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# Oral nutritional supplements in patients with cystic fibrosis: research results

Vera V. Zarubina[1], Olga V. Vysokolova[1], Mariya A. Mukhina[1], Elena E. Yakushina[1], Tatiana N. Kekeeva[1], Irina P. Vitkovskaya[2, 3]

[1] Morozov Children's Municipal Clinical Hospital, Moscow, Russia;
[2] Russian Research Institute of Health, Moscow, Russia;
[3] The Russian National Research Medical University named after N.I. Pirogov, Moscow, Russia

## ABSTRACT

***BACKGROUND:*** The nutritional status of patients with cystic fibrosis significantly affects their survival and the function of all organs, particularly the lungs. Due to increased protein and energy needs, these patients often require high-calorie and high-protein oral nutritional supplements (ONS).

***AIM:*** To assess the tolerability, efficacy, and safety of the ONS containing whey protein and soy lecithin.

***MATERIALS AND METHODS:*** The data of 14 patients with mixed form of cystic fibrosis and nutritional deficiencies, aged between 6 and 16 years, were analyzed. Five patients received ONS containing whey protein and soy lecithin (Fresubin Protein®) as monotherapy (Group 1), four patients received the same therapeutic food together with emulsion of medium-chain triglycerides (Group 2), and five patients received ONS balanced in protein, fat, and carbohydrates (control group). The dynamics between percentile and Z-Scores of body mass index (BMI) at the beginning and at the end of the study period (day 180±2) were used as the main efficacy parameter of the investigated food. Body fat and lean body mass were assessed by caliperometry as additional efficacy parameters.

***RESULTS:*** All patients showed an increase in Z-Score and BMI percentile from baseline while taking ONS containing whey protein and soy lecithin both as monotherapy and in combination with medium-chain triglyceride emulsion. There were no statistically significant differences from the control group ($p$ >0.05). However, Group 1 (100% of patients) demonstrated positive changes in muscle mass gain, as evidenced by caliperometry data, which was statistically significant ($p$ <0.05) compared with the control group (20%). In Group 2, muscle gain was observed in 75% of the patients ($p$ >0.05).

***CONCLUSION:*** These findings suggest that protein-enriched ONS not only increase BMI but also contribute to muscle mass gain in patients with cystic fibrosis. New therapeutic approaches are needed, such as the inclusion of high-protein ONS in the diet to prevent muscle mass loss, along with the monitoring of body composition to improve control of disease progression.

**Keywords:** cystic fibrosis; nutritional support; oral nutritional supplements; malnutrition; whey protein.

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# Пероральное лечебное питание при муковисцидозе. Результаты научно-исследовательской работы

В.В. Зарубина[1], О.В. Высоколова[1], М.А. Мухина[1], Е.Е. Якушина[1], Т.Н. Кекеева[1], И.П. Витковская[2, 3]

[1] Морозовская детская городская клиническая больница, Москва, Россия;
[2] Центральный научно-исследовательский институт организации и информатизации здравоохранения, Москва, Россия;
[3] Российский национальный исследовательский медицинский университет имени Н.И. Пирогова, Москва, Россия

## АННОТАЦИЯ

**Обоснование.** Нутритивный статус пациентов с муковисцидозом влияет на выживаемость и поддержание функций всех органов, в частности лёгких. Повышенные потребности в белке и энергии у данной группы пациентов обусловливают необходимость назначения высококалорийных и высокобелковых специализированных продуктов лечебного питания (СПЛП).

**Цель исследования** — оценка переносимости, эффективности и безопасности применения СПЛП, содержащего белок молочной сыворотки и соевый лецитин.

**Материалы и методы.** Проанализированы данные 14 пациентов со смешанной формой муковисцидоза и недостаточностью питания в возрасте от 6 до 16 лет включительно. 5 пациентов получали СПЛП, содержащий белок молочной сыворотки и соевый лецитин, в качестве монотерапии (группа 1), 4 пациента получали этот же продукт лечебного питания совместно с эмульсией среднецепочечных триглицеридов (группа 2), 5 пациентов получали сбалансированный по белкам, жирам и углеводам СПЛП (группа контроля). В качестве основного параметра эффективности исследуемых продуктов использовали динамику между перцентилем и Z-Scores ИМТ (индекс массы тела) в начале и в конце исследовательского периода (день 180±2), в качестве дополнительно параметра эффективности оценивали жировую и тощую массу тела с помощью калиперометрии.

**Результаты.** На фоне приёма СПЛП, содержащего белок молочной сыворотки и соевый лецитин, как в виде монотерапии, так и совместно с эмульсией среднецепочечных триглицеридов у всех пациентов отмечено увеличение Z-Score и перцентиля ИМТ по сравнению с исходными данными, статистически значимых различий с группой контроля не выявлено ($p$ >0,05). Однако в группе 1 у 100% пациентов, по данным калиперометрии, отмечена положительная динамика в виде увеличения мышечной массы, которая была статистически значима ($p$ <0,05) по сравнению с группой контроля (20%). В группе 2 увеличение мышечной массы наблюдалось у 75% пациентов ($p$ >0,05).

**Заключение.** Полученные данные свидетельствуют, что применение СПЛП, представляющих собой белковый модуль, помимо повышения ИМТ способствует увеличению мышечной массы у пациентов с муковисцидозом. Целесообразно рассмотреть новые подходы к терапии пациентов с муковисцидозом: включение в диету высокобелковых СПЛП для предотвращения потери мышечной массы, мониторинг состава тела с целью улучшения контроля за течением заболевания.

**Ключевые слова:** муковисцидоз; нутритивная поддержка; пероральные питательные смеси; недостаточность питания; сывороточный протеин.

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# BACKGROUND

Cystic fibrosis (CF) is an inherited disorder of exocrine gland secretion caused by pathogenic variants in the *CFTR* gene. It is characterized by a chronic and progressive course with multiple organ involvement, including respiratory, digestive, and reproductive systems [1–5].

Exocrine pancreatic insufficiency, which results in malabsorption of proteins, fats, and fat-soluble vitamins, as well as elevated energy expenditure associated with dyspnea, cough, and chronic infectious pulmonary process, contributes to the development of nutritional deficiencies in patients with CF. This, in turn, may result in faster disease progression and reduced quality of life. However, optimal nutritional status in patients of this group is associated with improved lung function and increased survival [1, 2, 6–9].

From the moment of diagnosis, patients with CF are advised to consume a diet that provides a higher level of protein and energy than that recommended for healthy peers [1, 2, 6, 8–12]. In the Russian Federation, high-calorie oral nutritional supplements (ONS) are primarily used to address nutritional deficiencies in children aged one and above. These supplements are designed to ensure that the diet provides an adequate level of energy. Nevertheless, elevated energy and fat intake may be a contributing factor in the development of overweight and obesity in patients with CF, including those with latent CF, when the body mass index (BMI) is within the reference range but there is a deficiency in muscle mass. This may have a negative impact on the clinical outcomes. Indeed, an increase in body weight in patients with CF is not always associated with improved lung function. Patients with high lean body mass (musculoskeletal and visceral) were shown to have better lung function than patients with high body fat mass [10, 12]. Furthermore, several studies demonstrated a positive correlation between enhanced anabolism and protein supplementation in children with CF and growth retardation [10, 11]. In this context, given the increased protein losses associated with malabsorption and during episodes of catabolism in pulmonary exacerbations, protein intake in patients with CF may be increased by 50–100% compared with the age-related norm [1, 2, 6].

Currently, an analysis of the composition of the therapeutic foods included in the List of Specialized Therapeutic Foods for Disabled Children[1] reveals that Fresubin Protein® powder (Fresenius Kabi LLC, Germany) is the only product that is a protein module designed primarily to address protein deficiency. A literature review indicates that there are no clinical trials in the Russian Federation that assess the efficacy of modular protein formulas in patients with CF.

**The aim of the study** is to assess the tolerability, efficacy, and safety of ONS containing whey protein and soy lecithin, in children with CF in comparison with the long-established ONS approved by the Government of the Russian Federation.

# MATERIALS AND METHODS

## Study design

An open-label, single-center, prospective, randomized controlled study was conducted.

## Eligibility criteria

*Inclusion criteria:*

- patients of both sexes aged from 3 to 17 years;
- CF diagnosed in accordance with federal clinical guidelines;
- BMI below the 25$^{th}$ percentile, BMI Z-score/age <–1;
- signed informed consent from the patient's parents or a patient between the ages of 14 and 17.

*Exclusion criteria:*

- adverse events while taking special formulas or refusal to take such formulas;
- individual intolerance to the components of the investigated product;
- refusal by the patient's parent or a patient between the ages of 14 and 17 to participate in the clinical trial;
- any clinically significant laboratory or vital sign abnormality that, in the opinion of the study physician, prevents the safe participation of the patient in the study and/or has the potential to affect the results of the study;
- failure of the patient/parents, in the opinion of the study physician, to comply with the procedures of the protocol;
- termination of the clinical trial by the sponsor or regulatory authorities.

## Study setting

The clinical trial was conducted in an outpatient setting at the Morozovskaya Children's City Clinical Hospital of the Moscow City Health Department. The study population comprised patients diagnosed with CF, who were registered with the Medical and Genetic Department at the aforementioned institution.

## Study duration

The study period was 180 days and included five visits to the study physician: visit 1 (day 0), visit 2 (day 45±2), visit 3 (day 90±2), visit 4 (day 135±2), and visit 5 (day 180±2). Data were collected at all visits, including information on any complaints, medical history, assessment of the food diary, evaluation of concomitant therapy, registration of adverse events, and physical examination with assessment of physical development (measurement of height, weight,

[1] Order of the Government of the Russian Federation dated December 11, 2023, No. 3551-r "On Approval of the List of Specialized Therapeutic Foods for Disabled Children". Available from: https://www.consultant.ru/document/cons_doc_LAW_464007/ Access date: 03.09.2021.

**Table 1.** Study design

| Medical manipulations | Visit 1 (day 0) | Visit 2 (day 45±2) | Visit 3 (day 90±2) | Visit 4 (day 135±2) | Visit 5 (day 180±2) |
|---|---|---|---|---|---|
| Complaints, history | + | + | + | + | + |
| Nutrition diary assessment | + | + | + | + | + |
| Assessment of concomitant therapy | + | + | + | + | + |
| Recording of adverse events | + | + | + | + | + |
| Physical examination with assessment of physical development (height, weight, and body mass index) | + | + | + | + | + |
| Assessment of organoleptic properties of oral nutritional supplements | – | + | – | – | – |
| Caliperometry | + | – | + | – | + |

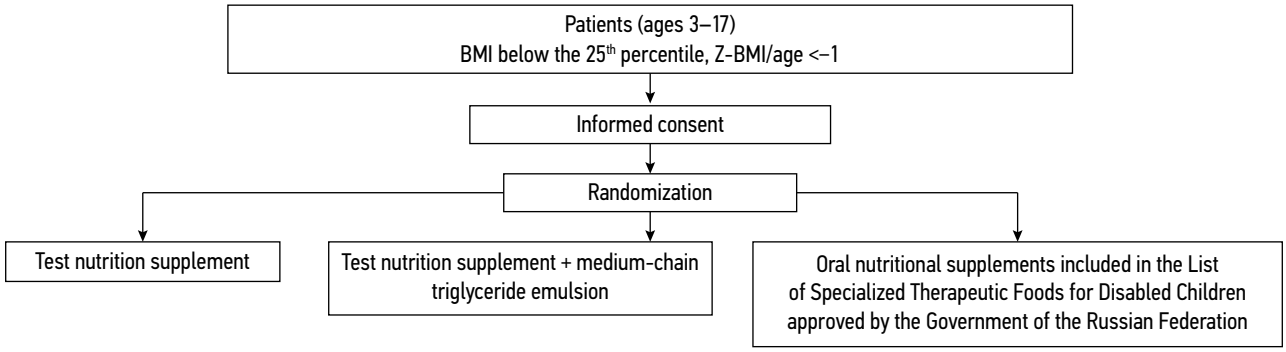


**Fig. 1.** Study design: ONS — oral nutritional supplements; BMI — body mass index.

and BMI). At visit 2, organoleptic properties of the ONS were additionally evaluated. At visits 1, 3, and 5, body composition was assessed by caliperometry. The study design is shown in Table 1 and Fig. 1.

## Intervention description

Prior to the start of the study, children who met the inclusion criteria were asked to taste the foods studied. All those who found the investigated ONS acceptable for consumption were then randomized. The randomization procedure was performed using a random number table.

All study participants were advised to adhere to their current dietary regimen, maintain a food diary, and calculate the energy value of the diet, including the proportion of proteins, fats, and carbohydrates consumed. The ratio of proteins, fats, and carbohydrates in the diet of the study participants corresponded to the age-related norms in CF, including an increased consumption of high-quality protein up to 20% and fats up to 35–40% of daily calorie intake. The ONS was permitted to be used in any form preferred by the child, including as a stand-alone product or added to milk porridges, soups, and drinks. The amount of supplemental food was determined based on the degree of nutritional deficiency and appetite. The daily amount of the ONS was divided into two or three equal portions. In addition to the nutritional support, all patients received the previously prescribed basic treatment (pathogenetic therapy, antibacterial therapy, enzyme replacement therapy, necessary symptomatic therapy, or kinesiotherapy).

## Main study outcome

The changes between BMI percentile and BMI Z-score at visit 1 (day 0) and visit 5 (day 180±2) relative to the baseline were used as the main efficacy parameter of the studied products.

The main safety parameter was the comparative incidence and development of adverse events.

## Additional study outcomes

The secondary efficacy point was defined as the changes between the caliperometry measures, including triceps skinfold (TSF) and shoulder muscle circumference (SMC), during visit 1 (day 0) and visit 5 (day 180±2) relative to the baseline.

## Subgroup analysis

Patients of both sexes diagnosed with CF and malnutrition who met the inclusion criteria were included in the clinical trial. A total of 14 patients aged 6 to 16 years were screened and divided into three groups (Table 2):

- Group 1 (*n*=5) comprised children with CF who received ONS containing whey protein and soy lecithin — Fresubin Protein® (Fresenius Kabi LLC, Germany);
- Group 2 (*n*=4) comprised children with CF who received test ONS in conjunction with an emulsion of medium-chain triglycerides;
- the control group (*n*=5) consisted of children with CF who were administered a balanced ONS included in the List of Specialized Therapeutic Foods for Disabled Children approved by the Government of the Russian Federation.

**Table 2.** General characteristics of the groups

| Study group | *n* | Median age (years) | Female patients (%) | Male patients (%) |
|---|---|---|---|---|
| Group 1: patients with cystic fibrosis receiving test nutrition supplement | 5 | 13 | 60 | 40 |
| Group 2: patients with cystic fibrosis receiving test nutrition supplement + medium-chain triglyceride emulsion | 4 | 12,5 | 25 | 75 |
| Control group: patients with cystic fibrosis receiving a balanced oral nutritional supplement | 5 | 10 | 40 | 60 |

**Table 3.** Comparative characteristics of oral nutritional supplements

| Oral nutritional supplement | Test nutrition supplement | Balanced oral nutritional supplement (control group) | Medium-chain triglyceride emulsion |
|---|---|---|---|
| Type of supplement | Modular formula containing only protein. It is used to supplement artificial or regular therapeutic diets | Standardized, balanced formula that can be used to supplement dietary intake or regular therapeutic feeding, or as a sole source of nutrition | Modular formula containing only fats (medium-chain triglycerides). It is used to supplement artificial or regular therapeutic diets |
| Presentation | Dry, 300 g | Dry, 322 g | Liquid, 250 ml |
| Protein | | | |
| Protein profile | Milk whey | Casein | |
| Fats, g in 100 g or 100 ml | 1 | 18.2 | 47.1 |
| Carbohydrates, g in 100 g or 100 ml | ⩽1 | 56.6 | — |
| Energy, g in 100 g or 100 ml | 360 | 463 | 450 |

The comparative characteristics of the ONS are shown in Table 3.

## Methods for registration of outcomes

Body weight and height were estimated using Auxology v. 1.0 b17® (Pfizer, 2003). A BMI Z-score of –1.0 to –1.9 indicated mild malnutrition, a Z-score of –2.0 to –2.9 indicated moderate malnutrition, and a Z-score of <–3.0 indicated severe malnutrition [13, 14].

Fat and lean (fat-free) body weight was estimated by caliperometry (TSF, mm). Upper arm circumference (UAC, cm) and SMC (cm) were measured using the following formula: SMC=UAC–0.314×TSF. Skinfold thickness was measured in the standing position at a standard point: above the triceps of the shoulder, midway between the acromial and ulnar processes, with the arm lowered and relaxed. Measurements were performed on the right and left arm using an electronic digital caliper KEC-100-1-I-D (JSC "TVES Tulinovsky Instrument-Making Plant," Russia).

The taste qualities of the products were evaluated according to a five-point scale, with "5" indicating an excellent rating, "4" indicating a good rating, "3" indicating a neutral rating, "2" indicating a dislike, and "1" indicating a strong dislike. In the event that a child was unable to provide a rating, the "eat–don't eat" system was employed.

## Statistical analysis

Statistical processing of data was performed using the Microsoft Office Excel. Descriptive statistics were used with the main criteria: arithmetic mean, standard deviation, median, minimum and maximum, and determination of 95%, 99%, and 99.9% confidence intervals. The Wilcoxon test was used to compare related samples in the same group. The non-parametric Mann–Whitney test was used to compare differences between groups. Results were considered statistically significant at $p < 0.05$.

# RESULTS

## Primary and secondary findings

The results of the study are presented in Tables 4–6.

At the start of the study period, the minimal and maximal BMI Z-scores ***in Group 1*** were –1.98 and –1.02, respectively. Additionally, the minimal BMI percentile was 2.37, with the maximum observed at 15.45. The minimal TSF thickness was recorded at –6.0 mm, the minimal SMC at 13.6 cm, the maximal TSF thickness at 12.0 mm, and the maximal SMC at 19.2 cm. At the end of the study period, the minimal and maximal BMI Z-scores within the same group were –1.06 and 0.39, respectively. The minimal and maximal BMI percentiles were 14.45 and 65.16, respectively. The minimal TSF thickness was 6.0 mm, the minimal SMC

**Table 4.** Results of scientific research in Group 1

| Patient | Age (years) | Body mass index Z-score | Centile | Triceps skinfold (mm) | Arm muscle circumference (cm) | Arm muscle circumference (cm) |
|---|---|---|---|---|---|---|
| *Visit 1 (day 0)* | | | | | | |
| 1 | 13 | –1.02 | 15.45 | 12 | 23 | 19.2 |
| 3 | 14 | –1.25 | 10.64 | 10 | 21 | 17.86 |
| 4 | 9 | –1.31 | 9.55 | 8 | 19 | 16.48 |
| 5 | 7 | –1.86 | 3.19 | 6 | 15.5 | 13.6 |
| 6 | 16 | –1.98 | 2.37 | 7 | 21 | 18.8 |
| Median | | –1.31 | 9.55 | 8 | 21 | 17.86 |
| Mean | | –1.48 | 8.24 | 8.6 | 19.9 | 17.18 |
| Standard deviation | | 0.41 | 5.46 | 2.40 | 2.83 | 2.26 |
| Minimum | | –1.98 | 2.37 | 6 | 15.5 | 13.6 |
| Maximum | | –1.02 | 15.45 | 12 | 23 | 19.2 |
| *Visit 5 (day 180±2)* | | | | | | |
| 1 | 13 | 0.39 | 65.16 | 10 | 25 | 21.8 |
| 3 | 14 | –1.05 | 14.75 | 8 | 22 | 19.4 |
| 4 | 9 | –0.96 | 16.8 | 9 | 20 | 17.17 |
| 5 | 7 | –1.06 | 14.45 | 8 | 17 | 14.4 |
| 6 | 16 | –1.02 | 15 | 6 | 24 | 22.1 |
| Median | | –1.02 | 15 | 8 | 22 | 19.4 |
| Mean | | –0.74 | 25.232 | 8.2 | 21.6 | 18.97 |
| Standard deviation | | 0.63 | 22.33 | 1.48 | 3.2 | 3.24 |
| Minimum | | –1.06 | 14.45 | 6 | 17 | 14.4 |
| Maximum | | 0.39 | 65.16 | 10 | 25 | 22.1 |

was 14.40 cm, whereas the maximal TSF thickness was 10.0 mm, and the maximal SMS was 22.10 cm. At the start of the study, all patients exhibited a BMI value that was below the 25$^{th}$ percentile (100%). The median BMI percentile was –9.55, whereas the median BMI Z-score was –1.31. By the end of the study period, one patient with CF (20%) exhibited a BMI value above the 25$^{th}$ percentile. The median BMI percentile was –15.0, while the median BMI Z-score was –1.02. At the start of the study, the median TSF thickness was 8 mm, a measurement that remained constant at the end of the study period. The median SMC at the start of the study was 17.86 cm and increased to 19.40 cm at the end of the study period.

At the start of the study period, the minimal and maximal BMI Z-scores ***in Group 2*** were –1.90 and –1.0, respectively. Additionally, the minimal BMI percentile was 2.90, with the maximum observed at 15.82. The minimal TSF thickness was recorded at 5.0 mm, the minimal SMC at 14.43 cm, the maximal TSF thickness at 12.0 mm, and the maximal SMC at 20.11 cm. At the end of the study period, the minimal and maximal BMI Z-scores within the same group were –1.79 and –0.75, respectively. The minimal and maximal BMI percentiles were 3.68 and 22.52, respectively. The minimal TSF thickness was 5.0 mm, the minimal SMC was 14.43 cm, whereas the maximal TSF thickness was 14.0 mm, and the maximal SMS was 21.80 cm. At the start of the study, all patients exhibited a BMI value that was below the 25$^{th}$ percentile (100%). The median BMI percentile was –4.26, whereas the median BMI Z-score was –1.74. At the end of the study, all patients (100%) had a BMI value below the 25th percentile. The median BMI percentile was –7.09, whereas the median BMI Z-score was –1.47. At the start of the study, the median TSF thickness was 6.50 mm and decreased to 6.0 mm at the end of the study. The median SMC at the start of the study was 17.91 cm and increased to 19.25 cm at the end of the study.

At the start of the study period, the minimal and maximal BMI Z-scores ***in the control group*** were –2.28 and –1.12, respectively. Additionally, the minimal BMI percentile was 1.13, with the maximum observed at 13.23. The minimal TSF thickness was recorded at 4.0 mm, the minimal SMC at 14.43 cm, the maximal TSF thickness at 10.0 mm, and the maximal SMC at 16.26 cm. At the end of the study period, the minimal and maximal BMI Z-scores within the same group were –2.46 and –0.83, respectively. The minimal and maximal BMI

**Table 5.** Results of scientific research in Group 2

| Patient number | Age (years) | Body mass index Z-score | Centile | Triceps skinfold (mm) | Arm muscle circumference (cm) | Arm muscle circumference (cm) |
|---|---|---|---|---|---|---|
| *Visit 1 (day 0)* | | | | | | |
| 2 | 12 | –1.6 | 5.48 | 7 | 19.8 | 17.6 |
| 12 | 15 | –1 | 15.82 | 6 | 22 | 20.11 |
| 13 | 9 | –1.88 | 3.04 | 5 | 16 | 14.43 |
| 14 | 13 | –1.9 | 2.9 | 12 | 22 | 18.23 |
| Median | | –1.74 | 4.26 | 6.5 | 20.9 | 17.91 |
| Mean | | –1.59 | 6.81 | 7.5 | 19.95 | 17.59 |
| Standard deviation | | 0.80 | 6.11 | 4.3 | 9.25 | 8.12 |
| Minimum | | –1.9 | 2.9 | 5 | 16 | 14.43 |
| Maximum | | –1 | 15.82 | 12 | 22 | 20.11 |
| Maximum | | –1.02 | 15.45 | 12 | 23 | 19.2 |
| *Visit 5 (day 180±2)* | | | | | | |
| 2 | 12 | –1.51 | 6.5 | 5 | 21 | 19.4 |
| 12 | 15 | –0.75 | 22.52 | 7 | 24 | 21.8 |
| 13 | 9 | –1.79 | 3.68 | 5 | 16 | 14.43 |
| 14 | 13 | –1.43 | 7.69 | 14 | 23.5 | 19.1 |
| Median | | –1.47 | 7.09 | 6 | 22.25 | 19.25 |
| Mean | | –1.37 | 10.09 | 7.75 | 21.12 | 18.68 |
| Standard deviation | | 0.72 | 8.59 | 5.0 | 9.96 | 8.77 |
| Minimum | | –1.79 | 3.68 | 5 | 16 | 14.43 |
| Maximum | | –0.75 | 22.52 | 14 | 24 | 21.8 |
| Maximum | | 0.39 | 65.16 | 10 | 25 | 22.1 |

percentiles were 1.0 and 20.39, respectively. The minimal TSF thickness was 5.0 mm, the minimal SMC was 14.43 cm, while the maximal TSF thickness was 12.0 mm, and the maximal SMS was 16.23 cm. At the start of the study, all patients exhibited a BMI value that was below the 25$^{th}$ percentile (100%). The median BMI percentile was –4.32, whereas the median BMI Z-score was –1.72. At the end of the study, all patients (100%) had a BMI value below the 25$^{th}$ percentile. The median BMI percentile was –14.96, whereas the median BMI Z-score was –1.04. At the start of the study, the median TSF thickness was 5.0 mm and increased to 7.0 mm at the end of the study. The median SMC at the start of the study was 15.70 cm and increased to 15.80 cm at the end of the study.

The changes in the nutritional status indicators while using the ONS are shown in Table 7 and Fig. 2.

The changes in the SMC are shown in Fig. 3. Data from the comparative analysis are presented in Tables 8, 9.

### Adverse events

No adverse events were reported in this study.

## DISCUSSION

### Summary of the primary study results

The administration of ONS containing whey protein and soy lecithin both as monotherapy and in conjunction with medium-chain triglyceride emulsion, resulted in a notable increase in Z-score and BMI percentile in all patients when compared to the baseline. No statistically significant differences were observed between the study groups and the control group ($p$ >0.05). Nevertheless, in Group 1, the caliperometry data indicated a positive trend, as evidenced by the increase in SMC (100%), which was statistically significant ($p$ <0.05) in comparison to the control group (20%). In Group 2, an increase in SMC was observed in 75% of patients ($p$ >0.05).

In addition, all patients rated the organoleptic properties of test nutrition supplement highly, with an average score of 5.0 on a five-point scale. The average rating of the organoleptic properties of the ONS, an emulsion of medium-chain triglycerides, was 3.0 points, whereas that of the balanced ONS was 3.8 points.

**Table 6.** Results of scientific research in control group

| Patient number | Age (years) | Body mass index Z-score | Centile | Triceps skinfold (mm) | Arm muscle circumference (cm) | Arm muscle circumference (cm) |
|---|---|---|---|---|---|---|
| *Visit 1 (day 0)* | | | | | | |
| 8 | 10 | –1.52 | 6.5 | 10 | 19.4 | 16.26 |
| 9 | 10 | –1.72 | 4.32 | 9 | 18.5 | 15.67 |
| 10 | 6 | –2.28 | 1.13 | 5 | 16 | 14.43 |
| 11 | 6 | –2.21 | 1.35 | 4 | 17 | 15.7 |
| 7 | 11 | –1.12 | 13.23 | 5 | 17.8 | 16.23 |
| Median | | –1.72 | 4.32 | 5 | 17.8 | 15.7 |
| Mean | | –1.77 | 5.3 | 6.6 | 17.74 | 15.65 |
| Standard deviation | | 0.48 | 4.95 | 2.7 | 1.31 | 0.74 |
| Minimum | | –2.28 | 1.13 | 4 | 16 | 14.43 |
| Maximum | | –1.12 | 13.23 | 10 | 19.4 | 16.26 |
| *Visit 5 (day 180±2)* | | | | | | |
| 8 | 10 | –1.04 | 14.96 | 12 | 20 | 16.23 |
| 9 | 10 | –0.99 | 16.05 | 12 | 20 | 16.23 |
| 10 | 6 | –2.46 | 1 | 5 | 16 | 14.43 |
| 11 | 6 | –0.83 | 20.39 | 6 | 17 | 15.1 |
| 7 | 11 | –1.13 | 12.86 | 7 | 18 | 15.8 |
| Median | | –1.04 | 14.96 | 7 | 18 | 15.8 |
| Mean | | –1.29 | 13.052 | 8.4 | 18.2 | 15.558 |
| Standard deviation | | 0.66 | 7.27 | 3.36 | 1.78 | 0.78 |
| Minimum | | –2.46 | 1 | 5 | 16 | 14.43 |
| Maximum | | –0.83 | 20.39 | 12 | 20 | 16.23 |

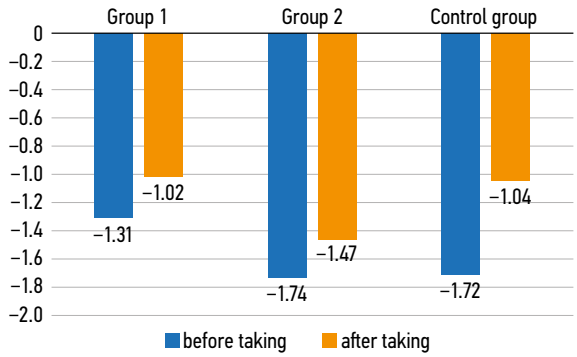


**Fig. 2.** Dynamics of body mass index (Z-score, median).

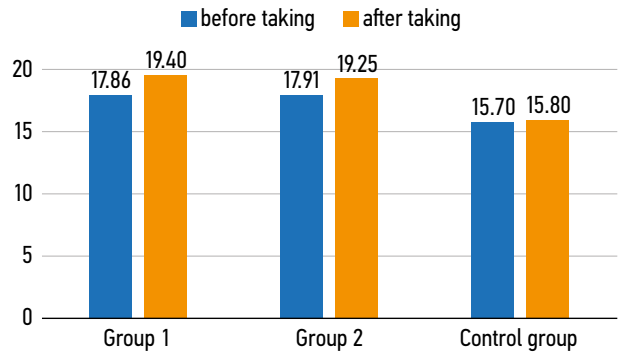


**Fig. 3.** Dynamics of shoulder muscle circumference, cm (median).

## Discussion of the primary study results

In consideration of the findings of the literature review, it was evident at the start of the study that there were no long-term, randomized controlled trials in the Russian Federation that had been conducted to assess the efficacy of ONSs in patients with CF. Our research provided the first data on the use of the ONS, which is a protein module, in patients with CF in the Russian Federation. Similar studies with a duration of 180 days were not described in the literature.

The findings indicate that the use of ONSs, which are protein modules, in conjunction with an elevated BMI, is associated with an increase in muscle mass in patients with CF. In this regard, novel strategies for the management of CF warrant consideration, including the incorporation of high-protein ONSs into the diet to prevent muscle mass loss and the monitoring of body composition to enhance disease control.

The analysis of the protein concentration ratio in therapeutic food products included in the List of Specialized Therapeutic Foods for Disabled Children indicates that test nutrition

**Table 7.** Dynamics of nutritional status

| Severity of malnutrition | Z-score | Group 1 (*n*/%) | | Group 2 (*n*/%) | | Control group (*n*/%) | |
|---|---|---|---|---|---|---|---|
| | | Before taking ONS | After taking ONS | Before taking ONS | After taking ONS | Before taking ONS | After taking ONS |
| Mild | From –1 to –1.9 | 5/100 | 3/60 | 5/100 | 3/75 | 3/60 | 2/40 |
| Moderate | From –2 to –2.9 | — | — | — | — | 2/40 | 1/20 |
| Severe | <–3 | — | — | — | — | — | — |
| None | ±1 | — | 2/40 | — | 1/25 | — | 2/40 |

*Note. ONS — oral nutritional supplement.*

**Table 8.** Comparative analysis (dynamics between visits 1 and 5, Wilcoxon t-test)

| Группы | Body mass index Z-score | Arm muscle circumference | Triceps skinfold |
|---|---|---|---|
| Within group 1 | $p < 0.05$ | $p < 0.05$ | $p > 0.05$ |
| Within group 2 | $p < 0.05$ | $p < 0.05$ | $p > 0.05$ |
| Within control group | $p > 0.05$ | $p > 0.05$ | $p < 0.05$ |

**Table 9.** Comparative analysis (dynamics between visits 1 and 5, U-criterion)

| Визиты | Group 1 | Control group | Group 2 | Control group | Group 1 | Group 2 |
|---|---|---|---|---|---|---|
| *Body mass index Z-score* | | | | | | |
| 1 | $p > 0.05$ | | $p > 0.05$ | | $p > 0.05$ | |
| 5 | $p > 0.05$ | | $p > 0.05$ | | $p > 0.05$ | |
| *Arm muscle circumference* | | | | | | |
| 5 | $p < 0.05$ | | $p > 0.05$ | | $p > 0.05$ | |

supplement is the most protein-concentrated, thereby making it the most clinically and economically justified ONS for patients who require an increased protein intake [5].

### Study limitations

A potential limitation of this study is the small sample size, which may have affected the statistical data. This is due to the rare incidence of CF, which is classified as an orphan disease, as well as the limited number of patients who met the inclusion criteria.

## CONCLUSION

The use of ONSs, which are a protein module, was demonstrated to increase both BMI and muscle mass in patients with CF. This may, in turn, lead to improvements in disease control and quality of life of patients in this group.

## ADDITIONAL INFORMATION

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**Competing interests.** The authors declare that they have no competing interests.

**Authors' contribution.** All authors confirm compliance of their authorship with the international ICMJE criteria. The largest contribution is distributed as follows: V.V. Zarubina — analysis of the obtained data, writing the article; T.N. Kekeeva, I.P. Vitkovskaya — scientifi c editing of the article; M.A. Mukhina, E.E. Yakushina, O.V. Vysokolova — patient consultation, obtaining data for analysis.

**Ethics approval.** The present study protocol was approved by the local Ethics Committee of the Morozov Children's Municipal Clinical Hospital (No. 179-1 by 15.12.2022).

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## AUTHORS' INFO

*** Vera V. Zarubina,** MD;
address: 1/9, 4th Dobryninskij lane, 119049 Moscow, Russia;
ORCID: 0000-0002-9724-7653;
eLibrary SPIN: 5364-9263;
e-mail: vv.zarubina@gmail.com
**Olga V. Vysokolova,** MD;
ORCID: 0000-0003-4155-2226;
eLibrary SPIN: 1632-7821;
e-mail: opopova@morozdgkb.ru
**Mariya A. Mukhina,** MD;
ORCID: 0000-0002-8329-386X;
eLibrary SPIN: 8391-1228;
e-mail: mariemuch@yandex.ru
**Elena E. Yakushina,** MD;
ORCID: 0000-0001-7090-0395;
eLibrary SPIN: 2942-1154;
e-mail: e.e.yakushina@gmail.com
**Tatiana N. Kekeeva,** MD;
ORCID: 0000-0002-4986-5748;
eLibrary SPIN: 5818-1395;
e-mail: kekeeva.genetic@gmail.com
**Irina P. Vitkovskaya,** MD, Cand. Sci. (Medicine), Associate Professor;
ORCID: 0000-0002-0740-1558;
eLibrary SPIN: 2970-0361;
e-mail: vip-dzm@mail.ru

## ОБ АВТОРАХ

*** Зарубина Вера Владимировна;**
адрес: Россия, 119049, Москва, 4-й Добрынинский переулок, д. 1/9;
ORCID: 0000-0002-9724-7653;
eLibrary SPIN: 5364-9263;
e-mail: vv.zarubina@gmail.com
**Высоколова Ольга Владимировна;**
ORCID: 0000-0003-4155-2226;
eLibrary SPIN: 1632-7821;
e-mail: opopova@morozdgkb.ru
**Мухина Мария Алексеевна;**
ORCID: 0000-0002-8329-386X;
eLibrary SPIN: 8391-1228;
e-mail: mariemuch@yandex.ru
**Якушина Елена Евгеньевна;**
ORCID: 0000-0001-7090-0395;
eLibrary SPIN: 2942-1154;
e-mail: e.e.yakushina@gmail.com
**Кекеева Татьяна Николаевна;**
ORCID: 0000-0002-4986-5748;
eLibrary SPIN: 5818-1395;
e-mail: kekeeva.genetic@gmail.com
**Витковская Ирина Петровна,** канд. мед. наук, доцент;
ORCID: 0000-0002-0740-1558;
eLibrary SPIN: 2970-0361;
e-mail: vip-dzm@mail.ru

* Corresponding author / Автор, ответственный за переписку