The effect of vitamin D provision on biomarkers of inflammation in bronchial asthma in children

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Annotation

Introduction. Asthma is a widespread disease in childhood and has a persistent tendency to increase. Therefore, the search for factors influencing this process, as well as biomarkers reflecting the degree of asthma control, is an urgent problem.

Objective. To study the relationship of vitamin D levels with the serum periostin and TGF-β1 concentration in children with asthma.

Materials and methods. The cross-sectional (one-stage) study included 80 children aged 6 to 17 years (average age — 12±3.2 g). The subjects were divided into 2 groups: children with asthma — group 1 (n = 40); group 2 — the control group (n = 40). In all children, the assessment of the concentration of 25(OH)D, periostin and TGF-β1 in the blood serum was studied.

Results. Median (Me) 25(OH) in patients with asthma was statistically significantly lower than in children of the comparison group (16.7 ng/ml, versus 25.7 ng/ml, p = 0.017), and did not depend on the severity of the disease, corresponded to a deficiency condition in both mild (16.2 ng/ml) and with an average severity of asthma (16.8 ng/ml) (p = 0.041). Me of periostin in 1st group was within the normal range (730.2 ng/ml), but statistically significantly exceeded the indicator of 2nd group (539.7 ng/ml, $p < 0.05$) and did not depend on the age and duration of asthma. High rates of periostin were observed in children with moderate severity of asthma with a disease experience of 4–6 years (617.2 ng/ml). Me of TGF-β1 in both groups corresponded to normal values (309.0 and 369.6 pg/ml, respectively, $p > 0.05$) and did not depend on the age and duration of asthma.

Conclusions. VD deficiency is registered in children with asthma 2 times more often than in healthy children in Ryazan region. The serum concentration of periostin increased in proportion to the severity of asthma. Vitamin D deficiency can be one of the risk factors for the development of asthma and lead to an imbalance in the periostin and TGF-β system.

Keywords: asthma, vitamin D, periostin, transforming growth factor β1, children.

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Влияние обеспеченности организма витамином D на биомаркеры воспаления при бронхиальной астме у детей

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Аннотация

Актуальность. Бронхиальная астма (БА) является широко распространенным в детском возрасте заболеванием и имеет стойкую тенденцию к росту. Поэтому поиск факторов, влияющих на этот процесс, а также биомаркеров, отражающих степень контроля БА, является актуальной проблемой.

Цель. Изучить взаимосвязь уровня витамина D с концентрацией периостина и TGF-β1 в сыворотке крови у детей с БА.

Материалы и методы. В поперечное (одномоментное) исследование были включены 80 детей в возрасте от 6 до 17 лет (средний возраст — 12±3,2 г.). Обследуемые были распределены на 2 группы: дети с БА — 1-я группа (n = 40); 2-я группа — контрольная группа (n = 40). У всех детей проводили оценку концентрации 25(OH)D, периостина и TGF-β1 в сыворотке крови.

Результаты. Медиана (Me) 25(OH)D витамина D у пациентов с БА была статистически значимо ниже, чем у детей группы сравнения (16,7 нг/мл, против 25,7 нг/мл, p = 0,017), и не зависела от тяжести течения заболевания, соответствовала дефицитному состоянию как при легкой степени (16,2 нг/мл), так и при средней степени тяжести БА (16,8 нг/мл) (p = 0,041). Me периостина в 1-й группе была в пределах нормы (730,2 нг/мл), но статистически значимо превышала показатель 2-й группы (539,7 нг/мл, p < 0,05) и не зависела от возраста и длительности БА. Высокие показатели периостина имели дети со средней степенью тяжести БА при длительности заболевания 4–6 лет (617,2 нг/мл). Me TGF-β1 в обеих группах соответствовала нормальным значениям (309,0 и 369,6 пг/мл соответственно, p > 0,05) и не зависела от возраста и длительности БА.

Заключение. В г. Рязани у детей с БА дефицит VD регистрируется в 2 раза чаще, чем у здоровых детей. Показатели периостина в сыворотке крови возрастали пропорционально степени тяжести БА. Дефицит витамина D может выступать одним из факторов риска развития БА и приводить к дисбалансу в системе периостина и TGF-β.

Ключевые слова: бронхиальная астма, витамин D, периостин, трансформирующего фактора роста β1, дети.

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INTRODUCTION

Bronchial asthma (BA) is one of the most common chronic diseases in children population and characterized by the presence of respiratory symptoms such as wheezing, shortness of breath, chest tightness, cough that are varied in time and intensity [1]. Internal (predominantly genetic) and external factors (allergens, tobacco smoke, industrial dust, atmospheric pollution) are involved in the development of asthma. The prevalence of BA increases from year to year and a rapid growth is particularly noted in children population that prompts a further search for factors, contributing to this trend as well as biomarkers, demonstrating the level of asthma control [2–4].

Periostin is one of markers of allergic inflammation, which is a protein of the epithelium extracellular matrix with a molecular weight of 90 kDa, belonging to the Fasciolide family. Periostin is expressed by osteoblasts, localized in fetal tissues, embryonic periosteum, placenta, heart valves, adrenal tissue, lungs and thyroid [5–6]. In BA the synthesis of periostin is carried out by fibroblasts, epithelial and endothelial cells as well as bronchial smooth muscle cells [7]. Periostin is involved in the acute phase of inflammation in BA, providing synthesis and secretion by eosino-

phils of IL-6 and IL- 8 interleukins, which transform β-1 and β-2 growth factors, cysteine leukotrienes and prostaglandin E2. Periostin forms congestion in the basement bronchial membrane in the chronic phase of inflammation, providing its thickening and remodeling. Periostin gene expression is under the control of numerous cytokines and hormones. Periostin expression regulators include bone morphogenetic proteins (type 2 and 4) platelet-derived growth factor, vascular endothelial growth factor, connective tissue growth factor-2, angiotensin II, IL-3, IL-4, IL-6 and IL-13. Literature data of recent years point out that patients with a higher concentration of periostin in the blood serum are characterized by a frequent persistence of bronchial inflammation, also higher probability of connective tissue restructuring of epithelium submucosal layer (remodeling) [8, 9].

In recent years, a special attention is paid to tissue growth factors in the study of processes of remodeling the respiratory tract in asthma. TGF-β1 is one of cytokines, involved in the process. Produced by epithelial cells of the bronchial mucosa, inflammatory infiltrate cells, TGF-β1 has a pronounced immunoregulatory, antiproliferative and regenerating effect. This cytokine correlates with increased activity of Th17, aggravating inflammation in the respiratory tract. Moreover, there are data, indicating the inhibitory effect of TGF-β1 on relaxation of smooth bronchial muscles by induction of shortening smooth muscle fibers and increasing bronchial hyperreactivity [10].

The role of vitamin D (VD) in the development and control of BA remains an active area of research. VD is a pleiotropic hormone, which, along with the regulation of calcium and phosphorus metabolism, has a strong immunomodulatory effect [11]. VD is able to inhibit the function of T-helpers type 2 (Th2-cells), and also the proliferation and differentiation of B-cells into plasma cells that causes a decrease in the secretion of immunoglobulins E (IgE) [12]. It is known that Th2-response plays a crucial role in all allergic diseases. Therefore, a growing interest in the impact of VD on the pathogenesis of chronic inflammation in BA is justified [13]. In БА VD, by affecting VD receptors (VDR), reduces hypertrophy of bronchial smooth muscles, hyperplasia of goblet cells, subepithelial collagen deposition and fibroblast activity that leads to a lower rate of remodeling process [14, 15].

Thus, study of the relationship between VD concentration and inflammation biomarkers in BA is a relevant objective.

OBJECTIVE OF THE STUDY

Study the relationship of vitamin D level with the serum periostin and TGF-β1 concentration in children with BA.

MATERIALS AND METHODS

One-stage single-site randomized study involved 80 children aged 6-17 (average age — 12 ± 3,2), including girls — 29 (36,0 %), boys — 51 (64,0 %), permanently residing in Ryazan. The children were divided into 2 groups: group 1 (main group) included 40 children with BA, group 2 contained 40 children (control group) (Table 1). The main group is divided into 2 subgroups: 1а — children with moderate asthma (n = 23, 57,5 %), 1б — children with a mild disease (n = 17, 42,5 %).

The study plan was approved by the local Ethics Committee, FSBEI HE RyazSMU of the Ministry of Health of Russia (Protocol of 09.03.2021). The parents of all the children, taking part in the study,

Table 1. **Characteristics of the study participants**
Таблица 1. **Характеристика участников исследования**

Indocator	Group 1 (n = 40)	Group 2 (n = 40)	p
Age, years	12,0±2,8	11,9±3,3	0,96
Girls, n (%)	15 (37,5 %)	14 (35,0 %)	0,12
Boys, n (%)	25 (62,5 %)	26 (65,0 %)	0,20

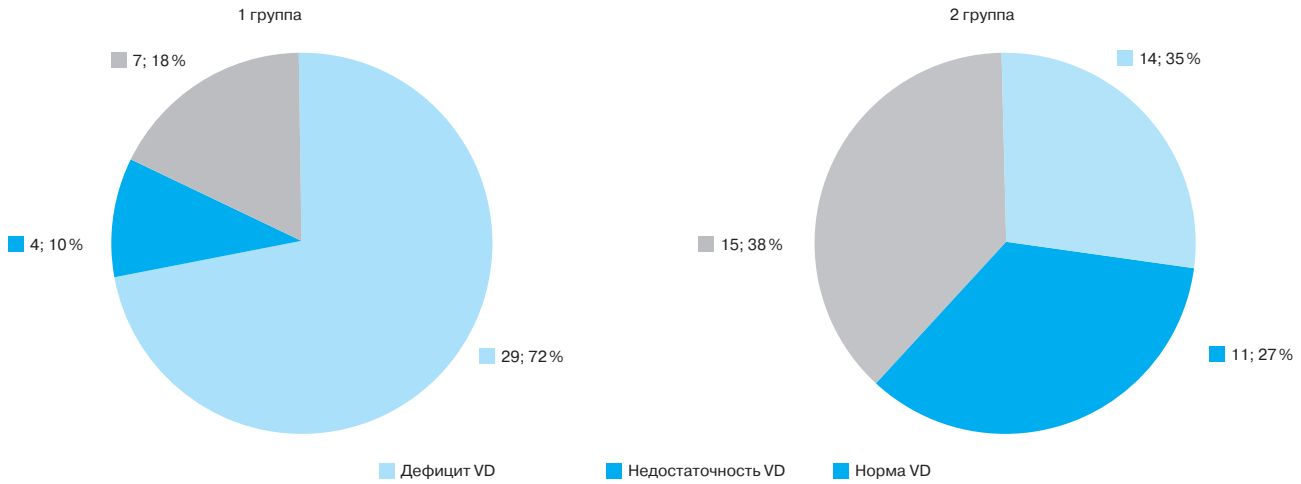

Fig. 1. **Provision of the examined children with VD**
Рис. 1. **Обеспеченность обследованных детей VD**

were familiarized with the regulation of the study and signed an informed consent.

SBI "City children's clinic № 3» (chief medical officer — A. O. Burdukova), Central research laboratory of FSBEI HE RyazSMU of the Ministry of Health of Russia (the head of the laboratory — candidate of medical science, associate professor A. A. Nikiforov) were bases to conduct the study.

Criteria for inclusion in the study: the established diagnosis of "bronchial asthma" for at least 1 year, verified according to GINA2022 [16] and Federal clinical guidelines [1]; patient age of 5-17 years; obtaining informed consent from parents and patients for the study.

Exclusion criteria: the presence of malignant neoplasm in the surveyed, an acute disease or exacerbation of other chronic diseases, endocrine or genetic pathology, surgery for the past 4 weeks, intake of anti-spasmatic drugs, disorders of calcium-phosphorus metabolism.

Material sampling was in March-April, 2021. Serum concentration 25(OH) D, periostin, TGF-β1 were determined by the ELISA method, using "25OH Vitamin D Total ELISA Kit" (DIAsourceImmunoAssaysSA, Belgium),

«ELISA Kit for Periostin», (Cloud-Clone Corp., USA), "ELISA Kit for Transforming Growth Factor Beta 1" (Cloud-Clone Corp., USA) in the Central Research laboratory, FSBEI HE RyazSMU of the Ministry of Health of Russia with further calculation of the median and interquartile range (Me; 25–75%). The obtained results were evaluated according to the National Program "Vitamin D insufficiency in children and adolescents in the Russian Federation: modern approaches to correction" (2018). Concentration 25(OH)D > 30 ng/mL was considered as the normal level, moderate deficiency — 21–30 ng/ml, severe deficiency — < 20 ng/ml [17]. Periostin value in the serum samples/plasma in 500-fold dilution: 132,4~859,6 ng/ml. TGF-β1 value in 3-fold dilution in the serum/plasma: 82,4~702,4 pg/ml [18].

Statistical data processing was conducted using MS Excel 2016 and Statistica 6.0 standard software packages. Shapiro-Wilk tests were used to analyze the normality of parameter distribution. Continuous variable was presented as the median (Me) with interquartile range (25–75 percentile). Categorial variables were determined in as a percentage (%). The assessment of differences between groups was conducted using non-parametric Mann-Whitney (U-test) and Pearson's (χ^2) tests with corrections for small samples. Differences were considered significant at $p < 0,05$.

STUDY RESULTS AND THEIR DISCUSSION

The examination revealed that most children had low level of 25(OH)D in the blood serum. At the same time, VD deficiency was recorded twice as often as in the control group ($p = 0,002$) (fig. 1).

The median of 25(OH)D in the group of children with BA was 1,5 times as low as in the control group and corresponded to the deficient condition — 16,7 ng/ml [7,1; 22,8] versus 25,7 ng/ml [17,4; 34,2] in group 2, respectively (p = 0,017).

The severity of the disease in children did not depend on the concentration of 25(OH)D in the blood serum in the main study group. Me in children with mild BA was 16,2 ng/ml [13,5; 22,8]), versus 16,8 ng/ml [13,9; 21,6] in the moderate severity (p = 0,041). 11,7 % (n = 2) of children with mild and 21,7 % (n = 5) with moderate asthma had optimal VD vitamin sufficiency. 37,5 % (n = 15) of children of the control group had normal VD-status.

Me 25(OH)D did not reach optimal values in any age category of children with BA, however, the rate in group 1 with teenage children was statistically significantly lower than in the control group (p < 0,05) (Table 2).

Periostin median in the group of children with BA was statistically much higher than the rate of the control group — 730,0 ng/ml [390,8; 1109,7] versus 536,7 ng/ml [452,0; 666,2] in group 2, respectively (p = 0,044) (fig. 2).

In the group of children with BA 30,0 % (n = 12) had the increased level of periostin. Periostin Me was 593,0 ng/ml [318,0; 846,3] with mild BA versus 751,0 ng/ml [505,0; 1140,0] with moderate BA (p = 0,027). 23,5 % (n = 4) of children with mild and 34,7 % (n = 8) with moderate asthma experienced the increased level of periostin (p > 0,05). 15,0 % (n = 6) of children in the control group had the same increased level. This is probably due to the activity of bone metabolism during active growth.

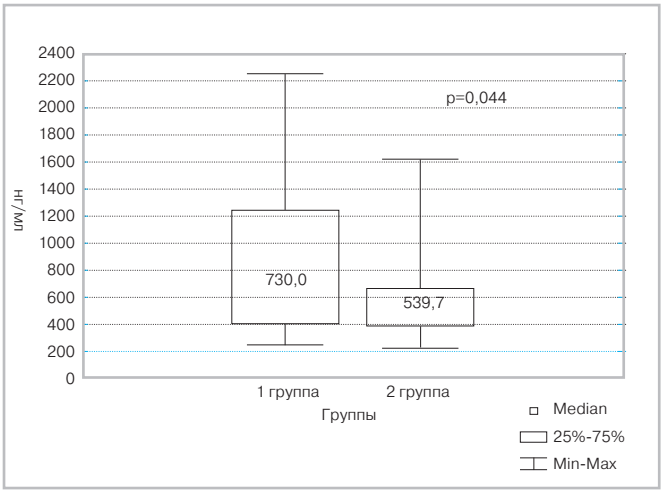

Fig. 2. **Median periostin in the blood serum of the examined children (ng/ml)**
Рис. 2. **Медиана периостина в сыворотке крови у обследованных детей (нг/мл)**

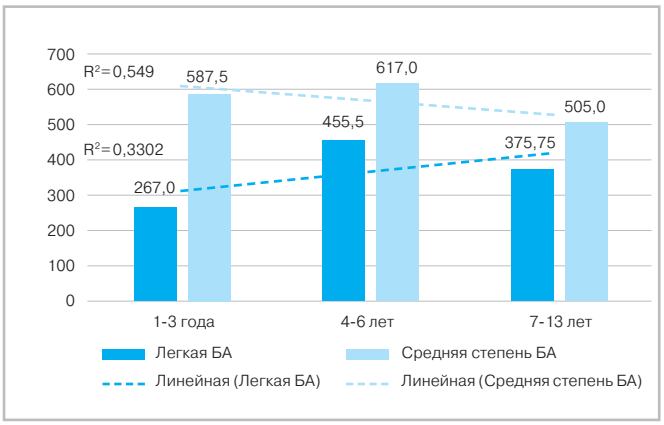

Fig. 3. **Median periostin in blood serum in children with asthma depending on the duration of the disease (ng/ml)**
Рис. 3. **Медиана периостина в сыворотке крови у детей с БА в зависимости от длительности заболевания (нг/мл)**

Table 2. **Median 25(OH)D in the blood serum of the examined children (ng/ml)**
Таблица 2. **Медиана 25(OH)D в сыворотке крови у обследованных детей (нг/мл)**

Age, years (n)	Group 1 Me [25 %; 75 %]	Group 2 Me [25 %; 75 %]	p
5–6 years (n = 3)	16,8 [16,8; 16,8]	32,7 [25,0; 40,4]	>0,05
7–9 years (n = 19)	19,4 [15,7; 30,5]	31,1 [21,1; 40,1]	>0,05
10–14 years (n = 36)	16,7 [13,7; 21,9]	25,3 [17,7; 33,5]	>0,05
15–17 years (n = 22)	13,5 [11,7; 16,9]	24,4 [16,6; 26,8]	<0,05

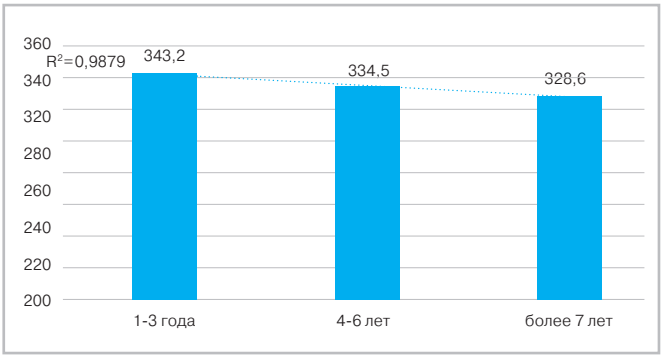

Fig. 4. **Median TGF-β1 in blood serum in children depending on the duration of AD (pg/ml) (p > 0.05)**
Рис. 4. **Медиана TGF-β1 в сыворотке крови у детей в зависимости от длительности БА (пг/мл) (p > 0,05)**

Me of periostin did not depend on the duration of the disease among children with BA, but this rate was higher (p >0,05) with moderate BA (fig. 3).

No clear correlation was found in the analysis of the relationship between the level of periostin and VD (Table 3).

The median of TGF-β1 in both groups of the examined children corresponded to normal values: 309,0 pg/ml [210,9; 408,6] and 355,0 pg/ml [257,4; 426,8], respectively (p > 0,05). However, Me TGF-β1 was statistically significantly lower among children with mild BA than in moderate asthma (300,9 [154,5; 342] pg/ml), versus 369,6 [296,1; 455,7] mg/ml, respectively, and lower than in children of the control group (355,0 pg/ml [257,4; 426,8]) (p < 0,05).

Me TGF-β1 in the blood serum was within the normal values in children with BA, and the lowest rate was noted with the duration of BA more than 7 years, which may indicate the properly selected anti-inflammatory therapy and high patient compliance (p > 0,05) (fig. 4).

Published meta-analysis of recent literature review indicate the presence of low VD sufficiency among pediatric patients with BA. The works by Wang Q et al. (2021) note that the level of 25(OH)D in the blood serum was much lower in children with BA (5 711 participants) than in children without asthma (21 561 people) [19]. The same results were obtained by Russian researchers (S. S. Masalskiy et al., 2018) [20]. The findings coincide with the conclusions of these authors — low VD sufficiency was detected in more than 70% of the examined children with BA.

The relationship between the level of periostin in the blood serum and the presence of BA is also being actively discussed. Inoue T. et al. (2016) noted that the concentration of periostin in the blood serum was higher in children with BA, compared to children with no allergic diseases. The authors also pointed to the need for determining periostin content in the blood serum to diagnose and monitor BA in children [21]. The works by Song J. S. et al. (2015) found that a high level of periostin in the blood serum in children with BA was associated with hyperreactivity of the respiratory tract [22, 23] S. S. Masalskiy and others. (2018) revealed that the level of serum periostin was significantly higher in children with BA, compared to healthy children, and directly correlated with the severity of BA [24]. In our study the level of periostin in the blood serum in children with BA was also statistically much higher than the rate of children in the control group, though, these figures were within the normal values and the concentration of periostin

Table 3. **Distribution of children by level 25(OH)D and periostin in blood serum in children with asthma**
Таблица 3. **Распределение детей по уровню 25(OH)D и периостина в сыворотке крови у детей с БА**

Rate	Increase in the concentration of periostin in the blood serum, n (%)	Normal concentration of periostin in the blood serum, n (%)	p
Severe VD deficiency, (n = 29)	10 (34,5 %)	19 (65,5 %)	> 0,05
Moderate VD deficiency, (n = 4)	1 (25,0 %)	3 (75,0 %)	> 0,05
Norm of VD, (n = 7)	1 (14,3 %)	6 (85,7 %)	> 0,05

in children with moderate BA was statistically significantly higher than in a mild degree of the disease, though both the rates were within the normal values.

It is considered that TGF-β1 plays a central role in the pathogenesis of remodeling the respiratory tract in BA, which can occur at any age, regardless of the severity degree and is caused by complex pathogenetic interactions between different biologically active molecules and external triggers. The work by N. L. Potapova, I. N. Gaymolenko (2019) revealed a significant difference in the content of serum TGF-β1 in children with BA, compared to the group of healthy children [10]. Our study has not found incidents of the increased content of serum TGF-β1 in either patients with BA or the controlled group. In this case, patients with mild BA had the level of TGF-β1 statistically much lower than in the moderate severity of the disease.

CONCLUSIONS:

1. The incidence of vitamin D deficiency in children with BA from Ryazan was recorded twice as often as in healthy children, and it did not depend on the severity of asthma.
2. Periostin rate in the blood serum increased in proportion to the severity of BA.
3. Vitamin D deficiency may be one of risk factors for developing BA, causing imbalance in the system of periostin and TGF-β.
4. It is advisable to monitor the level of 25(OH) D in the blood serum with subsequent correction in children with BA.

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THE AUTHORS' CONTRIBUTION TO THE WORK

Natalia A. Belykh – development of the concept and design of the study, editing the text of the article.

Inna V. Pisnyur – review of publications on the topic of the article, collection of material, statistical data processing, text preparation, writing and editing of the text of the article.

Aleksandr A. Nikiforov, Larisa V. Nikiforova – conducting research, analyzing the data obtained.

ВКЛАД АВТОРОВ В РАБОТУ

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