

## ОГЛЯДИ

### THE ROLE OF OBESITY IN THE DEVELOPMENT OF VITAMIN D DEFICIENCY RICKETS IN CHILDREN\*

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At present, insufficiency and, for the most part, deficiency of vitamin D is a pandemic that covers a large part of the general population, including children and adolescents, pregnant and lactating women. The D-hormone deficiency (more often referred to as vitamin D deficiency) in children takes the lead among the main problems of the World Health Organization [1].

Vitamin D deficiency rickets is one of the most common diseases among children of the first years of life in many countries around the world. Vitamin D deficiency rickets makes a significant contribution to the pathology structure not only in infants, but also has an adverse effect on the further development of the child and formation of osteopenies in adulthood [2].

Taking into account the modern ideas about metabolism and physiological functions of cholecalciferol, the importance of its deficiency in the pathogenesis of vitamin D deficiency rickets obviously needs to be considered not so much from the point of insufficient income into the child's body, but with regards to the characteristics of vitamin D metabolism under the influ-

ence of exo- and endogenous factor combination leading to the development of pathological process. It is very important to understand the aforementioned nosological unit as a metabolism disorder, and not just as a D-deficiency state. According to ICD-10, rickets does not refer to the hypovitaminosis chapter, but to the chapter of the endocrine system and metabolism diseases [3].

Thus, vitamin D metabolism, deposition, bioavailability and its biological role are dependent on the size of adipose tissue [4].

The problem of obesity and overweight in children is alarming in many countries around the world. Despite all the achievements and scientific developments in the world, the number of children with obesity is increasing. Our country is not an exception, as during the period of 2002–2012 the number of such children has almost doubled [5].

The significance of this problem is confirmed by the WHO data, according to which the number of infants and young children (0 to 5 years old) with overweight or obesity worldwide increased from 32 million in 1990 to

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42 million in 2013 (World Health Organization, 2013).

The maximum load on bone tissue is observed during the period of intense growth, which is characteristic for young children. This makes this age group particularly vulnerable to metabolic bone formation disorders. It is known that for the given child group the vitamin D and Ca deficiency, which is clinically manifested by the rickets development, leads to serious health effects throughout life. The problem of this disease requires special attention, first of all, in infants [6].

The rickets process formation is determined by the interaction of many factors that affect the calcium and phosphorus balance in the baby's body. Not new is the information that the risk of developing rickets from the child's side is a large body weight at birth (over 4 kg) and a significant increase in body weight (over 1 kg per month) during the first months of life [7]. In the available reference sources we have not found an explanation for this, and, unfortunately, this aspect is not involved in the peculiarities of preventive and curative measures optimization for these children in our country. And only today, the results of scientific works related to studies of the pathogenetic association of vitamin D deficiency and obesity reveal to us the multi-vector cause-and-effect links and prospects for further research [8].

In modern conditions, the risk factors for vitamin D deficiency rickets have undergone further study due to changes in socio-economic, environmental conditions of life, health state of women of childbearing age, peculiarities of physical development and infant feeding [9].

Thus, modern studies indicate that obesity is one of the risk factors for vitamin D deficiency in children [10]. Recent studies have shown that people who have excessive body weight, unlike people of normal weight, need higher doses of vitamin D to achieve the same levels of serum vitamin D [11]. According to the clinical recommendations of the International Endocrinology Society, which are based on the principles of evidence-based medicine, obese individuals in their age group require at least 2–3 times more vitamin D to provide the body with its adequate supply [1]. The results of other studies agree with this statement, and

supplement it with data that the dose of vitamin D preparations should be 1.5 times higher for people with overweight in relation to persons with normal body weight [12].

The population studies which were held in pediatrics and studied the association of obesity with vitamin D deficiency, received the following results. In over 50% of Norwegian children and adolescents with overweight, a low 25(OH)D status was detected, 19% of which had vitamin D deficiency [13]. The analysis of vitamin D availability among American children has shown that vitamin D deficiency was reported in 29% of overweight, 34% of obese children, and 49% of highly obese patients, which significantly differed from that of vitamin D in children with body weight, corresponding to their age norm [14]. The study of the above mentioned relation among Italian children showed that only 19% of them were adequately provided with vitamin D, while almost half of the patients examined had a deficiency status [15]. In African American adolescents with obesity, a correlation of low values of serum 25(OH) D with adiponectin, BMI, insulin resistance was observed [16]. Similar conclusions (connection of vitamin D deficiency with obesity markers) have been demonstrated among children living in the Caucasus, in tropical conditions (Malaysia, Colombia), Brazil [17–20].

Despite the growing amount of scientific evidence on this issue and some successes, it should be noted that the ground of the association between obesity and vitamin D deficiency is not completely clear. The pathogenetic interaction between obesity and vitamin D deficiency is probably predetermined by several mechanisms. Firstly, in case of obesity, vitamin D, which is a fat-soluble substance, is distributed in a considerable amount of adipose tissue, which leads to a decrease in its concentration in the blood plasma [8]. Secondly, with excessive body weight there is a limitation of vitamin D bioavailability, caused by vitamin D capture with adipocytes and depositing in adipose tissue. There are scientific papers claiming that there is a direct proportional correspondence between vitamin D deficiency and clinical and laboratory markers of obesity, such as body mass index (BMI), waist circumference and the

percentage of total body fat in adults and children [21, 22]. Thirdly, there is a genetic proof that the increase in BMI leads to a decrease in vitamin D levels in blood serum [4]. Fourthly, in relation to infants it is proved that one of the significant risk factors for the development of vitamin D-deficiency rickets in modern conditions is the accelerated rate of weight gain and growth [23]. It is also very important fact that an increase in the load on the bone system is observed at overweight.

Adipose tissue in the modern sense is not only a source of energy in the body, but also a true endocrine organ that produces and affects the secretion of a wide range of mediators that regulate the function of adipose tissue and important distant organs, i.e. the liver, pancreas, the cardiovascular system and skeletal muscles. According to the reference data, adipose tissue adipocytes secrete more than 50 biologically active substances, which differ significantly in structure and functions, among them cytokines, chemokines, growth factors, complementary system molecules and hormones. These biologically active factors affect the severity of the processes in many organs directly or due to neuroendocrine mechanisms. In metabolic disorders such as obesity, an increase of the size of adipocytes results in dysfunction in the adipose tissue, and in the shift in the secretory profile with growing release of proinflammatory adipokines [24].

Recent studies have shown that adipose tissue may be the direct target of vitamin D physiological actions. It has been proved that vitamin D can affect obesity through numerous mechanisms, including protein expression, oxidative stress, inflammation and cellular metabolism [25]. Recent data focus on the use of 1.25 (OH)<sub>2</sub>D<sub>3</sub> (calcitriol, an active vitamin D metabolite) in regulating adipose tissue inflammation in obesity by reducing proinflammatory cytokines that are secreted in adipose tissue. In addition, new perspectives in the context of obesity and related pathophysiological disorders open the participation of calcitriol in the adipokine expression modulation, a decrease of the monocyte set by human preadipocytes, and the resumption of glucose absorption in adipocytes [26]. There is an evidence that vitamin D affects body fat, preventing adipogenetic trans-

cription factors and lipid accumulation during adipocyte differentiation. Thus, vitamin D deficiency can lead to violation of the normal metabolic function of adipose tissue. Taking into account the importance of this tissue in the energy balance, lipid metabolism and inflammation in obesity, an understanding of the vitamin D action mechanisms in adipocytes can have a significant impact on the maintenance of metabolic health [27].

Given the references data, spirited debate has been held upon the negative impact of excess fat on catabolism growth and the formation of vitamin D inactive forms, its excessive deposition in the adipose tissue, and a decrease in the activity of 1 $\alpha$ -hydroxylase in liver infiltrated by fat. On the other hand, the wide representativity and expression ability of vitamin D receptors in adipose tissue involved in lipogenesis, lipolysis and adipogenesis, and increased parathyroid hormone levels noticed at vitamin D deficiency and activating lipogenesis allow vitamin D to be considered as an independent risk factor of adipose tissue accumulation [28].

The pathophysiological relationship between obesity and bone tissue is complex, and remains an active focus of many studies. According to references data, obesity probably affects bone metabolism through several mechanisms. It is known that adipocytes and osteoblasts are derived from a common multipotent mesenchymal stem cell. Thus, obesity can increase differentiation of adipocytes and accumulation of fat, while reducing differentiation of osteoblasts and bone formation speed. Another link is traced to the fact that obesity is associated with chronic inflammation. Increase of circulating and tissue proinflammatory cytokines in obesity can affect the activity of osteoclasts and bone resorption by altering the NF- $\kappa$ B (rank)/RANK ligand/osteoprotegerin pathway receptor activator. In addition, excessive leptin secretion and/or reduction of adiponectin production by adipocytes in obesity can either directly affect the formation of bone tissue, or indirectly affect bone tissue resorption by regulating production of proinflammatory cytokines [29].

Currently, recommendations for treatment and prevention of vitamin D deficiency can

be found in international foreign guidebooks whose authors state that obese children need a higher dosage of vitamin D compared to those whose physical development is consistent with age [30]. Scientific reports suggest a negative correlation between BMI and increase in vitamin D status in response to an additional dose of cholecalciferol [31].

There is also evidence that vitamin D can make its contribution to regulating body weight during obesity, especially when combined with a limited energy diet. For this purpose, the use of cholecalciferol was proposed as a promising strategy for prevention of obesity, and development of complications associated with it [32].

As for associating vitamin D deficiency and obesity, despite some success, many issues have not yet been studied. Provisions that form the basis of the causal link of vitamin D deficiency and obesity have not been cleared [33]. It should be noted that all studies devoted to the above relationship were conducted in adults and older children. These scientific works do not have a definite conclusion. Results of recent researches show that association of vitamin D levels and obesity in children is a complex problem and needs further refinement.

The analysis of up-to-date references suggests that studies of biochemical calcium-phosphorus metabolism alone do not make it possible to assess vitamin D deficiency adequately. The emergence of available laboratory diagnostic methods, in particular, the determination of serum vitamin D levels, is an important aspect for timely detection of vitamin D deficiency among children of high risk concerning its development and monitoring of therapy. It should be noted that the functional indicator of vitamin D content in the human body is the level of 25(OH)D (intermediate biologically inactive transport form, calcidiol, 25-hydroxycalciferol, hydroxyvitamin D) circulating in the blood after the hydroxylation of the vitamin D metabolite in the liver. The total 25-hydroxyvitamin D contains total blood levels of 25(OH)D<sub>2</sub> and 25(OH)D<sub>3</sub>. The level of this substance reflects both the formation of vitamin D in the skin and its receipt with food [34].

Vitamin D deficiency is a clinical syndrome that develops as a result of lowering 25(OH)D

in blood serum. In recent years, the issue of normative values of hydroxyvitamin D level in children and adults has been actively discussed. At the same time, there is still a controversial issue regarding the level of 25(OH)D, which determines the presence of vitamin D deficiency. Views on the diagnostics of vitamin D deficiency have historically undergone a variety of changes. It should be noted that modern laboratory technologies allow to exclude the recently discovered inactive form of 3-epi-25(OH)D<sub>3</sub> from the total concentration of the total 25(OH)D, which according to the results of modern researches is determined in the blood of children under the age of 1 year. Therefore, this aspect is important for obtaining reliable results of 25(OH)D levels in serum in children of this age group [35]. The serum concentration of the total 25-hydroxyvitamin D is expressed in nanograms per milliliter (ng/ml) or in nanomolars per liter (nmol/l), with 1 ng/ml being 2.496 nmol/l [36].

To assess the status of vitamin D in a child's body today, scientists and clinicians use the classification according to which the result interpretation of the study of serum hydroxyvitamin D concentration is carried out regardless of the child's age. According to most international professional organizations, the deficit occurs when 25(OH)D is below 20 ng/ml (that is, below 50 nmol/l), 25(OH)D levels from 21 to 29 ng/ml (i.e., 52 to 72 nmol/l) can be considered as an indicator of relative vitamin D insufficiency, and the level of 30 ng/ml and above is sufficient (that is, close to normal). Vitamin D intoxication is observed when 25(OH)D level is higher than 150 ng/ml (374 nmol/l). The Endocrine Society, the Federal Commission for Nutrition in Switzerland (FCN), the Spanish Society for Research on Bone and Mineral Metabolism support the sufficiency point equal to 30 ng/ml, giving priority to optimal conditions for bone tissue mineralization, absorption of calcium in the intestines and inhibition of excessive secretion of PTH with mobilization of calcium from bones [37–42]. Classification data are based on the high prevalence of osteomalacia and rickets in patients with 25(OH)D levels of less than 20 ng/ml, and an increase in the incidence of non-mineralized osteoid in patients with se-

rum hydroxyvitamin D levels ranging from 20–30 ng/ml [43, 44].

Thus, the target concentration of vitamin D in serum for both children and adults should correspond to a level higher than 30 ng/ml (75 nmol/l) to ensure all positive effects of this vitamin on the human body. Current data of biochemical, observational, and randomized controlled tests show that serum 25(OH)D levels of at least 50 nmol/l are essential for normalizing parathyroid hormone (PTH) to minimize the risk of osteomalacia, and for optimal bone cell function [45, 46]. Adequate vitamin D levels are vital to the normal functioning of the endocrine system, not only in the bone tissue, but in the whole body as well. For a long time, there was no consensus on the optimal 25(OH)D levels in the population, and only now an interest to this problem is growing. It should be noted that the dispute about the threshold values of serum hydroxyvitamin D continues with regard to safety, maximum benefit to the body, and prevention of diseases associated with its deficiency status.

The most important disadvantage of the last decade's approach to correction of vitamin D status is the use of therapeutic agents on the basis of this vitamin without adequate laboratory confirmation of its deficiency. Of course, one cannot forget about the different technical possibilities in the past and present because the laboratory assessment of the vitamin D concentration in serum has become available to a practitioner relatively recently. However, even in modern conditions, experts continue to ignore this fact. According to references data, the assessment of 25(OH)D serum concentration for infants, children, adolescents, and pregnant women with at least one risk factor for low vitamin D status is recommended [47]. Recently, there has been a message about the necessity of an individual approach in vitamin D prescription (after determining the content of its active metabolites in blood) to correct vitamin D deficiency. According to the results of modern studies, it is known that every 100 IU (2500 ng) of vitamin D daily use increase the 25(OH)D level in blood serum for 1 ng/ml [38, 48].

The reference sources widely discuss the impact of both obesity itself, and the lack of

vitamin D on changes in carbohydrate and fat metabolism. Without exaggeration, it can be said that every disease, especially in young children, is accompanied by a greater or lesser degree of deviation from lipid metabolism rate. The lipid metabolism components play an essential role in the processes of metabolic adaptation of the body in normal and in many pathological conditions, which advances postprimary deviations in the lipid blood spectrum. The enhancement of lipid peroxidation, functional and structural disorders of the phospholipid spectrum of cell membranes are regarded as the main pathochemical mechanism of many pathological processes in childhood [49]. An analysis of reference sources has revealed crossed studies which tracked the association of serum levels of vitamin D and lipids in different age groups [50]. According to the latest data, associations have been established between the status of vitamin D in children aged from 9 months, and blood lipids, BMI: inversely proportional link of serum vitamin D concentrations with cholesterol levels (HDL cholesterol), cholesterol, and BMI [51]. Unfortunately, the study did not reveal the correlation between the above stated indicators in children of younger age.

Despite the fact that the problem of vitamin D deficiency rickets in young children is sufficiently described in reference literature, and nationwide programs for ante- and postnatal prophylaxis and treatment have been developed, however, the pathogenetic grounds of the disease remain the most complex and disputable.

In connection with the steady increase of frequency of this osteopathy development in children, special significance has the assessment of the health state in critical growth periods, one of which is the first year of life. The study of osteogenesis in children of this age group is an important task, since timely prevention of rickets, initiated at this age, allows to prevent the development of organic pathology of the bone system in the future [52].

As a result of the data obtained, it can be noted that the association of obesity with vitamin D deficiency, and, as a consequence, the rickets development in young children requires further careful study. Understanding the influ-



ence of adipose mass on bone tissue during its growth and development is a very important

aspect for further health and pharmacotherapy strategies to prevent bone disorders.

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## РОЛЬ ОЖИРІННЯ У РОЗВИТКУ ВІТАМІН D-ДЕФІЦИТНОГО РАХІТУ У ДІТЕЙ

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Вітамін D-дефіцитний рахіт є одним із самих розповсюджених захворювань серед дітей перших років життя у багатьох країнах світу. Важливим в даний час є розуміння вищевказаної нозологічної одиниці як обмінного порушення, а не тільки як D-дефіцитного стану. В сучасних умовах фактори ризику вітамін D-дефіцитного рахіту зазнали подальшого вивчення. Результати досліджень вказують, що ожиріння являється одним із факторів ризику дефіциту вітаміну D у дітей. Існують докази того, що метаболізм даної речовини, депонування, біодоступність та біологічна роль знаходяться в залежності від об'єму жирової тканини. Патогенетичний взаємозв'язок між ожирінням та дефіцитом вітаміну D, напевно, зумовлений декількома механізмами. По-перше, при ожирінні вітамін D, який являється жиророзчинною речовиною, розподіляється в значному об'ємі жирової тканини, що призводить до зниження його концентрації в плазмі крові. По-друге, при надмірній масі тіла виникає обмеження біодоступності вітаміну D, що викликане захопленням вітаміну D адипоцитами та депонуванням в жировій тканині. По-третє, існують генетичні докази того, що збільшення значення ІМТ призводить до зниження рівня вітаміну D в сироватці крові. Останні дослідження показують, що жирова тканина може бути безпосереднім об'єктом фізіологічних дій вітаміну D. Доведено, що вітамін D може впливати на ожиріння через численні механізми, у тому числі на експресію білка, окислювальний стрес, запалення і клітинний метаболізм. На сьогоднішній день у переліку міжнародних зарубіжних посібників можна зустріти рекомендації з лікування та профілактики вітамін D-дефіцитних станів, автори яких вказують, що діти з ожирінням потребують більш високого дозування вітаміну D, порівняно з особами, чий фізичний розвиток відповідає віковій нормі. Розуміння впливу жирової маси на кісткову тканину в період її росту та розвитку являється дуже важливим аспектом для подальших стратегій з боку охорони здоров'я та фармакотерапії з метою попередження кісткових порушень.

Ключові слова: вітамін D-дефіцитний рахіт, ожиріння.

## THE ROLE OF OBESITY IN THE DEVELOPMENT OF VITAMIN D DEFICIENCY RICKETS IN CHILDREN

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Vitamin D deficiency rickets is one of the most common diseases among children of the first years of life in many countries around the world. It is very important to understand the aforementioned nosological unit as a metabolism disorder, and not just as a D-deficiency state. In modern conditions, the risk factors for vitamin D deficiency rickets have undergone further study. The results of the research indicate that obesity is one of the risk factors for vitamin D deficiency in children. Thus, vitamin D metabolism, deposition, bioavailability and its biological role are dependent on the size of adipose tissue. The pathogenetic interaction between obesity and vitamin D deficiency is probably predetermined by several mechanisms. Firstly, in case of obesity, vitamin D, which is a fat-soluble substance, is distributed in a considerable amount of adipose tissue, which leads to a decrease in its concentration in the blood plasma. Secondly, with excessive body weight there is a limitation of vitamin D bioavailability, caused by vitamin D capture with adipocytes and depositing in adipose tissue. Thirdly, there is a genetic proof that the increase in BMI leads to a decrease in vitamin D levels in blood serum. Recent studies have shown that adipose tissue may be the direct target of vitamin D physiological actions. It has been proved that vitamin D can affect obesity through numerous mechanisms, including protein expression, oxidative stress, inflammation and cellular metabolism. Currently, recommendations for treatment and prevention of vitamin D deficiency can be found in international foreign guidebooks whose authors state that obese children need a higher dosage of vitamin D compared to those whose physical development is consistent with age. Understanding the influence of adipose mass on bone tissue during its growth and development is a very important aspect for further health and pharmacotherapy strategies to prevent bone disorders.

**Key words:** vitamin D deficiency rickets, obesity.