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Cystic Fibrosis - Related Diabetes

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Title and Abstract

SUMMARY:
Cystic fibrosis (CF) is life-shortening autosomal recessive disease, caused by mutations in the cystic fibrosis transmembrane conductance regulator protein. The most common of CF complications is cystic fibrosis-related diabetes (CFRD). The pathophysiology of CFRD is complex. The best test for screening and diagnosis of CFRD is the oral glucose tolerance test (OGTT). Insulin therapy is a treatment of choice in CFDR pharmacotherapy. An inseparable element of CFRD therapy is also physical activity and diet.

Key words: cystic fibrosis-related diabetes, beta cells, insulin therapy

Cystic fibrosis (CF) is the most common life-shortening autosomal recessive disease among European population. The number of adults with CF continues to increase, while the number of children remains relatively stable. In 2019, adults were 56.0 percent of the CF population, compared with 31.1 percent in 1989 [1]. Patients usually demonstrate the following symptoms: persistent pulmonary infection, pancreatic insufficiency, and elevated sweat chloride levels. Most patients develop multisystem disease involving several organs. However, some patients may present mild or atypical symptoms [2].

CF is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Deranged chloride transport leads to thick, viscous secretions in the lungs, pancreas, liver, intestine, and reproductive tract. The diagnosis of CF is based upon the finding of genetic and/or functional abnormalities of the *CFTR* gene: in practice it is required to find clinical symptoms consistent with CF in at least one organ system and to document CFTR dysfunction (elevated sweat chloride, presence of two disease-causing mutations in the *CFTR* gene, or abnormal nasal potential difference). Sweat chloride testing is the most important diagnostic test and should be performed to clarify a diagnosis of CF, especially in infants with positive CF newborn screening results and in any patient with symptoms suggestive of CF [3].

The most common of cystic fibrosis complications is cystic fibrosis-related diabetes (CFRD), which affects 40–50% of CF adults. CFRD significantly impacts the pulmonary function and longevity of CF patients [4]. CFRD is associated with clinically important declines in pulmonary function and nutritional status, and with increased mortality.

The pathophysiology of CFRD is complex. The primary etiology is relative insulin insufficiency secondary to destruction of pancreatic islets, and to other factors that affect the function of the remaining beta cells. CFTR plays a dual role in insulin/glucagon hemostasis. Abnormal intracellular accumulation of chloride in β cells impairs their ability to depolarize in response to glucose, diminishing insulin release [5]. Insulin resistance, malabsorption, liver dysfunction and steroid therapy also may play a role in pathogenesis of CFRD [6]. It is worth underlying that CFRD combines the features of patients with type 1 and type 2 diabetes mellitus such as impaired insulin secretion and peripheral insulin resistance [7].

The risk factors of CFRD include: pancreatic insufficiency, increased age, frequent pulmonary exacerbations, female gender, impaired nutrition/growth, CF-related liver disease. The onset of CFRD is insidious due to the lack of clinical symptoms. For this reason it is advisable to perform screening tests. The best test for screening and diagnosis of CFRD is the oral glucose tolerance test (OGTT) [8].

CFDR - new pathophysiological data summarized in the table:

Table 1. CFDR - new pathophysiological data

organ	**defect**	**metabolic effect**
pancreas (exocrine)	↓ enzyme secreation	- malabsorption of fats, proteins and carbohydrates
pancreas (endocrine)	↓ beta cell mass ↓ alpha cell mass	- postprandial hyperglycemia - CFDR progression
intestines	malabsorption of fats and proteins accelerated glucose absorption ↓ GLP-1 activity	- rapid increase of postprandial glucose - ↓ insulin secretion - ↑ glucagon secretion
liver	↓ insulin clearance ↑ hepatic glucose production ↓ glycogen storage liver cirrhosis	- hyperglycemia - impaired response to hypoglycemia
fat tissue	↓ accumulation of fat	- ↓ glucose uptake
muscles	↓ muscle mass	- ↓ glucose uptake
adrenal glands	↑ cortisol secretion in response to infalmmation	- “stress” hyperglycemia

How is CFDR diagnosed?

- random plasma glucose concentration ≥200 mg/dL (11.1 mmol/L)
    - in patients on enteral tube feedings, CFRD may be diagnosed if mid- or post-feeding plasma glucose levels are ≥200 mg/dL on two separate days
- OGTT ≥200 mg/dL (11.1 mmol/L)
- fasting plasma glucose ≥126 mg/dL (7.0 mmol/L)
- HbA1c ≥6.5 percent

Nowadays, continous glucose monitoring system (CGMS) may also be helpful to diagnose CFDR [9].

What are the manin goals of treatment for CFDR?

- improving the nutritional status
- good metabolic control

- elimination of acute and chronic diabetes complications
- mental well-being
- life extension

Insulin therapy is a treatment of choice in CFDR pharmacotherapy. It is referred to administrate insulin by means of multiple injections or to use insulin pumps. CFDR characteristic feature is the dynamics of glycemic changes. Moreover, insulin requirements may vary: respiratory tract infections increase insulin requirement, whereas vomiting or diarrhea causes a decrease. During clinical stability, patients with CFRD typically require 0.5 to 0.8 units/kg/day. Insulin doses should be adjusted up to the maximum that can be safely tolerated to eliminate the catabolic effects of CFRD. Considerably higher insulin doses may be required during acute pulmonary exacerbations or other stress conditions. During hospitalizations and when glucocorticoids are used, the starting dose for basal insulin is generally 0.2 units/kg. Most patients also require prandial insulin during intercurrent infections [8, 9].

An inseparable element of CFRD therapy is also physical activity, which should be undertaken regularly. However, in the case of physical exertion it is especially important to ensure proper glycemia before, during and after exercise. Regular exercise is beneficial to aerobic capacity and lung health. Exercise alone can be used as an ACT (airway clearance technique), which promotes the removal of mucosal cilia [10]. The benefits from including physical exercise training in an individual's regular care may be influenced by the type and duration of the training programme. Aerobic training is advisable for people with CF. For this reason the following forms of exercises may be recommended: continuous activity at a low to moderate intensity, such as jogging, cycling, swimming or walking [11].

According to dietary recommendations, energy intake for patients with CFRD constitutes 120–150% of such intake for healthy people in the same age, sex and body weight. 40% of energy intake should come from fat, but with adequate supplementation of unsaturated fatty acid and limited content of saturated fatty acid to prevent the development of cardiovascular diseases. Protein requirement is about 200% of norm for healthy population. Carbohydrates should be ingested in every meal in the similar portion for prevention of hypoglycemia and hyperglycemia. Carbohydrates dose is individual for every patient [12].

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