EDITORIAL

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VITAMIN D DEFICIENCY IN YOUNG CHILDREN. THE REALITIES OF TODAY

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The article presents a review of the literature on the clinical aspects of assessing vitamin D deficiency in young children by the concentration of 25(OH)D (hydroxycalciferol) in blood serum. The purpose of the review was to familiarize pediatric specialists with the real state of affairs in assessing the clinical significance of diagnosing vitamin D status, its relationship with the prevention of deficient rickets, ways of correcting and choosing the dose of calciferol. A daily dose of 400 IU of vitamin D for young children is effective and safe in preventing deficient rickets. Higher subsidized doses of calciferol have not been shown to be more effective. In addition, they can potentially lead to toxic levels of vitamin D metabolites in the blood. When using lower daily doses (less than 400 IU), an adequate prophylactic effect may not be achieved. Determination of the level of circulating serum hydroxycalciferol, which characterizes the status of vitamin D in the body, is not recommended for routine examination and as a standard for diagnosing deficient rickets in young children. Calciferol has multilateral effects, modulates not only phosphorus-calcium metabolism, but also affects other systems and functions of the body, in particular, ontogenesis and the immune system. According to foreign literature, all infants should receive vitamin D for the prevention of rickets, treatment from the age of one month. This is most reliably identified for children, probably at risk. Convincing data indicating a positive protective effect on diabetes mellitus D on unforeseen pathology, for example, the frequency of exclusion of pneumonia, infectious diarrhea, atopic dermatitis in infancy, has not yet been obtained.

Keywords: early age; vitamin D; 25(OH)D (hydroxycalciferol); deficiency rickets; prevention.

НЕДОСТАТОЧНОСТЬ ВИТАМИНА D У ДЕТЕЙ РАННЕГО ВОЗРАСТА. РЕАЛИИ СЕГОДНЯШНЕГО ДНЯ

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В статье представлен обзор литературы, посвященный клиническим аспектам оценки недостаточности витамина D у детей раннего возраста по концентрации 25(OH)D (гидроксикальциферола) в сыворотке крови. Обзор знакомит специалистов педиатрического профиля с реальным положением вещей в оценке клинической значимости диагностики статуса витамина D, ее связи с проведением профилактики дефицитного рахита, путей коррекции и выбора дозы кальциферола. Для профилактики дефицитного рахита ежедневная доза 400 МЕ витамина D для детей раннего возраста эффективна и безопасна. Более высокие дотационные дозы кальциферола не показали свою высокую эффективность. Кроме того, они потенциально могут привести к токсическому уровню метаболитов витамина D в крови. При использовании более низких суточных доз (менее 400 МЕ) адекватный профилактический эффект может быть не достигнут. Уровень циркулирующего в сыворотке гидроксикальциферола, характеризующего статус витамина D в организме, не рекомендуется определять при рутинном обследовании и в качестве стандарта при диагностике дефицитного рахита у детей раннего возраста. Кальциферол обладает многосторонними эффектами, модулирует не только фосфорно-кальциевый обмен, но влияет и на другие системы и функции организма, в частности онтогенез и иммунную систему. По данным зарубежной литературы, все дети грудного возраста должны получать витамин D для профилактики рахита начиная с месячного возраста. Наиболее надежно это доказано для детей, относящихся к группам риска. Настоятельно рекомендуется универсальная добавка витамина D до 12-месячного возраста детям, находящимся на грудном или смешанном вскармливании. В возрасте старше 12 мес. рекомендовано дополнительное назначение витамина D детям из групп риска.

Ключевые слова: ранний возраст; витамин D; 25(OH)D (гидроксикальциферол); дефицитный рахит; профилактика.

In recent years, the world has significantly shown increased interest in the study of vitamin D (calciferol) and its wide-ranging role in ensuring the vital activity of the body. This was related to the study of vitamin D supplementation in children and the need to correct calciferol deficiency. Such increased attention also naturally affected early childhood. This is due to active measures implemented in many countries to prevent, first of all, rickets in this age group. This interest is largely associated with the recent practical opportunity to assess objectively the body's calciferol levels by determining the concentration of its metabolite 25(OH)D (hydroxycalciferol D_2 and D_3) circulating in the blood serum. The interest in this problem is to some extent fueled by companies producing vitamin D preparations.

This review presents the current state of affairs among pediatric specialists in the world and Russian health care in assessing the clinical significance of determining vitamin D status based on the blood level of 25(OH)D in children and ways to correct its deficiency. Vitamin D deficiency (rickets) is a representative clinical manifestation of vitamin D deficiency. Despite the multitudes of publications discussing the biological activities of calciferol that affect various body functions, including children (immunity, ontogenesis processes, etc.), there is currently no convincing scientific evidence, from the standpoint of evidence-based medicine, of the relationship between vitamin D deficiency and other non-rachitic pathology. However, some clinical aspects of the association of vitamin D status with rickets remain controversial. Several established opinions, especially those prevailing in Russian pediatrics in relation to this pathology, have no scientific justification at all. The review also considers some aspects of the possible effects of prophylactic doses of vitamin D on the growth processes of children and morbidity with infectious and non-infectious diseases.

In the selection of publications for the review, we used a standard search strategy in scientific electronic databases Medline, Google Scholar (Google Academy), and eLibrary.ru. In line with the research goal, the search and selection of literary sources were also performed on the websites of organizations, institutions, and communities involved in the development of recommendations, analyzing the current literature and compiling systematic reviews, particularly in the accessible (open) part of the Cochrane Library. First, we selected high-quality clinical trials that, in terms of their methodological level, meet current requirements and criteria for the evidence of the results obtained [2]. Priority was given to individual randomized clinical trials (RCTs), results of systematic reviews, meta-analyses, and publications of the Cochrane Collaboration. Our analysis also included modern national and international clinical guidelines that met the modern requirements of evidence-based medicine.

Clinical aspects of assessing vitamin D status in early childhood

The advent of the possibility of determining 25(OH)D levels in the blood serum created the prerequisites for the assessment of vitamin D status in the body and population by the concentration of this metabolite in practice. This has led to various proposals for the correction of vitamin D levels in the body, including young children, based only on indicators of insufficient circulating 25(OH)D. In most cases, such advice was not subsequently confirmed by RCTs. Epidemiological studies have also shown the prevalence of such deviations in all age groups in various populations in both economically developed and developing countries in northern and tropical regions [4, 10, 25, 28, 32]. Despite the obvious association, no evidence presents an absolute dose-dependent response to changes in serum 25(OH)D concentrations from taking vitamin preparations [31]. The 25(OH)D level is determined by the initial level of this precursor of the active metabolite D, dose of the administered drug, amount of the final active endogenous metabolite $1,25(OH)_2D_3$ produced, demographic characteristics, and number of other factors [25, 30, 31, 33, 34]. In addition, the levels of this metabolite depend on the method of determination, seasonality, nature of the underlying disease, and therapy, especially in cases of malabsorption. In accordance with the recommendations for determining the level of 25(OH)D, if the child received one or another vitamin D-containing drug or was exposed to ultraviolet radiation, then the assessment of vitamin D status should be performed no earlier than 3 mon after the withdrawal of such exposures. Thus, the pharmacokinetics of vitamin D and its blood levels depend on many factors that affect absorption, distribution, metabolism, and excretion and routes of administration. All the listed links of kinetics are largely genetically determined processes [1, 8, 10, 12, 31, 38]. Serum 25(OH)D concentration, having a multifactorial (polygenic) nature, is not always closely associated with the occurrence of rickets. Thus, understanding that 25(OH)D is neither a synonym nor a marker of the physiological function of vitamin D is extremely important, as it is not the

main active form of vitamin D [7]. A review showed no significant correlation between serum 25(OH)D levels and the concentration of the final vitamin D metabolite $1,25(OH)_2D$ [31]. Often, in children with low levels of 25(OH)D, rickets does not develop, and conversely, in some cases, a sufficient level of 25(OH)D does not prevent the development of rickets, especially in infants born prematurely [7, 28]. The main cause of rickets in children born prematurely is a deficiency in calcium, phosphorus, and magnesium, and not calciferol. In this regard, it is currently not recommended to determine routinely the concentration of 25(OH)D when examining children and when diagnosing rickets [27, 28].

For a long time, the discussion continued on classifying vitamin D status in children according to the serum concentration of 25(OH)D [27]. Nevertheless, an agreement has recently been reached on such a distribution [27, 28]. According to the consensus, vitamin D supplementation in children is considered sufficient if the total 25(OH)D (D_2 and D_3) concentration exceeds >50 nmol/L (20 ng/mL). A level of 30–50 nmol/L (12–20 ng/mL) indicates calciferol deficiency, and when the serum 25(OH)D level is <30 nmol/L (12 ng/mL), vitamin D deficiency occurs. Concentration >250 nmol/L (100 ng/mL) is regarded as excessive, and if it is accompanied by hypercalcemia, hypercalciuria, and parathyroid hormone suppression, calciferol intoxication is diagnosed. Thus, based on the presented modern data, determining the serum concentration of 25(OH)D and its interpretation are appropriate for assessing vitamin D status in an individual and population, but not for an individual choice of a prophylactic dose of calciferol and diagnosis of rickets.

Issues on vitamin D deficiency, its prevention and treatment, judging by the publications, are currently receiving much attention globally. This is due to the establishment of the multifunctional role of calciferol in the body and the possibility of the laboratory assessment of the vitamin status individually. Vitamin D, in addition to calcium and phosphate homeostasis, is necessary for the development of the skeleton, successful functioning of activated B- and T-lymphocytes, insulin production, secretion of thyroid-stimulating hormone, and myocardial contractions [41]. However, rickets is naturally the focus of related publications, as a pathology most closely associated with a lack of calciferol in early childhood. Vitamin D deficiency in infants is traditionally explained by its low level in breast milk and the natural limitation of sun exposure [23]. Recently, some studies have indicated an increase in the incidence of rickets in children, even in economically developed countries, particularly in the UK, Canada, and USA [24, 40, 42, 43, 45]. This phenomenon is mainly contributed by the migration of families with dark skin, who are most prone to vitamin D deficiency under conditions of limited insolation.

The epithet “deficiency” has replaced the definition of “vitamin D-deficient” because, as already mentioned, not only vitamin D deficiency, but also insufficient intake of calcium, phosphorus, and magnesium plays a significant role in the occurrence of rickets [6, 28, 40].

The most frequently cited questions in current early life studies are as follows: What is the safest and most effective dose of vitamin D for preventing rickets and other diseases in young children? Until what age is it appropriate for children to take vitamin D supplements for prophylactic purposes? The search for answers to these questions is presented in this review.

Prevention of vitamin D deficiency in early childhood: dose selection

When choosing the sources discussing this issue, we preferred modern publications that meet the requirements for research work, that is, with a minimum probability of making systematic errors [2]. The review deliberately included publications relating to regions with living conditions close to the Russian climate (Finland, Great Britain, Canada, Germany, etc.). The need of a breastfed infant for calciferol supplementation was confirmed by all the analyzed studies. The results of RCTs aimed at evaluating the efficacy and safety of various vitamin D doses in young children are analyzed and presented. As an example, we cite tests conducted in countries similar to the Russian Federation in terms of climatic and geographical characteristics.

In Finland, a double-blind RCT was conducted among breastfed children [19]. The participants were distributed into three groups, depending on the daily dose of vitamin D_3, namely, 400, 1200, and 1600 IU. All children received the drug from the age of 2 weeks. A comparative evaluation was performed after 12 weeks of prophylaxis. The authors did not reveal differences in calcium and phosphorus metabolism and the state of the skeletal system assessed by computed tomography.

A similar double-blind RCT was conducted in Canada among children distributed into four groups depending on the daily dose of vitamin D_3 (400, 800, 1200, and 1600 IU) [13]. All participants were breastfed with the same type and timing of the introduction of complementary foods. The follow-up

was performed for 12 mon. The authors concluded that vitamin D doses >400 IU per day did not confer additional benefits on bone mineralization. A comparison of the same groups at age 3 years also did not differ in their anthropometric parameters, body composition, and characteristics of the skeletal system [13, 18]. In turn, Canadian researchers, based on the serum level of 25(OH)D, demonstrated no difference in the prophylactic effect when taking ergo- and cholecalciferol preparations [13–15].

A systematic review with a meta-analysis by the Cochrane Society demonstrated the effectiveness of a 400 IU dose of vitamin D for infants, including those at risk [36]. Other reviews have also provided information characterizing the situation with the supplementation of calciferol to young children in other world regions [26, 28, 29, 32]. In the available publications, no data are available on the possible toxic effect of the prophylactic dose of 400 IU. A Cochrane review on the safety of prophylactic doses of vitamin D reported no risk of hypercalciuria, hypercalcemia, hyperphosphatemia, and hypoparathyroidism. The authors compared the effects of conventional doses of vitamin D with placebo effects [20].

Summary data on the effect of various prophylactic doses of calciferol on calcium–phosphorus metabolism and bone mineralization are presented in several reviews, including the Global Consensus on the Prevention and Management of Nutritional Rickets [13, 26, 28]. From these reviews, there is no evidence that higher daily doses of vitamin D over the generally accepted recommended dose of 400 IU affect any long-term meaningful outcomes. Larger amounts may result in serum 25(OH)D concentrations that are potentially associated with side effects.

Although numerous studies have confirmed the usefulness of vitamin D supplementation during the first 12 mon of life, no convincing evidence has established the usefulness of supplementation to children older than 1 year. This is due to the difficulties in assessing the influence of risk factors at this age, taking into account the consumption of products-containing vitamin D, sun exposure, etc. [23]. Calciferol supplementation is important for children at risk. The risk factors for rickets include the following [23, 28]:

Newborns and infants:

• Maternal vitamin D deficiency during gestation and lactation (limited sun exposure, dark skin, veiling, repeated births, and low dietary intake of calciferol)

• Prolonged exclusive breastfeeding without vitamin D supplementation

• Prematurity and low body length not corresponding to the gestational age

Children older than 1 year:

• Limited sun exposure, dark skin, and cultural practices (closed clothing, etc.).

• Reduced intake of dietary vitamin D (prolonged exclusive breastfeeding without complementary foods, lack of foods rich in calciferol and calcium in the diet, and starvation).

• Chronic diseases of the digestive system (such as malabsorption, exocrine pancreatic insufficiency, and biliary tract obstruction) and impaired hydroxylation of vitamin D metabolites (chronic liver or kidney disease).

• Iatrogenic factors (such as intake of rifampicin, isoniazid, and anticonvulsants).

The ultimate goal of scientific evidence on the efficiency and safety of medicines is their practical applicability. In this sense, it is of interest to analyze clinical guidelines for the prophylactic use of calciferol in young children from different regions. Currently, a sufficient number of clinical recommendations are available worldwide, both national and global (multinational), and their main provisions are based on contemporary principles of evidence-based medicine. We considered it interesting to compare the recommendations in these sources on the daily preventive use of vitamin D with Russian guidelines presented in the national program [5].

In the USA, the American Academy of Pediatrics indicated 400 IU in the first year of life, regardless of the type of feeding, and 400 IU at age >1 year [41].

In North America, the Institute of Medicine (USA) indicated 400 IU. In children aged >1 year, 600 IU was indicated by supplementation or with food [21].

In the DACH region (Germany, Austria, and Switzerland), the DACH Nutrition Society indicated 400 IU in the first year of life and then 800 IU [16].

In the European Union, the European Food Safety Authority (EFSA) indicated 400 IU up to 1 year of age and then 600 IU [39].

In the Northern region of Europe, EFSA indicated 400 IU in the first year of life and thereafter [11].

In the United Kingdom, the Scientific Advisory Committee on Nutrition indicated 200–400 IU in the first year of life and then 400 IU [22, 35].

Japan indicated 100 IU from birth to the age of 6 mon, 200 IU for mon 6–12, and 100–220 IU at age >1 year [37].

The World Health Organization (WHO) indicated 200 IU in the first year of life and later [29, in

the text of the reference source to the Food and Agricultural Organization/WHO recommendations of 2004].

The Global Consensus on the Prevention and Management of Nutritional Rickets (consensus was attended by representatives of the Asia-Pacific region, Japan, Latin America, Australia, India, Africa, China, British Commonwealth, and Europe) indicated 400 IU for the first 12 mon, regardless of the type of feeding, and then 600 IU either as supplementation or with food [28].

In the Russian Federation, National Program indicated 1000 IU in the first year of life or 1500 IU (for children aged 6–12 mon in the European North of Russia) and 1000 IU later [5].

The data presented demonstrate almost complete unanimity among international countries in the dose of vitamin D supplementation for children, especially in the first year of life. The exceptions are Japan and Russia. The low recommended prophylactic doses of calciferol for Japanese children can be explained by the national nutritional aspects characteristic of both nursing mothers and children aged >1 year. The widespread use in the diet of seafood and vegetables rich in vitamins D_3 and D_2, as well as calcium, largely meets the needs of the child, including through breast milk. Moreover, the doses recommended by the Russian program raise doubts in terms of reliability and validity. This is due to the complexity of the analysis of this publication. In the document, unlike international ones, there are no references to the publication of primary materials, which were the basis of the recommendations. These references are absent not only in the program itself but also in the publication preceding this document [3]. This refers to actual data obtained in various regions of Russia. In this regard, we could not, from the standpoint of modern requirements, assess the methodological level of these original studies, the validity of the results, and reliability and correctness of the conclusions. In addition, no information is available in the program proving the advantage in terms of the efficacy and safety of the proposed prophylactic doses of vitamin D over the prophylaxis scheme previously generally accepted in Russia.

Calciferol has multilateral effects and not only modulates phosphorus–calcium metabolism but also affects other systems and functions of the body, particularly ontogenesis and immune system. Thus, trials aimed at studying the effect of vitamin D on the disease course were of interest. A Cochrane systematic review [20] analyzed the possible effect of vitamin D supplementation on the linear growth of children. The review included 60 RCTs. The authors did not find evidence for such influences. The same review examined the association of vitamin D supplementation with atopic diseases (allergic rhinitis and bronchial asthma), type 1 diabetes mellitus, and other autoimmune disorders. Calciferol supplementation had no significant effect on these diseases. Later, similar results were demonstrated by two double-blind RCTs with placebo [9, 17]. An RCT conducted in Australia found no difference in the incidence of atopic dermatitis and sensitization in children aged 6 mon who received a calciferol supplement at a dose of 400 IU, compared with placebo [33]. Another review from the Cochrane Library studied the effect of vitamin D supplementation on the incidence of infectious diseases in children from birth to age 5 years. Pneumonia and intestinal infections were chosen as objects of the study. The authors did not find evidence that vitamin D supplementation positively affects the incidence of this pathology [44].

Thus, according to international literature, all infants should receive vitamin D for the prevention of rickets, starting from age 1 month. This is most reliably proven for children at risk. Convincing evidence of a positive protective effect of vitamin D supplementation on other pathologies, such as the incidence of pneumonia, infectious diarrhea, and atopic dermatitis in infancy, has not yet been obtained. A daily dose of 400 IU of vitamin D for young children is effective and safe in preventing rickets. Supplementation with higher doses of calciferol is not effective compared with the conventional regimen. In addition, they have the potential to lead to toxic blood levels of vitamin D metabolites and hypercalcemia. When using lower daily doses (<400 IU), an adequate prophylactic effect may not be achieved.

A universal vitamin D supplementation is highly recommended up to age 12 mon for breastfed or mixed-fed children. There is no consensus on the need for additional supplementation for children who are bottle-fed with calciferol-enriched mixtures. At age >12 mon, vitamin D supplementation is recommended for children at risk. However, no convincing evidence supports the objectivity of the 12-month threshold. It appears that this age is taken arbitrarily; thus, it can be considered appropriate to supplement vitamin D until the age of 24 mon. Determining the level of the 25(OH)D metabolite circulating in the blood serum, which characterizes the status of vitamin D, is not recommended for use either as a routine method for examining children or for diagnosing rickets in young children.

ADDITIONAL INFORMATION

Author contributions. All authors confirm that their authorship complies with the ICMJE criteria. All authors have made a significant contribution to the development of the concept, research, and preparation of the article and have read and approved the final version before its publication.

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