

Characteristics of bone mineral density and its biochemical markers in children with bronchial asthma

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Abstract

Patients with asthma are at increased risk of developing osteopenia due to decreased bone mineral density (BMD). Particular attention is given to the role of vitamin D, whose deficiency is associated with the management of symptoms and bone health.

Study Objective. To study BMD and its biochemical markers, with an emphasis on vitamin D status and intake in children with asthma in the Moscow region.

Materials and Methods. Anamnestic, questionnaire, and laboratory methods were used, including assessment of nutritional impact, grade D, biochemical markers of bone metabolism, and molecular genetic analysis. Mineral support was obtained using X-ray densitometry. Data were statistically processed using SPSS Statistics 26 (IBM) using parametric and nonparametric methods at a significance level of $p < 0.05$.

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Results. The included study included 100 children with asthma, 15 % of whom had AD, and showed decreased BMD of varying severity. Most patients had low vitamin D levels, which were gradually adjusted and required oral cholecalciferol. High-dose inhaled glucocorticosteroids were associated with a more frequent decrease in BMD, while higher BMD values were recorded in children with moderate physical activity. The level of 25(OH)D was significantly lower in patients with asthma carrying the GG genotype of the *VDR* (FokI) gene polymorphism compared to those with the AA and AG genotypes. No relevant medical studies on bone health were identified.

Conclusion. This study confirms a significant decrease in BMD in children with asthma compared to those in medical settings and reveals significant changes in biochemical markers of bone metabolism. Low vitamin D levels and limited physical activity in this group of patients necessitate comprehensive treatment and correction of metabolic changes to prevent long-term complications, including osteoporosis. A multidisciplinary approach that combines stress management, nutritional status improvement, and physical activity is essential to BMD and reduce the risk of bone disease in adulthood.

Keywords: bronchial asthma, children, bone mineral density, vitamin D, risk factors

Conflict of Interest

Smolkin Yu. S. is a member of the editorial board; the authors assure that the article has undergone all stages of peer review.

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Характеристика минеральной плотности кости и ее биохимических маркеров у детей с бронхиальной астмой

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Аннотация

Актуальность. Пациенты с бронхиальной астмой имеют повышенный риск развития остеопении в результате снижения минеральной плотности кости (МПК). Особое внимание уделяется роли витамина D, недостаток которого ассоциирован с низким контролем симптомов астмы и ухудшением состояния костной ткани.

Цель исследования. Изучение состояния МПК и ее биохимических маркеров, с акцентом на изучении содержания и метаболизма витамина D у детей Московской области, страдающих бронхиальной астмой.

Материалы и методы. В исследовании использованы анамнестический, анкетно-опросный и лабораторные методы, включая оценку нутритивного статуса, уровня витамина D, биохимических маркеров костного обмена и молекулярно-генетический анализ. Минеральная плотность кости определялась методом рентгеновской денситометрии. Данные статистически обрабатывались с помощью SPSS Statistics 26 (IBM) с использованием параметрических и непараметрических методов при уровне значимости $p < 0,05$.

Результаты. В исследование включены 100 детей с бронхиальной астмой, у 15% которых выявлено снижение МПК различной степени выраженности. У большинства пациентов уровень витамина D был низким, что сопровождалось недостаточным поступлением кальция и колекальциферола с пищей. При применении высоких доз ингаляционных глюкокортикостероидов (от 400 мкг и выше в сутки) чаще отмечалось снижение МПК. Среди детей с умеренной физической активностью показатели МПК были выше. Уровень 25(OH)D был значимо ниже у пациентов с БА с генотипом GG полиморфного варианта гена *VDR* (FokI) по сравнению с носителями генотипов AA и AG. Значимого влияния проанализированных генетических факторов на состояние костной ткани выявлено не было.

Заключение. Данное исследование подтверждает снижение МПК у детей с бронхиальной астмой по сравнению со здоровыми сверстниками и выявляет значимые изменения биохимических маркеров костного обмена. Низкий уровень витамина D и ограничение физической активности у этой группы пациентов подчеркивают необходимость комплексного мониторинга и коррекции метаболических нарушений для предотвращения долгосрочных осложнений, включая остеопороз. Важно применять мультидисциплинарный подход, сочетающий контроль воспаления, оптимальный нутритивный статус и физическую активность, что способствует сохранению МПК и снижению рисков костных заболеваний в зрелом возрасте.

Ключевые слова: бронхиальная астма, дети, минеральная плотность кости, витамин D, факторы риска

Конфликт интересов

Смолкин Ю. С. — член редакционной коллегии; авторы заверяют, что статья прошла все этапы рецензирования.

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List of Abbreviations:

BMD:	bone mineral density
BA:	bronchial asthma
BMC:	bone mineral content
ICS:	inhaled glucocorticosteroids
BMI:	body mass index

Список сокращений:

МПК:	минеральная плотность кости
БА:	бронхиальная астма
СМК:	содержание минералов в кости
ИГКС	ингаляционные глюкокортикостероиды
ИМТ	индекс массы тела

INTRODUCTION

The state of bone metabolism in childhood plays a key role in ensuring normal physical development, preventing musculoskeletal disorders, and reducing the risk of osteoporosis in adulthood. The formation of bone mineral density (BMD) in children and adolescents depends on many factors, including genetic characteristics, level of physical

activity, diet, hormonal status, and the effects of external factors [1].

In recent years, there has been increased interest in researching patterns of BMD changes in children, as early deviations can cause serious long-term consequences [2]. Particular attention is drawn to the problem of reduced BMD in children with chronic diseases, particularly bronchial asthma [3]. Bronchial

asthma (BA) is one of the most common chronic respiratory diseases, most often debuting in childhood, and can not only be accompanied by respiratory disorders, but also affect other systems of the sick child's body, including bone tissue [3]. For a long time, asthma and osteopenic conditions were considered separate pathological processes, and when treating children with asthma, clinicians traditionally focused on assessing and correcting respiratory function [4]. However, the use of glucocorticosteroids (GCS), reduced physical activity, and chronic inflammation can all potentially contribute to bone metabolism disorders and a decrease in BMD [5]. Such data can be found in numerous publications, which show that children with asthma have a more frequent and pronounced decrease in BMD than their healthy peers, especially against the background of a long-term course of the disease and the use of high cumulative doses of inhaled GCS [6]. In recent years, the role of vitamin D in allergic diseases, including in children with asthma, has been actively studied, and the relationship between insufficient vitamin D levels and poor control of asthma symptoms has already been confirmed [7, 8].

THE OBJECTIVE OF THIS WORK is to study the state of the BMD, its biochemical markers, and vitamin D status in children in the Moscow region suffering from bronchial asthma.

This study was approved by the Local Ethics Committee of the Moscow Region State Budgetary Healthcare Institution "NIKID MH MO" No. 12 on December 22, 2021.

STUDY OBJECT. One hundred children with asthma were examined. 73 (73%) boys and 27 (27%) girls (the average age of patients was 12.8 ± 3.6 years, median age was 14.0 years (10.4; 16.0) were among them. Inclusion criteria: diagnosis of asthma, age under 18 years, informed consent signed by parents (guardians). Exclusion criteria: presence of concomitant chronic microbial-inflammatory, autoimmune, or hereditary diseases. The control group of children aged 6 to 18 years consisted of 61 children. Among

the healthy children examined ($n = 61$), there were 37 boys (60.7%) and 24 girls (39.3%), with a mean age of 12.1 ± 3.4 and a median age of 11 years.

METHODS USED IN THE STUDY

1. Anamnestic method, including analysis of medical history, life history, and family history as part of the verification of the diagnosis of asthma.
2. A questionnaire survey method was used to assess the consumption of foods containing calcium and vitamin D. Calcium consumption was assessed using a questionnaire, recording the daily dose of calcium supplements and calculating its intake from food based on data from a 3-day food diary. Calcium intake was calculated using the computer program Mobile Android application "Formula for slimness for children and adolescents" [9].
3. The anthropometric parameters of patients were assessed using the Quetelet body mass index (BMI) ($\text{weight (kg)} / \text{height}^2 \text{ (m)}^2$). A percentile system was used to assess the nutritional status of children. Values in the range from the 25th to the 75th percentile were considered normal. The target values for children and adolescents were those corresponding to normal values for healthy children of the same sex and age, i.e., the 50th percentile. To assess the height and weight indicators of young children (under 2 years of age), the weight-for-height index (WHI) was used ($\text{actual weight} / \text{ideal weight for height and gender} \times 100\%$). Overweight and obesity in children aged 5 to 19 years are defined as follows: overweight — if the BMI for the corresponding age exceeds the median value specified in the Standard Indicators of Physical Development of Children by more than one standard deviation; and obesity — if the excess of the median value specified in the Standard Indicators of Physical Development of Children is more than two standard deviations.

4. Vitamin D levels were assessed based on the blood content of its intermediate metabolite, 25(OH)D calcidiol, and vitamin D concentration. The concentration of 25(OH)D calcidiol was determined using an enzyme-linked immunosorbent assay (ELISA) kit from Euroimmun AG (Germany). The results of 25(OH)D level determination were interpreted in accordance with the guidelines of the International Society of Endocrinology (2011) and the European Consensus Recommendations: severe deficiency — 25(OH)D level below 10 ng/mL; deficiency — 10 to 20 ng/mL; insufficiency — 21–29 ng/mL; normal content — 30–100 ng/mL, a level above 100 ng/mL was considered excessive, requiring correction of the vitamin D dose [10]. Assessment of vitamin D content by enzyme-linked immunosorbent assay in the laboratory of the Federal Budgetary Institution Central Research Institute of Epidemiology of Rospotrebnadzor.
5. Determination of biochemical markers related to bone formation (ionized calcium, total calcium, osteocalcin, alkaline phosphatase, acid phosphatase, C-terminal telopeptides of type I collagen, parathyroid hormone, creatinine, calcitonin) was performed by enzyme-linked immunosorbent assay in the laboratory of the Federal State Budgetary Institution Central Research Institute of Epidemiology of Rospotrebnadzor.
6. Molecular genetic analysis was performed on total DNA isolated from whole blood leukocytes using a standard phenol-chloroform extraction method. The polymorphism of cytochrome P450 biotransformation genes was studied by PCR using primers selected for the study. Genes and polymorphisms for study: 1. *CALCR* (c.1340C>T) — encodes the calcitonin hormone receptor, which is involved in the control of calcium homeostasis [11]; 2. *COL1A1* (c.104-441G>T) — encodes the amino acid sequence of the alpha-1 chain of type 1 collagen protein [12]. 3. *VDR* (c.1206T>C(A>G), c.152T>C, c.1174+283G>A, c.1025-49G>T) — various polymorphisms of the vitamin D receptor gene that affect the regulation of metabolic processes, immune response, and bone metabolism [13].
7. Imaging method. Bone mineral density (BMD) was determined using dual-energy X-ray absorptiometry (DXA) in the lumbar spine (L2–L4), and bone mineral content (BMC) in children over 6 years of age was measured using a DEXXUM device (South Korea). Children were classified as being at risk if they had a decrease in BMD (Z-score <–1) (risk group for mineralization and linear growth disorders according to methodological recommendations) [15].
8. Statistical methods. Statistical data processing was performed using the SPSS Statistics 26 (IBM) software package. The normality of distribution was checked using the Shapiro-Wilk test and descriptive statistics analysis. Parametric (mean and standard deviation) and nonparametric statistics (median, 1st and 3rd quartiles) were used to describe quantitative data). Frequency tables and contingency tables indicating numbers and percentages (%) were used to describe qualitative data. The Mann–Whitney nonparametric test was used to test differences in quantitative characteristics. To test for differences in qualitative characteristics, Pearson's chi-square independence test and the z-test for equality of proportions were used. Differences were considered statistically significant at $p < 0.05$.

STUDY RESULTS

The group examined during 2024 consisted of 100 children from the Moscow region suffering from asthma. Of these, 73 (73%) were boys and 27 (27%) were girls. The average age of patients with BA was

Table 1. **BMD (g/cm²), BMC (g), and Z-score indicators in children with BA and in the control group, Me (Q1; Q3)***
(authors' table)Таблица 1. **Показатели МПК (BMD) (г/см²), СМК (BMC) (г), Z-score у детей с БА и в группе контроля, Ме (Q1; Q3)*** (таблица авторов)

Indicator	Patients with BA (n = 100)	Healthy (n = 61)	p-value
BMD (g/sm ²)	0,91 (0,77; 1,14)	0,83 (0,70; 1,00)	p=0,043
BMC (g)	40,38 (32,11; 59,36)	32,15 (24,86; 51,72)	p=0,007
BMD Z-score	0,35 (-0,45; 1,00)	-0,20 (-0,60; 0,60)	p=0,100

* The Mann-Whitney test was used.

12.8±3.6 years, with a median age of 14.0 years (Q_1 — 10.4 and Q_3 — 16.0). Children with signs of obesity were divided into groups according to age: 30 (30%) children were in the first group (6–11 years old), and 70 (70%) children were in the second group (12–18 years old). The severity of bronchial asthma was determined according to clinical guidelines and distributed as follows: mild severity 35 (35%), moderate severity 34 (34%), severe 31 (31%).

In the group of patients with BA, normal BMD (-1 Z-score values) were obtained in 85 (85%) patients, a decrease in BMD (<-1 Z-score) was found in 13 (13%) children, and a decrease in BMD (<-2 Z-score) was found in 2 (2%). Thus, in the vast majority of children with BA examined, BMD remained within the reference range for their age, but 15% of children showed signs of BMD decrease of varying severity.

No significant differences in Z-score BMD values were found between children with BA and the control group, but BMD values in the group of children with BA were significantly higher than in the control group ($p = 0.043$) (Table 1).

When comparing BMD values in groups of patients receiving high-dose inhaled corticosteroids, no significant decrease in bone density ($Z\text{-score} \leq -2$) was observed, indicating an increased risk of osteopenia or osteoporosis. In this case, data from patients receiving inhalation therapy for more than 12 months were considered, so the patient groups

were further divided by age: under 10 years and over 10 years. In patients under 10 years of age, the Z-score distribution across the low- and high-dose ICS categories is similar: the majority of children in both groups have a Z-score above -1.0 , and there is no proportion of patients with a significant decrease in bone density ($Z\text{-score} \leq -2.0$). In children over 10 years of age, there are also no significant differences between low- and high-dose ICS: cases of $Z\text{-score} \leq -2.0$ are isolated, while the majority of patients in both groups have a Z-score above -1.0 , indicating preserved or only slightly decreased bone mineral density (Table 2).

In the group from 6 to 12 years old, overweight was present in 9 children (9%), obesity — in 11 (11%); in the group from 12 to 18 years old, overweight was present in 15 children (15%), obesity — in 6 children (6%) (Table 3).

The study results of biochemical parameters in patients with BA revealed comparable levels of vitamin D in the blood compared to healthy children, but lower levels of calcitonin, ionized calcium and creatinine, both in the overall group and in the 6–11 and 12–18 year old groups (Tables 4, 5). The synthesis and secretion of calcitonin is regulated by the level of calcium in the blood; its concentration in the blood is very low (a value below the limit has not been established), therefore, even a slight change in the concentration of calcitonin requires medical attention, since calcitonin increases the flow of calcium from the

Table 2. **Calculation of the combined dose of ICS* — Densitometry (Z-score)** (authors' table)**
 Таблица 2. **Расчет сопряженности дозы ИГКС* и плотности костной ткани (Z-score)** (таблица авторов)**

Age/Doses			Bone density according to Z-score n (%)			
			≤-2,0	-1,9 — -1,0	>-1,0	p-value
Up to 10 years	ICS doses	Low	-	1 (50)	9 (56,3)	p=0,867
		High	-	1 (50)	7 (43,8)	
Over 10 years old	ICS doses	Low	-	4 (40)	30 (54,5)	p=0,407
		High	1 (100)	6 (60)	25 (45,5)	

* ICS — inhaled glucocorticosteroids.

** Pearson's chi-square test was used.

blood into the bones, which inhibits resorption (destruction, decrease in mineral density) of the bone, that is, the action of calcitonin is aimed at reducing the level of calcium in the blood and inhibiting bone demineralization [16].

A decrease in osteocalcin and acid phosphatase with age was found in both BA and healthy children, which is probably the age norm [13]. In the group of healthy children, the level of C-terminal telopeptides decreased.

Table 3. **Anthropometric data of patients with bronchial asthma and healthy children depending on age, Me (Q1; Q3)* (authors' table)**
 Таблица 3. **Антропометрические данные пациентов с бронхиальной астмой и здоровых детей в зависимости от возраста, Me (Q1; Q3)* (таблица авторов)**

Indicator	6–11 years		12–18 years		p-value
	BA (1)	Healthy (2)	BA (3)	Healthy (4)	
BMI, percentile	89,63 (53,88; 98,14)	29,8 (3,9; 56,7)	68,40 (30,05; 91,98)	27,45 (12,7; 66,3)	p ₁₋₂ <0,001 p ₃₋₄ =0,001 p ₁₋₃ =0,026 p ₂₋₄ =0,639
BMI, z-score	1,29 (0,10; 2,11)	-0,53 (-1,76; 0,17)	0,47 (-0,56; 1,38)	-0,78 (-1,25; 0,14)	p ₁₋₂ <0,001 p ₃₋₄ =0,001 p ₁₋₃ =0,017 p ₂₋₄ =0,846
Number of overweight and obese children, n (%)	20 (20%)	3 (4,8%)	21 (21%)	33 (4,8%)	—
Increase, percentile	81,02 (46,39; 92,54)	46,6 (20,8; 81,7)	74,85 (47,42; 88,36)	64,9 (42,3; 77,3)	p ₁₋₂ =0,010 p ₃₋₄ =0,160 p ₁₋₃ =0,423 p ₂₋₄ =0,323
Increase, z-score	0,89 (-0,10; 1,47)	-0,03 (-0,41; 0,95)	0,67 (0,04; 1,25)	0,39 (-0,19; 0,75)	p ₁₋₂ =0,035 p ₃₋₄ =0,156 p ₁₋₃ =0,414 p ₂₋₄ =0,574

* The Mann-Whitney test was used.

Table 4. **Biochemical marker indicators $M \pm m$, Me (Q1; Q3), of patients with bronchial asthma and healthy children in the overall group* (authors' table)**
 Таблица 4. **Показатели биохимических маркеров $M \pm m$, Me (Q1; Q3), пациентов с бронхиальной астмой и здоровых детей в общей группе* (таблица авторов)**

Indicator	Bronchial asthma	Healthy	p-value
Vitamin D (N 30–70 ng/ml)	24,05 (19,85; 30,10)	21,90 (14,50; 27,60)	p = 0,050
Calcitonin, 0–79 pg/L	2,00 (2,00; 2,55)	11,00 (11,00; 11,00)	p < 0,001
Osteocalcin*, ng/ml	91,00 (49,50; 118,00)	85,00 (67,00; 113,00)	p = 0,727
C-terminal telopeptides*, ng/ml	1,63 (1,11; 2,19)	1,64 (1,24; 1,99)	p = 0,656
Parathyroid hormone (N 1.72–6.68 pmol/L)	3,75 (2,65; 4,57)	3,57 (2,54; 4,80)	p = 0,733
Total Ca, (N 2.2–2.7 mmol/L)	2,37 (2,33; 2,44)	2,40 (2,36; 2,43)	p = 0,208
Ca 2+, (N 1.22–1.37 mmol/L)	1,27 (1,21; 1,30)	1,31 (1,29; 1,35)	p < 0,001
Alkaline phosphatase (N 97–361 U/L)	189,50 (107,50; 259,50)	203,00 (128,00; 242,00)	p = 0,974
Creatinine, (N 27–62 μ mol/l)	51,00 (42,55; 65,05)	54,20 (50,20; 65,10)	p = 0,019
Acid phosphatase, (N <6 U/L)	5,10 (3,90; 6,45)	5,60 (4,30; 6,40)	p = 0,644

* The Mann-Whitney test was used.

Among patients with BA, doses of cholecalciferol were extremely low and significantly different from those received by healthy children, and did not depend on age. Calcium intake from food was also insufficient and did not meet the recommended age-specific standards (Tables 6, 7). The approximate daily calcium intake requirements for children, depending on age, are as follows: up to 3 months — 400 mg of calcium per day; from 4 to 6 months — 500 mg per day; 7 to 12 months — 600 mg per day; 1 to 3 years — 800 mg per day; 3 to 7 years — 900 mg per day; 7 to 11 years — 1100 mg per day; 11 to 18 years — 1200–1300 mg per day [15].

Vitamin D and calcium intake did not affect BMD. Vitamin D and calcium intake was lower in patients with asthma (Table 8).

Patients with moderate physical activity had better BMD indicators compared to patients with low physical activity (Table 9).

The frequency of *CALCR*, *COL1A1*, and *VDR* gene genotypes in patients with bronchial asthma and healthy children did not differ (Table 10).

The level of 25(OH)D was significantly lower in patients with BA with the GG genotype of the polymorphic variant of the *VDR* (FokI) gene compared to carriers of the AA (p = 0.010) and AG (p = 0.010) genotypes (Table 11). Healthy children with the AA genotype of the *VDR* (FokI) polymorphism had low osteocalcin levels and high alkaline phosphatase values, indicating active bone resorption processes.

The study found that patients with BA had low vitamin D levels (25.2 ± 8.8 ng/ml), comparable to those of the control group, and no supplementation with cholecalciferol and calcium from food (183.1 ± 93.9 mg). Vitamin D levels were significantly lower in patients with BA with the GG genotype of the polymorphic variant of the *VDR* (FokI) gene compared to carriers of the AA (p = 0.010) and AG (p = 0.010) genotypes. Patients with BA also had lower levels of calcitonin, ionized calcium, and creatinine, both in the general group and in the 6–11 and 12–18 age groups. BMD and BMC levels were higher in children with BA compared to the control group, which was primarily due to high nutrition-

Table 5. **Biochemical marker indicators $M \pm m$, Me (Q1; Q3), of patients with bronchial asthma and healthy children by age* (authors' table)**Таблица 5. **Показатели биохимических маркеров $M \pm m$, Me (Q1; Q3), пациентов с бронхиальной астмой и здоровых детей в зависимости от возраста* (таблица авторов)**

Indicator	6–11 years		12–18 years		p-value
	BA (1) (n=30)	Healthy (2) (n=31)	BA (3) (n=70)	Healthy (4) (n=30)	
Vitamin D (N 30–70 ng/ml)	25,35 (21,40; 30,00)	21,90 (14,50; 27,60)	23,25 (18,50; 30,80)	22,20 (13,70; 28,30)	$p_{1-2} = 0,077$ $p_{3-4} = 0,217$ $p_{1-3} = 0,508$ $p_{2-4} = 0,885$
Calcitonin, 0–79 pg/L	2,05 (2,00; 3,70)	11,00 (11,00; 11,00)	2,00 (2,00; 2,00)	11,00 (11,00; 11,00)	$p_{1-2} < 0,001$ $p_{3-4} < 0,001$ $p_{1-3} = 0,009$ $p_{2-4} = 0,422$
Osteocalcin*, ng/ml	97,00 (84,00; 122,00)	97,00 (75,00; 119,00)	79,00 (42,00; 110,00)	70,50 (35,00; 107,00)	$p_{1-2} = 0,756$ $p_{3-4} = 0,758$ $p_{1-3} = 0,043$ $p_{2-4} = 0,015$
C-terminal telopeptides*, ng/ml	1,69 (1,52; 2,16)	1,79 (1,50; 2,03)	1,61 (0,96; 2,25)	1,25 (0,91; 1,74)	$p_{1-2} = 0,829$ $p_{3-4} = 0,236$ $p_{1-3} = 0,323$ $p_{2-4} = 0,004$
Parathyroid hormone, (N 1.72–6.68 pmol/L)	3,91±1,63 3,75 (2,97; 4,31)	3,46±1,40 2,90 (2,40; 4,79)	3,98±1,88 3,77 (2,64; 4,83)	4,18±1,62 4,05 (3,34; 4,80)	$p_{1-2} = 0,306$ $p_{3-4} = 0,443$ $p_{1-3} = 0,845$ $p_{2-4} = 0,075$
Total Ca, (N 2.2–2.7 mmol/L)	2,38 (2,34; 2,47)	2,39 (2,36; 2,42)	2,36 (2,32; 2,42)	2,40 (2,36; 2,44)	$p_{1-2} = 0,821$ $p_{3-4} = 0,117$ $p_{1-3} = 0,168$ $p_{2-4} = 0,641$
Ca 2+, (N 1,22–1,37 mmol/L)	1,27 (1,19; 1,30)	1,31 (1,29; 1,35)	1,27 (1,23; 1,30)	1,32 (1,29; 1,34)	$p_{1-2} < 0,001$ $p_{3-4} < 0,001$ $p_{1-3} = 0,327$ $p_{2-4} = 0,891$
Alkaline phosphatase, (N 97–361 U/L)	229,50 (202,00; 266,00)	215,00 (199,00; 280,00)	148,50 (94,00; 254,00)	120,00 (66,00; 217,00)	$p_{1-2} = 0,735$ $p_{3-4} = 0,154$ $p_{1-3} = 0,003$ $p_{2-4} < 0,001$
Creatinine, (N 27–62 μ mol/l)	39,80 (35,10; 46,80)	51,30 (49,10; 54,20)	61,05 (45,60; 69,60)	65,20 (59,00; 72,20)	$p_{1-2} < 0,001$ $p_{3-4} = 0,068$ $p_{1-3} < 0,001$ $p_{2-4} < 0,001$
Acid phosphatase, (N <6 U/L)	6,55 (5,90; 7,20)	6,10 (5,60; 6,90)	4,50 (3,60; 5,90)	4,30 (3,20; 5,20)	$p_{1-2} = 0,390$ $p_{3-4} = 0,229$ $p_{1-3} < 0,001$ $p_{2-4} < 0,001$

* The Mann-Whitney test was used.

al status especially in the 6–12 age group, where overweight and obesity were more common than in the 12–18 age group. However, in the group of patients receiving high doses of ICS, a significant decrease in BMD indicators was observed. BMI (%) and BMI Z-score in patients with BA were higher in the 6–11 and 12–18 age groups, as well as in groups with different BMD. Patients with moderate physi-

cal activity had optimal BMD indicators compared to patients with low physical activity.

DISCUSSION

The data obtained as a result of this study indicate a decrease in BMD indicators in children suffering from bronchial asthma compared to their healthy peers. Significant differences in the levels

Table 6. **Calculation of indicators of daily cholecalciferol dose intake, calcium intake from food in patients with bronchial asthma and healthy children* (authors' table)**Таблица 6. **Расчет показателей приема суточной дозы колекальциферола, поступления кальция с пищей у пациентов с бронхиальной астмой и здоровых детей* (таблица авторов)**

Indicator	Age, years		p-value
	6–11 (n=30)	12–18 (n=70)	
Daily intake of vitamin D Me (Q1–Q3), IU	0,00 (0,00; 500,00)	0,00 (0,00; 0,00)	p=0,638
Daily intake of Ca with food Me (Q1–Q3), mg	150,00 (100,00; 200,00)	150,00 (100,00; 250,00)	p=0,546

* The Mann-Whitney test was used.

Table 7. **Indicators of daily cholecalciferol dose intake and calcium intake from food in children with bronchial asthma depending on age* (authors' table)**Таблица 7. **Показатели приема суточной дозы колекальциферола, поступления кальция с пищей у детей с бронхиальной астмой в зависимости от возраста* (таблица авторов)**

Indicator	Bronchial asthma	Healthy	p-value
Daily intake of vitamin D M±m, Me (Q1–Q3), IU	0,00 (0,00; 0,00)	500,00 (0,00; 1000,00)	p=0,001
Daily intake of Ca with food M±m, Me (Q1–Q3), mg	150,00 (100,00; 230,00)	400,00 (300,00; 800,00)	P<0,001

* The Mann-Whitney test was used.

Table 8. **BMD in patients with BA and healthy children depending on daily cholecalciferol intake and calcium intake from food* (authors' table)**Таблица 8. **МПК у пациентов с БА и здоровых детей в зависимости от приема суточной дозы колекальциферола, поступления кальция с пищей* (таблица авторов)**

Indicator	Z-score densitometry				p-value
	≤ -1,0	≤ -1,0	> -1,0+	> -1,0+	
	BA (1) (n=15)	Healthy (2) (n=11)	BA (3) (n=85)	Healthy (4) (n=50)	
Vitamin D intake per day Me (Q1–Q3), IU	0,00 (0,00; 0,00)	0,00 (0,00; 500,00)	0,00 (0,00; 0,00)	500,00 (0,00; 1000,00)	p ₁₋₂ = 0,172 p ₃₋₄ = 0,002 p ₁₋₃ = 0,614 p ₂₋₄ = 0,419
Dietary intake of Ca per day Me (Q1–Q3), mg	200,00 (120,00; 230,00)	200,00 (100,00; 300,00)	150,00 (100,00; 220,00)	500,00 (300,00; 800,00)	p ₁₋₂ = 0,529 p ₃₋₄ < 0,001 p ₁₋₃ = 0,559 p ₂₋₄ = 0,001

* The Mann-Whitney test was used.

of calcitonin, ionized calcium, and other markers of bone metabolism have been identified, emphasizing the need for regular monitoring of bone metabolism in this category of patients. Timely

correction of identified disorders is vital for preventing long-term complications, including osteoporosis. It has also been established that patients with BA have low levels of 25 (OH)D levels in

Table 9. **BMD in patients with BA depending on physical activity* (authors' table)**
 Таблица 9. **МПК у пациентов с БА в зависимости от физической активности* (таблица авторов)**

Physical activity, n (%)	Z-score densitometry			p-value
	≤ -1,0	> -1,0+	Total	
Low (lack of daily walks)	11 (18,3)	49 (81,7)	60 (100)	p=0,050
Moderate (daily walks, physical education classes at school)	4 (10,3)	35 (89,7)	39 (100)	
High (exercise 3-4 times a week)	0 (0)	1 (100)	1 (100)	

* Pearson's chi-square test was used.

the blood and low intake of cholecalciferol and calcium from food, which is probably due to existing dietary restrictions in these patients and it dictates the need for comprehensive preventive measures aimed at eliminating deficiencies in these patients in order to control the symptoms of bronchial asthma.

Interestingly, a decrease in cholecalciferol intake and a reduction in its metabolite blood concentration are convincingly associated with a decrease in

calcitonin. Low cholecalciferol intake and decreased calcidiol levels may correlate with limited physical activity, presumably due to families discouraging children with bronchial asthma from engaging in normal physical activity. Studies confirming this global trend have been published in several countries.

The authors tend to associate the recorded isolated indicators of decreased BMD in children receiving ICS for at least 1 year not with the effects of the drugs, but rather with the uncontrolled course of the

Table 10. **Distribution of *CALCR*, *COL1A1*, and *VDR* gene polymorphisms in patients with bronchial asthma and healthy children* (authors' table)**
 Таблица 10. **Распределение полиморфизма генов *CALCR*, *COL1A1* и *VDR* у пациентов с бронхиальной астмой и здоровых детей* (таблица авторов)**

Indicator, n (%)		BA	Healthy	p-value
<i>CALCR</i>	CC	6 (6,0)	3 (4,9)	p=0,731
	TC	43 (43,0)	23 (37,7)	
	TT	51 (51,0)	35 (57,4)	
<i>COL1A1</i>	GG	62 (62,0)	43 (70,5)	p=0,389
	GT	33 (33,0)	17 (27,9)	
	TT	5 (5,0)	1 (1,6)	
<i>VDR TaqI</i>	TT	42 (42,0)	24 (39,3)	p=0,536
	TC	49 (49,0)	34 (55,7)	
	CC	9 (9,0)	3 (4,9)	
<i>VDR FokI</i>	AA	31 (31,0)	22 (36,1)	p=0,734
	AG	47 (47,0)	25 (41,0)	
	GG	22 (22,0)	14 (23,0)	
<i>VDR BsmI</i>	AA	9 (9,00)	3 (4,9)	p=0,616
	AG	50 (50,0)	33 (54,1)	
	GG	41 (41,0)	25 (41,0)	
<i>VDR ApaI</i>	TT	16 (16,0)	11 (18,0)	p=0,931
	CA	61 (61,0)	37 (60,7)	
	CC	23 (23,0)	13 (21,3)	
Total		100 (100)	61 (100)	

* Критерий независимости хи-квадрат Пирсона.

Table 11. **Biochemical indicators Me (Q1–Q3) of patients with bronchial asthma and healthy children depending on VDR (FokI) genotypes* (authors' table)**
 Таблица 11. **Биохимические показатели Me (Q1–Q3)) пациентов с бронхиальной астмой и здоровых детей в зависимости от генотипов гена VDR (FokI)* (таблица авторов)**

Indicator		25(OH)D, ng/ml			
Gene		n1	Bronchial asthma	n2	Healthy
VDR FokI	AA (1)	31	25,50 (21,20; 31,30)	22	25,20 (19,40; 30,20)
	AG (2)	47	23,20 (20,20; 30,80)	25	16,00 (13,10; 25,90)
	GG (3)	22	21,35 (14,90; 27,10)	14	22,65 (14,50; 24,80)
p-value		p ₁₋₂ = 0,434 p ₁₋₃ = 0,010 p ₂₋₃ = 0,037			p = 0,140
Indicator		Calcitonin, pg/L			
Gene		n1	Bronchial asthma	n2	Healthy
VDR FokI	AA (1)	31	2,00 (2,00; 2,10)	22	11,00 (11,00; 11,00)
	AG (2)	47	2,00 (2,00; 2,70)	25	11,00 (11,00; 11,00)
	GG (3)	22	2,00 (2,00; 2,60)	14	11,00 (11,00; 12,90)
p-value		p = 0,762			p = 0,054
Indicator		Ionized calcium, mmol/L			
Gene		n1	Bronchial asthma	n2	Healthy
VDR FokI	AA (1)	31	1,24 (1,20; 1,30)	22	1,33 (1,29; 1,35)
	AG (2)	47	1,27 (1,24; 1,31)	25	1,32 (1,27; 1,34)
	GG (3)	22	1,27 (1,22; 1,31)	14	1,31 (1,29; 1,33)
p-value		p = 0,244			p = 0,604
Indicator		Total calcium, mmol/l			
Gene		n1	Bronchial asthma	n2	Healthy
VDR FokI	AA (1)	31	2,37 (2,34; 2,44)	22	2,41 (2,38; 2,44)
	AG (2)	47	2,37 (2,33; 2,44)	25	2,38 (2,34; 2,41)
	GG (3)	22	2,36 (2,31; 2,49)	14	2,40 (2,34; 2,44)
p-value		p = 0,950			p = 0,365
Indicator		Osteocalcin, ng/ml			
Gene		n1	Bronchial asthma	n2	Healthy
VDR FokI	AA (1)	31	70,00 (38,00; 121,00)	22	89,50 (70,00; 113,00)
	AG (2)	47	92,00 (64,00; 116,00)	25	74,00 (47,00; 97,00)
	GG (3)	22	94,00 (44,00; 130,00)	14	113,00 (85,00; 143,00)
p-value		p = 0,468			p ₁₋₂ = 0,147 p ₂₋₃ = 0,008 p ₁₋₃ = 0,177

Table 11. **Biochemical indicators Me (Q1–Q3) of patients with bronchial asthma and healthy children depending on VDR (FokI) genotypes* (authors' table)**
 Таблица 11. **Биохимические показатели Me (Q1–Q3)) пациентов с бронхиальной астмой и здоровых детей в зависимости от генотипов гена VDR (FokI)* (таблица авторов)**

Indicator		Acid phosphatase, U/L			
Gene		n1	Bronchial asthma	n2	Healthy
VDR FokI	AA (1)	31	4,90 (3,70; 7,00)	22	5,95 (4,90; 6,60)
	AG (2)	47	5,90 (4,00; 6,70)	25	5,20 (4,10; 5,80)
	GG (3)	22	4,55 (4,00; 5,70)	14	6,15 (4,30; 7,20)
p-value		p=0,494			p=0,126
Indicator		C-terminal peptides, ng/ml			
Gene		n1	Bronchial asthma	n2	Healthy
VDR FokI	AA (1)	31	1,63 (0,96; 2,01)	22	1,82 (1,21; 2,15)
	AG (2)	47	1,76 (1,36; 2,34)	25	1,43 (1,24; 1,74)
	GG (3)	22	1,51 (1,11; 2,30)	14	1,65 (1,49; 2,02)
p-value		p=0,467			p=0,283
Indicator		Parathyroid hormone, pmol/L			
Gene		n1	Bronchial asthma	n2	Healthy
VDR FokI	AA (1)	31	3,44 (2,43; 4,38)	22	3,51 (2,52; 4,80)
	AG (2)	47	3,83 (2,95; 4,84)	25	4,10 (2,80; 4,80)
	GG (3)	22	3,60 (2,37; 4,83)	14	3,20 (2,20; 4,30)
p-value		p=0,318			p=0,611
Indicator		Alkaline phosphatase, U/L			
Gene		n1	Bronchial asthma	n2	Healthy
VDR FokI	AA (1)	31	173,00 (111,00; 240,00)	22	214,00 (199,00; 267,00)
	AG (2)	47	223,00 (117,00; 270,00)	25	155,00 (72,00; 200,00)
	GG (3)	22	148,50 (94,00; 235,00)	14	232,00 (128,00; 265,00)
p-value		p=0,216			p ₂₋₃ = 0,085 p ₁₋₂ = 0,014 p ₁₋₃ = 0,669
Indicator		Creatinine, μmol/l			
Gene		n1	Bronchial asthma	n2	Healthy
VDR FokI	AA (1)	31	51,90 (39,90; 66,80)	22	52,20 (50,20; 59,20)
	AG (2)	47	47,90 (39,80; 64,70)	25	56,40 (50,90; 67,00)
	GG (3)	22	58,40 (48,90; 62,50)	14	60,90 (49,40; 71,50)
p-value		p=0,299			p=0,134

* Comparison of indicators by gene groups was performed using the Kruskal-Wallis test (p-values without index); if statistically significant differences were detected, pairwise comparisons were performed using the Mann-Whitney test (p-values with indexes).

disease, which determines restrictions in nutrition and physical activity, which probably leads to a decrease in bone mineral density.

Importantly, the proportion of BMD reduction (Z-score < -1) in the groups of children with BA and the group of healthy children was comparable, indicating the maintenance of adequate bone tissue in the majority of patients with BA receiving medium and low doses of ICS while adhering to modern standards of treatment and prevention. Moreover, in the examined group of children with BA, higher absolute values of BMD and its mineralization of BMD and BMC were observed compared to the control group, which can be explained by both the higher proportion of older children in the study group and high BMI.

Thus, the study results confirm the importance of a multidisciplinary approach in the management of children with bronchial asthma, including not only the control of bronchial inflammation and rational drug therapy, but also ensuring optimal nutritional status and physical activity. These measures help maintain bone mineral density and reduce the risk of developing bone complications in adulthood.

A promising direction for further study is the identification of early prognostic biomarkers of decreased bone density, as well as the evaluation of the effectiveness of comprehensive programs for the restoration of bone metabolism in children with severe forms of bronchial asthma.

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Ekaterina S. Nikonova — patient enrollment, manuscript preparation, evaluation and editing, preparation, creation, and presentation of the published work.

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