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SEASONAL DYNAMICS OF THE LEVEL OF CALCIDIOL IN CHILDREN WITH CYSTIC FIBROSIS LIVING IN THE SOUTH OF RUSSIA

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СЕЗОННАЯ ДИНАМИКА УРОВНЯ КАЛЬЦИДИОЛА У ДЕТЕЙ С МУКОВИСЦИДОЗОМ, ПРОЖИВАЮЩИХ НА ЮГЕ РОССИИ

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The study included 78 children: 38 patients with cystic fibrosis (CF) (median age 8.2 [4.9–13.8] years) and 40 healthy children (median age 7.66 [2.0–12.1] years), living in the Stavropol region during 2018–2019. Vitamin D sufficiency was assessed by the content of calcidiol – 25(OH)D in blood plasma. Seasonal fluctuations in the level of calcidiol during the year in children with CF were more pronounced than in children from the control group – 12.2 [7.6–20.2] ng/ml in winter, 29.8 [21.3–37 .9] ng/ml in spring, 33.2 [26.5–39.1] ng/ml in summer and 22.6 [11.4–30.5] ng/ml in autumn, in healthy children the level is 25(OH)D during 2018 was 34.8 [24.8–53.1] ng/ml in winter, 31.1 [24.6–44.6] ng/ml in spring, 30.4 [23.3–35.3] ng/ml in summer and 41.9 [32.1–55.2] ng/ml in autumn. Serum calcidiol levels were significantly lower in CF children compared to the control children group in winter ($p=0.007$) and autumn ($p=0.04$). During the study, the number of children with vitamin D deficiency and severe vitamin D deficiency significantly decreased. At the beginning of the study, severe vitamin D deficiency was detected in 40 % of patients with CF; after adjusting the dose of vitamin received in spring ($p<0.005$) and summer ($p<0.005$), it was not found in any of the children. On the contrary, the frequency of normal vitamin D sufficiency increased significantly by 36.7 % in spring ($p<0.05$), by 50 % in summer ($p<0.01$), and by 16.7 % in autumn ($p>0.05$), compared with the first determination of 25(OH)D in winter. Thus, the frequency of vitamin D deficiency in CF patients is statistically significantly higher than in healthy children. The problem of vitamin D deficiency in children with CF is quite relevant due to the low awareness of CF patients and their parents about the critical role of cholecalciferol in this disease.

Keywords: cystic fibrosis, vitamin D, 25(OH)D, preventive dose, cholecalciferol

В исследование включено 78 детей: 38 пациентов с муковисцидозом (МВ) (медиана возраста 8,2 [4,9–13,8] лет) и 40 здоровых детей (медиана возраста 7,66 [2,0–12,1] лет), проживающих в Ставропольском крае. Оценка обеспеченности витамином D проводилась по содержанию кальцидиола – 25(OH)D в плазме крови. Сезонные колеба-

ния уровня кальцидиола в течение года у детей с МВ были более выраженными, чем у детей из группы контроля, – 12,2 [7,6–20,2] нг/мл в зимнее время, 29,8 [21,3–37,9] нг/мл в весеннее время, 33,2 [26,5–39,1] нг/мл летом и 22,6 [11,4–30,5] нг/мл осенью, у здоровых детей уровень 25(OH)D в течение 2018 года составил 34,8 [24,8–53,1] нг/мл в зимнее время, 31,1 [24,6–44,6] нг/мл в весеннее время, 30,4 [23,3–35,3] нг/мл в летнее время и 41,9 [32,1–55,2] нг/мл в осеннее время года. Уровни кальцидиола сыворотки были значимо ниже у детей с МВ, по сравнению с детьми из группы контроля в зимнее время (p=0,007) и осеннее время года (p=0,04). В ходе исследования количество детей, имеющих дефицит и тяжелый дефицит витамина D, значимо снизилось, в начале исследования тяжелый дефицит витамина D был выявлен у 40 % больных с МВ, после коррекции получаемой дозы витамина весной (p<0,005) и летом (p<0,005) не был обнаружен ни у одного ребенка. Частота нормальной обеспеченности витамином D, напротив, значимо возросла – на 36,7 % весной (p<0,05), на 50 % летом (p<0,01) и на 16,7 % осенью (p>0,05), по сравнению с первым определением 25(OH)D зимой. Таким образом, частота дефицита витамина D у пациентов с МВ статистически значимо превосходит таковую у здоровых детей. Проблема дефицита витамина D у детей с МВ достаточно актуальна ввиду низкой осведомленности пациентов с МВ и их родителей о важной роли холекальциферола при данном заболевании.

Ключевые слова: муковисцидоз, витамин D, 25(OH)D, профилактическая доза, холекальциферол

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CF – cystic fibrosis
CFTR – cystic fibrosis transmembrane conductance regulator
ELISA – enzyme-linked immunosorbent assay
25(OH)D – calcidiol

Cystic fibrosis (CF) is the most common monogenic genetic disease among Caucasians, caused by a mutation in the CFTR gene (transmembrane conductance regulator of CF), leading to a sharp reduction in the duration and quality of life without adequate treatment. According to neonatal screening, the prevalence of pathology in Russia reaches, on average, 1 case per 10 thousand newborns [1–3].

Dysfunction of CFTR, a chloride channel in epithelial cells of exocrine glands, leads to their damage due to impaired transport of excessively viscous secretions [4, 5]. The variety of clinical manifestations of CF (chronic upper and lower respiratory tract infection, exocrine and endocrine pancreas insufficiency, liver pathology, gastrointestinal tract damage, male infertility, pseudo-barter syndrome, etc.) is determined by a wide range of mutations in the CFTR gene, to date more than 2,000 mutations have been detected [4].

A decrease in absorption accompanies CF and various metabolic disorders of vitamin D. Modern studies show that up to 90 % of patients have serum calcidiol levels (25(OH)D) of less than 30 ng/ml (75 nmol/l) [6–8]. Due to the multi-systemic nature of the non-calcemic effects of vitamin D, it is possible to say with certainty about the adverse effects of its deficiency in CF patients – progression of chronic upper and lower respiratory tract infection, reduced muscle strength, osteopenia and osteoporosis [9–11].

Peculiarities of the geographical position of Russia determine the high frequency of vitamin D deficiency in the population, but in patients with CF vitamin D deficiency is also determined by additional risk factors [12, 13]. First, secondary deficiency of fat-soluble vitamins, incl. vitamin D, in CF is a characteristic manifestation of malabsorption [14, 15]. In addition, in patients with CF, the hydroxylation of cholecalciferol in the liver is impaired. R.K. Lark, etc., has expressed views on the accelerated release of vitamin D before exposure to 25-hydroxylase of the liver as a result of the enterohepatic discharge. Increased oxidative activity and activity of cytochrome P450 (CYP24A1) results in accelerated degradation of metabolized 25(OH)D. Among the causes of vitamin D deficiency, there is also a decrease in the number of receptors for vitamin D in the target tissues, mainly in the intestine [1, 9].

In patients with CF, endogenous vitamin D synthesis may be reduced, as many patients avoid exposure to sunlight due to increased photosensitivity due to certain antibiotics. CF patients who are exposed to UV rays often have a thin subcutaneous fat layer that is unable to store the required amounts of cholecalciferol, further exacerbating the problem. Decreased storage of synthesized and consumed vitamin D may be associated with reduced vitamin D-binding protein (DBP) levels in CF patients [1, 5, 8].

The close relationship between vitamin D availability, pulmonary function, the severity of the inflammatory process, and the frequency of exacerbations of chronic bronchopulmonary infection cause research interest in studying seasonal changes in vitamin D status in patients with CF.

The study aimed to study seasonal fluctuations in the level of calcidiol in children with CF in the South of Russia and to analyze the effectiveness of preventive and therapeutic dosages of cholecalciferol.

Material and Methods. The study included 78 children living in the Stavropol Territory. The study was conducted during 2018–2019; blood sampling was carried out quarterly.

The analyzed group included 38 patients with CF aged 0 to 18 years. All patients were diagnosed according to the national consensus «Cystic fibrosis: definition, diagnostic criteria, therapy» and the recommendations of the European CF Society [4]. The age of the examined patients (of which 19 (50.0 %) were boys and 19 (50.0 %) girls) averaged 8.9±4.6 years. The median age was 8.2 [4.9–13.8] years.

The control group is represented by children without chronic diseases, aged 0 to 18 years (n=40, of which 16 (40.0 %) were boys and 24 (60.0 %) girls). The mean age of these children was 7.6±4.6 years. The median age was 7.66 [2.0–12.1] years.

The level of vitamin D was assessed by the content of its intermediate metabolite, calcidiol (25(OH)D), in the blood plasma. The concentration was determined at the center of the Moscow State Scientific Center by enzyme immunoassay (ELISA) using kits from EuroimmunAG (Germany), an EnSpire plate spectrofluorimeter (PerK iN Elmer, Finland), a Biosan Laboratory Centrifuge LMC-3000 centrifuge and a Thermo-Shaker Biosan PST-60-thermoshaker. HL-4 during 2018 (Winter: Jan–Feb 2018, Spring: May 2018, Summer: Aug–Sep 2018, Fall: Nov 2018).

The results were interpreted based on the recommendations of the International Society of Endocrinologists (2011) and the recommendations of the European Consensus: serious deficit – 25(OH)D level less than 10 ng/ml; deficit – 10 to 20 ng/ml; insufficiency – 21–29 ng/ml; normal content 30–100 ng/ml, a level of more than 100 ng/ml has been rated as excessive, requiring a dosage of cholecalciferol [7, 16].

The physical development of children under five years of age was assessed using the WHO Anthro (version 3) and WHO AnthroPlus for children over five.

Statistical data was processed using the AtteStat-software package STATISTICS v.10.0 (StatSoft Inc., USA). The correspondence of the statistical distribution of empirical indicators to the theoretical Gaussian normal distribution was assessed using the Shapiro – Wilk test. Quantitative data that did not conform to normal distribution law was shown as median, lower and upper quarters: Q1 (25 %) and Q3 (75 %). Quantitative data subject to normal distribution law was shown as arithmetic mean (M) and standard deviation (SD).

The Mann – Whitney test was used to estimate the statistical significance of the differences in quantitative data between two unrelated groups in a statistical comparison. The test χ^2 was used to estimate the statistical significance of quality differences when all the absolute values in the contingency table were above 10; if the absolute values in the contingency table were between 5 and 10, The Yates-corrected χ^2 test was used; if absolute values were less than 5, the Fisher exact test was used. The discrepancies were considered statistically significant at $p<0.05$.

Results and Discussion. As a result of the analysis of the data obtained during the study, it was revealed that the minimum level of calcidiol in children with CF was observed in the winter season ($p<0.05$ when compared with the level of calcidiol in the spring, summer and autumn seasons). It should be noted that in patients with CF, seasonal fluctuations in the level of calcidiol were more pronounced during the year – 12.2 [7.6–20.2] ng/ml in winter, 29.8 [21.3–37.9] ng/ml in spring, 33.2 [26.5–39.1] ng/ml in summer and 22.6 [11.4–30.5] ng/ml in autumn, in healthy children the level of 25(OH)D during 2018 was 34.8 [24.8–53.1] ng/ml in winter, 31.1 [24.6–44.6] ng/ml in spring, 30.4 [23.3–35.3] ng/ml in summer and 41.9 [32.1–55.2] ng/ml in autumn. Serum calcidiol levels were significantly lower in children with CF compared with children from the control group in the winter ($p=0.007$) and autumn ($p=0.04$) seasons. Thus, the level of 25(OH)D in patients with CF at different times of the year varies widely and is 5–65 % lower (in summer and winter, respectively) than in healthy children.

When comparing the results between boys and girls in the same groups, no significant differences were found – so the median of calcidiol in patients with CF in the winter season was 11.1 [7.6–12.8] ng/ml in boys and 12.5 [7.6–20.0] ng/ml in girls ($p=0.2$), in the control group, the median of calcidiol in the winter season in boys and girls was 34.6 [22.3–37.3] ng/ml and 35.7 [24.1–49.9] ng/ml, respectively ($p=0.1$). For the rest of the year, the medians of calcidiol in boys and girls in the analyzed groups also did not differ significantly.

Figure 1 compares the incidence of severe deficiency, deficiency, insufficiency, and normal vitamin D supply in sick and healthy children.

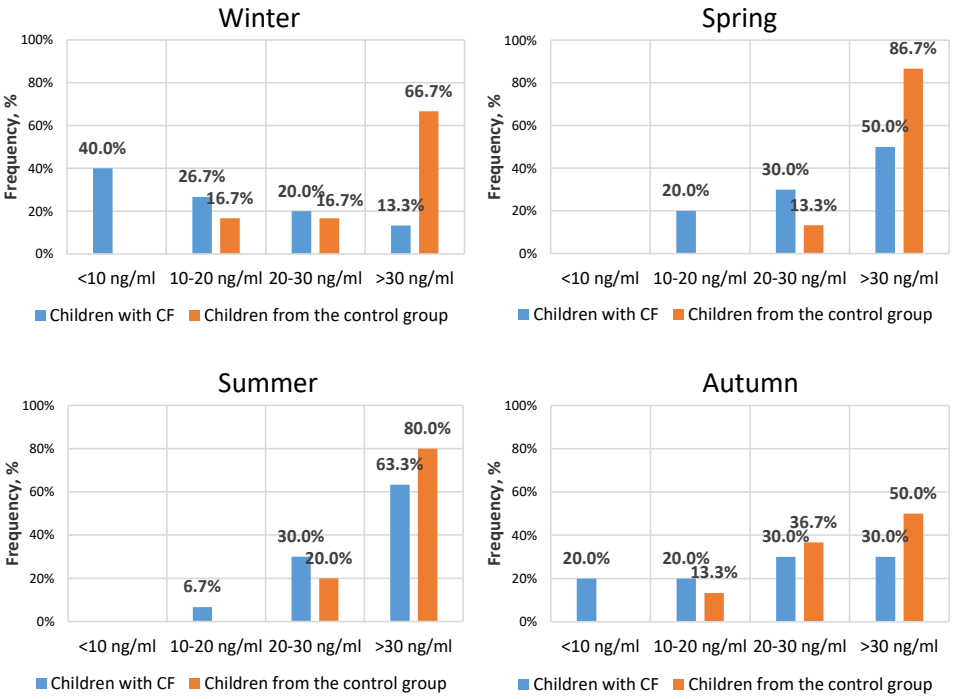

Fig. 1. Frequency of different levels 25(OH)D in children with CF and children from the control group, depending on the time of year

The comparative analysis demonstrates significant differences in the incidence of vitamin D insufficiency and deficiency in CF patients and healthy children. In general, the frequency of vitamin D deficiency (level below 20 ng/ml) in CF patients significantly exceeds that in healthy children at any time of the year, except for summer – 20 (66.7 %) and 5 (16.7 %) in winter ($p<0.005$); 6 (20.0 %) and 0 (0 %) in springtime ($p<0.01$); 12 (40.0 %) and 4 (13.3 %) in autumn, respectively ($p<0.02$).

The proportion of CF patients with insufficient levels of 25(OH)D was the highest in the winter season, reaching the lowest value in summer – 36.7 %. The proportion of children from the control group with an insufficient level of 25(OH)D also significantly decreased in summer

compared to winter and spring. The increase in the number of children with CF with vitamin D deficiency and insufficiency in the autumn-winter period emphasizes the importance of drug prevention of hypovitaminosis D during this season.

A moderately positive correlation was found between age and vitamin D levels both in patients with CF (r=–0.44; p=0.014) and in healthy children (r=–0.71; p=0.0001). An analysis of the age characteristics of vitamin D supply showed that the median 25(OH)D decreases with age, both in sick and healthy children (Fig. 2).

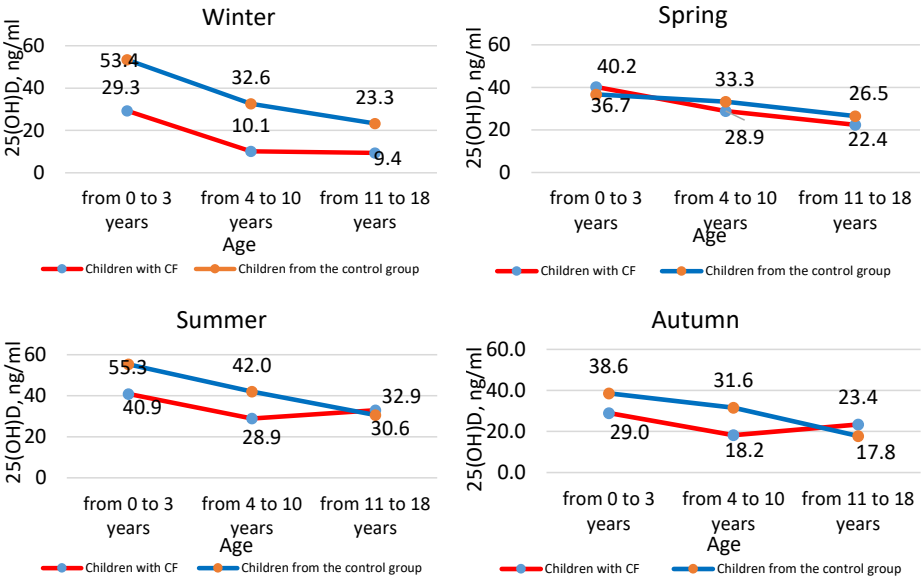

Fig. 2. Level 25(OH)D in children with CF and children from the control group of different ages, depending on the time of year

Among children under three years of age, differences between serum calcidiol levels in patients with CF and the control group are not significant during most of the year, except for winter (p=0.01). In patients with CF from 4 to 10 years (p=0.001 in winter, p=0.04 in summer, p=0.01 in autumn) and from 11 to 18 years (p=0.01 in winter) season, p=0.03 in autumn), the content of calcidiol in the blood for most of the year was statistically significantly lower than in the group of healthy children, which emphasizes the need for mandatory intake of vitamin D supplements in patients with cystic fibrosis older than four years and adolescents. The identified age-related features reflect a typical pattern for Russian children of a decrease in vitamin D supply, which has been repeatedly demonstrated in other studies [6, 7, 12, 13]. These age-related features are explained by the fact that the prophylactic use of cholecalciferol preparations in the first year of life makes it possible to achieve relatively high calcidiol numbers. However, in the future, it progressively decreases, accompanied by the development of deficiency and vitamin D deficiency by school age. At the same time, CF patients, due to the above reasons, have a much higher risk of developing hypovitaminosis D and are characterized by lower levels of 25(OH)D throughout all periods of childhood.

Analysis of the effect of sunshine duration on the level of 25(OH)D in children with CF and children from the control group showed that in children with CF, there is a moderate correlation between the concentration of calcidiol in the blood serum and the period of sunshine (r=0.5, p=0.0001), in children from the control group, there is no trend towards an increase in the provision of calcidiol with an increase in the length of daylight hours (r=–0.06, p=0.5).

To explain the contradiction, we analyzed the duration of sunshine and the average concentration of 25(OH)D in children with CF and children from the control group receiving and not receiving cholecalciferol preparations.

The analysis showed that children in the control group taking vitamin D (Fig. 3) do not correlate with plasma calcidiol level and sunshine period (g=–0.12, p=0.4), and patients with CF have r=0.4, p=0.001.

Children not taking vitamin D showed a stronger correlation between calcidiol and sunshine in the CF group (g=0.7, p=0.0001), while healthy children not taking vitamin D

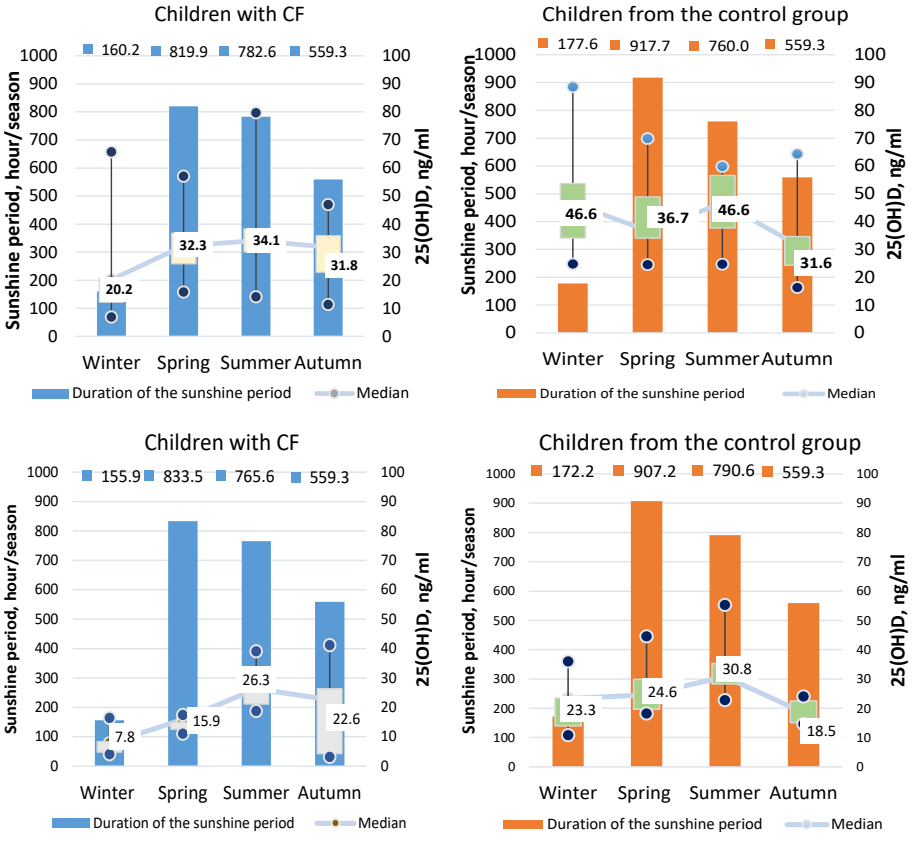

Fig. 3. Analysis of the effect of the duration of sunshine on the level of 25(OH)D in children taking and not taking cholecalciferol

had no significant correlation (r=0.3, p=0.09). Thus, during the study, the natural sun is the predominant way to obtain vitamin D in children with CF, probably due to malabsorption and the inability to use vitamin D from food effectively.

The most important part of the analysis was comparing calcidiol levels in healthy and CF patients depending on cholecalciferol intake and daily dose. During the study, the proportion of children with CF taking cholecalciferol after informing their parents about vitamin D adequacy increased from 57 % to 73 % (p>0.05). The number of control children receiving cholecalciferol drugs remained at the same level as at the beginning of the study.

Average doses of cholecalciferol received by children with cystic fibrosis during most of the year were higher than those of healthy children. They were prescribed following the recommendations of the National Consensus «Cystic fibrosis: definition, diagnostic criteria, therapy» and the National Programme «Vitamin D Deficiency in Children and Adolescents of the Russian Federation: Modern Approaches to Correcting the Situation [4, 13].

At the beginning of the study, doses of cholecalciferol in patients with CF were lower than recommended – 1076±661 IU/day and even slightly lower than in healthy children – 1184±342 IU/day (p=0.073). Subsequently, the prescriptions were corrected, and the dosages of vitamin D preparations in the spring season in patients with CF began to exceed the dosages of children from the control group – 3080±1288 IU/day and 1469±531 IU/day, respectively (p=0.0007). Patients with CF at the first stage received increased doses of cholecalciferol to correct vitamin D deficiency and insufficiency. Later, as a risk group for the formation of hypovitaminosis D – in the summer, the average doses were 1543±952 IU/day in patients with CF and 1400±447 IU/day in children from the control group (p=0.436), in the autumn season – 2113±2075 IU/day in patients with CF and 1350±516 IU/day in children from the control group (p=0.131).

The distribution of children from the analyzed group and the control group (Fig. 1) indicates a significant decrease in the number of children with vitamin D deficiency and a severe deficiency during the study, so at the beginning of the study, severe vitamin D deficiency was detected in 40 % of patients with CF, after correction the received dose of vitamin in spring (p<0.005) and summer (p<0.005) was not detected in any child. The appearance in autumn (p>0.05, compared with the winter season) of children with calcidiol deficiency indicates mainly a decrease in the adherence of the patients' parents to the drug prevention of hypovitaminosis D, as well as the essential role of reducing the intensity of natural insolation in the provision of patients with CF with vitamin D considering the phenomenon of malabsorption. The frequency of normal vitamin D supply, on the contrary, significantly increased by 36.7 % in spring (p<0.05), by 50 % in summer (p<0.01) and by 16.7 % in autumn (p>0.05), compared with the first determination of 25(OH)D in winter.

According to various studies, about 90 % of patients with CF have exocrine pancreatic insufficiency and require an additional intake of fat-soluble vitamins (A, D, E and K). However, even with supplementation of standard multivitamin complexes soluble in fat, many patients still suffer from vitamin D deficiency [4]. Fat-soluble vitamin deficiency was observed in all age groups of patients, including children in the first months of life [6, 7].

A study by Daley T. et al. found that despite the addition of cholecalciferol, 7 % of patients with CF had a serious vitamin D deficiency (25(OH)D < 11 ng/ml), and 90 % had a vitamin D deficiency (25(OH)D < 30 ng/ml) where 36.7 % to 86.7 % of patients with CF had insufficient levels of vitamin D, despite taking cholecalciferol [16]. Boyle M. P. et al. (USA) showed that despite a 4.5-fold increase in vitamin D dosage, about half of adult CF patients failed to reach the target level of 25(OH)D > 30 ng/ml [17].

The prevalence of vitamin D deficiency/deficiency in CF patients in different countries ranged from 23 % to 95 % [16–18]. The available data vary widely: researchers from the United Kingdom (UK 54°N) report a prevalence of vitamin D deficiency in 87 % of patients, while Australian researchers (Australia 25°S) Prevalence of vitamin D deficiency is reported in 3 % of patients with CF, probably due to the different geographical location of these countries [19]. People living in northern latitudes are at increased risk of developing vitamin D deficiency due to reduced exposure to natural UV radiation, as an endogenous synthesis of vitamin D drops dramatically from the end of September to the beginning of March, which is also true for the Stavropol Territory, in 45 NL [13].

To date, there are not so many studies on the prevalence of vitamin D deficiency among pediatric CF patients in the Russian Federation. In patients with cystic fibrosis living in Moscow and the Moscow region, it has been shown that, depending on the time of year, 50–75 % of patients with CF had a 25(OH)D level of less than 30 ng/ml [6]. According to the results of a study conducted in St. Petersburg, vitamin D levels of less than 30 ng/ml were detected in 80.4 % of children with cystic fibrosis, which also correlates with the results of our study and indicates the need for drug prevention of hypovitaminosis D in children with CF despite the geographical location of the region [20, 21].

Conclusions. According to the study's results, an insufficient level of vitamin D in the blood serum was detected with a frequency of 36.7 % to 86.7 % in children with CF and from 13.3 % to 50.0 % in healthy children, depending on the season, living in the Stavropol edge. The frequency of vitamin D deficiency in patients with CF is statistically significantly higher than in healthy children at any time of the year except summer. The level of 25(OH)D in children with CF reached the norm only in the summer, while in the population of healthy children, the median of vitamin D was above 30 ng/ml throughout the year. The median level of 25(OH)D in winter and autumn was significantly higher in children from the control group. The median 25(OH)D decreases with age in both sick and healthy children, which reflects a typical pattern for Russian children of a decrease in vitamin D sufficiency. Its seasonal fluctuations. There is a correlation between the level of natural insolation and the concentration of 25(OH)D serum, clearly shown in the group of children without the additional intake of cholecalciferol preparations. The problem of vitamin D deficiency in children with CF is quite relevant due to the low awareness of CF patients and their parents about the critical role of cholecalciferol in this disease, given its non-classical effects, especially immunotropic effect, which requires the achievement of optimal levels of blood calcidiol.

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