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Current dietary recommendations for patients with cystic fibrosis

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Abstract

Cystic fibrosis (CF) is classified as metabolic and multisystem disease with autosomal recessive inheritance caused by mutations in the gene located on chromosome 7 encoding cystic fibrosis transmembrane conductance regulator (CFTR) protein. CFTR is a transmembrane chloride channel of epithelial cells and affects the activity of the mucous membrane of the sweat glands, airway epithelium, pancreatic ducts, vas deferens, bile ducts and intestines. In CF, increased concentration of chlorides in the sweat, pancreatic insufficiency and impaired absorption are observed as well as changes in the respiratory system related to, among others, impaired airway patency, weakening of the mucociliary clearance mechanism and the development of bacterial infections. CF is a chronic condition requiring comprehensive therapy. Nutritional treatment is an essential element of CF therapy. Malnutrition is a common complication in patient with CF and eating disorders. The majority of patients with CF have higher energy, protein and fat needs. In addition, supplementation with enzyme preparations, vitamins, sodium chloride, as well as the use of high-energy nutrients is recommended. The aim of the study was to evaluate current nutritional

recommendations of patients with CF.

Keywords: cystic fibrosis, nutritional treatment, supplementation

Cystic fibrosis (CF) is a genetic disorder inherited in an autosomal recessive manner. It is the most common genetic disease among Caucasians leading to death at an early age. The multidisciplinary approach to CF treatment has allowed to extend the median survival to 37 years [1]. It is estimated that the disease affects 70,000 to 100,000 people in the world [1, 2], according to the European Cystic Fibrosis Society Patient Registry there were 44,719 people living with CF in Europe in 2016 [3]. CF mostly concerns children and young adults, the average age at diagnosis is 4.1 years [3]. CF is caused by a mutation in a single gene located on chromosome 7q31 [4] encoding the CFTR (cystic fibrosis transmembrane regulator) membrane protein, which is the chloride channel of the epithelial cell membrane.

CFTR affects the activity of the mucous membrane of sweat glands, airway epithelium, pancreatic ducts, vas deferens, bile ducts and intestines [5], which is why cystic fibrosis is classified as a multisystem disorder. Over 2000 different mutations have been identified in the CFTR gene [1], the most frequent being the phenylalanine deletion at position 508 (p.Phe508del also known as F508del). As a result of CFTR gene mutation, defective protein is synthesised, chlorine transport from the cell is impaired and there is increased absorption of sodium into the cell, which results in decreased amount of water in the exocrine gland secretions. In CF, increased concentration of chlorides in the sweat, pancreatic insufficiency and impaired absorption are observed as well as changes in the respiratory system related to, among others, impaired airway patency, weakening of the mucociliary clearance mechanism and the development of bacterial infections.

Nutritional treatment in a CF patient should be introduced as soon as possible after the diagnosis and subsequently monitored and corrected throughout the entire patient's life. The proper nutritional condition affects the course of the disease and the treatment process, as well as the overall survival and the patient's quality of life. European Society for Clinical Nutrition and Metabolism European Society for Clinical Nutrition and Metabolism (ESPEN) recommends regular assessment of anthropometric parameters reflecting the state of nutrition, to promptly identify those patients in whom nutritional treatment should be intensified. In infants and children up to 2 years of age who suffer from cystic fibrosis, the evaluation of the nutritional condition is performed on the basis of percentile ranks. The score ≥ 50th percentile for the body mass and height determined for a healthy population of the same age indicates adequate nutritional status. Measurements are carried out every 1-2 weeks until the body reaches normal weight and height and subsequently every month for one year. In the case of older children (from 2 to 18 years of age), ESPEN recommends the assessment of nutritional status using BMI. The score > 50th percentile for BMI determined for a healthy population of the same age indicates adequate nutritional status. In adult women, BMI ≥ 22

kg/m^2 is considered as the optimal nutritional status, in men it is BMI ≥ 23 kg/m^2. In older children and adults, routine and regular assessment of the nutritional status should be carried out every 3 months [6].

Malnutrition in cystic fibrosis is not always correlated with low BMI. In a study conducted on a group of 86 CF patients, it was demonstrated that BMI failed to detect fat-free body mass (FFM) in 58% of subjects [7]. Therefore, BMI should be carefully interpreted in the assessment of nutritional status in cystic fibrosis patients due to the high variability of body fat mass and FFM levels [6]. Malnutrition in CF patients leads to muscle atrophy, also involving respiratory muscles, which results in impaired lung function.

Hauschild et al. (2018) performed a 36-month observational study in a group of 38 children aged 1 - 15 years suffering from CF. These researchers found a correlation between low BMI and reduced FEV1 (forced expiratory volume in 1 second) and no correlation with increased frequency of pulmonary exacerbations, hospitalisations and Pseudomonas aeruginosa infections [5].

Barni et al. (2017) conducted a study involving a group of 73 patients ≥ 16 years of age with clinically stable CF and found that malnutrition is a common complication in these age groups, despite the available dietary recommendations. They showed that malnutrition is associated with age, clinical stage of CF and lung function impairment. Schwachman and Kulczycki scale was used to assess the clinical stage of CF, while the impairment of lung function was assessed on the basis of FEV1 [10]. In turn, Neri et al. (2019) conducted a cross-sectional study to assess the nutritional status of CF patients. They demonstrated that the majority of patients had adequate nutritional status as well as calorie and macroelement intake. They stressed that in order to determine the possibility of reducing the complications of malnutrition in people with CF at a later age, new studies should be carried out involving pre-school children [11].

Apart from the assessment of nutritional status by means of anthropometric measurements, proper monitoring of patients with cystic fibrosis also includes the assessment of the function of the pancreas by determining the concentration of elastase in the faeces. This examination should be performed annually and during the period of weight loss or insufficient weight gain. It is also recommended to perform complete blood count and determine the levels of iron, fat-soluble vitamins, calcium, electrolytes and liver enzymes once a year. Beginning at 10 years of age it is recommended to perform an annual oral glucose tolerance test (OGTT). In addition, it is advisable to monitor FEV1 every 3 months in all patients [12].

Breastfeeding is recommended in CF infants. There was an improvement in lung function and a reduced risk of developing infection in CF and breastfed children compared to those receiving modified milk [12]. If it becomes necessary to provide additional feeding, the youngest patients should receive mixtures of modified milk appropriate to their age and specially prepared for CF patients [13].

Patients with cystic fibrosis have a higher energy demand compared to the general population. This is mainly due to the pathophysiology of the disease associated with, among other factors, increased resting energy expenditure due to increased respiratory muscle work, impairment of the exocrine function of the pancreas and the presence of inflammation in the

body. The daily energy requirement of CF patients is 120-150% of that of a healthy person [6].

The daily dietary intake od a CF patient should include 35-40% fats, 20% proteins and 40-45% carbohydrates. The percentages refer to daily energy requirements. Optimal protein requirements in cystic fibrosis are much higher than in other chronic inflammatory diseases [8]. This is mainly due to the disturbed balance between the anabolic and catabolic protein reactions, as well as to the impaired ability to digest peptides and the greater need for protein due to the presence of chronic inflammation. Perhaps a change of protein to hydrolysed proteins or free amino acids, while optimizing pancreatic enzyme substitution, may affect protein metabolism in people suffering from cystic fibrosis, which is crucial in preventing muscle mass loss. However, there are no recommendations for optimal protein consumption in cystic fibrosis [8].

Due to the lack of detailed guidelines for the management of people with cystic fibrosis and abnormal fasting glucose or abnormal glucose tolerance, standard nutritional recommendations are used [14]. In the case of patients with Cystic Fibrosis - Related Diabetes (CFRD), it should be noted that dietary restrictions cannot be applied, because the course of the disease in people with malnutrition is much more severe [15].

The goal of nutritional care in CFRD is to achieve and maintain a good nutritional status as well as normalise the level of blood glucose [14].

In result of excessive sweating, poor intestinal absorption and chronic inflammation, CF patients have an increased need for: sodium, calcium, zinc, iron and selenium [12]. ESPEN recommends supplementation of sodium (in the form of sodium chloride) in breastfed infants at a dose of 1-2 mmol/kg/day, and in the case of vomiting, diarrhoea, fever, hot weather and in infants with a stoma the dose should be increased to 4 mmol/kg/month/d. NaCl is administered t infants in the form of a 10% solution (1 ml of 10% NaCl = 100 mg NaCl), taking into account all sources of NaCl intake [13]. For older children and adults in stressful situations, when excessive sweating is expected, the sodium supply can be increased by salting foods and selecting sodium rich foods such as salty snacks, yellow cheese, multi-electrolyte fluids or ready-made sodium chloride preparations [12]. ESPEN recommends the consumption of food that is rich in calcium due to the frequent osteoporosis and osteopenia and a high risk of bone fractures in children and adults with CF and, in case of a small consumption, oral calcium supplements and annual monitoring of blood calcium concentration are advised [12]. Although the guidelines of The European Cystic Fibrosis Society recommend the use of bisphosphonates in certain groups of children and adolescents with CF, ESPEN recommends that clinicians consider the benefits versus the risk when deciding on the use of bisphosphonates in the prevention of bone mineral density loss in adult patients [12]. Due to safety concerns, the use of bisphosphonates in children remains controversial [12]. Sands et al. (2015) assessed the correlation between diet and bone mineral density in a group of 89 children with cystic fibrosis aged 10 to 18 years. They showed that patients with CF did not adhere to their dietary recommendations. Dietary deficiencies in energy, protein, calcium and vitamin D3 were observed. An excessive consumption of

phosphorus was demonstrated. Significant differences were observed between girls and boys. A lower mean bone mineral density (BMD) and tendency to BMD decrease with age were observed. The nutritional status assessed on the basis of BMI showed a correlation with BMD, which requires intensive nutritional therapy in accordance with the developed recommendations [16].

In patients with CF, iron is supplemented in the case of its actual deficiency that does not result from chronic inflammation [12]. Zinc supplementation is recommended in CF patients and in the states of increased demand, i.e. in patients with visual impairment, a tendency to frequent infections, delayed puberty and growth disorders. Zinc is best administered over a period of 6 months, in infants up to 2 years of age and with risk factors for zinc deficiency at a dose of 1 mg/kg/month/d, in children from 2 to 18 years of age at a dose of 15 mg/day and in adults at a dose of 25 mg/day [12]. It is not recommended to routinely supplement selenium and glutathione in CF patients [12].

In adults and children with CF, due to pancreatic exocrine insufficiency and inadequate sun exposure, a deficiency of fat-soluble vitamins is common. It is recommended to monitor the concentration of fat-soluble vitamins in CF patients once a year, and 3-6 months after dose modification [12]. Vitamin supplements should be taken together with food rich in fat and pancreatic enzymes to improve their absorption. ESPEN recommends regular supplementation of vitamin K1 in doses adapted to age and the risk of deficiency: neonates 0.3 - 1 mg/day, older children and adults 1 - 10 mg/day. Therefore regular supplementation of the following vitamins is recommended: vitamin E in order to maintain the serum α-tocopherol to cholesterol ratio above 5.4 mg/g, supplementation of vitamin D to maintain the blood levels of 25-hydroxy-vitamin D above 20 ng/ml (50 nmol/L) and vitamin A to achieve the optimal range of serum retinol concentrations, as in the healthy population [12]. Despite the recommended daily supplementation of vitamin D3, CF patients still have to cope with a significant deficiency. It has been demonstrated that the deficiency of vitamin D3 is associated with an increased frequency of pulmonary exacerbations and increased colonisation with pathogenic bacteria [17]. In addition, in younger patients, lower levels of vitamin D3 are associated with lower FEV1 [4] [17]. This is probably related to the immunomodelling role of vitamin D3 in mitigating the progression of lung disease in cystic fibrosis. It was observed that vitamin D reduces the proliferation of B lymphocytes, plasma cells as well as differentiation and secretion of immunoglobulins. Moreover, in vitro studies on the bronchial epithelial cells obtained from CF patients showed that vitamin D3 increases the level of cathelicidin, which is an antimicrobial agent effective against Pseudomonas aeruginosa [17]. Uncomplicated cystic fibrosis is rarely associated with water-soluble vitamin deficiency (e.g. vitamin B12, folic acid, vitamin C). According to ESPEN guidelines, all women planning to get pregnant are recommended to take 400 mcg of folic acid daily before and during the first trimester of pregnancy to prevent neural tube defects. Lifetime supply of 100 mg of vitamin B12 every month applies to patients after extensive resection of the ileum In vitamin C deficiency prevention, it is recommended to consume food that is rich in vitamin C, and in the case inadequate intake, oral supplementation [12].

ESPEN suggests considering supplementation of essential fatty acids and fat-soluble vitamins in CF patients with liver disease and hepatic steatosis [12]. Low values of linoleic acid (LA) in CF patients were correlated with poor lung condition and impaired growth in infants and children, while low docosahexaenoic acid (DHA) and high arachidonic acid (AA) values were associated with impaired bone mineral density both in children and young adults with CF [12]. Altered EFA levels were also correlated with impaired renal function, liver function and immunological function [12]. The results obtained in a small number of studies suggest that supplementing the diet with essential unsaturated fatty acids may improve lung function. However, as the evidence is still insufficient, there are no specific recommendations regarding fatty acid supplementation to improve lung function or anti-inflammatory activity in children or adults with CF [12]. According to the Polish Cystic Fibrosis Society, supplementation of docosahexaenoic acid, preferably in its pure form, is justified [13].

In all patients who have been diagnosed with exocrine pancreatic insufficiency, the administration of oral pancreatic enzymes is recommended. Pancreatic enzymes are administered in the form of enteric capsules, which prevents them from being inactivated by gastric acid and ensures delivery of active enzymes to the distal part of the gastrointestinal tract. The addition of a proton pump inhibitor may improve the efficacy of pancreatic enzymes [12]. Enzymatic preparations must always be taken before a meal, with an additional dose administered in the middle of a larger meal, and if eating lasts longer than 30 minutes, also at the end of the meal [18]. Enzymes should not by administered with snacks that do not contain fats and proteins. Capsules must not be crushed or kept in the mouth. If the patient has problems swallowing, the capsule can be opened and then administered on an acidic product [18]. The recommended dose of pancreatic enzymes is determined individually and depends on the amount of fat in the food, age and body weight of the patient. The efficacy of treatment with pancreatic enzymes should be assessed and possibly corrected at each follow-up visit in infants and children up to 2 years of age, every 3 months in older children and every 6 months in adults [12]. The dose of the preparations that is considered adequate is the one that provides a reduction in fat loss with stool, which is clinically manifested by the normalisation of the number and consistency of stools, disappearance of bloating and abdominal pain and constant weight gain in children or its maintenance in adults [13]. Too small doses of pancreatic enzymes may cause persistent steatorrhoea [13]. The dose of 10 thousand lipase units/kg/day must not be exceeded because it was found that taking high doses of pancreatic enzymes is the main risk factor for fibrosing colonopathy [18].

When a properly balanced diet, supplemented with pancreatic enzymes and fat-soluble vitamins, does not allow for the achievement of optimal nutritional status in a CF patient, invasive methods, including enteral and parenteral nutrition, should be considered. Enteral nutrition can be carried out using a nasogastric tube or gastrostomy (PEG) [13]. Indications for the application of percutaneous endoscopic gastrostomy are the expected long-term therapy and lack of efficacy and patient's acceptance of nutrition through a nasogastric tube [13]. Except for a limited number of cases, the use of parenteral nutrition is not recommended in CF due to the risk of complications, high costs and difficulty in administering [12].

The increase in the number of cystic fibrosis patients with overweight or obesity is worrying. In a cohort study of 909 CF patients followed up in the years 1985-2011, the percentage of underweight patients decreased from 20.6% to 11.1%, while the number of overweight and obese patients increased from 7% to 18.4%. [19]. There are concerns about the long-term health effects of the recommended high-calorie and high-fat diet in cystic fibrosis. Higher intake of saturated fats in CF patients favours the development of obesity and exacerbations of inflammation. Obesity in cystic fibrosis, as in healthy people, increases the risk of cardiovascular disease, insulin resistance, metabolic syndrome and diabetes [8]. Current evidence suggests that in the routine care of patients with cystic fibrosis, greater emphasis should be placed on the intake of high-quality protein and the assessment of body composition, instead of BMI, to induce an increase the lean body mass while preventing central obesity [8].

Antibiotics are only a part of the treatment of pulmonary exacerbations of cystic fibrosis. Physiotherapy, clearing the airways, nutritional supplementation and proper treatment of diabetes also play an important role in the therapy. Nutritional support should be optimised due to increased energy demand, catabolism and reduced appetite [20]. In the course of exacerbation of pulmonary cystic fibrosis, in the case of CFRD, insulin requirements may be up to several times higher compared to the basal insulin dose and must be adjusted after the completion of treatment [20]. The increase in insulin requirements is also caused by corticosteroids, most often used temporarily in pulmonary cystic fibrosis.

ESPEN and the Polish Cystic Fibrosis Society guidelines do not recommend the use of probiotics in CF patients. Despite the encouraging preliminary results, a limited number of studies does not justify the addition of probiotics to current CF treatment protocols [21].

Summary

Cystic fibrosis is an incurable disease that limits life expectancy and leads to worsening of the lung function. The patient's nutritional status affects the functioning of the respiratory system, which is why the prevention of eating disorders is such an important element of therapy. Nutritional treatment is a key component of CF treatment affecting the course of the disease. In the majority of patients with cystic fibrosis, the diet should be high-energy, rich in protein and rich in fat. Moreover, the supplementation with enzyme preparations, vitamins, sodium chloride and the use of high-energy nutrients is often recommended.

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