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VITAMIN D – EFFICACY, TOXICITY AND SAFETY: REVIEW

***Abstract:** Over the past decade, the popularity of vitamin D has increased many times over. Today, there are a huge number of publications on the undoubted benefits of taking vitamin D (25 (OH) D), on its positive effect on the immune system, functioning and homeostasis of the body. Vitamin*

D deficiency is an urgent and actively discussed topic all over the world, since deficiency of it causes conditions such as rickets in children, osteomalacia, increased susceptibility to respiratory infections, the risk of autoimmune, cardiovascular diseases, kidney diseases, and also, which is very importantly, the risk of cancer, diabetes and tuberculosis. **Purpose:** To study the clinical manifestations and toxic properties of vitamin 25 (OH) D, safe dosages according to international recommendations, comparing a review of existing literature on clinical trials. **Research methodology:** To search for articles, we use the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Library, search for medical databases including MEDLINE, PubMed, and EMBASE, as well as the Google Scholar search system.

Keywords: 25(OH)D; hypervitaminosis D; toxic properties of vitamin D; Intoxication, nephrocalcinosis, hypercalcemia, children, rickets

Introduction

In the past, vitamin D deficiency has been associated with osteoporosis in adults and rickets in children. The origin of the term “rickets” remains unclear. Most likely, it comes from the German word “wricken”, which translates as “twisted”. Rickets was known as “the English disease” [1].

One of the founders of a detailed description of rickets is the British Daniel Whistler and orthopedic physician Francis Glisson, who lived in the mid-17th century [2,3].

Although there was an earlier description of bone changes in the Romans and Greeks in the 1-2 century AD. For example, the ancient Roman physician Soranus noted that bone deformities in Roman children are more common than in the Greeks, referring to low education and poor hygiene by Roman mothers. Also, his contemporary Galen described the classic clinic of rickets [4].

In the 19th century, the pathophysiology of rickets was not yet understood. It has been suggested that rickets may be due to tuberculosis or congenital syphilis. Of course, these diseases played an undeniable role in the development of rickets, especially among the poor people. Not knowing the basics of the pathophysiology of rickets, for the treatment and straightening of bent legs it was even proposed to do cauterization, hung by the legs, and applied medical tires (cautery, splinting, and even pendulous suspension) [5].

In 1919, Mellanby was the first to link a group of fats that were allocated as

“growth promoting” fats for the prevention of rickets, calling it the 4th vitamin. He stated: “Rickets is a deficiency disease which develops in consequence of the absence of some accessory food factor or factors. It therefore seems probable that the cause of rickets is a diminished intake of an anti-rachitic factor, which is either fat-soluble factor A, or has a similar distribution to it” [6].

To clarify this issue, in 1922, Elmer McCollum neutralized vitamin A from fish oil. So, it was proved that not vitamin A is responsible for the cure for rickets, but another one, previously unknown vitamin. Since it was the fourth vitamin discovered by science, it was called the fourth letter of the Latin alphabet - vitamin D [7].

Benefits of Vitamin D in brief

Vitamin D is known to inhibit proliferation and induce differentiation of cells of various lines, and is also important for the regeneration of the epithelial barrier and the maturation of immune cells [8]. The immunomodulatory role of vitamin D is proved by the high content of vitamin D receptors (VDR) in macrophages, dendritic cells, T and B lymphocytes, which play an important role in the fight against bacteria, autoimmune and chronic inflammatory diseases [9]. Vitamin D deficiency increases the incidence of respiratory diseases [10, 11].

Table 1

Randomized, controlled trials of vitamin D efficacy in respiratory infections in children

Autors	Publication Year	Disease or Study pathogen	Dose of vitamin D (IU)	Duration	Efficiency
Manaseki-Holland S. et al [12]	2010	Recurrent pneumonia	100,000 once	3 weeks	+ ¹
Urashima M. et al [13]	2010	Influenza A	1200 daily	4 months	+
Holland S. et al. [14]	2012	Pneumonia	100,000 quarterly	18 months	- ²
Majak P. et al. [15]	2011	Prevent Asthma	500 daily	6 months	+
Kerley C. P. et al. [16]	2015	Asthma	2000 daily	15 weeks	-

1 During treatment with vitamin D drugs, a positive effect was noted

2 Vitamin D was not effective

As can be seen from table 1, in most cases, the effectiveness of vitamin D has a positive effect on respiratory diseases in children, but it was also noted that there was no effect during the study, possibly due to the severity of the disease and the selection of dosages, which requires further detailed research.

Hypervitaminosis D and the manifestation of its toxic properties

In August 1931, there was a publication in the Edinburgh Medical Journal by Lewis Thatcher, MD, Physician, Royal Edinburgh Hospital for Sick Children, which described the case of a child dying from hypervitaminosis D. In his study, he said that the boy was 18 months old and was admitted to the hospital in October 1930 with complaints of weakness, lethargy, lack of appetite and weight loss. At the time of the examination, he weighed about 7 kg (15.5 lb), and at birth he had 3.8 kg (8.5 lb), he had a noticeable weight loss, he was pale, the bones were thinned, the muscles were weak and hypotrophic. Body length and head circumference were normal.

The mole was opened at 1.27 sm (0.5 Inch), the edges are moderately supple. There were no particular signs of rickets. From the anamnesis of life and illness, it was known that the child was born healthy, from 5 months after weaning from breastfeeding, he did not gain well in weight, had difficulty digestion, received diluted cow's milk, pieces of meat, and orange juice in his diet. At 13 months, he had moderate diarrhea. After recovery and before admission to the hospital, he received irradiated ergosterol.

At night, he had a temperature to 37.5 * C (99.6F). In the morning, the condition worsened sharply, the patient became apathetic, vomiting because of the increasing temperature, blood urea increased 3 times. The patient responded well to therapy. In urinalysis, he noted moderate albuminuria, bacteria, and a small number of red blood cells. Bacterial culture of urine yielded mixed results: Staph, alb., Streptococci, and B. Pyocyaneus. Pyelonephritis was exposed. But since the disease did not have a completely clear course, a congenital anomaly of the kidneys was assumed. After 12 days of hospitalization, the patient died [17].

An autopsy showed calcium deposition in both kidneys, which was visible even to the naked eye with a grayish-granular shape in the medulla of the kidneys, at the

bases of the pyramids. Most of the deposits were in the collecting tubules. Also, small purulent foci of infection in the kidneys were found, which explained pyuria. But most likely it was like a secondary infection. The bladder, ureters, spleen were not changed. The cerebral cortex is not affected, macroscopic deposits of calcium were found throughout the medulla oblongata [17].

Barrueto F. et al. published a unique case report on an acute overdose of vitamin D in a 2-year-old child in the journal "Pediatrics". It is reported that the mother of the child went to the emergency department with complaints of vomiting, constipation, lethargy, and abdominal pain. Upon examination by a doctor, a slight increase in blood pressure was noted. Recommendations were given with a diagnosis of constipation, but the next day the child's condition worsened, he was disturbed by severe abdominal pain and he was hospitalized. In this case, the mother denied any manifestations of diarrhea, fever, seizures.

She gave an over-the-counter vitamin D (Raquiferol) to enhance her baby's health and bones. The child took 1 ampoule of vitamin D (2 drops per day was recommended) for 4 days (in one ampoule 600,000 IU), i.e. a total of 2,400,000 IU. The examination was as follows: the child's weight was 14.5 kg (90th percentile), blood pressure was increased to 39/98 mm Hg, body temperature was 36.1 * C (97.6F), heart rate 88 beats per minute, respiratory rate was 16 breaths per minute. Other vital indicators were normal.

Only serum Ca² concentration of 14.4 mg / dL was increased by laboratory investigation (normal: 8.4–10.2 mg / dL), and on the second day, the calcium level increased to 15.0 mg / dL, on the 4th day – it decreased to 13.9 mg / dL, and at discharge was 11 mg / dL. Vitamin D levels on the first day were 106 ng / mL, then rose sharply to 470 ng / mL, and on discharge dropped slightly to 389 ng / mL. The child was given emergency measures, which are intravenously administered fluids - 5% dextrose solution, furosemide, calcitonin, and intravenously administered hydrocortisone. The child was released from the hospital after 2 weeks with improvement [18].

In another study, 27 clinically confirmed cases of vitamin D intoxication associated with hypercalcemia and / or hyperphosphatemia were analyzed, which

showed that 85.7% of the patients had complaints of vomiting, anorexia - 57.1%, weight loss - 47.6%, dehydration - 42.8%, polyuria / polydipsia - 38%, and constipation was 33.3%. Severe condition associated with severe hypercalcemia was in 6 cases (22.2%), the patients were hospitalized and successfully treated with bisphosphonates, intravenous hydration and furosemide therapy. The average hospital stay was 9 days. A serious complication in patients was nephrocalcinosis, diagnosed 7 patients (25.9%). Follow-up observation was for 1.3 years. Over time, there was no manifestation of hypercalcemia, but nephrocalcinosis persisted in 6 patients [19].

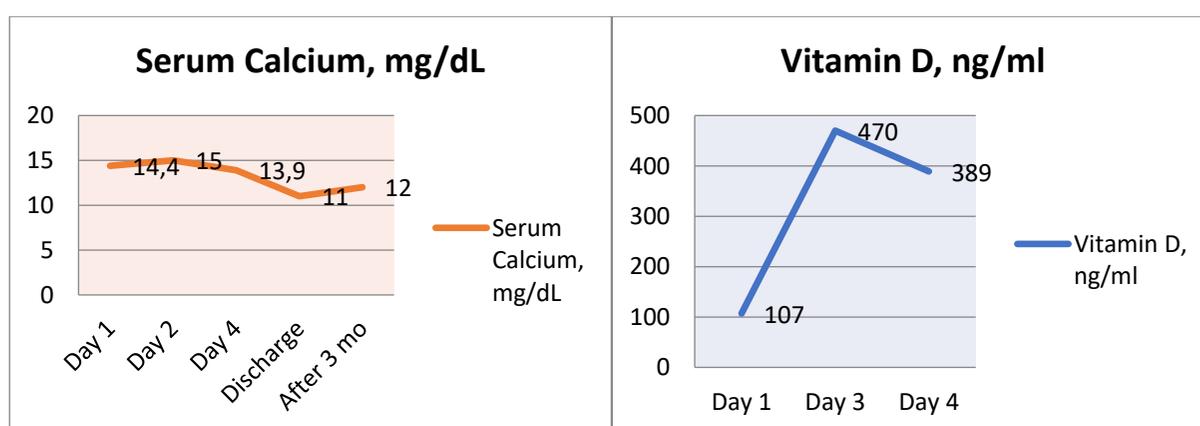


Fig. 1. The dynamics of serum calcium and vitamin D levels in this patient

Recommended safe dosages of vitamin D for children (minimum, maximum, optimum)

Nowadays, there is no unified classification according to the level of vitamin D deficiency. Many international recommendations consider the serum level of 25 (OH) D below 10 ng / mL (25 nmol / L) to be deficiency. According to the recommendations of the Endocrine Society, the serum levels of 25 (OH) D of at least 30 ng / mL (75 nmol / L) is considered optimal. And in its recommendations, the Endocrine Society defined serum 25 (OH) D <20 ng / mL, and insufficiency as 21–29 ng / mL as vitamin D deficiency [20]. The Global Consensus Recommendations on Prevention and Management of Nutritional Rickets has determined that sufficiency is > 20 ng / mL (50 nmol / L), insufficiency, 12-20 ng / mL (30-50 nmol

/l) and deficiency, $<12 \text{ ng / mL}$ (30 nmol / L), and intoxication can occur at a level of $> 100 \text{ ng / mL}$ (250 nmol / L) [21].

We would also like to add the recommended safe upper dosage limits for vitamin D, at which no toxic properties were observed. For children up to 1 month - 1000 IU / day , from 1 month to 10 years - 2000 IU / day , from 10 years to 18 - 4000 IU / day [22-24].

In conclusion, at present time, throughout the world, the majority of the population has a widespread deficiency of vitamin D. There is no doubt that the effectiveness of taking vitamin D preparations has a positive effect on the human body and this is proved by many randomized controlled trials. But it should be noted that the uncontrolled intake of vitamin D preparations, without previous laboratory-confirmed data on its deficiency, can lead to its toxic effects, which were described in this review. When prescribing vitamin D preparations, it is necessary to take into account the individual characteristics of the child, clearly explain to parents about the possible symptoms in case of overdose, adhere to international recommendations for safe dosages with the possibility of laboratory control of its level.

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