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VITAMIN D, OBESITY AND BONE HEALTH IN CHILDREN: THE ROLE OF METABOLIC SYNDROME AND MASLD

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This article provides a narrative review of recent scientific literature regarding the complex interrelationship between vitamin D status, obesity, and bone health in the pediatric population. Vitamin D plays a pivotal role in calcium and phosphorus homeostasis, bone mineralization, and the regulation of bone turnover through osteoblast and osteoclast activity. A deficiency in this essential micronutrient during childhood can impair bone development and lead to conditions such as rickets, osteopenia, and osteoporosis. The high prevalence of vitamin D deficiency in children is associated with inadequate sun exposure, poor dietary intake, sedentary lifestyle, and underlying metabolic disturbances.

A key focus of the review is the impact of obesity on vitamin D metabolism and skeletal health. Obesity not only reduces vitamin D bioavailability due to its sequestration in adipose tissue but also contributes to chronic low-grade inflammation and metabolic dysregulation, which adversely affect bone structure and function. Emerging evidence highlights that while higher body mass was once considered protective against bone fragility, recent studies suggest that excessive visceral fat, particularly in the presence of metabolic syndrome (MetS), may compromise bone quality and increase fracture risk.

The article also explores the implications of metabolic dysfunction-associated steatotic liver disease (MASLD), which is increasingly diagnosed in overweight and obese children. MASLD may disrupt the newly recognized liver-bone axis, thereby contributing to altered bone remodeling and reduced bone mineral density. Furthermore, studies show that vitamin D deficiency is closely associated with the presence and severity of MASLD, suggesting a bidirectional relationship.

The authors underscore the potential of vitamin D supplementation and lifestyle interventions, including improved nutrition and physical activity, as viable strategies to mitigate the adverse effects of obesity and MetS on pediatric skeletal health. The need for further clinical and translational research is emphasized to better understand the interactions among vitamin D status, adiposity, liver function, and bone development in children and adolescents.

Key words: *vitamin D, obesity, children, bone tissue, osteoporosis, metabolic syndrome, MASLD.*

Наталя Гніда, Ігор Гнідой. Вітамін D, ожиріння і здоров'я кісток у дітей: роль метаболічного синдрому і MASLD

У статті представлено наративний огляд сучасної наукової літератури щодо складного взаємозв'язку між статусом вітаміну D, ожирінням і станом кісткової системи у дітей. Вітамін D відіграє ключову роль у підтриманні гомеостазу кальцію і фосфору, мінералізації кісток, а також регуляції процесів остеогенезу й резорбції кісткової тканини через вплив на остеобласти й остеокласти. Дефіцит цього важливого мікронутрієнта в дитячому віці може порушити нормальний розвиток скелету і спричинити рахіт, остеопенію та остеопороз. Висока поширеність дефіциту вітаміну D серед дітей пояснюється недостатнім впливом сонячного світла, незбалансованим харчуванням, малорухливим способом життя та метаболічними порушеннями.

Окрему увагу приділено впливу ожиріння на обмін вітаміну D і здоров'я кісткової системи. Надлишкова маса тіла знижує біодоступність вітаміну D через його накопичення у жировій тканині, а також супроводжується хронічним низькоінтенсивним запаленням і метаболічною дезрегуляцією, які негативно впливають на структуру та функцію кісткової тканини. Сучасні дослідження доводять, що попри раніше існуючу думку про «захисну роль» ожиріння для кісток, вісцеральне ожиріння, особливо в поєднанні з метаболічним синдромом, може знижувати якість кісткової тканини та підвищувати ризик переломів.

Розглянуто також роль метаболічно асоційованої стеатозної хвороби печінки (MASLD), що дедалі частіше діагностується у дітей із надмірною вагою. MASLD спричиняє порушення функціонування так званої «печінково-кісткової осі», що додатково поглиблює дисбаланс у кістковому ремоделюванні. Доведено, що дефіцит вітаміну D корелює з наявністю і тяжкістю MASLD, що свідчить про взаємозалежність цих станів.

Автори підкреслюють перспективність застосування вітаміну D та змін способу життя (раціонального харчування, фізичної активності) як ефективних підходів до профілактики порушень кісткової системи у дітей з ожирінням та метаболічними розладами. Наголошено на необхідності подальших досліджень для глибшого розуміння взаємодії між вітаміном D, жировою тканиною, функцією печінки та розвитком кісткової тканини в дитячому віці.

Ключові слова: *вітамін D, ожиріння, діти, кісткова тканина, остеопороз, метаболічний синдром, MASLD.*

Underground. One of the key roles in ensuring bone health is played by vitamin D. However, the implementation of its function is difficult in case of exposure to various adverse factors. These factors may include overweight and obesity. These conditions result from an imbalance between energy consumed (too much) and energy expended (too little). Globally, people are consuming foods and drinks that are more energy-dense (high in sugars and fats) and engaging in less physical activity [1], which requires less energy. Therefore, the prevalence of obesity is increasing at a very rapid rate, including among children and adolescents [2]. In turn, an increase in body weight in children entails an additional decrease in their physical functioning [3]. Previously, it was believed that bone tissue does not suffer; obesity in children and adolescents even contributes to an increase in bone mineral density (BMD). But today, the position of scientists on this issue is not unambiguous [4]. Similarly, the definition and criteria of metabolic syndrome in children and adolescents are currently not fully understood [5]. At the same time, it was found that the prevalence of metabolic dysfunction-associated fatty liver disease in cohort of Ukrainian children with overweight and obesity was 19%; vitamin D deficiency was associated with presence of this disease and can be supposed like risk factors for it [6]. These data highlight the need for further study of the mechanisms of interaction between obesity, vitamin D levels and skeletal health in children.

The **purpose** of this review article is to analyze modern studies of the dependence of bone conditions in children on the vitamin D level in their body and the presence of overweight and obesity.

Material and methods. The search query was conducted in the PubMed database with a depth of 3 years and included the words «vitamin D», «obesity», «bone», «child». Several hundred scientific articles were processed using a selective search method. Articles that dealt exclusively with early childhood, pregnant women, as well as genetic diseases, dental issues, etc., which did not correspond to the purpose of the search, were excluded. The final number of 46 sources was included in this narrative review.

Discussion. To structure the information obtained, we grouped the search results into blocks, which, in our opinion, logically follow from each other.

The Role of Vitamin D in Bone Metabolism

Investigations revealed the two major functions of vitamin D were to increase intestinal calcium and phosphate absorption and mobilize calcium from the skeleton to maintain calcium and phosphorus homeostasis [7; 8]. There is no doubt that the first of these functions has a positive effect on the condition of the bone, providing it with the main structural component. The bone inorganic matrix, composed of a combination of calcium and phosphorus salts, contributes to its hardness and rigidity [9]. The second function of vitamin D serves primarily to maintain a constant level of calcium in the blood. But it also contributes to the renewal of bone tissue. Both the bone modeling process and the bone remodeling process are important in maintaining bone health and the integrity and mechanical characteristics of the skeleton [10]. The dense, strong, and hardy nature of bone tissue allows it to form a framework that supports all the organs of the body and provides safe shelter for the most vital and delicate of them, such as the brain, heart, and lungs [9]. Not only that, but the skeleton is much more than a rigid scaffold for the body. It is a multifunctional organ that transforms the force created by muscle contraction into locomotion, contains the marrow where the blood cells are produced, serves as the main storage system for calcium and phosphorus that are key components of intracellular signaling pathways, is an essential part of the circulatory system, and has emerged in the last years as a previously unsuspected endocrine tissue [9]. Accordingly, with vitamin D deficiency, all these functions can be impaired. Therefore, vitamin D sufficiency is extremely important to maximize bone health throughout life [8]. Strong evidence has been obtained regarding the appropriate intake of calcium and vitamin D in children and adolescents to achieve proper peak bone mass [10]. A large cross-sectional analysis in 4,682 people aged 6 to 18 years showed a positive association of serum 25-hydroxyvitamin D with bone health measured by calcaneal quantitative ultrasound, in children and adolescents, particularly among those who had reached the post-pubertal stage [11].

The review [12] revealed that the central role for vitamin D in bone physiology is directed via osteoblasts and depends on their stage of development. VDRs and the vitamin-D-metabolizing enzymes

CYP27B1 and CYP24A1, known from the vitamin D endocrine system, are present and functional in osteoblasts. This uncovers a direct local role for 1α,25-OH2D3 vitamin D in osteoblast function, and expands the vitamin D action profile from endocrine regulation of calcium and phosphate homeostasis to an auto/paracrine regulatory network in bone. In this way, vitamin D controls the proliferation, apoptosis, differentiation, and mineralization of osteoblasts, as well as their gene profile and interaction with other factors that maintain healthy bone [12].

Vitamin D deficiency and osteoporosis in children and adolescents

Osteoporosis is a metabolic bone disorder which increases fragility fracture risk. Elderly individuals, especially postmenopausal women, are particularly susceptible to osteoporosis [13]. Although rare, osteoporosis in children and young adults is becoming increasingly evident [13; 14]. Pediatric osteoporosis is defined by both: 1) a clinically significant fracture history; and 2) a low BMD. Pragmatically, the diagnosis of osteoporosis is indicated by a BMD Z-score ≤ -2.0 and a clinically significant fracture history, defined as two or more long bone fractures by age 10 years, or three or more long bone fractures at any age up to 19 years. Additionally, the finding of one or more vertebral non-traumatic compression fractures is diagnostic of osteoporosis independent of BMD [15].

As childhood bone fragility has several etiologies, its management requires a thorough evaluation of all potentially contributing pathogenetic mechanisms [14]. Vitamin D deficiency may be among them [14]. It is frequent around the world especially in the pediatric population [16]. Besides, pediatric individuals are prone to imbalanced diets and picky eating behavior, and their diets may then become incomplete: the highest risk for deficiency is observed for iron, zinc and vitamin D [17].

It is established that vitamin D deficiency leads to secondary hyperparathyroidism, increasing bone resorption. As a result, this decreases bone mineral content and compromises architectural integrity increasing risk for fracture [8]. In a recent study, vitamin D deficiency correlated with almost five times the increased risk of pediatric low-energy fractures [18]. Therefore, lifestyle interventions including adequate nutrition with adequate calcium and vitamin D intake, as well as physical activity, are recommended for the prevention of osteoporosis and osteoporotic fractures [14].

Obesity and bone health in children

Unfortunately, the world still has the problem of malnutrition in its various forms: deficiencies, excesses, or imbalances in a person's intake of energy and/or nutrients, including important vitamins and minerals [1]. The most frequent consequences of malnutrition are thinness and stunting or, on the contrary, overweight. Moreover, an analysis of data from 3663 population-based studies with 222 million participants showed that the combined burden of underweight and obesity has increased in most countries, driven by an increase in obesity [19].

Current evidence suggests that childhood obesity has profound multifaceted effects on the developing musculoskeletal system, ultimately causing poor nutritional status during development [20]. A study was performed to compare parameters of bone metabolism in children 8–12 years of age with normal weight with overweight/obesity. The results showed that overweight/obesity may negatively affect bone health already at a young age [21].

Obesity, characterized by excessive fat accumulation, has been traditionally associated with higher bone mineral density. Also, recent data suggests a favorable bone microarchitecture profile in these patients. However, the increase in bone mineral density does not necessarily confer protection against fractures, and the risk of fractures may vary depending on the skeletal sites [22]. There have been publications suggesting that patients with a high body mass index (BMI) may have a higher bone fragility and fracture risk. However, some obese individuals with healthy metabolic profiles seem to be less at risk of bone fracture [23]. Therefore, the possible negative effects on the bones are not so much caused by obesity itself as by the presence of a concomitant metabolic syndrome.

Metabolic syndrome and its effects on bones

Metabolic syndrome (MetS) is a complex disorder characterized by abdominal obesity, elevated blood pressure, hyperlipidemia, and elevated fasting blood glucose levels. The diagnostic criteria for MetS in adults are well-established, but there is currently no consensus on the definition in children and adolescents [24]. The individual components of MetS together increase the risk of MetS-related disorders. The most common MetS-related diseases with a detrimental impact on bone quality are type 2 diabetes mellitus, cardiovascular diseases, osteoporosis [25].

The main negative effects of MetS on bone tissue are mediated by the increased differentiation of mesenchymal stem cells towards adipocytes at the expense of osteoblasts, reduced levels of physical activity with increased activity of osteoclasts, reduced intestinal calcium absorption and low-grade chronic inflammation [14]. We can see that some of these mechanisms, in turn, are mediated by vitamin D deficiency.

Obesity and vitamin D deficiency

The most common micronutrient deficiencies found in patients with obesity were vitamin D and calcium [26]. On the other hand, it has been proven that the high prevalence of vitamin D deficiency in children and adolescents attributed to an increase in the incidence of obesity [27]. That is, the relationship between obesity and vitamin D is intricate and bidirectional. Obesity can contribute to vitamin D deficiency, and vitamin D deficiency may exacerbate certain health risks associated with obesity [28].

In addition, vitamin D can both stimulate and inhibit adipogenesis [29]. Adipose tissue, for its part, acts both as a potential reservoir and as a site for vitamin D sequestration [28].

The most probable mechanism for vitamin D deficiency in adolescents with obesity, rather than altered metabolic, is the environmental factors (sedentary lifestyle and lack of adequate sunlight exposure) [30], which are relatively easy to adjust. In obesity with MetS, an additional mechanism appears, and it is much more difficult to adjust. This mechanism is that visceral adipose tissue may sequester vitamin D, leading to reduced availability for metabolic processes [28]. In turn, children and adolescents with severe vitamin D deficiency are more likely to have MetS than those with sufficient levels [31].

An increasing number of studies show how hypovitaminosis D in the pediatric age may play a role in the pathogenesis of metabolic disorders and lipid profile alterations [32]. A correlation between vitamin D levels and the lipid/atherosclerotic profile was recorded in children and adolescents with obesity [33]. In children with overweight or obesity, a positive association between 25(OH)D and biomarkers of inflammation caused by MetS was observed [34]. Metabolic disorders among the school-aged children with degrees I, II, and III obesity could affect the homeostasis of vitamin D metabolism related genes such as CYP27A1, CYP2R1, CYP27B1 etc. through abnormal DNA methylation, resulting in the disorders of vitamin D related metabolites to decrease vitamin D bioavailability with the BMI-independent manner [35]. In turn, the lower levels of vitamin D metabolites would affect the liver function to exacerbate the progression of obesity [35].

Metabolic dysfunction-associated steatotic liver disease (MASLD), osteoporosis, and vitamin D levels in children and adolescents

As a classical endocrine organ, the liver is involved in numerous pathophysiological regulatory processes. In addition, the liver also showed tight regulation of the newly defined endocrine organ, bone, which could be defined as the “liver-bone axis” [36]. Therefore, liver injury induced by different liver diseases can cause an imbalance in bone metabolism [36]. These diseases include MASLD.

MASLD is now identified as a hepatic sign of metabolic syndrome [37]. It has profound adverse effects on bone health and homeostasis. MASLD appears to be associated with changes in bone mineral density (BMD) and fracture rate [38]. At the same time, serum 25(OH)D concentrations were lower in children and adolescents with obesity and hepatic steatosis as compared to those without hepatic steatosis, with an inverse association between the severity of hepatic steatosis and serum 25(OH)D concentrations [39].

Prospects for the use of vitamin D for the prevention and treatment of detected disorders

Consequently, the research findings highlight an intricate association between vitamin D, obesity, MetS, and skeletal health [40]. It has been shown that low concentrations of 25(OH)D are associated with the risk of developing osteoporosis and other diseases, as well as complications characterized by bone metabolism disorders, and obesity and its complications [41]. This provides the prospect of using vitamin D for the prevention and/or treatment of skeletal disorders in patients with obesity and MetS [40]. Moreover, the fact that vitamin D's efficacy extends beyond bone health to include significant impacts on cellular and molecular pathways critical to MetS [42]. Not only that, the ubiquitous presence of the vitamin D receptor in the body has led to its redefinition from a steroidal hormone primarily involved in skeletal functions to a hormone with pleiotropic effects, exerting its influence on the circulatory, nervous, and immune systems. This has prompted investigations into its potential use in preventing and treating not only chronic metabolic disorders, but also cardiovascular diseases, infections, and allergic and autoimmune diseases, including in children [43].

An endocrine society clinical practice guideline suggests empiric vitamin D supplementation for children and adolescents aged 1 to 18 years to prevent nutritional rickets and because of its potential to lower the risk of respiratory tract infections [44, 45]. Adequate vitamin D and calcium supplementation, along with exercise training, may also attenuate the negative effects of obesity diets on bone health [46].

Conclusions and prospects:

1. A review of studies published over the past 3 years suggests that vitamin D has several mechanisms for influencing bone health, and its role is crucial in maintaining an optimal balance between osteoblasts and osteoclasts.

2. With vitamin D deficiency, this balance is disturbed, which leads to the prevalence of bone resorption and the development of osteopenia and osteoporosis, including in school-age children and adolescents.

3. In today's pediatric population, the prevalence of obesity is growing rapidly, which also has an impact on bone health, and, according to current data, it is assessed ambiguously.

4. It is assumed that abdominal obesity, which is a component of metabolic syndrome, has negative effects on bone tissue.

5. Abdominal obesity can cause vitamin D deficiency in the body even with sufficient dietary intake – due to the sequestration of the vitamin in visceral adipose tissue.

6. Particularly unfavorable is the presence of metabolic dysfunction-associated steatotic liver disease (MASLD).

7. Further research is needed on the complex relationships between vitamin D, bone, adipose tissue, and liver in school-age children and adolescents to develop optimal prevention and therapeutic strategies in this cohort of children.

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