10-20 years, 40% between 20-30 years and 50% over 30 years. The disease is found in 20% of the patients with CFRD mutations class I-III and only in 1.5% of the patients with CFRD mutations class IV-V. The incidence is higher in patients with liver disease in CF, and the association of diabetes with CF makes morbidity and mortality 6 times higher (3,4,5).

The risk factors involved in the CFRD association are: age, female gender, exocrine pancreatic insufficiency, altered exocrine pancreatic function and organ transplant.

The main cause in the emergence of CFRD is the insulin deficit – the consequence of the progressive loss of β pancreatic cells.

Specific CF factors determining fluctuations in the glucose metabolism are:

- lung infection and inflammation;
- increase in the energetic consumption;
- malnutrition;
- glucagon deficit;
- gastro-intestinal anomalies: malabsorption, gastric emptying disturbances and intestinal motility, liver disease (3,4,5).

CFRD presents clinical and biological particularities in comparison to type 1 and 2 (Table 1).

The CFRD pathophysiology is multifactorial, with genetic and environmental factors. Information plays an important role in the CFRD physiopathology, the glucose disturbances being more intense in patients with chronic inflammation and acute exacerbations of the chronic lung infection, and growing insulin resistance. Autoantibodies present in patients with diabetes mellitus type 1 are not detected in CFRD, and autoimmunity does not seem to play a significant role in the physiopathology of CFRD. Serum antibodies as a response to

Coresponding author:
Anton-Paduraru Dana-Teodora, „Gr. T. Popa" University of Medicine and Pharmacy, 16 Universitatii Str., Iasi

TABLE 1. *CFRD characteristics in comparison to diabetes mellitus type 1 and 2*

	Diabetes mellitus type 1	**Diabetes mellitus type 2**	**CFRD**
Onset	acute	insidious	insidious
Age of the onset	child and adolescent	adult	18-24 years
Positive Ab	yes	no	probably not
Insulin secretion	absent	low	severely low, but not absent
Sensitivity to insulin	sometimes low	severely low	sometimes low
Treatment	insulin	diet, oral antidiabetic medication	insulin
Microvascular complications	yes	yes	yes, but few
Macrovascular complications	yes	yes	no
Causes of death	cardiovascular disease, nephropathy	cardiovascular disease	lung disease

bacterial antigens (for example: anti-P. aeruginosa IgG ab) are involved in the emergence of CFRD and are significantly high 3-12 months before diabetes mellitus. This aspect suggests that chronic bacterial infection is the cause for progressive destruction of β pancreatic cells – Fig. 1 (4,6,7).

The onset of the disease is insidious, patients being asymptomatic for many years (at least 4 years). The average age of the onset is 18-21 years, being rarely under 10 years old. In girls, the age of the onset is smaller by 5-7 years in comparison to boys, probably because of the earlier debut of puberty

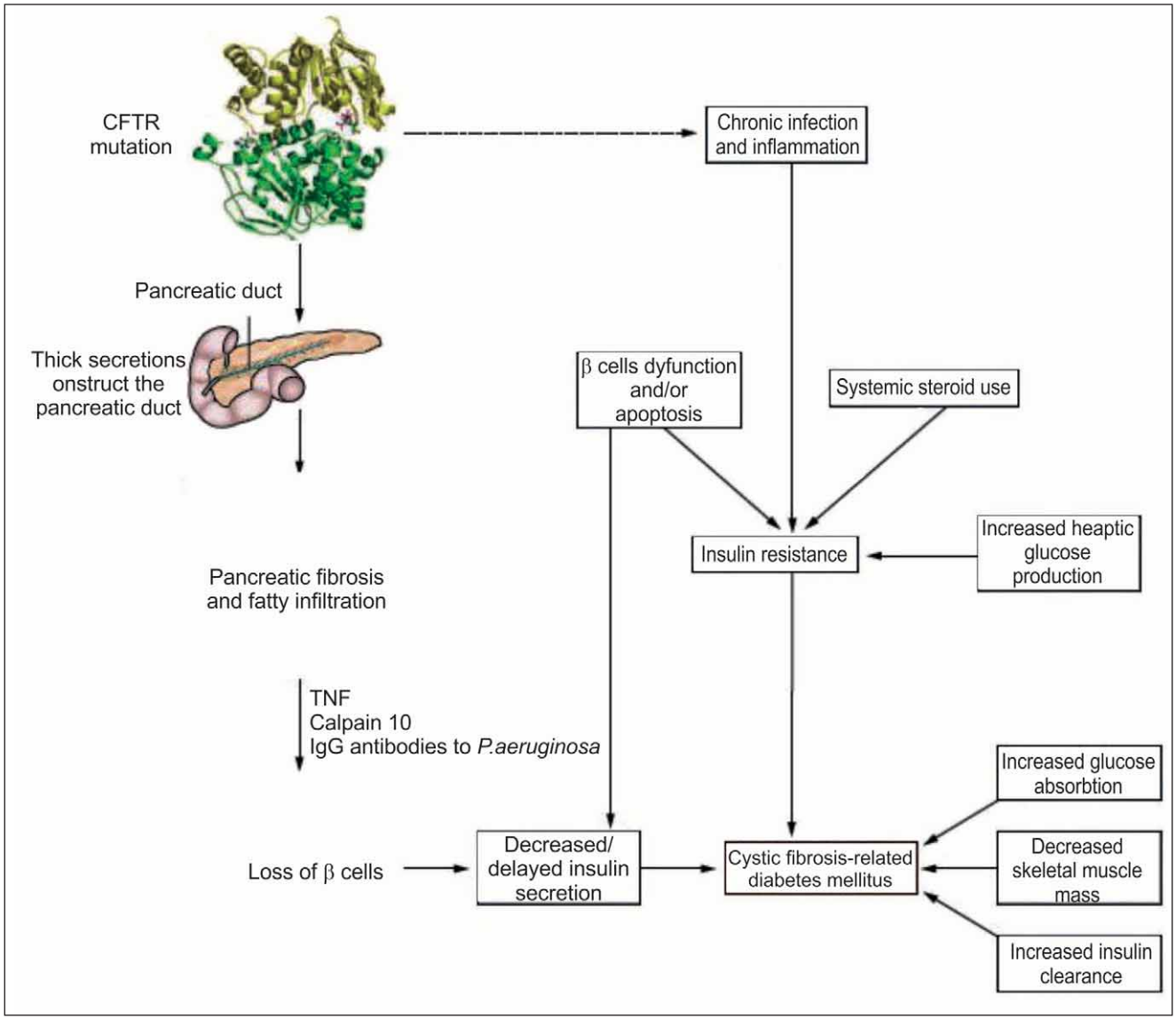

FIGURE 1. *CFRD Pathophysiology (7)*

and the association of the increased insulin resistance at this age.

The onset is more frequent in circumstances in which insulin resistance is higher:

- acute lung infections;
- severe chronic lung disease;
- treatment with glucocorticoids;
- carbohydrate supplements (oral, percutaneous, intravenous, gastrostoma);
- post-transplant immunosuppressive treatments (8,9).

The clinical picture includes classic symptoms for diabetes (polyuria, polydipsia, weight loss) as well as other symptoms: fatigue, alteration of the lung function without a direct connection to the exacerbation of the lung infection, late puberty (1,2,8).

The CFRD diagnosis implies the performance of:

– *the glycemia*: values of over 200 mg/ dl (mmol/ l) raises suspicion of diabetes, but normal values under 100 mg/dl (5.6 mmol/l) do not exclude the diagnosis either (1,2,10);

– the *oral glucose tolerance test (OGTT):* representing the standard test for the CFRD diagnosis. This will be performed annually in all children with CF over 10 years, and diabetes with a normal glycemia á jeun may be detected only based on the OGTT. The measurement of the insulin concentration every 30 minutes during the OGTT may be useful in determining the insulin deficit degree. The interpretation of the OGTT in CF is presented in table 2, and the behaviour depending on the test results in table no. 3 (1,2,6,11,12,13).

TABLE 2. *Interpretation of the OGTT in patients with CF*

	Glycemia á jeun mg/dl (mmol/l)	**Glycemia every 2 hours mg/dl (mmol/l)**
Normal tolerance	under 100 (under 5,6)	under 140 (7,8)
CFRD: – normal glycemia á jeun	under 126 (7)	over 200 (11,1)
– high glycemia á jeun	over 126 (7)	over 200 (11,1)
Low glucose tolerance	100-125 (5,6-6,9)	140-199 (7,8-11)

TABLE 3. *Behaviour depending on the OGTT results*

OGTT screening results	
NORMAL	To be repeated annually
LOW TOLERANCE	To be repeated after 1 year or earlier if the clinical parameters aggravate (lung function, unjustified weight loss)
CFRD	Monitoring glycemia for 2 weeks, nutritional journal; of the values are normal, the OGTT is to be repeated after 6 months

– *glycosylated hemoglobin (HbA1c)*: it is often normal because in CF the life expectancy of red blood cells is under 3 months, being affected by chronic infection, which alters the glycosylation or because intermittent hyperglycemia is not high or persistent enough to increase the HbA1c. Only 16% of the people with CF have high values at the time of the diagnosis (1,2,6).

The objectives of the CFRD treatment are:

- eradication of the hyper-/hypoglycemia symptoms;
- appropriate maintenance of the nutritional status, growth and lung function.

Insulin-therapy represents the only recommended medicamental therapy. It is useful in stabilizing the lung function and improving the nutritional status. The choice of the insulin type depends on the individual needs and patient's characteristics. Rapidly administrated insulin in 3-4 intakes/ day controls postprandial hyperglycemic episodes and allows a more flexible diagram. 1 UI covers 15 g of carbohydrates. The insulin dose will be adjusted depending on the carbohydrate intake and in the following circumstances:

- during enteral nutrition: an extra-dose of insulin may be necessary during and after nutrition sessions to cover the carbohydrate charge;
- in infectious exacerbations, even if the food intake decreases due to the loss of appetite;
- after liver/lung transplant, as the medication used for immunosuppression increases insulin-resistance or destroys (temporarily/ permanently) the function of pancreatic cells;
- the insulin necessary also grows in case of weight gain (1,2,6,14,15).

Oral antidiabetic medication is not approved by the CF Foundation Consensus. There are few studies on two classes of antidiabetics: antidiabetics that increase the insulin secretion (Glipizide, Glyburide) and antidiabetics that make cells more sensitive to insulin (Metformin), but they are not recommended because of the risk of side effects (lactic acidosis, nausea, diarrhea, abdominal discomfort) (1,2,14).

The objectives of nutritional therapy are:

- maintaining normal nutritional status;
- ensuring optimum growth and development;
- hyperglycemia control, minimizing the risk of chronic complications.

The factors that need to be taken into account are:

- appetite;
- nutritional status;
- lifestyle;

- socioeconomic conditions;
- psychological factors.

The diet recommendations in CF contradict the ones for diabetes mellitus type 1 and 2 and must be solved in favour of the ones for CF.

The hypercaloric diet rich in lipids maintaining the nutritional status must continue during CFRD. The increased caloric intake will be maintained both with simple and complex carbohydrates. Low glycemic index carbohydrates may be consumed and distributed equally during the day in order to optimize the glycemic control. A healthy diet must include a variety of foods of the 6 food groups (fruits, vegetables, dairies, grains, meat, oils) that provide the 6 types of nutrients (proteins, lipids, carbohydrates, vitamins, minerals, water) (1,2,6, 14,15,16).

Table 4 presents comparatively the dietetic recommendations in diabetes mellitus type 1 and 2 and in CFRD (1,2).

Foods containing carbohydrates affect the glycemic level, while foods containing proteins and lipids have a low effect. Still, lipids slow down the carbohydrate absorption in the bowel with indirect effect on the glycemia (Fig. 2). Foods rich in fibres do not have special effects on the glycemic level. Alcohol suppresses gluconeogenesis, having a hypoglycemic effect (6).

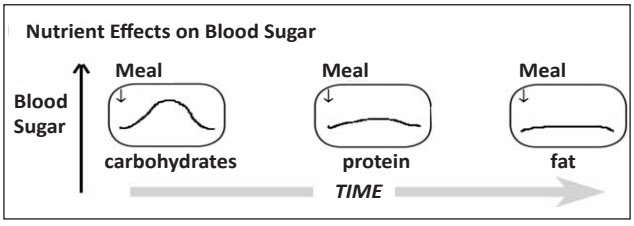

FIGURE 2. *Effects of foods on glycemia (6)*

Nutritional supplements must be included in the diet of patients with CFRD:

– suplplements that contain glucose polymers (Polycal, Maxijul, Nutren junior, Caloreen) will be administered during the meal due to the fact that being rapidly absorbed, they determine a quick increase in the glycemic level;

– milk-based polymeric supplements (Ensure, Scandishake, Fresubin) are most frequently used: they contain simple sugars with an impact on glycemia, but the presence of lipids and proteins, as well as the low content of carbohydrates lead to a lower increase in the glycemic level (1,2,16,17).

Enteral nutrition (through nasogastric tube or gastrostoma) is necessary to improve or maintain the nutritional status in CF. At the same time, OGTT must be performed in all patients proposed for enteral nutrition to exclude diabetes. In 64% of the cases, hyperglycemia is associated with the beginning of nocturnal nutrition. Pre- and post-enteral nutrition monitoring and at least one monitoring during enteral nutrition must become routine practice (1,2).

Parenteral nutrition is rarely indicated as a routine nutritional support. It is reserved on short term for patients with complications of the short bowel syndrome or postoperative complications. During parenteral nutrition, monitoring of the glycemic level is recommended every hour at the beginning, and then every 4-6 hours (1,2).

The glycemic changes during physical exercise depend on the level of the insulinemia, on the type of insulin, and on the time of the insulin intake. The glycemic level must be monitored before and after physical activity, taking into account that hypoglycemia can emerge 24-36 hours after physical exercise. Fast acting carbohydrate snacks are also necessary during and after physical exercise, hydration before, during and after physical exercise, as well as extra salt intake (1,2).

Lung transplant is not contraindicated in patients with CFRD. Patients with CFRD may have initially increased needs of post-transplant treatment due to the immunosuppressive medication.

TABLE 4. *Dietetic recommendations in diabetes mellitus type 1 and 2 and in CFRD*

	Diabetes mellitus type 1 and 2	**CFRD**
Calories	under 100% of the normal intake for the specific age and gender; sometimes caloric restrictions to prevent obesity	120-150% of the intake normal for the specific age and gender (to prevent malnutrition)
Lipids	30-35% of the necessary caloric intake	40% of the necessary caloric intake
Refined sugars	up to 10% of the necessary intake	no restrictions
Carbohydrates	50-55% of the necessary caloric intake	45-50% of the necessary caloric intake
Fibres	years of age + 5 g/day	– yes for the properly nourished – in malnourished, they compromise the energetic intake
Proteins	10-15% of the necessary caloric intake; up to 1 g/body kg/day	200% in comparison to the normal intake
Salt	under 6 g/day	increased necessary intake

There are situations in which the debut of post-transplant CFRD is precipitated by steroid pulsations for acute rejection, increased doses of Cyclosporine or Tacrolimus (17).

In patients with CF and hepatic affectation CFRD emergence has increased prevalence, even in small ages. Liver treatment is a solution for long-term evolution and periodical post-transplant test of glycemia will minimize the risk of complications on short or long term.

CFRD management includes glycemia monitoring during:

- infectious exacerbations: patients have hyperglycemia risk (the necessary insulin intake will be 4 times higher than the usual dose), and due to low appetite, solid foods are not tolerated, therefore fluids containing carbohydrates (milk, supplements) need to be ingested every 2-3 hours.
- corticosteroid treatment;
- after the beginning of enteral feeding (every 2-3 hours);
- before and after surgical procedures;
- hypoglycemia symptoms;
- pregnancy (1,2,15).

CFRD prognostic:

The diagnose of diabetes in patients with CF represents the development of the second chronic disease, with important psychological implications.

The presence of CFRD is associated with:

- alteration of the lung function: the rate of lung function decline is directly proportional to the degree of glucose tolerance and the insulin deficit;
- FEV1 72% in CF in comparison to 52% in CF associated to diabetes;
- poor nutritional status;
- decrease in the survival rate to 25%, in comparison to 60% in patients without CFRD.

Risk factors for complications are represented by the long-term evolution of diabetes mellitus and inappropriate glycemic control.

Microvascular complications emerge after 10 years of evolution of the CFRD, rarely during the first 5 years from the debut of diabetes. They are represented by: retinopathy (10-36%), microalbuminuria (10-21%), neuropathy (3-30%), gastropathy. No macrovascular complications have been reported until now (1,2,4,6).

CONCLUSIONS

CFRD remains one of the most important comorbidities in CF, associated with high mortality and morbidity due to the alterated lug disfunction and nutritional status. CFRD being a complication with insidious onset the glucose tolerance test remains the main screening instrument for the CFRD diagnosis. Early diagnose and appropriate therapeutic interventions can diminish the negative impact of diabetes on the lung function in CF.

Maintaining the optimum nutritional status in patients with CF remains the main treatment objective and can improve survival. Diet recommendations specific to diabetes mellitus type 1 and 2 are not applicable to patients with CFRD.

The complexity of the daily diet for CF (enzymatic substitution, multiple medication for the respiratory conditions, vitamins) is aggravated by the requirements for CFRD.

The treatment for CFRD calls for a multidisciplinary team, and insulin remains the most efficient pharmacological agent.

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