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BONE METABOLISM STATUS IN CHILDREN WITH CHRONIC RESPIRATORY DISEASES

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СОСТОЯНИЕ КОСТНОГО МЕТАБОЛИЗМА У ДЕТЕЙ С ХРОНИЧЕСКИМИ ЗАБОЛЕВАНИЯМИ ОРГАНОВ ДЫХАНИЯ

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This review focuses on the specific issues of bone metabolism in children with chronic respiratory diseases, namely, cystic fibrosis and bronchial asthma. The results of numerous studies show that patients with chronic bronchial and lung issues tend to develop a premature imbalance of bone remodeling, the clinical manifestations of which include osteopenia, osteoporosis and low-impact fractures. There is also a discussion offered around factors that have a certain effect on the bone metabolism status at the physiological level, as well as around the role of various pathogenetic mechanisms and medication therapy in affecting bone mineral density in pediatric patients suffering from cystic fibrosis and bronchial asthma.

Keywords: cystic fibrosis, bronchial asthma, osteopenia, osteoporosis, bone metabolism

Обзор посвящен особенностям костного метаболизма у детей с хроническими заболеваниями органов дыхания, а именно муковисцидозом и бронхиальной астмой. Согласно результатам многочисленных исследований, пациенты с хроническими заболеваниями бронхов и лёгких подвержены преждевременному развитию дисбаланса костного ремоделирования, что клинически проявляется в форме остеопении, остеопороза и низкоэнергетических переломов. Обсуждаются факторы, оказывающие влияние на состояние костного обмена на физиологическом уровне, а также роль различных патогенетических механизмов и лекарственной терапии в снижении минеральной плотности кости у пациентов детского возраста с муковисцидозом и бронхиальной астмой.

Ключевые слова: муковисцидоз, бронхиальная астма, остеопения, остеопороз, костный метаболизм

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BA – bronchial asthma
BMD – bone mineral density
BMI – body mass index
CF – cystic fibrosis
IGCS – inhaled glucocorticosteroids
IGF-1 – insulin-like growth factor 1
IGF-2 – insulin-like growth factor 2
GCS – glucocorticosteroids
M-CSF – macrophage colony-stimulating factor
M-CSFR – macrophage colony-stimulating factor receptor
NF-kB – transcription nuclear factor
OCN – osteocalcin

OPG – osteoprotegerin
OPN – osteopontin
PBM – peak bone mass
PG – pancreatic gland
PTH – parathormone
RANK – receptor activator of nuclear factor-kappa B
RANKL – receptor activator of nuclear factor kappa-B ligand
STH – somatotrophic hormone (growth hormone)
TGF-β – transforming growth factor-β
TNF-α – tumor necrosis factor-α
VDR – vitamin D receptor

Bone tissue is a dynamic system demonstrating high metabolic activity. This said, an integral feature of such a system will be continuous remodeling processes, which serve as the basis for bone restoration and mechanical strength maintenance. Besides, all this keeps the homeostasis of the most significant macro- and microelements (Calcium, Phosphorus, Zinc, Copper, etc.) [1, 2].

Patients with chronic respiratory diseases are susceptible to premature development of bone remodeling imbalance, which can be accounted for by a lower bone mineral density (BMD) due to the lack of capacity to arrive at its peak in childhood, as well as due to the predominance of osteoresorption, the latter condition being caused by the pathogenesis of the respiratory tract chronic inflammation [3]. A secondary, less often – primary, decrease in BMD develops, depending on the disturbance severity, manifested through osteopenia, osteoporosis, and low-impact fractures.

Children have a remodeling rate of around three times as high as that of adults. As puberty comes, it increases 4–6 times, associated with arriving at the maximum activity of bone metabolism and gaining peak bone mass (PBM) [4]. The peak of PBM in girls is reached earlier and lasts shorter than in boys, occurring at the ages 10–11 and 12–14 years, respectively [5]. The relationship between the weight and the bone mass observed through the active growth period is explained by the mechanical effect experienced by the developing bone.

Skinny children, therefore, have the biochemical activity of resorptive processes prevailing, whereas their BMD indicators are lower than their peers whose weight falls within the normal range. Overweight children have a low level of physical activity along with a high risk of falls and fractures, which, too, can affect the BMD [6, 7]. There are differences to be observed in the intestinal microbiota contents in patients with osteoporosis and healthy individuals, which are to be explained by specific nutrition patterns with a predominant intake of certain substances that have an impact on the microbiome amounts, its composition, and the metabolites it produces [8].

Bone remodeling occurs in the «basic multicellular units», including osteoclasts, osteoblasts, osteocytes, and the supporting tissue [9, 10]. Osteoblasts produce the bone matrix main proteins (Type I Collagen, osteocalcin (OCN), osteonectin (ONN), and osteopontin (OPN)) and stimulate its mineralization. Osteocytes get fixed on the bone surface through secreted proteins (OCN and OPN) and redirect calcium to the bone depot while their apoptosis activates regeneration [2, 11].

Locally, the critical role in remodeling regulation belongs to osteoblasts, the RANK/RANKL/OPG system, and the canonical Wnt-signaling system [1]. Osteoprotegerin (OPG) is a trap for the receptor activator of nuclear factor kappa-B ligand (RANKL), preventing its binding to the receptor activator of nuclear factor-kappa B (RANK) and the development of the RANK/RANKL set, i. e., the resorption activity has a proportional connection to the RANKL/OPG ratio (Fig. 1).

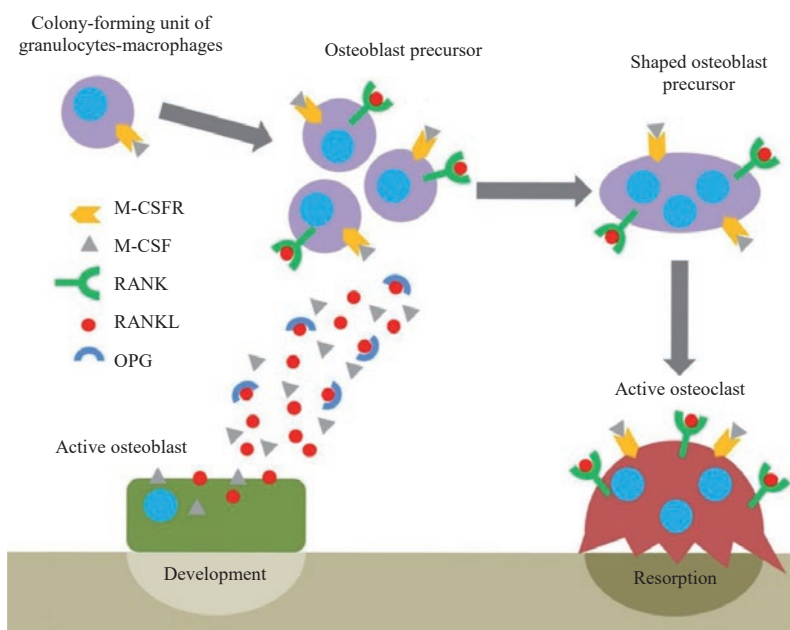


Fig. 1. The RANK/RANKL/OPG and M-CSF axis in osteoclast differentiation and activation (adapted from [1]).

Abbreviations: M-CSFR – macrophage colony-stimulating factor receptor; M-CSF – macrophage colony-stimulating factor; RANK – receptor activator of nuclear factor-kappa B; RANKL – receptor activator of nuclear factor kappa-B ligand; OPG – osteoprotegerin

As far as systemic regulators of bone metabolism are concerned, particular importance is attached to parathyroid hormone (PTH), calcitonin, active metabolites of vitamin D, glucocorticosteroids (GCS), sex hormones, somatotrophic hormone (STH), thyroxine, insulin, and growth factors (insulin-like growth factor-1 (IGF-1), insulin-like growth factor-2 (IGF-2) and transforming growth factor- β (TGF- β)) [9].

Bone metabolism activity is directly dependent on the status of phosphorus-calcium metabolism, vitamin D being its crucial regulator. The active metabolites of the latter (1.25(OH)₂D, 24.25(OH)₂D) enhance calcium and phosphorus absorption in the intestine and renal tubules, also controlling the intake of calcium into the cell through the stimulation of the synthesis of TRPV5 and TRPV6 and D9K and D28K calcium-binding carriers [12, 13].

Calcitriol activates the production of TGF- β and IGF-2, increases the density of IGF-1 receptors, and regulates the activity of the Wnt coreceptor gene while stimulating the proliferation and differentiation of osteoblasts. 1.25(OH)₂D, in turn, can stimulate the synthesis of RANKL, OCN, and Type I Collagen, suppress the production of OPG, and at the same time accelerate the differentiation of osteoclasts [13]. This dual effect serves as proof of an impact that involves the bone metabolism rate as a whole, with no predominant effect on individual links.

Calcidiol values go below the optimal level (under 30 ng/ml), and calcium reabsorption in the kidneys slows down, making it a potent stimulator for PTH release. The latter will mobilize calcium from the depot, activate its reabsorption in the distal tubules of the nephron and small intestine, and reduce the concentration of phosphates in the blood via suppressing tubular reabsorption and increasing their excretion with urine. PTH, therefore, offers short-term emergency control of phosphorus-calcium homeostasis while never replacing the contribution of vitamin D as its permanent regulator [13, 14].

The «golden standard» for diagnosing osteopenia and osteoporosis is osteodensitometry (dual-energy X-ray absorptiometry), which allows quantitative identification of the BMD [15]. Laboratory methods offer ways to carry out differential diagnostics to assess antiresorptive therapy's effectiveness and bone metabolism's intensity [11, 15]. Currently, the levels of osteocalcin, procollagen Type I N-propeptide in blood serum, and bone alkaline phosphatase are used as specific markers of bone formation. The resorption activity rate can be seen from factors like the level of Type I collagen C-telopeptide, tartrate-resistant acid phosphatase 5b (TRACP 5b) in blood serum, and the level of Type I collagen N-telopeptide in urine [16–18].

Even though the clinical significance of osteoporosis in adulthood is higher, the grounds for its development in the case of bronchopulmonary chronic pathology are shaped in childhood, long before respective clinical manifestations.

Nowadays, a limited number of studies are available that focus on the specific features of bone metabolism in children with CF and BA. Speaking of the adult population, however, the issue in question has been studied in more detail. There are some patterns of bone metabolism disorders revealing similarities on both age categories, which explains the reason for investigating this health issue in children within specifically designed studies.

Specific features of bone metabolism in patients with cystic fibrosis. The progress in treating cystic fibrosis (CF) witnessed in recent decades has inevitably

led to a longer life expectancy. During that time, the number of complications associated with CF increases. According to the data of the Register of CF Patients in the Russian Federation, within the period of 2011–2021 there was a decrease registered in the osteoporosis incidence affecting both adults (from 33.1 % down to 19.2 %) and children (from 4.6 % to 1.8 %) [15]. This is due to the improvements in the treatment mode – inhaled and intravenous antibacterial medications, mandatory intake of cholecalciferol (HCF) in preventive dosages, improved nutrition, and a higher level of physical development.

Nevertheless, children with CF still belong to the risk group given their lower BMD and developing osteoporosis, as well as low-impact fractures (cystic fibrosis bone disease) [19]. Several studies have pointed to questionable bone metabolism changes in children with CF [15, 20]. On the other hand, studies reveal a decrease in BMD with low concentrations of bone development markers and an increase in the resorption markers. This condition means disturbed bone remodeling growth and balance, which predicts later osteopenia and osteoporosis development [17, 18].

In the case of CF, osteoporosis is a classic example of a multifactorial disease [15]. The main factors of the BMD decrease in children with CF include the direct effect that the CFTR gene works on the bone tissue with a chronic microbial inflammatory process accompanied by D hypovitaminosis, reduced nutritional status and physical activity, delayed puberty with a need for lengthy intake of antibacterial medications and glucocorticosteroids, as well as immunosuppressive therapy at lung transplantation (Fig. 2) [21–23].

All these factors have the CFTR gene defect in their core. There is a proven connection between mutation and changes affecting bone metabolism, which is associated with CFTR and can be found on the surface of bone cells. The CFTR defect results in increased bone resorption through suppressed synthesis of osteoblastogenesis inducers, prostaglandins E₂, and OPG at increased production of the macrophage colony-stimulating factor (M-CSF), RANKL, proinflammatory cytokines, and the tumor necrosis factor- α (TNF- α). This affects the Wnt-signaling pathway with inhibited osteoblast differentiation and simultaneously excessive activation of osteoclasts [24].

Research outcomes show a decrease in OCN and OPG levels and an increased RANKL index in children with CF compared to a healthy population. The RANKL/OPG ratio should be expected to correlate with a low BMD index and may be an early predictor of a developing bone disease caused by CF. However, the study [25] showed that children with CF were not found to correlate serum bone markers (OCN, RANKL, OPG, and RANKL/OPG) and changes in BMD. During that, the forced expiratory volume₁ (FEV₁), the muscle mass, and the muscle strength were predictably associated with the BMD index.

The bone tissue status at CF is affected by chronic microbial inflammation in the respiratory tract, which is mainly decisive for the disease course and outcome forecast. *S. aureus* and *P. aeruginosa* are most often identified infections. In contrast, 2/3 of inflammation cases are caused by bacterial associations. Pathogenic microorganisms' persistent presence increases proinflammatory cytokines' activity (IL-1, IL-6, IL-8, IL-11, TNF- α , etc.).

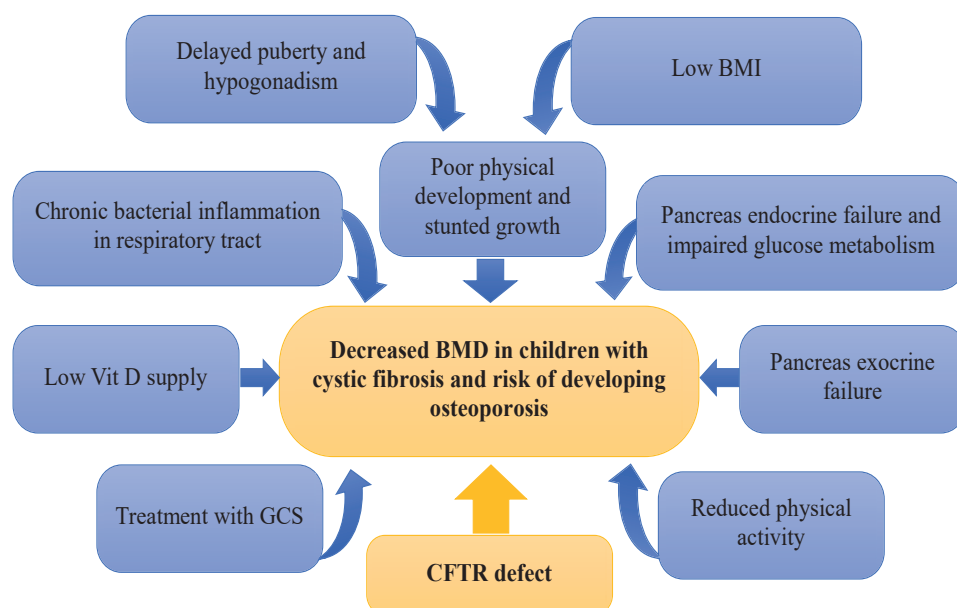


Fig. 2. Pathogenetic factors affecting BMD remodeling in cystic fibrosis (adapted from [19])

Lower microbial diversity, however, is also associated with higher levels of inflammation markers, which enhances bone resorption through the RANKL synthesis activation, also causing the RANK/RANKL/OPG system imbalance and disrupting the conventional Wnt signaling pathway of osteoblastogenesis regulation [23, 26, 27].

Vitamin D has a crucial role in bone metabolism in children with CF. Lack of 25(OH)D in blood serum (below 30 ng/ml) is diagnosed in 36.7–86.7 % of children suffering from CF who live in the South of Russia [28]. The obtained data reflect the results of the meta-analysis, which shows that 63 % of children and adolescents with CF suffered from low vitamin D levels within a year [29]. Vitamin D deficiency results in calcium malabsorption and increases its resorption from bones against developing secondary hyperparathyroidism, which can decrease BMD and promote osteoporosis progress.

This condition also leads to higher frequency fractures. Another issue associated with hypovitaminosis D is that respective patients reveal reduced levels of antimicrobial peptides, which – given chronic respiratory infection – leads to a significant increase in the rate and aggravation of infectious complications affecting children with CF [30]. Vitamin D deficiency in CF develops through several pathogenic links acting together.

Disturbance in the pancreas's exocrine function reduces the exogenous supply of fat-soluble vitamins and calcium. The resulting liver ailment often comes accompanied by a disturbed first stage of HCF-hydroxylation, which leads to a poor action of its effects. At the same time, notable here is an incomparably significant increase of blood serum 25(OH)D both in healthy children and children with CF against an intake of identical dosages of vitamin D [31]. When dealing with patients diagnosed with CF, it is essential to select the dosage of the drug on an individual basis, not only given the patient's age but also in taking into account factors like body weight and the severity of malabsorption syndrome in every single case [32].

Essential factors behind D hypovitaminosis are low levels of insolation, a lengthy intake of antibiotics, and inpatient treatment [33, 34].

A multicenter study involving adults with CF at pulmonary exacerbations showed the effectiveness of administering high doses of vitamin D (250 000 IU, single intake, orally) to prevent bone tissue damage [35].

Unlike deficiency conditions, no direct link was identified between the vitamin D receptor gene polymorphism and the risk of developing low BMD. However, each VDR genetic variant increases the risks of infection affecting the respiratory tract with a microorganism and serves as another reason to use GCS, which indirectly affects bone metabolism [36].

A thinning subcutaneous fat layer with lower levels of vitamin D-binding protein occurring due to digestive disorders will limit the capacity for depositing proper amounts of calcidiol [33, 34]. A low body mass index (BMI) directly correlates with the BMD Z-score. During that time, patients with a decreased BMI fail to gain sufficient PBM [37]. The slowed physical progress is reflected in the linear growth of the bone. A particular role here resides in genetic factors and the STH/IGF-1 axis, which, in the case of CF, is susceptible to suppression. STH replacement therapy improves growth and helps gain PBM during active growth, providing proper nutrition and adequate control of inflammation [38, 39].

Proper nutrition for children with CF implies a high-calorie diet enriched with animal protein and fats, mainly of plant origin [40]. A fat-rich diet facilitates bile secretion, while selecting the most bile-resistant intestinal microbiota, whose metabolites can accelerate osteoporosis development [8].

An essential aspect of the treatment for CF is the control of the levels of calcium-phosphorus in the diet, as well as substances linked with the absorption of these elements, namely, fats and vitamin D. An analysis of the nutrition for children with CF revealed a significant connection between calcium, phosphorus, vitamin D and various health indicators. While the average serum calcium levels and their intake fell within the normal range, one-third of the children were found to have hypercalciuria. However, despite some children being diagnosed with hypophosphatemia, most patients had elevated levels of alkaline phosphatase and hyperphosphaturia [41].

Studies carried out nowadays do not point to delayed puberty as an inevitable component of CF. CF-related liver diseases may account for the issue in question. Severe CF-associated diabetes mellitus and malnutrition aggravate chronic inflammation against the backdrop of long-term GCS therapy. Delayed puberty and hypogonadism can have an effect on the choice of

treatment for osteopenia cases, just like they are taken into account when interpreting the osteodensitometry findings [42].

Specific features of bone metabolism in patients with bronchial asthma. Bronchial asthma (BA), as defined according to the Global Initiative for Asthma (GINA) 2023, is a heterogeneous disease featuring chronic inflammation of the airways, respiratory symptoms such as attacks of obstructed breathing, suffocation, wheezing (whistling sound), shortness of breath, the feeling of chest congestion and cough. The clinical manifestations vary in time and intensity, manifesting with varying airway obstruction. Regardless of the severity and the volume of essential therapy, children with BA have no disturbance affecting their physiological patterns of bone metabolism and mineralization [43].

The risks of decreased BMD, excluding genetic predisposition, have two main reasons behind it – chronic inflammation in the bronchi and continuous use of drugs capable of hurting bone remodeling. The development of osteopenia and osteoporosis, resulting in low-impact bone fractures in patients with BA, is becoming more and more of an issue over age. This relevance is due to deteriorating life quality and an increasing rate of turning to emergency medical assistance and hospitalizations and related treatment costs [44].

GCS is fascinating when studying drugs capable of affecting bone metabolism. At the physiological level, endogenous GCS produces an anabolic effect, promoting the differentiation of osteoblasts and maintaining bone homeostasis. In the case of treatment with exogenous GCS, their concentration in the body exceeds the physiological levels. It works demonstrating the opposite effect – the differentiation and proliferation of osteoblasts drop, their apoptosis is induced due to inhibited main signaling pathways and proteins (IGF-1, Wnt signaling pathway, synthesis of bone morphogenetic proteins), stimulated somatostatin secretion and inhibited pulse STH release, its receptors and their binding activity, which – cooperating – lead to a slowdown in the linear bone growth [45].

Initially, long-term systemic therapy with GCS was considered the only meaningful factor behind changes affecting bone metabolism in the case of BA. These effects are most evident during the first six months following the start of GCS therapy. Further on, this phenomenon acquires some dose-dependent specifics [46]. Continuous use of low dosages of systemic GCS, along with respective frequent course treatment, leads to a decrease in the BMD and, as an effect, increases the risk of osteoporosis. During that, sporadic short courses at exacerbation periods do not typically significantly affect bone tissue and appear relatively safe [47]. However, reports are claiming undesirable effects produced even through short treatment courses, which cannot be taken into account when deciding on treatment tactics for mild exacerbations. After a five-day course of systemic treatment with GCS, for instance, children with BA were revealed to have a decrease in serum OCN, which took around a month to get back to the average values [48].

The introduction of inhaled GCS into modern BA treatment allowed localizing the effect of drugs while minimizing numerous risks of systemic therapy. The impact on bone metabolism, though, remains questionable. Depending on the delivery method, 10 % to 56 % of the drug's nominal dosage enters the lungs,

working a specific local anti-inflammatory effect before being absorbed into the blood circulation. Further on, systemic GCS releases its action with no organ-specific anti-inflammatory effect [49]. The study measured the risk of developing osteoporosis and low-impact fractures in patients with BA, depending on the treatment with modern oral GCS or IGCS [50].

Using IGCS was associated with a lower risk of osteoporosis. However, the high frequency of administering the drug, along with its cumulative dosage over the previous year, increased the risk in both cases. The impact on the fracture rate was similar – the dose-effect link between the frequency of use, the total dosage, and the risk of fractures in the two groups remained. Patients who were taking Budesonide as an IGCS were at a greater risk of developing osteoporosis, whereas the risks of having fractures revealed no dependence on the active substance.

A similar study involving a population of children with BA exposed no clinically significant association between IGCS therapy and fractures, in contrast to treatment with systemic GCS, which, when used, did entail a significantly higher risk of disturbed bone integrity, specifically in girls [51].

There is an evidence concerning the role of long-term (2+ years) therapy with medium and high dosages of Budesonide (≥ 400 mcg/day for children aged 6–11, and ≥ 800 mcg/day for 11+ year-olds) in reducing the BMD in children at the age of 7–17 suffering from moderate to severe bronchial asthma [52].

On the other hand, the issue of employing IGCS within the primary therapy for BA in children remains significant due to its negative effect on linear growth. Using IGCS in early childhood entails a BMD decrease and affects growth in the cohort of children under six. During that time, patients whose treatment length exceeded one year were found to have negative feedback on the IGCS cumulative dosage and the body length [53].

Data is available that reports a decrease in the growth rate by an annual average of 0.48 cm in the case of regular use of IGCS. Average dosages, in turn, slow down growth by 0.2 cm/year more if compared to low dosages of hormones. Prospective studies suggest a 1.1 cm decrease in the body length at the end of the six-year follow-up period in patients taking IGCS, unlike children receiving Nedocromil or placebo. Finally, the twelve-year longitudinal follow-up study results showed that the body length of adult patients with BA taking IGCS within their respective treatment in childhood was 1.2 cm shorter than in the control group [54].

There is a growing interest in studying the effect that mediators of allergic inflammation have on bone tissue, which is of importance when dealing with cases of atopic asthma. More and more studies nowadays report a link between the production of IL-31, IL-33, Th2, Th1, and Th17 cytokines and the development of osteopenic issues in patients with BA [55].

Once we touch upon the effect that the immune system and atopy have on the bone metabolism status, we cannot but mention the non-calcemic effects of 25(OH)D. Preventing excessive bone destruction, mediated through the immune response modulation, is a proven fact. The inactivation of NF- κ B promotes a decrease in the levels of proinflammatory cytokines (IL-1, IL-6, IL-12, IL-23, IL-17, TNF- α); the functional M1-polarization of monocytes and macrophages shifts towards M2-polarization; the pool of Th1 and Th17 gets decreased, with the Th2-mediated

immune response profile getting modulated, which has anti-inflammatory effects [56, 57]. From this point of view, improved levels 25(OH)D entails the reduction of the occurrence frequency of acute respiratory diseases and exacerbations of virus-induced BA, improved values, better symptom control and treatment effectiveness at any age, never affecting the severity of asthma, which, in turn, can prevent excessive and premature loss of BMD [58, 59].

The study [60] demonstrated that children with BA and delayed growth lack 25(OH)D. Children with BA, though, who featured no delay in growth, and children without BA yet with delayed development, were found to have vitamin D deficiency, elevated levels of IL-4 and CD23+ expression, and lower IL-10 levels.

Conclusion. Given the above, disturbed bone metabolism in children with chronic respiratory diseases is a multifactorial condition. Despite the constant expansion of the respective knowledge base and ongoing research, the ambiguity of the obtained data points to a need for multicenter studies and systematic research work. The factors behind the development of osteopenia and osteoporosis feature similarity, and despite the difference in the etiology of chronic respiratory issues, they do offer grounds for experimental modeling and clinical investigation into the pathogenetic mechanisms caused by chronic microbial and allergic inflammation, which, in turn, might help develop effective methods for the prevention and treatment of osteopenic conditions in childhood.

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