Transplantologiya. **2017;9(2):125-136.**

DOI:10.23873/2074-0506-2017-9-2-125-136

Nutritional status in patients with cystic fibrosis before and after lung transplantation

M.Sh. Khubutiya, M.E. Il'inskiy, A.A. Ryk, Yu.N. Lyashchenko

N.V. Sklifosovsky Research Institute for Emergency Medicine, Moscow, Russia

Correspondence to: Mogeli Sh. Khubutiya, Acad. of RAS, Professor, President of N.V. Sklifosovsky Research Institute for Emergency Medicine, Moscow, Russia, e-mail: sklifos@inbox.ru

Received: 14 December 2016

This review focuses on the nutritional status of patients with cystic fibrosis, systematic approach to monitoring and nutritional intervention in undernourished patients, and the maintenance of nutritional status before/after lung transplantation.

Keywords: cystic fibrosis, nutritional status, lung transplantation

Introduction

Cystic fibrosis, or mucoviscidosis (from mucus, viscidus), a hereditary autosomal recessive disease, the most common in the European population, is caused by the presence of mutations in the gene that codes for the transmembrane conductance regulator (the protein that regulates the transmembrane transport of sodium and chlorine ions through epithelial and other cell membranes). An impaired flow of H_2O and Cl ions across the cell membarane affects the respiratory, hepatobiliary, reproductive system, gastrointestinal tract, sweat glands, which is manifested specifically in the increased viscosity of mucous membrane secretions [1-3]. The thick secretions in the respiratory tract reduce the mucociliary clearance, thereby

increasing the risk of developing infection and inflammation. An impaired pulmonary function might lead to a deteriorated nutritional status and, consequently, increase the risk of unfavorable outcome of the disease [4, 5]. A partial obstruction of pancreatic ducts impedes the delivery of digestive enzymes, disrupts the absorption of key nutrients, and leads to pancreatic self-digestion as early as in the embryonic period [2, 6, 7].

Nutritional status characteristics in patients with cystic fibrosis

According to the epidemiological data of the European Cystic Fibrosis Society Patient Registry (ECFSPR) (2010), despite the increased number of patients whose nutritional status (NS) can be assessed as adequate; only 50% of patients can be referred to this category [8].

Malnutrition in patients with CF is caused by high energy requirements and its consumption while an inadequate nutrient intake. The increased energy consumption is associated with infectious inflammatory processes in the lungs, dyspnea, cough, using the metabolism-stimulating drugs (the therapy with corticosteroids and bronchodilators). The conducted studies revealed a direct correlation between a deficient pancreatic function and increased energy expenditures, the mechanism of this correlation not being entirely clear so far [3]. The main cause of energy loss is malabsorption as a result of exocrine pancreatic insufficiency due to a decreased number of digestive enzymes secreted into the gastrointestinal tract lumen [2]. Enzymatic insufficiency is not the only manifestation of the pancreas dysfunction. A bicarbonate deficiency and a decreased buffer capacity of secretions (alkalinization of the contents coming from the stomach to the duodenum) reduce the effect of endogenous and exogenous enzyme activities, increase the precipitation of bile salts [9, 10].

The extent of energy losses is increasing with the development of the digestive disorders that may be caused by the following factors: inflammatory bowel diseases, the syndrome of excessive bacterial growth in the small intestine, a decreased insulin secretion, and the insulin resistance (CF-related diabetes), and by hepatic dysfunction (CF-associated liver diseases) [11-13]. The incidence of diabetes in patients with CF increases with age (more than 50% of patients are older 40 years) [14]. Hyperglycemia enhances the bacterial colonization of the lungs, exacerbating the respiratory system dysfunction, increasing the risk of an adverse outcome [15]. Aimed at a timely detection of diabetes mellitus, the annual screening for glucose tolerance is made among CF patients aged from 10 years and older [16]. In addition to the individual approach to carbohydrate prescription, the patients with CF-related diabetes need the diet containing more proteins and essential fatty acids than the standard diet to maintain their optimal NS [17]. Signs of liver cirrhosis occur in about 5-10% of CF patients during the first 10 years of life. Later, the portal hypertension complicated by esophageal varices is revealed in many patients [18]. The decision on the additional prescription of essential fatty acids and fat-soluble vitamins to patients with liver abnormalities is made on individual basis, depending on the goals and tasks posed to the doctor [19, 20].

High energy consumption and energy losses can be compensated for by an adequate food intake. However, such psychosocial and medical factors as stress, depression, noncompliance with medical prescriptions, especially among children and adolescents, as well as a pulmonary insufficiency, gastroesophageal reflux, constipation, distal intestinal obstruction syndrome, excessive bacterial growth of intestinal flora, and side effects of drug

therapy, reduce appetite, and also negatively affect the possibility of adequate food intake and digestion [2, 3].

In addition to the aforementioned disorders, osteopenia and osteoporosis, which are associated with an increased risk of bone fractures, a decreased working ability, severe respiratory insufficiency, and a deficiency of essential fatty acids (EFA), are the most common among CF complications [21, 22].

Assessment and monitoring of nutritional status

The studies published in 2013-2014 showed that the height and the body weight of patients who reached the age of 4 years have a direct correlation with the lung function, the CF complication rates, survival to the age of 18. According to ECFSPR data, a low body mass index (BMI) in CF patients 6-fold increases the risk of developing severe lung dysfunctions compared to the patients with normal BMI [23, 24].

According to current recommendations, the main criteria of nutritional deficiency in CF patients over 18 years of age include the BMI lower than 18.5 kg/m^2, and a weight loss of 5% or more in the previous 2 months. The target BMI parameters are 22 kg/m^2 for women, 23 kg/m^2 for men [5, 25, 26].

In order to characterize the NS in adult CF patients, a 3-5-day diet composition should be analyzed, at least every 6 months. [27].

Attempts to apply different formulas for calculating metabolic requirements in children and adolescents with CF have not been successful. In the group of unstable patients, for example, at exacerbation of infectious complications the method of indirect calorimetry is preferable for use. Moreover, according to M.A. Thomson et al. (1995), metabolic changes in

early CF (the patients younger than 2 years) can be considered as an early indicator of the disease severity that precedes the clinical manifestations and is independent of the lung function [25, 28, 29].

The commonly assessed peripheral blood parameters include the total blood count, electrolytes, iron concentration, the level of fat-soluble vitamins, liver and pancreas function tests. Should laboratory facilities allow, then the blood plasma level of phospholipids and the content of fatty acids in erythrocytes are measured [25, 26, 30].

The body parameters of patients are assessed using anthropometry measures, dual-energy X-ray absorptiometry, bioelectrical impedance, air plethysmography and hydrometry [27]. A quantitative measurement of lean body mass (LBM) by means of dual-energy X-ray absorptiometry made it possible to reveal a number of additional characteristics of NS in CF patients with pancreatic dysfunction. S. Sheikh et al. (2014) noted that in the surveyed population (the patients aged from 5 to 21 years old) the low BMI values do not accurately reflect the LBM deficit, since the fat and lean body masses decrease disproportionately. Moreover, when comparing BMI and LBM, the most pronounced correlation with pulmonary system dysfunction was detected in the LBM measurement [31].

Maintaining adequate nutritional status

Over a long period of time, a low lipid-containing diet was recommended to reduce the steatorrhea severity in patients with CF. Initiated in 1980s, the active use of enzyme replacement therapy with enteric-coated enzymes made it possible to definitely improve the NS and the survival of patients [4, 32]. Currently, the standard approaches to maintaining an adequate NS imply high-calorie (high-lipid-containing) foods,

supplementary intake of fat-soluble vitamins and enzyme replacement therapy [33]. The target level of energy consumption in CF patients, according to the European recommendations, is 120-150% of the requirements for healthy people of similar age, gender, and anthropometric data. Energy expenditure at rest makes about 60-70% of the total energy requirements; physical activity-induced energy expenditure accounts for 10-25%, and diet-induced (thermogenesis) energy expenditure make 10% [25]. The protein needs of CF patients are also higher than the standard-recommended 0.83 g/kg per day for healthy adults. The protein : fat : carbohydrates ratio in the diet for children is 20% : 35-40% : 40-45%, respectively [33].

The patients in condition of increased sweating, malabsorption, and chronic infections need an additional intake of sodium chloride, calcium, iron, zinc, and selenium. An inadequate pancreatic function and impaired lipid absorption, rare and short stay in the sun results in the deficient vitamins A, D, E, and K in patients. The deficiency of water-soluble vitamins is rare in uncomplicated CF course; but among the patients who underwent the terminal ileum resection (meconium ileus), the consideration should be given to the supplemental intake of vitamin B_{12}, and in case of a planned pregnancy and during its first trimester, a daily intake of 400 μg of folic acid is indicated. The administration of vitamin C in a medicinal formulation may also be required if its content is low in the diet customary for a sick person [27].

In addition to the essential α-linolenic (ω-3) and linoleic (ω-6) fatty acids, the arachidonic (ω-6) and docosahexaenoic (ω-3) fatty acids became conditionally essential in various pathological processes. The decreased level of linoleic acid correlates with the severity of respiratory failure, the

growth and development rates in children and adolescents; and the low level of docosahexaenoic acid and the high level of arachidonic acid are associated with an impaired bone tissue mineralization. In addition, altered blood EFA concentrations are associated with impaired functions of the immune system, kidneys, and the liver [27]. In a number of small studies, the supplemental use of EFA in the patients has been found to improve the respiratory system function; and the regular addition of omega-3 fatty acids to the diet results in a decreased level of pro-inflammatory markers [34, 35]. Nevertheless, according to the conclusion made by the authors of the systematic review of the Cochrane Research Library (2013), currently there is insufficient evidence to recommend the addition of omega-3 fatty acids to all patients with CF [36].

According to the 2011 European Guidelines, the decision to prescribe bisphosphonates shall be taken after evaluating the bone tissue mineralisation using a serial bone densitometry or if the patent has the history of pathological fractures [37]. Regular physical exercise significantly increases the bone density [38].

A poor appetite has already been noted as one of malnutrition causes in CF patients. Several studies on the efficacy of using the appetite stimulants (megestrol acetate and cyproheptadine hydrochloride) indicate an improvement in appetite and an increase in body weight when these drugs are used [39].

Encouraging results have been obtained in a number of studies evaluating the efficacy of probiotics. Oral administration of living bacteria contributed to lower severity of acute gastroenteritis, a reduced incidence of pulmonary complications, and a decreased number of hospital admissions [40, 41].

Correction of NS impairments

The primary approach in the treatment of malnutrition in children and adults suffering from CF implies the diet changes in favor of the increased feeding frequency, food amount, and caloric value, including additional intake of fats (rich in linoleic acid vegetable oils, butter, etc.). An additional intake of linoleic acid can reduce the patient's need for high-calorie nutrition [42]. Of note, in order to reduce the risk of cardiovascular diseases when giving fats, the preference should be given to unsaturated fatty acids (UFAs) and, if possible, the use of trans fats and saturated fatty acids should be avoided [43, 44]. In order to increase the effect of dietary therapy, it is important to pay attention to training and counseling both the parents and their sick children, and also adult patients, to form proper eating habits [5, 25].

According to the Annual Report of the North American Cystic Fibrosis Foundation, 43% of patients need additional oral nutrition, and 11.4% require enteral tube feeding (45). The signs of persistent malnutrition, despite the increased caloric content of the daily diet and the corrected eating habits, with conducted optimized enzyme replacement therapy, make an indication to the use of oral supplemental liquid nutrition. Taking into account a wide range of different nutritional preparations produced by the food industry, it is desirable to individually select a product based on the organoleptic and emotional preferences of the patient. This type of supplementary food is used to increase the caloric content of the diet and to improve an inadequate consumption of such components as EFA by the patients [46, 47].

Diet optimization in adult CF patients with inadequate NS contributes to weight gain, but LBM remains unchanged. In order to increase the muscle mass, the supplemental nutrition should be combined with physical exercise. This treatment tactic helps to increase not only LBM, but also the maximal lung ventilation, tissue uptake of oxygen, and tolerance of physical loads [48, 49].

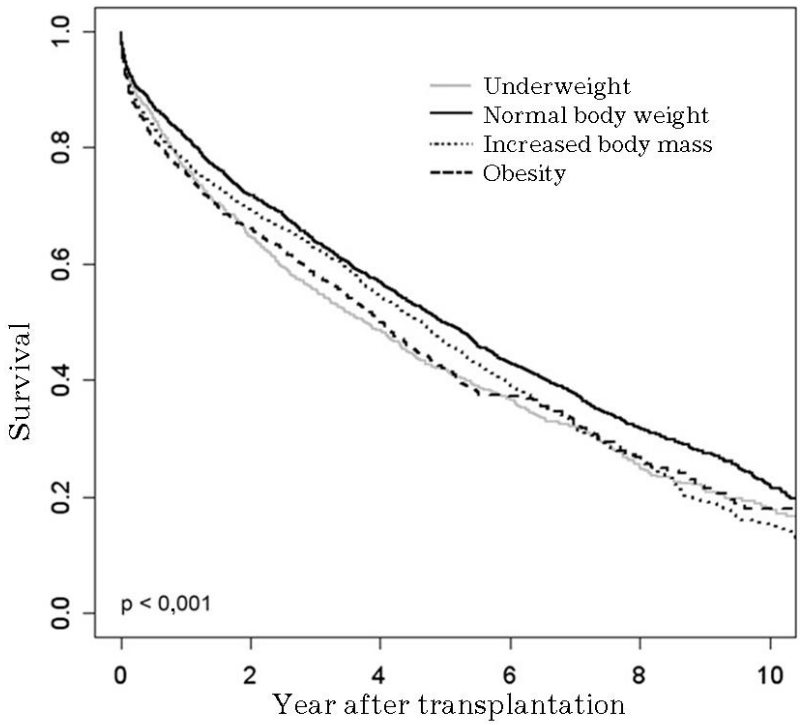
Should prolonged additional enteral feeding be necessary, gastrostomy is preferred. Being guided by an adequate assimilation, the volume of additional artificial nutrition is increased gradually. Night enteral feeding may be considered optimal, from the point of influencing the appetite during the day [50, 51]. Either a continuous (gravitational or pump) infusion, or a daily bolus injection of nutritional formula is used, or the combination of both. In most cases, patients well tolerate polymeric high-calorie formulae (1.5-2 Kcal/ml). The enzyme replacement therapy is usually used before the start and the end of the polymeric formula infusion. In severe pancreas functional disorders and a poor tolerance of polymeric formulae, elemental or semi-elemental formulae shall be used, their dose and time of administration being selected individually. Glucose tolerance disorders resulted from the increased energy consumption require additional monitoring of the hyperglycemia level and, if necessary, administering small doses of insulin to the patient [27, 31].

Parenteral nutrition is usually used in the patients with severely impaired NS being on the waiting list of LT and(or) with gastrointestinal tract dysfunction which do not allow the use of enteral nutrition. We should note that the use of parenteral nutrition is associated with an increased risk of sepsis; and the increase in the body weight of patients is transient [52].

Severe course of cystic fibrosis, and lung transplantation

Despite the increase in life expectancy in the general population of CF patients, the progression of pulmonary dysfunction leads to the need for transplantation almost in all patients with severe course of the disease [53, 54]. According to the Registry of the International Society of Heart and Lung Transplantation (ISHLT), approximately 3,700 LTs are registered annually in the world. Given that the registration on the site is a voluntary decision of transplantologists, the true number of transplants exceeds the Registry data. The median survival after LT in CF patients for the period from 1994 to 2010 (about 30% of all bilateral LTs) was 7.5 years, and 10.4 years for the patients who survived during the first 12 months, [55].

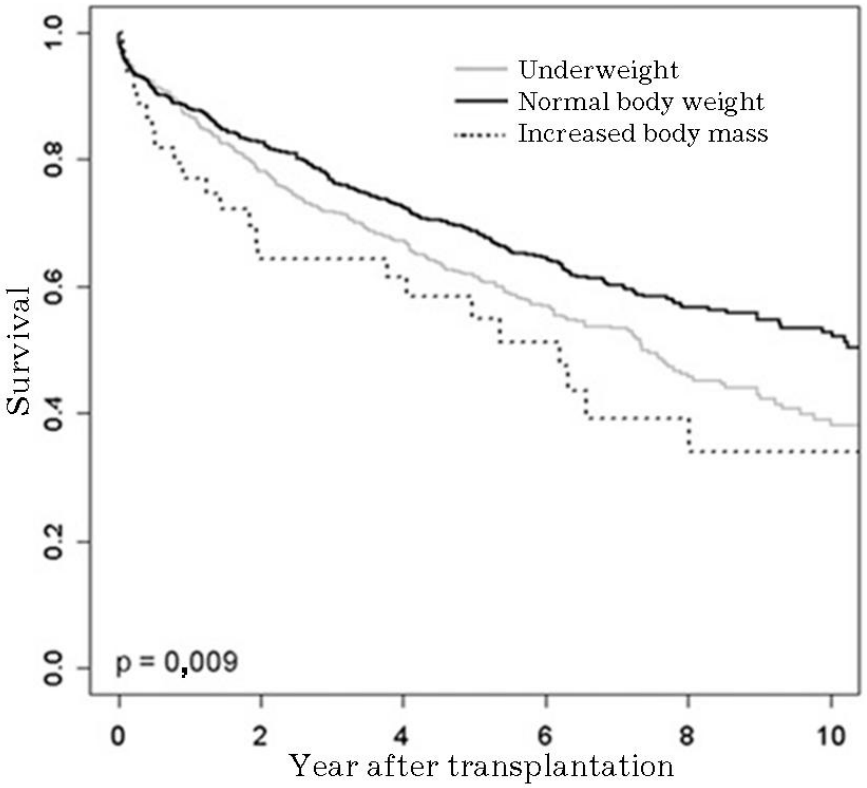
As already noted, the adequate nutrition is closely related to the pulmonary system function and the life expectancy of CF patients; and BMI serves one of the indicators characterizing the disease prognosis in adult patients [9]. In 2009, D.J. Lederer et al. published the study where analyzed the effect of BMI on LT outcomes [56]. In accordance with the criteria recommended by the World Health Organization, the patients were allocated into four groups: underweight (BMI under 18.5 kg/m^2), normal weight (BMI equal to 18.5-24.9 kg/m^2), increased BMI (25-29.9 kg/m^2, and obesity (BMI over 30 kg/m^2). CF, chronic obstructive pulmonary disease, and idiopathic pulmonary fibrosis were presented among the diseases requiring LT. The authors of the study found a significant increase in the risk of death in the groups of patients with BMI below or above the norm ($p<0.001$). Normal BMI was observed in 18% of CF patients only, 48% of patients were underweight (among 5978 patients aged 18 years and over, there were 960 patients with CF included in the study) (Fig.1).



Body mass	Year after transplantation					
	0	2	4	6	8	10
Underweight	862	583	445	272	136	49
Normal	2864	2056	1586	906	451	181
Increased	1644	1117	840	412	173	50
Obesity	608	393	280	151	66	23

Fig. 1. Survival of recipients after lung transplantation in groups with regard to Body Mass Index (modified; see ref. 56)

The risk of unfavorable outcome in recipients suffering from CF increased by 25% in case of inadequate body weight (confidence interval 4; 52%, p=0.02). Investigators also drew the attention to the fact that an increased risk of death was observed in the long term after LT due to chronic graft dysfunction and (or) infectious complications rather than in the early post-LT period (Fig. 2).



Body mass	Year after transplantation					
	0	2	4	6	8	10
Underweight	410	286	224	133	65	27th
Normal	519	390	309	194	107	52
Increased	34	19	18	12	7th	2

Fig. 2. Survival of patients with cystic fibrosis after lung transplantation with regard to Body Mass Index (modified; see ref. 56)

Thus, recovery of normal BMI values (18.5-24.9 kg/m^2) in the patients on the waiting list for LT is one of the ways to reduce the risk of adverse outcome after surgery. This is especially true for our country where, according to 2011 Russian Registry, the median BMI of adult CF patients was 18.5 kg/m^2 among men, and 18.9 kg/m^2 among women [57].

In conformity with the treatment program for CF patients on the waiting list for LT, J.J. Egan et al. (1997) recommended that gastrostomy

should be used in all the patients to maintain an adequate NS before and after surgery [58]. The most frequent complications of supplementary feeding via gastrostomy, in the authors' opinion, include the abdominal distension and vomiting caused by discordance between the rate of food intake and the rate of gastric emptying. Using prokinetics and reducing the amount of food allow these complications to be avoided. A diet rich in carbohydrates can cause an increased production of carbon dioxide and the aggravation of respiratory failure, which is the indication to the use of non-invasive ventilation [59].

Due to the lack of a sufficient evidence database, the approaches to maintain an adequate NS in CF patients immediately after LT are based on the standard recommendations for the population of general surgical patients and patients who underwent transplantation of other organs [60]. The oral diet in patients extubated on the 1^{st} or 2^{nd} day after surgery should be gradually expanded, depending on food absorption and digestion by the patients with a mandatory enzyme replacement therapy. Appetite is usually improving with the recovery of respiratory function and intestinal motility, with early activation of the patient [61].

Anorexia, taste alterations, nausea, vomiting, diarrhea, or constipation can be caused by drug therapy (drugs for the prevention and treatment of graft rejection, antibiotics, antifungal medications, etc.). If these complications develop or if a prolonged use of non-invasive/mechanical lung ventilation is necessary, a supplemental enteral nutrition (through gastrostomy, tube feeding) is used. One of the criteria to consider the gastrostomy closure is the achieved BMI over 19 kg/m^2 that is maintained for more than 3-6 months without supplemental nutrition [62].

The results of two studies demonstrating a significant increase in vitamin A and E levels in the post-LT patients served the basis for recommending the regular monitoring of fat-soluble vitamin levels in this patient population, depending on the results, dose adjustment, or withdrawal of an additional vitamin therapy [63, 64].

The immunosuppressive therapy and the treatment for acute pulmonary graft rejection, in particular the use of high doses of steroids, are associated with an increased risk of secondary diabetes mellitus or the decompensation of CF-related diabetes mellitus, and also increase the risk of osteoporosis [65, 66].

The most common gastrointestinal complications of the early postoperative period include oropharyngeal dysphagia, stomach bezoars, gastrostasis, gastroesophageal reflux disease, distal intestinal obstruction syndrome, constipation [67-70].

According to B.S. Quon et al. (2012), the CF patients undergoing LT have an increased risk of the renal injury development [71].

The immunosuppressive therapy increases the risk of foodborne infections such as salmonella and listeriosis [72, 73].

The use of dosed physical exercise to rehabilitate the patients with chronic pulmonary insufficiency has established itself as an effective and safe method of treatment. The need to develop an individual program of physical activity of a patient before and after LT is also beyond doubt, considering the tolerance of physical activity (resistance exercises, aerobic exercise, balance and flexibility training, etc.). Achieving the optimal level of strength and endurance helps to retain/increase LBM and contributes to the improvement of the postoperative treatment outcomes [74].

Thus, the correction of impaired nutrition status in CF patients, including the BMI kept at 22-23 kg/m^2 (giving the priority to increase the LBM values), an adequate enzyme replacement therapy, and the compensation of deficient micro- and macro-nutrients make the crucial tasks which solution would improve the quality of life, reduce the incidence of fatal complications, and improve patient survival after LT.

The authors state there is no conflict of interest to declare

References

1. Cohen-Cymberknoh M., Shoseyov D., Kerem E. Managing cystic fibrosis: strategies that increase life expectancy and improve quality of life. *Am J Respir Crit Care Med.* 2011;183(11):1463–1471. PMID:21330455 DOI:10.1164/rccm.201009-1478CI

2. Li L., Somerset S. Digestive system dysfunction in cystic fibrosis: challen-ges for nutrition therapy. *Dig Liver Dis.* 2014;46(10):865–874. PMID:25053610 DOI:10.1016/j.dld.2014.06.011

3. Culhane S., George C., Pearo B., Spoede E. Malnutrition in cystic fibrosis: a review. *Nutr Clin Pract.* 2013;28(6):676–683. PMID:24170579 DOI:10.1177/0884533613507086

4. Corey M., McLaughlin F.J., Williams M., Levison H. A comparison of survival, growth, and pulmonary function in patients with cystic fibrosis in Boston and Toronto. *J Clin Epidemiol.* 1988;41(6):583–591. PMID:3260274

5. Stallings V.A., Stark L.J., Robinson K.A. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic

review. *J Am Diet Assoc.* 2008;108(5):832–839. PMID:18442507 DOI:10.1016/j.jada.2008.02.020

6. Petrova N.V., Ginter E.K. Molecular-genetic aspects of cystic fibrosis. In: Kapranov N.I., Kashirskaya N.Yu., eds. *Cystic Fibrosis.* Moscow: MEDPRAKTIKA-M Publ., 2014. 37–80. (In Russian).

7. Andersen D.H., Dorothy H. Cystic fibrosis of the pancreas and its relation to celiac disease: a clinical and pathological study. *Am J Dis Child.* 1938;56(2):344–399. DOI:10.1001/archpedi.1938.01980140114013

8. Stephenson A.L., Mannik L.A., Walsh S., et al. Longitudinal trends in nutritional status and the relation between lung function and BMI in cystic fibrosis: a population-based cohort study. *Am J Clin Nutr.* 2013;97(4):872–877.

9. Amelina E.L., Gembitskaya T.E., Chermenskaya A.G. Features of cystic fibrosis in adults. In: Kapranov N.I., Kashir-skaya N.Yu., eds. *Cystic Fibrosis.* Moscow: MEDPRAKTIKA-M Publ., 2014. 548–575. (In Russian).

10. Robinson P.J., Smith A.L., Sly P.D. Duodenal pH in cystic fibrosis and its relationship to fat malabsorption. *Dig Dis Sci.* 1990;35(10):1299–1304. PMID:2120019

11. Perano S., Rayner C.K., Couper J., et al. Cystic fibrosis related diabetes – a new perspective on the optimal management of postprandial glycemia. *J Diabetes Complicat.* 2014;28(6):904–911. PMID: 25060530 DOI:10.1016/j.jdiacomp.2014.06.012

12. Debray D., Kelly D., Houwen R., et al. Best practice guidance for the diagnosis and management of cystic fibrosis-associated liver disease. *J Cyst Fibros.* 2011;10(Suppl 2):S29–S36. PMID:21658639 DOI:10.1016/S1569-1993(11)60006-4

13. Kashirskaya N.Yu. Pancreatic lesions, changes in the hepatobiliary system in patients with cystic fibrosis. In: Kapranov N.I., Kashirskaya N.Yu., eds. *Cystic Fibrosis.* Moscow: MEDPRAKTIKA-M Publ., 2014. 295–345. (In Russian).

14. Moran A., Dunitz J., Nathan B., et al. Cystic fibrosisrelated diabetes: current trends in prevalence, incidence, and mortality. *Diabetes Care.* 2009;32(9):1626–1631. PMID:19542209 DOI:10.2337/dc09-0586

15. Waugh N., Royle P., Craigie I., et al. Screening for cystic fibrosis-related diabetes: a systematic review. *Health Technol Assess.* 2012;16(24):iii-iv,1–179. PMID:22572153 DOI:10.3310/hta16240

16. Moran A., Pillay K., Becker D.J. ISPAD Clinical Practice Consensus Guidelines 2014. Management of cystic fibrosis related diabetes in child-ren and adolescents. *Pediatr Diabetes.* 2014;15(Suppl 20):65–76. PMID:25182308 DOI:10.1111/pedi.12178

17. Moran A., Brunzell C., Cohen R.C., et al. Clinical care guidelines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. *Diabetes Care.* 2010;33(12):2697–2708. PMID:21115772 PMCID:PMC2992215 DOI:10.2337/dc10-1768

18. Colombo C., Battezzati P.M., Crosignani A., et al. Liver disease in cystic fibrosis: a prospective study on incidence, risk factors, and outcome. *Hepatology.* 2002;36(6):1374–1382. PMID:12447862 DOI:10.1053/jhep.2002.37136

19. Lindblad A., Glaumann H., Strandvik B. Natural history of liver disease in cystic fibrosis. *Hepatology.* 1999;30(5):1151–1158. PMID:10534335 DOI:10.1002/hep.510300527

20. Van Biervliet S., Van Biervliet J.P., Robberecht E., Christophe A. Fatty acid composition of serum phospho-lipids in cystic fibrosis (CF) patients with or without CF related liver disease. *Clin Chem Lab Med.* 2010;48(12):1751–1755. PMID:20961201 DOI:10.1515/CCLM.2010.336

21. Conway S.P., Morton A.M., Oldroyd B., et al. Osteoporosis and osteopenia in adults and adolescents with cystic fibrosis: prevalence and associated factors. *Thorax.* 2000;55(9):798–804. PMID:10950902

22. Gronowitz E., Lorentzon M., Ohlsson C., et al. Docosahexaenoic acid is associated with endosteal circumference in long bones in young males with cystic fibrosis. *Br J Nutr*. 2008;99(1):160–167. PMID:17697399 DOI:10.1017/S000711450780105X

23. Yen E.H., Quinton H., Borowitz D. Better nutritional status in early childhood is associated with improved clinical outcomes and survival in patients with cystic fibrosis. *J Pediatr*. 2013;162(3):530–535. PMID:23062247 DOI:10.1016/j.jpeds.2012.08.040

24. Kerem E., Viviani L., Zolin A., et al. Factors associated with FEV1 decline in cystic fibrosis: analysis of the ECFS Patient Registry. *Eur Respir J.* 2014;43(1):125–133. PMID:23598952 DOI:10.1183/09031936.00166412

25. Sinaasappel M., Stern M., Littlewood J., et al. Nutrition in patients with cystic fibrosis: a European Consensus. *J Cyst Fibros.* 2002;1(2):51–75. PMID:15463811

26. Smyth A.R., Bell S.C., Bojcin S., et al. European cystic fibrosis Society standards of care: best practice guidelines. *J Cyst Fibros.* 2014;13(Suppl 1):S23–S42. PMID:24856775 DOI:10.1016/j.jcf.2014.03.010

27. Turck D., Braegger C.P., Colombo C., et al. ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children,

and adults with cystic fibrosis. *Clin Nutr.* 2016;35(3):557–577. PMID:27068495 DOI:10.1016/j.clnu.2016.03.004

28. Thomson M.A., Bucolo S., Quirk P., Shepherd R.W. Measured versus predicted resting energy expenditure in infants: a need for reappraisal. *J Pediatr.* 1995;126(1):21–27. PMID:7815217

29. Thomson M.A., Wilmott R.W., Wainwright C., et al. Resting energy expenditure, pulmonary inflammation, and genotype in the early course of cystic fibrosis. *J Pediatr.* 1996;129(3):367–373. PMID:8804325

30. Wood L.G., Gibson P.G., Garg M.L. Circulating markers to assess nutritional therapy in cystic fibrosis. *Clin Chim Acta.* 2005;353(1-2):13–29. PMID:15698587 DOI:10.1016/j.cccn.2004.11.002

31. *Cystic Fibrosis Trust.* Nutritional management of cystic fibrosis. London, UK, 2002.

32. Powers S.W., Mitchell M.J., Patton S.R., et al. Mealtime behaviors in families of infants and toddlers with cystic fibrosis. *J Cyst Fibros.* 2005;4(3):175–182. PMID:15982934 DOI:10.1016/j.jcf.2005.05.015

33. Gaskin K.J. Nutritional care in child-ren with cystic fibrosis: are our patients becoming better? *Eur J Clin Nutr.* 2013;67(5):558–564. PMID:23462946 DOI:10.1038/ejcn.2013.20

34. Olveira G., Olveira C., Acosta E., et al. Fatty acid supplements improve respiratory, inflammatory and nutritional parameters in adults with cystic fibrosis. *Arch Bronconeumol.* 2010;46(2):70–77. PMID:20045240 DOI:10.1016/j.arbres.2009.11.001

35. Keen C., Olin A.C., Eriksson S., et al. Supplementation with fatty acids influences the airway nitric oxide and inflammatory markers in patients with cystic fibrosis. *J Pediatr Gastroenterol Nutr.* 2010;50(5):537–544. PMID:20639712 DOI:10.1097/MPG.0b013e3181b47967

36. Oliver C., Watson H. Omega-3 fatty acids for cystic fibrosis. *Cochrane Database Syst Rev.* 2013;11:CD002201. PMID:24282091 DOI:10.1002/14651858.CD002201.pub4

37. Sermet-Gaudelus I., Bianchi M.L., Garabédian M., et al. European cystic fibrosis bone mineralisation guidelines. *J Cyst Fibros.* 2011;10(Suppl 2):S16–S23. PMID:21658635 DOI:10.1016/S1569-1993(11)60004-0

38. *Cystic Fibrosis Trust.* Bone minera-lisation in cystic fibrosis. London, UK, 2007.

39. Chinuck R., Dewar J., Baldwin D.R., Hendron E. Appetite stimulants for people with cystic fibrosis. *Cochrane Database Syst Rev.* 2014;7:CD008190. PMID:25064192 DOI:10.1002/14651858.CD008190.pub2

40. Bruzzese E., Raia V., Gaudiello G., et al. Intestinal inflammation is a frequent feature of cystic fibrosis and is reduced by probiotic administration. *Aliment Pharmacol Ther.* 2004;20(7):813–819. PMID:15379842 DOI:10.1111/j.1365-2036.2004.02174.x

41. Bruzzese E., Raia V., Spagnuolo M.I., et al. Effect of Lactobacillus GG supplementation on pulmonary exacerbations in patients with cystic fibrosis: a pilot study. *Clin Nutr.* 2007;26(3):322–328. PMID:17360077 DOI:10.1016/j.clnu.2007.01.004

42. Kindstedt-Arfwidson K., Strandvik B. Food intake in patients with cystic fibrosis on an ordinary diet. *Scand J Gastroenterol.* Suppl. 1988;143:160–162. PMID: 3164504

43. Smith C., Winn A., Seddon P., Ranganathan S. A fat lot of good: balance and trends in fat intake in children with cystic fibrosis. *J Cyst Fibros.* 2012;11(2):154–157. PMID:22119390 DOI:10.1016/j.jcf.2011.10.007

44. Woestenenk J.W., Castelijns S.J., van der Ent C.K., Houwen R.H. Dietary intake in children and adolescents with cystic fibrosis. *Clin Nutr.* 2014;33(3):528–532. PMID:23920501 DOI:10.1016/j.clnu.2013.07.011

45. *Cystic Fibrosis Foundation Patient Registry.* Annual Data 2012. Bethesda, Maryland, 2013.

46. Steinkamp G., Demmelmair H., Rühl-Bagheri I., et al. Energy supple-ments rich in linoleic acid improve body weight and essential fatty acid status of cystic fibrosis patients. *J Pediatr Gastroenterol Nutr.* 2000;31(4):418–423. PMID:11045840

47. Rettammel A.L., Marcus M.S., Farrell P.M., et al. Oral supplementation with a high-fat, high-energy product improves nutritional status and alters serum lipids in patients with cystic fibrosis. *J Am Diet Assoc.* 1995;95(4):454–459. PMID:7699188 DOI:10.1016/S0002-8223(95)00121-2

48. Alison J.A., Donnelly P.M., Lennon M., et al. The effect of a comprehensive, intensive inpatient treatment program on lung function and exercise capacity in patients with cystic fibrosis. *Phys Ther.* 1994;74(6):583–591. PMID:8197244

49. Heijerman H.G. Chronic obstructive lung disease and respiratory muscle function: the role of nutrition and exercise training in cystic fibrosis. *Respir Med.* 1993;87(Suppl B):49–51. PMID:8234970

50. Williams S.G., Ashworth F., McAlweenie A., et al. Percutaneous endoscopic gastrostomy feeding in patients with cystic fibrosis. *Gut.* 1999;44(1):87–90. PMID:9862831

51. Rosenfeld M., Casey S., Pepe M., Ramsey B.W. Nutritional effects of long-term gastrostomy feedings in children with cystic fibrosis. *J*

Am Diet Assoc. 1999;99(2):191–194. PMID:9972186 DOI:10.1016/S0002-8223(99)00046-2

52. Allen E.D., Mick A.B., Nicol J., McCoy K.S. Prolonged parenteral nutrition for cystic fibrosis patients. *Nutr Clin Pract.* 1995;10(2):73–79. PMID:7731428 DOI:10.1177/011542659501000273

53. Avdeev S.N. Lung transplantation in cystic fibrosis. In: Kapranov N.I., Kashirskaya N.Yu., eds. *Cystic Fibrosis.* Moscow: MEDPRAKTIKA-M Publ., 2014. 595–611. (In Russian).

54. Spahr J.E., Love R.B., Francois M., et al. Lung transplantation for cystic fibrosis: current concepts and one center's experience. *J Cyst Fibros.* 2007;6(5):334–350. PMID:17418647 DOI:10.1016/j.jcf.2006.12.010

55. Stehlik J., Edwards L.B., Kuche-ryavaya A.Y., et al. The Registry of the International Society for Heart and Lung transplantation: 29th adult lung and heart-lung transplant report – 2012. *J Heart Lung Transplant.* 2012;31(10):1073–1086. PMID:22975095 DOI:10.1016/j.healun.2012.08.002

56. Lederer D.J., Wilt J.S., D'Ovidio F., et al. Obesity and underweight are associated with an increased risk of death after lung transplantation. *Am J Respir Crit Care Med.* 2009;180(9):887–895. PMID:19608717 DOI:10.1164/rccm.200903-0425OC

57. The register of patients with cystic fibrosis in the Russian Federation. 2011. *Pulmonology.* 2014; Suppl. Available at: http://mukoviscidoz.org/doc/registr/Registr_end_2011.pdf

58. Egan J.J., Woodcock A.A., Webb A.K. Management of cystic fibrosis before and after lung transplantation. *J R Soc Med.* 1997;90(Suppl 31):47–58. PMID:9204012

59. Elborn J.S., Jagoe T., Shale D.J. Metabolic and respiratory consequences of a glucose load in hypoxic patients with cystic fibrosis. *Ulster Med.* 1992;61(2):188–192. PMID:1481313

60. Hirche T.O., Knoop C., Hebestreit H., et al. Practical Guidelines: Lung Transplantation in Patients with Cystic Fibrosis. *Pulm Med.* 2014;2014:621342. PMID:24800072 DOI:10.1155/2014/621342

61. Tynan C., Hasse J.M. Current nutrition practices in adult lung transplantation. *Nutr Clin Pract.* 2004;19(6):587–596. PMID:16215158 DOI:10.1177/0115426504019006587

62. Kalnins D., Wilschanski M. Maintenance of nutritional status in patients with cystic fibrosis: new and emer-ging therapies. *Drug Des Devel Ther*. 2012;6:151–161. PMID:22787388 DOI:10.2147/DDDT.S9258

63. Ho T., Gupta S., Brotherwood M., et al. Increased serum vitamin A and e levels after lung transplantation. *Transplantation.* 2011;92(5):601–606. PMID:21841542 DOI:10.1097/TP.0b013e31822790e3

64. Stephenson A., Brotherwood M., Ro-bert R., et al. Increased vitamin A and E levels in adult cystic fibrosis patients after lung transplantation. *Transplantation.* 2005;79(5):613–615. PMID:15753854

65. Hadjiliadis D., Madill J., Chaparro C., et al. Incidence and prevalence of diabetes mellitus in patients with cystic fibrosis undergoing lung transplantation before and after lung transplantation. *Clinical Transplantation.* 2005;19(6):773–778. PMID:16313324 DOI:10.1111/j.1399-0012.2005.00420.x

66. Gottlieb J., Ballmann M., von Mallinckrodt C., et al. Lung transplantation in cystic fibrosis – a position paper. *Pneumologie.* 2009;63(8):451–460. PMID:19670104 DOI:10.1055/s-0029-1214821

67. Gilljam M., Chaparro C., Tullis E., et al. GI complications after lung transplantation in patients with cystic fibrosis. *Chest.* 2003;123(1):37–41. PMID:12527600

68. Atkins B.Z., Petersen R.P., Daneshmand M.A., et al. Impact of oropharyngeal dysphagia on long-term outcomes of lung transplantation. *Ann Thorac Surg.* 2010;90(5):1622–1628. PMID:20971276 DOI:10.1016/j.athoracsur.2010.06.089

69. Dellon E.S., Morgan D.R., Mohanty S.P., et al. High incidence of gastric bezoars in cystic fibrosis patients after lung transplantation. *Transplantation.* 2006;81(8):1141–1146. PMID:16641599 DOI:10.1097/01.tp.0000205813.54136.85

70. Mendez B.M., Davis C.S., Weber C., et al. Gastroesophageal reflux disease in lung transplant patients with cystic fibrosis. *Am J Surg.* 2012;204(5):e21–e26. PMID:22921151 DOI:10.1016/j.amjsurg.2012.07.019

71. Quon B.S., Mayer-Hamblett N., Aitken M.L., Goss C.H. Risk of post lung transplant renal dysfunction in adults with cystic fibrosis. *Chest.* 2012;142(1):185–191. PMID:22222189 DOI:10.1378/chest.11-1926

72. Outbreak of Salmonella serotype Javinia infections. Orlando, Florida, June 2002. *MMWR Morb Mortal Wkly Rep.* 2002;51(31):683–684. PMID:12233909

73. Goulet V., Hebert M., Hedberg C., et al. Incidence of listeriosis and relate-d mortality among groups at risk of acquiring listeriosis. *Clin Infect Dis.* 2012;54(5):652–660. PMID:22157172 DOI:10.1093/cid/cir902

74. Mathur S., Hornblower E., Levy R.D. Exercise training before and after lung transplantation. *Phys Sportsmed.* 2009;37(3):78–87. PMID:20048531 DOI:10.3810/psm.2009.10.1732