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Decreased Bone Mineralization in Children with Inflammatory Bowel Diseases

Maria I. Erokhina[1]*, Niso D. Odinaeva[1,2], Elena I. Kondratieva[1,3], Anatoli I. Khavkin[1,4], Ekaterina A. Yablokova[1,5], Elena K. Zhekaite[1]

[1] *Research Clinical Institute of Childhood of the Ministry of Healthcare of the Moscow Region, Mytishchi, Russian Federation*
[2] *Moscow Regional Research and Clinical Institute, Moscow, Russian Federation*
[3] *Research Center for Medical Genetics, Moscow, Russian Federation*
[4] *Belgorod State National Research University, Belgorod, Russian Federation*
[5] *I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russian Federation*

Aim: to assess bone mineral density (BMD) in children with inflammatory bowel diseases (IBD) and analyse the factors influencing it.
Materials and methods. The study included 113 patients with IBD (58 with Crohn's disease and 55 with ulcerative colitis) and 61 healthy children (control group). All the participants had a comprehensive assessment of BMD by means of dual-energy X-ray absorptiometry (DEXA), as well as measurement of vitamin D levels, biochemical markers of bone metabolism, dietary calcium intake, and physical activity.
Results. Decreased BMD of varying degrees was identified in 39.8 % of patients with IBD, which is substantially more frequent than in the control group (p = 0.001). Significant predictors of decreased BMD were established: disease duration exceeding 3 years, high clinical and endoscopic activity, low calcium intake (*Me*) 300 mg/day vs 550 mg/day in the control group (p < 0.001), and dose-dependent effect of glucocorticoid therapy.
Conclusion. Low bone mass build-up in children with IBD is a multifactorial process associated with disease activity and duration, dietary restrictions, and treatment modalities, underscoring the need for multidisciplinary monitoring of bone tissue status in this patient group.
Keywords: Crohn's disease, inflammatory bowel diseases, children, osteoporosis, ulcerative colitis
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Снижение минерализации костной ткани у детей с воспалительными заболеваниями кишечника

М.И. Ерохина[1]*, Н.Д. Одинаева[1,2], Е.И. Кондратьева[1,3], А.И. Хавкин[1,4], Е.А. Яблокова[1,5], Е.К. Жекайте[1]

[1] *ГБУЗ Московской области «Научно-исследовательский клинический институт детства Министерства здравоохранения Московской области», Мытищи, Российская Федерация*
[2] *ГБУЗ «Московский областной научно-исследовательский клинический институт им. М.Ф. Владимирского», Москва, Российская Федерация*
[3] *ФГБНУ «Медико-генетический научный центр им. академика Н.П. Бочкова», Москва, Российская Федерация*
[4] *ФГАОУ ВО «Белгородский государственный национальный исследовательский университет», Белгород, Российская Федерация*
[5] *ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет), Москва, Российская Федерация*

Цель: изучение состояния минеральной плотности кости (МПК) и факторов, влияющих на ее формирование, у детей с воспалительными заболеваниями кишечника (ВЗК).
Материалы и методы. В исследование включены 113 пациентов с ВЗК (58 с болезнью Крона и 55 с язвенным колитом) и 61 здоровый ребенок (контрольная группа). Всем участникам проведена комплексная оценка МПК методом двухэнергетической рентгеновской абсорбциометрии (DEXA), уровня витамина D, биохимических маркеров костного метаболизма, уровня потребления кальция с пищей и физической активности.
Результаты. Снижение МПК различной степени выявлено у 39,8 % пациентов с ВЗК, что достоверно чаще, чем в контрольной группе (p = 0,001). Установлены значимые предикторы снижения МПК: длительность заболевания

более 3 лет, высокая клинико-эндоскопическая активность, низкое потребление кальция (*Me*) 300 мг/сут против 550 мг/сут в контроле ($p < 0,001$) и дозозависимое влияние глюкокортикостероидной терапии.
Выводы. Формирование низкой костной массы у детей с ВЗК является мультифакторным процессом, ассоциированным с активностью и длительностью заболевания, диетическими ограничениями и характером терапии, что обосновывает необходимость мультидисциплинарного мониторинга состояния костной ткани в данной группе пациентов.
Ключевые слова: болезнь Крона, воспалительные заболевания кишечника, дети, остеопороз, язвенный колит
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.
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Introduction

Inflammatory bowel diseases (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), as well as undifferentiated colitis and a number of monogenic gastrointestinal disorders, represent a group of severe chronic immune-mediated conditions primarily affecting the gastrointestinal tract (GIT), with both common and distinguishing clinical features [1].

A significant increase in IBD incidence has been observed across all age groups, especially affecting children: in 25 % of cases, the disease onset occurs during childhood and adolescence, which is associated with a poorer prognosis, high risk of complications and surgical interventions, as well as delayed growth and development [1, 2]. Long-term systemic inflammatory activity, driven by the ongoing pathological process in the GIT and dysbiosis, is a key mechanism underlying the development of multiple organ manifestations in patients with IBD. In particular, this category of patients is characterised by impaired gut-bone axis, which leads to decreased bone mineral density and increased risk of fractures. The incidence of decreased bone mineral density among patients with IBD varies by region and amounts to as much as 40 % in adults and 36 % in children [3, 4]. According to data from different authors, decreased BMD figures are characteristic of Russian children aged 5–18 without somatic comorbidities (malabsorption, hepatitis, thyrotoxicosis, diabetes mellitus, etc.) [5].

The disease activity leading to restrictive diets, reduced physical activity, lack of insolation, side effects of medications including corticosteroids, as well as the presence of comorbidities and extraintestinal manifestations are the primary pathophysiological factors contributing to the development of osteoporosis. In accordance with the world's practice, bone mineral composition is assessed by means of dual-energy X-ray absorptiometry (DEXA). This test is particularly indicated for children with severe IBD on long-term or repeated corticosteroid therapy; if abnormalities are detected, treatment is supplemented with calcium and vitamin D.

Aim of the study: to investigate the condition and remodeling of bone tissue in children with inflammatory bowel diseases living in the Moscow Region, depending on the nosological entity, sex, age, and ongoing treatment.

Materials and methods

The study enrolled 174 children aged from 6 to 17 years 11 months 30 days, residing in the Moscow Region and undergoing examination at the gastroenterological and consultative-diagnostic departments of the Scientific Research Clinical Institute of Childhood of the Ministry of Health of the Moscow Region (Director: Odinaeva N.D., Dr. Sci. (Med.), Professor) from March 2022 to February 2023. The main group was composed of 113 children with IBD. The comparison group consisted of 61 healthy children. The IBD diagnosis was formulated on the grounds of comprehensive analysis of clinical manifestations, medical history data, laboratory and endoscopic tests in accordance with the Federal Clinical Recommendations. Pediatric indices with score-based grading were used to assess clinical activity of the disease in accordance with universally accepted criteria: PCDAI (CD: <10 – remission, 10–30 – mild/moderately severe, 30–100 – severe activity) and PUCAI (UC: 10–35 – minimal, 36–65 – moderately severe, 65–85 – severe activity). To determine endoscopic activity, SES-CD (CD) and UCEIS (UC) indices were used, where scores reflected severity: SES-CD (>15 – severe, 7–14 – moderately severe, 3–6 – mild, less than 2 points – endoscopic remission) and UCEIS (7–8 – high, 5–6 – moderate, 2–4 – minimum, 0–1 – remission). All patients received treatment in accordance with clinical recommendations.

The main group consisted of 113 children with inflammatory bowel diseases (58 children with CD and 55 with UC; 59 boys (52.2 %) and 54 girls (47.8 %)). The control group included 61 healthy children: 37 (60.7 %) boys and 24 (39.3 %) girls (Table 1). Inclusion criteria for the control group: absence of acute, chronic, somatic, and infectious diseases affecting the child's growth and development; provision of informed consent. In the IBD group of children, the median (*Me*) age was 14.5 years, whereas in the group of healthy children, *Me* was 11 years.

Gender analysis showed a predominance of males in the control group and among patients with CD, while girls predominated in the UC group. Patients with IBD and healthy children were divided into two groups based on sex and age: Group 1: 6–11 years, Group 2: 12–18 years. Adolescents were more often found among patients with IBD, whereas the control group was basically made up of children aged 6–11 (Table 1).

Study design: a point prevalence, interventional, prospective, non-randomised study.

The participation of all children in the study was confirmed by signed by parents or legal representatives. The study was approved by the Ethical Committee of the Scientific Research Clinical Institute of Childhood of the Ministry of Health of the Moscow Region (Report No. 2 dated 22.12.2021).

All the children underwent assessment of their physical development using anthropometric data analysed with the WHO Anthro software (https://www.who.int/tools/child-growth-standards/software). The children's physical development was assessed by means of body mass index (BMI) by Quetelet (mass(kg)/height(m^2)) using percentile systems (https://www.who.int/tools/child-growth-standards/standards/weight-for-age). Values within the range from the 25th to 75th percentile were accepted as normal. The target value for children and adolescents with IBD corresponded to normal figures for healthy children of the same age and sex — the 50th percentile.

Bone mineral density (BMD) was assessed by dual-energy X-ray absorptiometry (DEXA) at a single site — the lumbar spine (L_I–L_{IV}) — with the DEXXUM 3 Osteo Sys device (South Korea). According to the criteria of the International Society for Clinical Densitometry (ISCD) [6], decreased BMD in children is defined by a Z-score for bone mineral content (BMC) or by areal bone mineral density (Areal BMD) of ≤ –2.0 standard deviations (SD). Clinical picture and the fracture history are also taken into account for diagnosing osteoporosis. A Z-score is a deviation of the individual value from the mean age norm in children of the corresponding sex and age. Z-score value above –1.0 SD is considered normal, values from –1.0 to –2.0 SD indicate decreased mineral density.

Osteoporosis is diagnosed when BMD, Z-score is ≤ –2.0, in combination with a clinically significant fracture history, which includes: 1) two or more long bone fractures by the age of 10; 2) three or more long bone fractures before the age of 19. In absence of other causes, one or more compression fractures of the spine is also indicative of osteoporosis [5, 7]. When conducting densitometry, assessment was made of BMD (g/cm^2) and BMC (g).

To evaluate vitamin D status, the blood concentration of its intermediate metabolite — calcidiol 25(OH)D was measured by enzyme-linked immunosorbent assay.

Table 1. General characteristics of the examined patients with inflammatory bowel diseases and children from the comparison group, *n* (%)

Таблица 1. Общая характеристика обследованных пациентов с воспалительными заболеваниями кишечника и детей группы сравнения, *n* (%)

Diagnosis / *Диагноз*	IBD / *ВЗК*	CD / *БК*	UC / *ЯК*	Control / *Контроль*
Groups / *Группы*	113 (64.9)	58 (51.3)	55 (48.7)	61 (35.1)
Boys / *Мальчики*	59 (33.9)	37 (21.3)	22 (12.6)	37 (21.6)
Girls / *Девочки*	54 (31.6)	21 (11.9)	33 (19)	24 (13.8)
Age, years / *Возраст, годы, Me* (Q1; Q3)	14.5 (6.0; 17.8)	15.1 (12.8; 17.1)	13.3 (9.8; 16.3)	11.0 (9.3; 15.1)
Age groups: / *Возрастные группы:*				
Group 1 (6–11 years) / *Группа 1 (6–11 лет)*	33 (29.2)	11 (19)	22 (40)	33 (54.1)
Group 2 (12–18 years) / *Группа 2 (12–18 лет)*	80 (70.8)	47 (81)	33 (60)	28 (45.9)

Note: *IBD — inflammatory bowel diseases, CD — Crohn's disease, UC — ulcerative colitis.*
Примечание: *ВЗК — воспалительные заболевания кишечника, БК — болезнь Крона, ЯК — язвенный колит.*

Biochemical evaluation of bone metabolism included measurements of blood serum levels for total and ionized calcium, inorganic phosphorus, creatinine, alkaline phosphatase (ALKP), parathyroid hormone, calcitonin, osteocalcin and C-terminal telopeptides by enzyme-linked immunosorbent assay at the CMD laboratory.

Calcium intake was assessed using a questionnaire, recording the daily dose of calcium supplements and calculating its dietary intake from the data of a 3-day food diary.

Physical activity levels were evaluated through questionnaires for parents. Based on the obtained data on the duration and frequency of exercise during the day, all subjects were classified into three groups according to WHO recommendations for children aged 5–17 years: low: <60 min/day,<3 days/week; moderate: ≥60 min/day, 3–6 days/week; high: ≥60 min/day of moderate to high intensity, every day [8–10].

Statistical analysis was performed using specialised software (IBM SPSS Statistics 13.3, BioStat, MedCalc and Microsoft Excel). Median (*Me*), as well as lower and upper quartiles, Q1 (25 %) and Q3 (75 %), were used as measures for the description of the initial sample. When comparing medians, Mann – Whitney *U*-test was applied. Kruskal – Wallis non-parametric one-way analysis of variance was used (pairwise comparison by the Mann – Whitney test). Differences were considered statistically significant at $p < 0.05$.

Results of the study

According to medical history data and anthropometry results, median IBD duration at the time of the study was 1.5 years. Extraintestinal manifestations were documented in 23 % of patients: joint pathology occurred most often (42.3 %), mucous membrane involvement was less frequent (26.9 %), skin and hepatobiliary system involvement was observed in 11.5 %, and the incidence rates were comparable between the CD and UC groups. Complicated course of disease was diagnosed in 16.8 % of patients, and the prevalence of complicated disease was significantly higher in the CD group, as compared to the UC group (27.6 % and 5.5 % respectively; $p < 0.01$). The analysis of physical development by standardised Z-scores of body mass index (BMI SDS) revealed some differences: body weight deficit was more often recorded among patients with CD (34.5 % vs 20 % in the UC group; $p = 0.04$). The height of patients with UC was less significant (*Me*) 158 cm, than that of patients with CD (*Me*) 163 cm ($p = 0.015$). The difference in height is explained by differences in the children's ages within the groups.

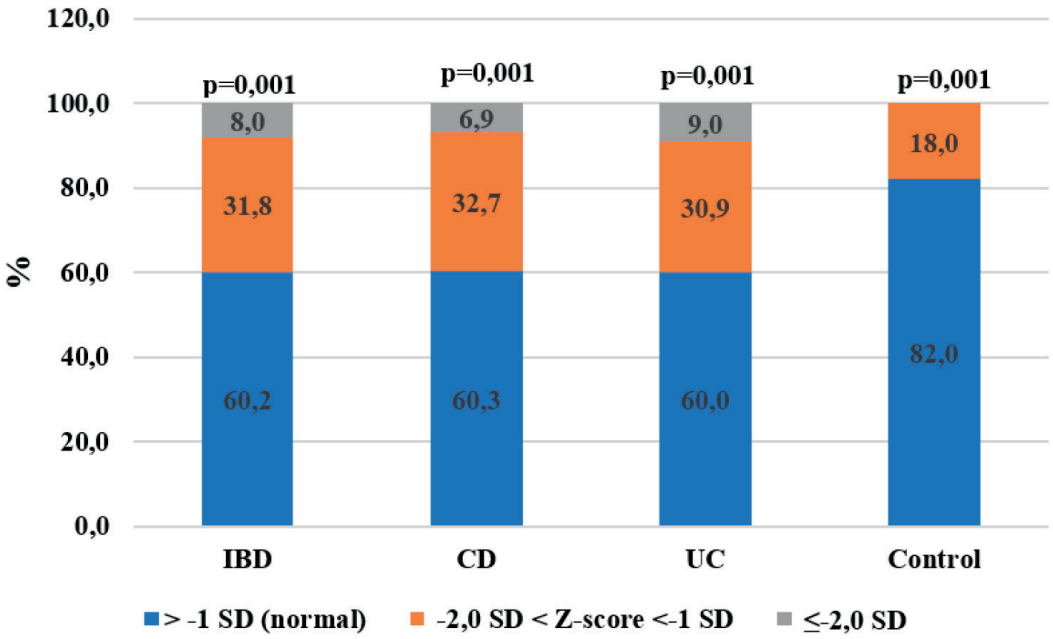
Clinical characteristics of lesion localisation demonstrated differences between IBD nosological entities. Among patients with CD ($n = 58$), ileocolitic lesion (L3) was the most frequent phenotype – 62.1 % of cases, isolated colitis (L2) was observed in 13.8 %, terminal ileitis (L1) – in 10.3 %, extended lesion – ileocolitis + upper sections (L3 + L4) in 13.8 %. Among patients with UC ($n = 55$), severe pancolitis (E4) was the most common form of the disease, identified in 61.8 % of patients. Extensive lesion (E3) was diagnosed in 12.8 % of patients, left-sided lesion – in 21.8 %, and proctitis – in 3.6 %.

According to the PCDAI/PUCAI clinical indices, most patients (74.3 %) had minimal disease activity, while 25.7 % exhibited moderate activity. No severe disease activity was identified. Endoscopic examination confirmed the presence of inflammation in 74.3 % of subjects (mild – 33.6 %, moderately severe – 34.5 %, severe – 6.2 %). The response to steroid therapy showed steroid dependence in 44.2 % of patients and steroid resistance in 11.5 %.

A good response to glucocorticoids (GCS) was documented in medical history for 23 % of patients, while 21.2 % had no history of GCS use. Pharmacotherapy for patients included the following medications: Mesalazine (used by 90.9 % of patients with UC and 36.2 % with CD), thiopurines (used by 75.2 % of all the patients with IBD; 77.6 % with CD and 72.7 % with UC), and GCS were used by 78.7 % (69 % with CD and 89 % with UC). Genetically engineered biologic therapy (GEBT) was indicated to 79.6 % of patients with IBD and it was used more frequently in the CD group (87.9 %) than in the UC group (70.9 %). GEBT arsenal included TNF-α inhibitors (International nonproprietary name (INN): infliximab, adalimumab), α4β7 integrin antagonists, (INN: vedolizumab), IL-12/IL-23 antibodies (INN: ustekinumab).

Bone mineral density in the examined children

When comparing Z-score levels of BMD in the lumbar spine (L_I–L_{IV}) of healthy children and patients with IBD (both as the entire group and divided by nosological entities – CD and UC), it was established that among patients with IBD, normal BMD (>–1 Z-score) was recorded in 68 (60.2 %) children, decreased BMD (–2.0 SD < Z-score <–1 SD) in 36 (31.8 %) children, and considerably decreased BMD (≤–2.0 SD) in 9 (8 %) patients ($p = 0.001$). Normal BMD (>–1 Z-score) among the healthy children was found in 50 (82 %) individuals ($p = 0,001$). Decreased BMD level (–2.0 SD < Z-score <–1 SD,) in the group of children with IBD (31.8 %) was significantly ($p = 0.03$) predominant in comparison with children from the control group (Fig. 1). A considerably decreased BMD



Figire 1. BMD indicators in the examined children
Note: IBD — inflammatory bowel diseases, CD — Crohn's disease, UC — ulcerative colitis.
Рисунок 1. Показатели МПК у обследованных детей
Примечание: ВЗК — воспалительные заболевания кишечника, БК — болезнь Крона, ЯК — язвенный колит.

indicator, Z-score below –2.0 SD, was noted only in children from the main group and was absent in the control group ($p < 0.001$). Patients with different IBD forms did not diverge from each other in frequency or degree of BMD decrease, but they differed significantly from the group of healthy children in this respect (Fig. 1).

At the time of comparative analysis of densitometry data at the lumbar spine level (L_I–L_{IV}) between healthy children and patients with IBD (both in the entire group and in CD and UC nosological entities), the following was detected: BMD, Z-score and BMC (g) were significantly lower in the entire IBD group compared to the control group

Table 2. Bone mineral density indicators (BMD, *Z*-score, BMD, g/cm^2, BMC, g) in the group of children with IBD (in the entire group and by nosological entities) and in the control group, *Me* (Q1; Q3)
Таблица 2. Показатели минеральной плотности кости (BMD, *Z*-score, BMD, г/см^2, BMC, г) в группе детей с ВЗК (в целом и по нозологическим формам) и в группе контроля, *Me* (Q1; Q3)

Indicator / *Показатель*	IBD$_{(1)}$ / *ВЗК*$_{(1)}$, *n* = 113	CD$_{(2)}$ / *БК*$_{(2)}$, *n* = 58	UC$_{(3)}$ / *ЯК*$_{(3)}$, *n* = 55	Control$_{(4)}$ / *Контроль*$_{(4)}$, *n* = 61	*p*
BMD, *Z-score*	–0.5 (–1.4; –0.1)	–0.5 (–1.4; –0.4)	–0.5 (–1.5; 0.4)	–0.2 (–0.6; 0.75)	$p_{1-4} = 0.031$ $p_{2-4} = 0.028$ $p_{3-4} = 0.028$
BMD, g/cm^2 / *г/см*^{2}	0.70 (0.86; 1.10)	0.70 (0.83; 1.00)	0.70 (0.85; 1.10)	0.90 (0.70; 1.10)	$p_{2-4} < 0.180$ $p_{3-4} < 0.169$
BMC, g / *г*	35.4 (42.0; 61.0)	35.4 (43.1; 60.9)	35.4 (42.0; 59.1)	39.4 (41.3; 57.4)	$p_{1-4} < 0.001$ $p_{2-4} < 0.690$ $p_{3-4} < 0.890$

Note: *Mann – Whitney U-test was applied; IBD — inflammatory bowel diseases, CD — Crohn's disease, UC — ulcerative colitis.*
Примечание: *применялся критерий Манна — Уитни; ВЗК — воспалительные заболевания кишечника, БК — болезнь Крона, ЯК — язвенный колит*

($p = 0.031$ and $p < 0.001$). Children from the control group had significantly higher BMC values. BMD (g/cm^2) did not differ significantly between the entire IBD group and the control group. No differences were detected in BMD (Z-score), BMC (g), and BMD (g/cm^2) between patients with CD and UC. Decreased BMD was significantly more prevalent in all groups of patients with IBD compared to the control group (Table 2).

For an accurate assessment of Z-score, accounting for age and sex, the participants were divided into two age groups: 6–11 years and 12–18 years. In children with IBD aged 6–11, BMD values were significantly higher in girls, with

Table 3. BMD, g/cm^2, BMC, g/cm, and BMD, Z-score in children with inflammatory bowel diseases and in the control group, *Me* (Q1; Q3)

Таблица 3. BMD, г/см^2, BMC, г/см и BMD, Z-score у детей с воспалительными заболеваниями кишечника и группы контроля, *Me* (Q1; Q3)

Indicator / *Показатель*	6–11 years / *лет*		12–18 years / *лет*		*p*
	IBD$_{(1)}$ / *ВЗК*$_{(1)}$	Control$_{(2)}$ / *Контроль*$_{(2)}$	IBD$_{(3)}$ / *ВЗК*$_{(3)}$	Control$_{(4)}$ / *Контроль*$_{(4)}$	
BMD, g/cm^2 / *г/см^2*	0.4 (–0.7; 0.9)	0.9 (0.6; 08)	0.7 (0.86; 1.1)	1.0 (0.9; 1.4)	$p_{1-2} = 0.004$ $p_{3-4} < 0.001$ $p_{1-3} < 0.001$ $p_{2-4} = 0.762$
BMC, g / *г*	30.2 (13.2; 28.6)	36.8 (18.7; 30.7)	35.4 (42.0; 61.0)	41.6 (40.1; 58.2)	$p_{1-2} = 0.011$ $p_{3-4} = 0.049$ $p_{1-3} < 0.001$ $p_{2-4} < 0.001$
BMD, *Z*-score	–0.5 (1.5; –0.4)	–0.1 (–0.7; 0.9)	–0.5 (–1.4; –0.1)	–0.1 (–0.5; 0.5)	$p_{1-2} = 0.002$ $p_{3-4} < 0.001$ $p_{1-3} = 0.195$ $p_{2-4} = 0.214$

Note: *Mann – Whitney U-test was applied; IBD – inflammatory bowel diseases.*
Примечание: *применялся критерий Манна – Уитни; ВЗК – воспалительные заболевания кишечника.*

Table 4. Physical development indicators for patients with inflammatory bowel diseases depending on bone mineral density (*Z*-score), *Me* (Q1; Q3)

Таблица 4. Показатели физического развития пациентов с воспалительными заболеваниями кишечника в зависимости от минеральной плотности кости (*Z*-score), *Me* (Q1; Q3)

Indicator / *Показатель*	≤–1 Z-score	>–1 Z-score (normal / *норма*)	*p*
IBD / ВЗК			
BMI / *ИМТ*, z-score	–0.80 (–1.25; 0.25)	–0.16 (–1.02; 0.68)	0.036
Height / *Рост*, z-score	–0.27 (–0.74; 0.25)	0.15 (–0.53; 0.87)	0.032
CD / БК			
BMI, percentiles / *ИМТ, процентили*	14.96 (3.29; 27.09)	62.16 (17.62; 77.04)	0.020
BMI SDS / *ИМТ SDS*, z-score	–1.06 (–1.84; –0.61)	–0.55 (–1.13; 0.37)	0.029
Height, cm / *Рост, см*	161.00 (152.50; 174.25)	167.00 (161.00; 173.00)	0.044
Height / *Рост*, z-score	37.84 (28.43; 59.87)	59.64 (33.36; 84.85)	0.035
UC / ЯК			
BMI, percentiles / *ИМТ, процентили*	14.96 (3.29; 27.09)	62.16 (17.62; 77.04)	0.020
BMI / *ИМТ*, z-score	–1.06 (–1.84; –0.61)	–0.55 (–1.13; 0.37)	0.029
Height, cm / *Рост, см*	142.00 (132.00; 162.00)	160.50 (143.00; 169.50)	0.044
Height / *Рост*, z-score	–0.15 (–1.33; 0.15)	0.25 (–0.43; 1.03)	0.035

Note: *Mann – Whitney U-test was applied; IBD – inflammatory bowel diseases, CD – Crohn's disease, UC – ulcerative colitis, BMI – body mass index, BMI SDS z-score – body mass index, standard score, z-score.*
Примечание: *применялся критерий Манна – Уитни; ВЗК – воспалительные заболевания кишечника, БК – болезнь Крона, ЯК – язвенный колит, ИМТ – индекс массы тела, ИМТ SDS – индекс массы тела (стандартное отклонение).*

a median (*Me*) of 0.71 g/cm², compared to boys of the same age group, who had *Me* 0.58 g/cm² ($p < 0.001$). No significant differences in BMD were identified between age and sex groups in healthy children during comparative analysis.

The comparison of BMD, BMC and Z-score indicators in healthy children and patients with IBD across different age groups revealed significant differences. The values of BMD, g/cm², BMC, g/cm, and BMD, Z-score were higher in healthy children (Table 3).

The assessment of physical development indicators in patients with IBD showed dependence on BMD indicators. A group of children with normal BMD (Z-score > –1.0) had significantly higher Z-score values for body mass index (BMI) and height than patients with decreased BMD (Z-score ≤ –1.0) (Table 4). This pattern was characteristic of both CD and UC: in both nosological subgroups, higher values of physical development indicators were observed in a group with the preserved bone mineral density.

A decreased level of physical activity in patients with IBD and in the control group (Table 5) was accompanied by a decreased BMD, Z-score ($p < 0.05$).

The analysis identified several reliable factors affecting BMD (Z-score). The comparison of BMD, Z-score showed that in patients with a long-standing disease history (>3 years) it was –0.90 (–1.15; –0.40), while in patients with a shorter disease history of less than 3 years it was –0.40 (–1.02; 0.12), $p = 0.048$. A relationship was established between the severity of clinical and endoscopic disease activity and the indicators of BMD (Z-score). Patients with minimal disease activity and slight endoscopic changes had higher BMD, Z-score values (*Me*: –0.4 and –0.5, respectively) compared to patients with moderate IBD clinical activity and

Table 5. Physical activity levels in patients with inflammatory bowel diseases and children from the control group, depending on bone mineral density (BMD, *Z*-score), *Me* (Q1; Q3)

Таблица 5. Уровень физической активности пациентов с воспалительными заболеваниями кишечника и детей контрольной группы в зависимости от минеральной плотности кости (BMD, *Z*-score), *Me* (Q1; Q3)

Physical activity indicator / *Показатель физической активности*	IBD / *ВЗК*		Control group / *Контроль*	
	***n* (%)**	**BMD, Z-score**	***n* (%)**	**BMD, Z-score**
$Low_{(1)}$ / *Низкая*$_{(1)}$	55 (48.7)	–1.4 (–1.8; –1)	27 (44.3)	–0.2 (–0.8; 0.7)
$Moderate_{(2)}$ / *Умеренная* $_{(2)}$	35 (31)	–0.5 (–0.7; 0.3)	24 (39.3)	–0.15 (–0.7; 0.5)
$High_{(3)}$ / *Высокая*$_{(3)}$	23 (20.3)	–0.2 (–0.6; 0.9)	10 (16.4)	0.05 (–0.6; 1.0)
p	$p_{(1–2)} < 0.001$ $p_{(2–3)} = 0.048$ $p_{(1–3)} = 0.034$		$p_{(1–2)} = 0.501$ $p_{(2–3)} = 0.012$ $p_{(1–3)} = 0.027$	

Note: *Mann — Whitney U-test was applied; IBD — inflammatory bowel diseases.*

Примечание: *применялся критерий Манна — Уитни; ВЗК — воспалительные заболевания кишечника.*

Table 6. Bone mineral density values (BMD, *Z*-score) depending on clinical and endoscopic activity of the disease

Таблица 6. Показатели минеральной плотности кости (BMD, *Z*-score) в зависимости от клинической и эндоскопической активности заболевания

Activity / *Активность*	***n* (%)**	**BMD, *Z*-score, *Me* (Q1; Q3)**	***p***
Clinical / *Клиническая*			
Minimal / *Минимальная*	84 (74.3)	–0.40 (–1.35; 0.50)	0.022
Moderate / *Умеренная*	29 (25.7)	–0.70 (–1.50; –0.25)	
Severe / *Тяжелая*	0		
Endoscopic / *Эндоскопическая*			
Remission/mild / *Ремиссия/легкая*	67 (59.3)	–0.50 (–1.37; 0.40)	0.037
Moderately severe/severe / *Умеренная/тяжелая*	46 (40.7)	–0.80 (–1.40; –0.27)	

Note: *Mann — Whitney U-test was applied.*

Примечание: *применялся критерий Манна — Уитни.*

Table 7. Bone mineral density values (BMD, *Z*-score) depending on inflammatory process localisation
Таблица 7. Показатели минеральной плотности кости (BMD, *Z*-score) в зависимости от локализации воспалительного процесса

Extent of lesion / *Распространенность поражения*	*n* (%)	BMD, *Z*-score, *Me* (Q1; Q3)	*p*
CD / *БК*			
Terminal ileitis — L1 + Isolated colitis — L2 / *Терминальный илеит — L1 + Изолированный колит — L2*	14 (24.1)	–0.8 (–1.2;–0.2)	0.071
Ileitis and colitis — L3 + Ileocolitis + upper sections — L3 + L4 / *Илеит и колит — L3 + Илеоколит + верхние отделы — L3 + L4*	44 (75.9)	–0.7 (–1.4;–0.4)	
UC / *ЯК*			
Pancolitis — E4 + Extensive — E3 / *Панколит — E4 + Распространенный — E3*	41 (74.6)	–0.9 (–1.5; 0.3)	0.001
Left-sided — E2 + Proctitis — E1 / *Левосторонний — E2 + Проктит — E1*	14 (25.4)	–0.3 (–1.2; 0.45)	

Note: *Mann — Whitney U-test was applied; CD — Crohn's disease, UC — ulcerative colitis.*
Примечание: *применялся критерий Манна — Уитни; БК — болезнь Крона, ЯК — язвенный колит.*

more pronounced endoscopic changes (Me: –0.7 and –0.8), $p < 0.05$ (Table 6).

Also, a relationship was detected between the extent of the lesion and BMD indicators ($p < 0.05$) in patients with UC: larger lesion extent was associated with lower bone density. However, no statistically significant correlation between the extent of the lesion and BMD was detected in patients with CD (Table 7).

The effect of therapy on BMD was assessed, particularly regarding the use of GEBT and GCS. The analysis showed that GCS use was associated with a significant decrease in BMD in children with IBD. At the same time, no statistically significant relationship between GEBT use and BMD indicators was identified (Table 8).

A cumulative dose representing the total dose of all therapy courses in absolute values (mg) and adjusted for body weight (mg/kg) was calculated for each patient receiving systemic GCS. Higher cumulative doses of GCS were recorded in patients with decreased BMD values (Z-score ≤ –1) compared to patients with normal BMD values (Z-score > –1). In absolute values: 2200 (1700; 2900) mg vs 1400 (820; 1200) mg; $p = 0.012$. Adjusted for body weight: 85 (39; 93) mg/kg vs 33 (28;56) mg/kg, $p = 0.028$.

Biochemical indicators of bone tissue remodeling in the study groups

When comparing bone remodelling markers in the entire group of patients with IBD and in healthy children, it was shown that the levels of calcitonin ($p > 0.001$) and ionized calcium ($p = 0.036$) were lower in IBD patients, while the level of parathyroid hormone was higher in the IBD group ($p < 0.001$) (Table 9).

The analysis of biochemical markers of bone metabolism revealed the following age-related peculiarities in patients with IBD (Table 10). A significant increase in parathyroid hormone levels ($p = 0.004$) and a decrease in ionized calcium levels ($p = 0.036$) were recorded in the older group of patients with IBD compared to the control group. Calcitonin levels were significantly

Table 8. Bone mineral density values (BMD, *Z*-score) depending on the use of GEBT and GCS in treatment schemes
Таблица 8. Показатели минеральной плотности кости (BMD, *Z*-score) в зависимости от использования в схемах лечения ГИБТ и ГКС

Treatment protocol with the use of / *Протокол лечения с использованием*	*n* (%)	BMD, *Z*-score, *Me* (Q1; Q3)	*p*
GCS / *ГКС*			
Used / *Применялось*	89 (78.8)	–0.9 (–1.2; 0.2)	0.001
Not used / *Не применялось*	24 (21.2)	–0.5 (–1.0; –0.1)	
GEBT / *ГИБТ*			
Used / *Применялось*	90 (79.6)	–0.7 (–1.45; –0.15)	0.069
Not used / *Не применялось*	23 (20.4)	–0.6 (–1.3; –0.1)	

Note: *Mann — Whitney U-test was applied; GCS — glucocorticoids, GEBT — genetically engineered biologic therapy.*
Примечание: *применялся критерий Манна — Уитни; ГКС — глюкокортикостероиды, ГИБТ — генно-инженерная биологическая терапия.*

Table 9. Biochemical markers of patients with inflammatory bowel diseases and healthy children in the entire group, *Me* (Q1; Q3)*

Таблица 9. Биохимические маркеры пациентов с воспалительными заболеваниями кишечника и здоровых детей в общей группе, *Me* (Q1; Q3)*

Indicator / *Показатель*	IBD / *ВЗК*	Control / *Контроль*	*p*
25(OH)D, ng/mL / *нг/мл* (N 30–70)	22.60 (17.77; 31.30)	21.90 (14.50; 27.60)	0.111
Calcitonin, pg/L / *Calcitonin, pg/L* (N 0–79)	10.2 (2.3; 10.2)	11.0 (11.0; 11.0)	<0.001
Osteocalcin, ng/mL** / *Остеокальцин, нг/мл***	93.0 (61.0; 136.0)	85.0 (67.0; 113.0)	0.401
C-terminal telopeptides, ng/mL** / *С-концевые телопептиды, нг/мл***	1.59 (1.14; 2.32)	1.64 (1.24; 1.99)	0.514
Parathyroid hormone, pmol/L / *Паратиреоидный гормон, пмоль/л* (N 1,72–6,68)	4.86 (3.30; 6.73)	3.60 (2.50; 4.80)	<0.001
Total Ca, mmol/L / *Ca общий, ммоль/л* (N 2,2–2,7)	2.40 (2.31; 2.52)	2.40 (2.36; 2.43)	0.655
Ca $^{2+}$, ммоль/л / *Ca $^{2+}$, mmol/L* (N 1,22–1,37)	1.26 (1.27; 1.31)	1.31 (1.29; 1.35)	0.036
Alkaline phosphatase, U/L / *Щелочная фосфатаза, Ед/л* (N 97–361)	180 (105; 246)	203 (128; 242)	0.631
Creatinine, umol/L / *Креатинин, мкмоль/л* (N 27–62)	58.5 (52.5; 64.8)	54.2 (50.2; 65.1)	0.384

Note: *Mann – Whitney U-test was applied; N – normal values, IBD – inflammatory bowel diseases. * The manufacturer's reference values were used. ** Reference values for osteocalcin and C-terminal telopeptides are not available.*
Примечание: *Применялся критерий Манна – Уитни; N – нормальные значения, ВЗК – воспалительные заболевания кишечника. * Использовали референсные значения производителя. ** Для показателей остеокальцина и С-концевых телопептидов референсные значения отсутствуют.*

decreased in patients with IBD compared to healthy children in both age groups ($p < 0.001$). Bone turnover indicators characterising osteogenesis (osteocalcin, alkaline phosphatase and C-terminal telopeptides) were significantly higher in the younger age group, both in IBD patients and in the control group ($p < 0.05$). The levels of calcidiol were found to be higher in IBD patients in the 6–11 age group ($p = 0.001$).

An analysis of the relationship between bone mineral density indicators and calcium intake levels was performed in 113 patients with IBD and 61 healthy children (control group). Average daily calcium dietary intake was calculated based on the questionnaire data. It was established that the values of calcium intake in the control group were higher than those in patients with IBD: 300 (200; 400) mg/day vs 550 (300; 800), $p < 0,001$. A possible cause is the limitation of dairy product consumption in the diet of patients with IBD.

Low calcium intake had a direct effect on bone mineral density: patients with decreased BMD (Z-score ≤ –1.0) showed significantly lower calcium intake compared to patients with normal bone mass (Z-score > –1 SD) and the control group ($p < 0.001$) (Fig. 2).

Discussion

The analysis of bone mineral density and its remodelling markers in patients with IBD and children from the control group residing in the Moscow Region revealed several peculiarities in the clinical course of the disease in this cohort. In particular, a high prevalence of decreased BMD in children with IBD was established, confirming the hypothesis of a negative effect of severe bowel inflammation on bone metabolism. The identified incidence rate of decreased BMD (40 %) corresponds to the figures regarding adult patients reported in the literature [9–12, 17]. The results of densitometry show a significant decrease in bone mineral density in patients with IBD compared to healthy children. Significantly lower values of BMD, Z-score ($p = 0.031$) and BMC ($p < 0.001$) were observed in patients with IBD. Comparison with the control group, in which BMD, BMC and Z-score values were significantly higher ($p < 0.05$), confirms the negative effect of IBD on bone metabolism, indicating impairment in the processes of bone remodelling. It is important to note that the identified disturbances did not show statistically significant differences between the nosological entities of IBD (Crohn's disease and ulcerative colitis) and age groups. The obtained data are consistent with the results of other authors' studies [17–20].

Gender-specific differences in bone metabolism were found: BMD indicators are significantly higher in prepubescent girls with IBD than in boys ($p < 0.05$). The finding confirms the theory of early development of sexual differences in bone remodelling and may be explained by the protective effects of estrogens on bone tissue, even in the presence of chronic inflammation [21–24].

Physical development parameters are significant markers of bone disorders in patients with IBD.

Table 10. Biochemical markers in patients with inflammatory bowel diseases and healthy children, depending on age, *Me* (Q1; Q3)

Таблица 10. Биохимические маркеры пациентов с воспалительными заболеваниями кишечника и здоровых детей в зависимости от возраста, *Me* (Q1; Q3)

Indicator / *Показатель*	6–11 years / *лет*		12–18 years / *лет*		*p*
	$IBD_{(1)}$ / *ВЗК*$_{(1)}$	$Control_{(2)}$ / *Контроль*$_{(2)}$	$IBD_{(3)}$ / *ВЗК*$_{(3)}$	$Control_{(4)}$ / *Контроль*$_{(4)}$	
25(OH)D, ng/mL / *нг/мл*	29.60 (23.80; 46.71)	21.9 (14.5; 27.6)	21.50 (16.76; 28.93)	22.2 (13.7; 28.3)	$p_{(1–2)} = 0.001$ $p_{(1–3)} = 0.001$ $p_{(2–4)} = 0.885$ $p_{(3–4)} = 0.685$
Calcitonin, pg/L / *Кальцитонин, пг/л*	10.2 (7.4; 10.2)	11.0 (11.0; 11.0)	10.2 (1.9; 10.2)	11.0 (11.0; 11.0)	$p_{(1–2)} < 0.001$ $p_{(1–3)} = 0.363$ $p_{(2–4)} = 0.422$ $p_{(3–4)} < 0.001$
Osteocalcin, ng/mL / *Остеокальцин, нг/мл*	118.0 (99.0; 148.0)	97.0 (75.0; 119.0)	86.0 (55.00; 130.00)	70.5 (35.0; 107.0)	$p_{(1–2)} = 0.069$ $p_{(1–3)} = 0.003$ $p_{(2–4)} = 0.015$ $p_{(3–4)} = 0.155$
C-terminal telopeptides, ng/mL / *С-концевые телопептиды, нг/мл*	2.13 (1.46; 2.58)	1.79 (1.50; 2.03)	1.55 (0.99; 2.22)	1.25 (0.91; 1.74)	$p_{(1–2)} = 0.171$ $p_{(1–3)} = 0.012$ $p_{(2–4)} = 0.004$ $p_{(3–4)} = 0.185$
Parathyroid hormone, pmol/L / *Паратиреоидный гормон, пмоль/л*	3.55 (2.76; 5.00)	2.90 (2.40; 4.80)	5.40 (3.74; 7.21)	4.41 (3.30; 4.80)	$p_{(1–2)} = 0.154$ $p_{(1–3)} = 0.008$ $p_{(2–4)} = 0.075$ $p_{(3–4)} = 0.004$
Total Ca, mmol/L / *Са общий, ммоль/л*	2.42 (2.34; 2.52)	2.39 (2.36; 2.42)	2.39 (2.30; 2.53)	2.40 (2.36; 2.44)	$p_{(1–2)} = 0.186$ $p_{(1–3)} = 0.375$ $p_{(2–4)} = 0.641$ $p_{(3–4)} = 0.856$
Ca^{2+}, mmol/L / *ммоль/л*	1.30 (1.27; 1.36)	1.31 (1.29; 1.36)	1.28 (1.29; 1.35)	1.32 (1.29; 1.34)	$p_{(1–2)} = 0.797$ $p_{(1–3)} = 0.027$ $p_{(2–4)} = 0.891$ $p_{(3–4)} = 0.036$
Alkaline phosphatase, U/L / *Щелочная фосфатаза, Ед/л*	234 (199; 306)	215 (199; 280)	127 (95; 224)	120 (66; 217)	$p_{(1–2)} = 0.378$ $p_{(1–3)} < 0.001$ $p_{(2–4)} < 0.001$ $p_{(3–4)} = 0.155$
Creatinine, μmol/L / *Креатинин, мкмоль/л*	51.10 (47.50; 54.90)	51.3 (49.1; 54.2)	61.10 (55.60; 67.60)	65.20 (59; 72.20)	$p_{(1–2)} = 0.369$ $p_{(1–3)} < 0.001$ $p_{(2–4)} < 0.001$ $p_{(3–4)} = 0.076$

Note: *Mann — Whitney U-test was applied; IBD — inflammatory bowel diseases.*
Примечание: *применялся критерий Манна — Уитни; ВЗК — воспалительные заболевания кишечника.*

Physical development indicators (Z-score, BMI, and height) were significantly higher in patients with retained BMD (Z-score > –1.0) compared to those with decreased BMD. This pattern was observed in both nosological entities (Crohn's disease and ulcerative colitis), demonstrating the universal nature of the identified relationship. The identified relationship between the parameters of physical development and the condition of bone tissue in patients with inflammatory bowel diseases is scientifically grounded and confirmed by a number of studies [25–27].

Physical activity level had a considerable effect on bone mineral density in the examined children: low physical activity was reliably associated with decreased BMD indicators (BMD, Z-score; $p < 0.05$), as previously demonstrated in a study by Vanhelst et al. in 2023 [28].

Factors negatively affecting bone mineral density were identified: disease duration exceeding 3 years, moderate and average clinical and endoscopic activity in IBD, and the extensive nature of mucous lesions in the colon in ulcerative colitis. At the same time, no statistically significant relationship

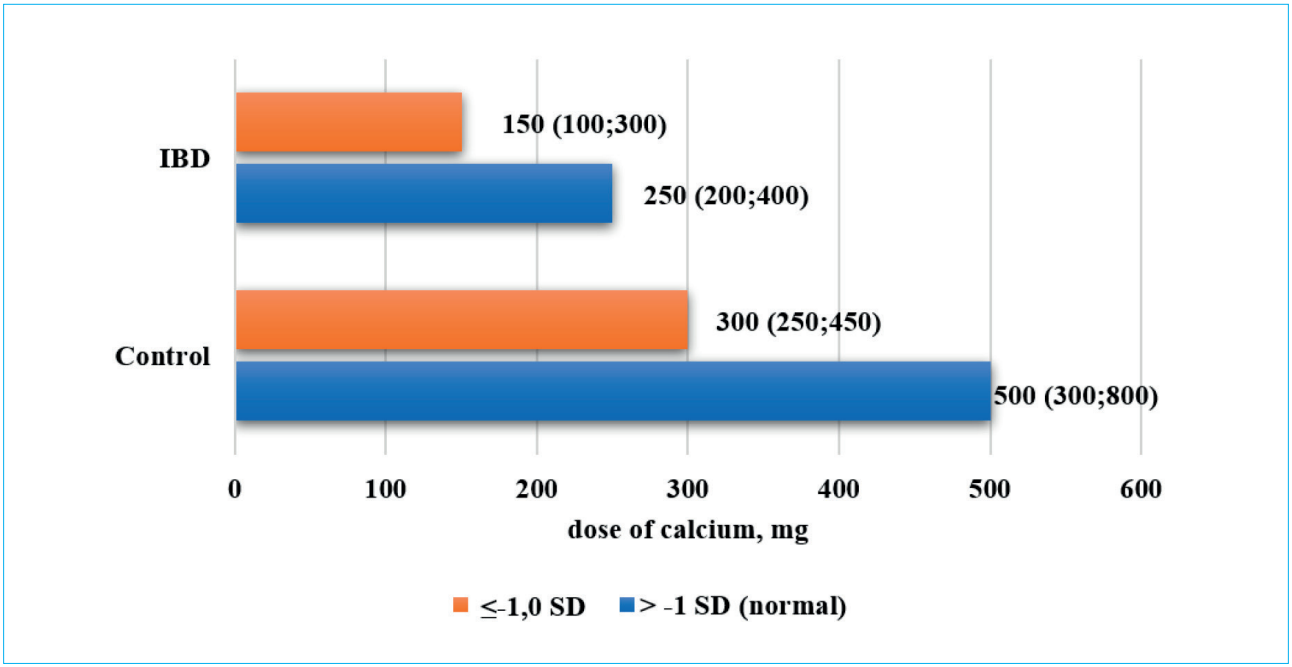


Figure 2. Bone mineral density in patients with IBD and the control group depending on dietary calcium intake, *Me* (Q1; Q3)

Note: IBD — inflammatory bowel diseases.

Рисунок 2. Поступление кальция с пищей у пациентов с ВЗК и различной минеральной плотностью кости и группы контроля, *Me* (Q1; Q3)

Примечание: ВЗК — воспалительные заболевания кишечника.

between the extent of the process and BMD indicators was detected in patients with Crohn's disease. The obtained data are consistent with the results of other authors' studies [12, 14, 21, 29–31], which have shown that high clinical and endoscopic activity of IBD, as well as extensive localisation of inflammation, are associated with decreased BMD Z-score. The established relationship between clinical and endoscopic activity of the disease and BMD indicators demonstrates that systemic and local inflammation, as well as malabsorption, negatively affect bone mineral density in children with IBD.

Therapeutic regimens based on genetically engineered biological drugs and glucocorticoids have a multidirectional influence on bone mineral density indicators. In our study, the use of genetically engineered biologic therapy (GEBT) was not associated with decreased BMD indicators (BMD, Z-score). In accordance with the data from literature, the study shows the absence of a negative effect of GEBT on bone metabolism and densitometry values due to the blocking of the key proinflammatory cytokine TNF-α [13–15]. Using the example of osteo-immunological diseases, including rheumatoid arthritis and ankylosing spondyloarthritis, positive effect of medications with anti-TNF activity on BMD indicators was demonstrated, confirming the advisability of early use of genetically-engineered biological agents for the prevention of a serious complication — systemic osteoporosis — in this patient group [16].

Despite the widespread implementation of genetically engineered biologic therapy, the need for steroids remains high due to their proven effectiveness in inducing remission in inflammatory bowel diseases, especially in children with high disease activity who require high doses and pulse therapy. The use of GCS had a considerable negative effect on bone tissue status ($p = 0.001$). Moreover, dose-dependent effect was noted: high cumulative doses caused a more pronounced decrease in BMD (BMD, Z-score), $p < 0.05$.

The obtained results are consistent with the data of other researchers, who observed a similar pattern both in inflammatory bowel diseases and in rheumatic diseases [32, 33].

The assessment of biochemical markers of bone metabolism revealed age-related peculiarities of bone tissue remodelling in patients with IBD. Osteoresorption processes were predominant in pubertal patients, as indicated by increased parathyroid hormone levels and decreased concentrations of calcitonin and ionized calcium ($p < 0.05$). In contrast, the processes of osteogenesis dominated in younger children, evidenced by increased levels of osteocalcin, alkaline phosphatase and decreased bone resorption, as indicated by C-terminal telopeptide levels. Vitamin D concentrations were

also significantly higher in the younger age group ($p = 0.001$). The obtained data are consistent with the results of studies, demonstrating the activation of osteoresorptive mechanisms in IBD [4, 35].

Age-related peculiarities of bone metabolism, particularly the predominance of resorption during puberty, have also been described in [34–36], showing the relationship between hormonal developments and changes in the balance of bone remodelling.

The obtained data confirming the absence of influence of biochemical markers of bone remodelling on bone mineral density indicators (BMD) point to dynamic processes of bone tissue renewal in patients with IBD and are consistent with the results of other studies emphasising that these parameters provide independent information on bone tissue status [37].

The analysis of the diet showed that patients with IBD had lower intake of calcium compared to healthy children, which was related to the elimination diet and restrictions in the use of dairy products. This deficiency, in turn, correlated with decreased BMD and likely caused the observed changes: lower calcium levels and increased parathyroid hormone levels in blood serum. Moreover, calcium intake was significantly lower in the group of patients with IBD and decreased BMD (Z-score ≤ -1.0) than in patients with normal BMD (BMD, Z-score). The obtained data are consistent with the results of other studies confirming the influence of dairy products consumption on bone health in children.

Conclusion

The conducted study confirmed high prevalence of decreased bone mineral density in children with IBD in the Moscow Region, indicating the negative effect of chronic inflammation on bone metabolism.

A set of risk factors was established, including disease activity and duration, physical development level, calcium intake deficiency, low physical activity, and dose-dependent effect of glucocorticoid therapy.

Age- and gender-related peculiarities in bone remodelling were identified.

The obtained data highlight the need for a multidisciplinary approach to the management of patients with IBD, focusing on inflammation control, correction of nutritional deficiencies and prevention of therapy-related adverse effects on bone tissue status.

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Information about the authors

Maria I. Erokhina* — Researcher at the Department of Pediatrics, a gastroenterologist at the Department of Gastroenterology, Scientific Research Clinical Institute of Childhood of the Ministry of Health of the Moscow Region.
Contact information: m.ero@mail.ru;
141009, Mytishchi, Kominterna str., 24A, build. 1.
ORCID: https://orcid.org/0000-0003-3441-4626

Niso D. Odinaeva — Dr. Sci. (Med.), Director, Research Clinical Institute of Childhood of the Ministry of Healthcare of the Moscow Region; Professor of the Department of Pediatrics, Moscow Regional Research and Clinical Institute.
Contact information: mz_nikid_info@mosreg.ru;
141009, Mytishchi, Kominterna str., 24A, build. 1.
ORCID: https://orcid.org/0000-0001-5214-8072

Elena I. Kondratyeva — Dr. Sci. (Med.), Professor, Deputy Director, Research Clinical Institute of Childhood of the Ministry of Healthcare of the Moscow Region; Head of the Scientific and Clinical Department of Cystic Fibrosis, Head of the Department of Genetic and Respiratory Diseases, Institute of Higher and Continuing Professional Education, Research Center for Medical Genetics.
Contact information: elenafpk@mail.ru;
141009, Mytishchi, Kominterna str., 24A, build. 1.
ORCID: https://orcid.org/0000-0001-6395-0407

Anatoly I. Khavkin — Dr. Sci. (Med.), Professor, Head of the Department of Gastroenterology and Dietetics named after A.V. Mazurin, Research Clinical Institute of Childhood of the Ministry of Healthcare of the Moscow Region; Professor of the Department of Pediatrics with a Course in Pediatric Surgical Diseases, Medical Institute, Belgorod State National Research University.
Contact information: khavkin@nikid.ru;
141009, Mytishchi, Kominterna str., 24A, build. 1.
ORCID: https://orcid.org/0000-0001-7308-7280

Ekaterina A. Yablokova — Cand. Sci. (Med.), Docent, Senior Researcher at the Department of Pediatrics, Research Clinical Institute of Childhood of the Ministry of Healthcare of the Moscow Region; Associate Professor at the Department of Pediatric Diseases, N.F. Filatov Clinical Institute of Children's Health, I.M. Sechenov First Moscow State Medical University (Sechenov University).
Contact information: yablokova_e_a@staff.sechenov.ru;
141009, Mytishchi, Kominterna str., 24A, build. 1.
ORCID: https://orcid.org/0000-0003-3364-610X

Elena K. Zhekaite — Cand. Sci. (Med.), Senior Researcher at the Department of Hereditary and Metabolic Diseases, Pediatrician at the Cystic Fibrosis Department, Research Clinical Institute of Childhood of the Ministry of Health of the Moscow Region.
Contact information: mz_nikid_otd_mv@mosreg.ru;
141009, Mytishchi, Kominterna str., 24A, build. 1.
ORCID: https://orcid.org/0000-0001-5013-3360

Сведения об авторах

Ерохина Мария Ильинична* — научный сотрудник отдела педиатрии, врач-гастроэнтеролог гастроэнтерологического отделения, ГБУЗ «Научно-исследовательский клинический институт детства Министерства здравоохранения Московской области».
Контактная информация: m.ero@mail.ru;
141009, г. Мытищи, ул. Коминтерна, 24а, стр. 1.
ORCID: https://orcid org/0000-0003-3441-4626

Одинаева Нисо Джумаевна — доктор медицинских наук, директор, ГБУЗ Московской области «Научно-исследовательский клинический институт детства Министерства здравоохранения Московской области»; профессор кафедры педиатрии, ГБУЗ «Московский областной научно-исследовательский клинический институт им. М.Ф. Владимирского.
Контактная информация: mz_nikid_info@mosreg.ru;
141009, г. Мытищи, ул. Коминтерна, 24а, стр. 1.
ORCID: https://orcid org/0000-0001-5214-8072

Кондратьева Елена Ивановна — доктор медицинских наук, профессор, заместитель директора, ГБУЗ Московской области «Научно-исследовательский клинический институт детства Министерства здравоохранения Московской области»; руководитель научно-клинического отдела муковисцидоза, заведующая кафедрой генетики болезней дыхательной системы Института высшего и дополнительного профессионального образования, ФГБНУ «Медико-генетический научный центр имени академика Н.П. Бочкова».
Контактная информация: elenafpk@mail.ru;
141009, г. Мытищи, ул. Коминтерна, 24а, стр. 1.
ORCID: https://orcid org/0000-0001-6395-0407

Хавкин Анатолий Ильич — доктор медицинских наук, профессор, заведующий кафедрой гастроэнтерологии и диетологии им. А.В. Мазурина, ГБУЗ Московской области «Научно-исследовательский клинический институт детства Министерства здравоохранения Московской области»; профессор кафедры педиатрии с курсом детских хирургических болезней Медицинского института, ФГАОУ ВО «Белгородский государственный национальный исследовательский университет».
Контактная информация: khavkin@nikid.ru;
141009, г. Мытищи, ул. Коминтерна, 24а, стр. 1.
ORCID: https://orcid org/0000-0001-7308-7280

Яблокова Екатерина Александровна — кандидат медицинских наук, доцент, ведущий научный сотрудник отдела педиатрии, ГБУЗ Московской области «Научно-исследовательский клинический институт детства Министерства здравоохранения Московской области»; доцент кафедры детских болезней, Клинический институт детского здоровья им. Н.Ф. Филатова, ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет).
Контактная информация: yablokova_e_a@staff.sechenov.ru;
141009, г. Мытищи, ул. Коминтерна, 24а, стр. 1.
ORCID: https://orcid org/0000-0003-3364-610X

Жекайте Елена Кястутисовна — кандидат медицинских наук, старший научный сотрудник отдела наследственных и метаболических болезней, врач-педиатр отделения муковисцидоза, ГБУЗ «Научно-исследовательский клинический институт детства Министерства здравоохранения Московской области».
Контактная информация: mz_nikid_otd_mv@mosreg.ru;
141009, г. Мытищи, ул. Коминтерна, 24а, стр. 1.
ORCID: https://orcid org/0000-0001-5013-3360

* Corresponding author / Автор, ответственный за переписку

Authors' contributions

Concept and design of the study: Erokhina M.I., Odinaeva N.D., Kondratieva E.I., Khavkin A.I., Yablokova E.A., Zhekaite E.K.
Collection and processing of materials: Erokhina M.I., Zhekaite E.K.
Statistical processing: Erokhina M.I., Yablokova E.A., Zhekaite E.K.
Writing: Erokhina M.I.
Editing: Erokhina M.I., Kondratieva E.I., Khavkin A.I., Yablokova E.A.
Checking the layout and coordinating it with the author's team: Erokhina M.I.

Вклад авторов

Концепция и дизайн исследования: Ерохина М.И., Одинаева Н.Д., Кондратьева Е.И., Хавкин А.И., Яблокова Е.А., Жекайте Е.К.
Сбор и обработка материалов: Ерохина М.И., Жекайте Е.К.
Статистическая обработка: Ерохина М.И., Яблокова Е.А., Жекайте Е.К.
Написание текста: Ерохина М.И.
Редактирование: Ерохина М.И., Кондратьева Е.И., Хавкин А.И., Яблокова Е.А.
Проверка верстки и ее согласование с авторским коллективом: Ерохина М.И.

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