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Hypervitaminosis D in the pediatric population

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Abstract

Vitamin D is a fat-soluble vitamin that plays a huge role in the metabolism of bones and teeth, which is especially important among pediatric patients. Its deficiency in the developmental period is associated with a decrease in bone mass, bone mineralization disorders, as well as the development of rickets.

In addition, vitamin D has an immunomodulatory effect, and its reduced level correlates with a higher incidence of certain autoimmune diseases and cancer. However, it is worth noting that nowadays, in the era of high availability of over-the-counter (OTC) drugs and dietary supplements, not only hypovitaminosis D can be dangerous and pose a significant clinical problem. More and more parents decide to administer exogenous vitamin D preparations, often without prior consultation with a doctor to determine the optimal dose or duration of supplementation. Unfortunately, it happens that over-the-counter supplements contain a higher dose of vitamin D than the manufacturer suggests. This is very often due to inadequate control of supplement production. Restrictions similar to those in the case of drug production should be sought. It should be remembered that the human body, thanks to exposure to sunlight, under the influence of UV radiation, is able to synthesize endogenous vitamin D on its own. Another source of vitamin D is many foods such as fatty fish, eggs, mushrooms or dairy products, which should be in the diet of every person, especially a child. Therefore, it becomes necessary to define uniform recommendations for doctors and parents regarding vitamin D supplementation in children, as well as to educate the public about possible toxic effects resulting from excessive supply.

Keywords: hypervitaminosis D, children, toxicity, supplementation

1. Admission

Vitamin D belongs to the group of fat-soluble vitamins. Although its various, health-promoting effects have long been known, it still remains the subject of many scientific studies. It is known to play an important role in bone metabolism and thus calcium-phosphate metabolism, which is particularly important among the pediatric population. Proper vitamin D levels enable the proper development of bones and teeth, protect against the development of rickets, and thus are important for the proper growth of the child. On the other hand, its immunomodulatory and anti-cancer properties have been proven, which seems to be particularly important in the era of increasing incidence of autoimmune diseases and cancer. The basic, endogenous source of vitamin D for the human body is synthesis, made possible by skin exposure to sunlight, and more specifically to UV radiation. In addition to the skin, the liver and kidneys are also involved in its metabolism. It is a complex process in which many enzymes are involved. Exogenous vitamin D comes from the diet, mainly fish, eggs and dairy products, as well as widely marketed preparations including both supplements and medicines. Given that some medications are currently available over the counter, the risk of improper vitamin D supplementation is high. It includes a high dose that is not adapted to the age and demand, and a prolonged time of administering the preparations to the child. The growing awareness and fear of parents about the well-known effects of deficiency leads to more frequent self-use of vitamin D in the youngest, which entails the need to draw attention and educate them that hypervitaminosis can also lead to serious health disorders and even be life-threatening. Toxic levels of vitamin D contribute to an imbalance in calcium and phosphate metabolism, disrupting the functioning of many organs, including the kidneys, bones, parathyroid glands, nervous and digestive systems (1-6).

There is a need to monitor 25-hydroxyvitamin D levels in infants and children who receive long-term vitamin D supplementation at or above the currently recommended upper level intake. Vitamin D poisoning can range from mild, which can be ignored, to severe life-threatening symptoms (19).

2. Aim and methodology of work

The aim of the study is to present the problem of hypervitaminosis D in the paediatric population. The research method used was a literature review.

3. State of the art

3.1 What is hypervitaminosis D?

It is vitamin D poisoning (VDT) most often resulting from the supply of too high or too frequent doses of this substance in the form of various preparations. It is worth noting that exposure to sunlight or a varied diet are completely safe and necessary to ensure healthy levels of this vitamin. Although we are dealing with a deficiency much more often, there are more and more descriptions of poisoning cases in the literature, also among pediatric patients. The first step to establish a diagnosis is a medical history with the parent and, if possible, with the patient, followed by a physical examination of the child. The final method, which clearly allows to determine the excess level of vitamin D, is the determination of serum concentration of 25(OH)D, i.e. calcidiol. Toxicity is said to occur when the concentration of this metabolite exceeds 100 ng/ml (1). Other sources indicate 150 ng/ml as a dangerous and highly harmful value (2, 3, 4, 7).

3.2 Causes of hypervitaminosis D

Products enriched with this vitamin have been available in stores for a long time. This applies to milk, including milk for babies and children, and other dairy products. There are reports of a population in which at least 56 people developed VDT due to production errors with food, of which 41 were hospitalized and 2 died. Studies have shown significant differences between the dosage stated on the product packaging and the actual dose. This confirms production errors, the minimization of which requires optimisation of the control of products released for circulation (6). In healthy individuals, exogenous VDT is usually caused by long-term use (months) of mega doses of vitamin D, but not by abnormally high skin sun exposure or eating a varied diet. The human body can regulate the amount of previtamin D (tachysterol and lumisterol) produced in the skin by ultraviolet-B radiation. A varied diet usually does not provide large amounts of vitamin D, and vitamin D boosts are modest (13). Although rare, cases of vitamin D poisoning, which manifest as dramatic life-threatening symptoms, continue to occur in children. What's more, recent studies in infants raise the potential need to monitor vitamin D levels when doses at or above the currently recommended upper range are used. More research is needed to clarify these findings (18).

In the United States, hypervitaminosis developed in people drinking vitamin D-fortified milk from a local dairy, and analysis showed abnormalities in current doses. This situation contributed to the ban on milk fortifications and became an alarm for doctors about the potentially dangerous effects of high doses of vitamin D (2). Manufacturing errors can be successfully eliminated.

A bigger problem nowadays is the high availability of various preparations, the desire to protect the child from the effects of deficiency and the dosage on one's own, without medical indications. In 2015, a pediatric case of VDT was reported in an infant with severe hypercalcemia. The serum concentration of 25(OH)D was 293 ng/ml. The child was dehydrated, vomiting, presenting symptoms of hypervitaminosis D. A conversation with the mother showed that she was giving 50,000 IU of the vitamin per day, which is much higher than the recommended dose for an infant. Two other cases of infants with VDT are described in Bilbao. The children also presented similar symptoms as above, their parents also admitted to administering much higher than recommended doses of vitamin D, used over-the-counter preparations, leading to hypercalcemia in the range of 15–21 mg/dL total calcium and hypervitaminosis 25(OH)D: 644–680 ng/ml in both children (7). The risk group for VDT is also children with rickets treated parenterally with a high, single dose of vitamin D. Although such treatment is justified, it may result in symptoms of poisoning and significantly elevated levels of 25(OH)D (6). The need for hospitalization occurred in the case of 9 newborns in one of the French hospitals. The children were between 25 and 105 days of age, and the main indication for treatment in the ward was severe dehydration due to oral intake of 600,000 IU of vitamin D orally. During the diagnosis, it turned out that among young patients, as many as 7 out of 9 had nephrocalcinosis, which was confirmed by abdominal ultrasound (8). It is worth remembering that VDT may have an endogenous basis, the possibility of overproduction or disorders of vitamin D degradation should always be ruled out, which may occur in some systemic diseases, lymphoproliferative or paraneoplastic syndromes. A genetic basis is also possible, including mutations in the CYP24A1 or SLC34A1/A3 genes (2, 9, 11). A high serum 25(OH)D concentration without accompanying symptoms and an aggravating history should raise suspicions of a false positive result and be re-verified, as the cause may be an imperfection in immunological tests, i.e. laboratory error. In this case, it is called pseudohypervitaminosis D (10).

3.3 Epidemiology

Hypervitaminosis D is relatively rare in the paediatric population, but it is nevertheless a significant problem today. The widespread use of vitamin D has already contributed to 25,397 cases of toxicity between 2000 and 2014. By comparison, between 2000 and 2005, the annual average cases of vitamin D toxicity was 196, and between 2005 and 2011, there was a significant increase in exposure, resulting in a new annual average of 4,535 cases (5). In a study conducted in Lithuania, it was noted that hypervitaminosis D was most common in young children. The same conclusions can be drawn from a retrospective study in Romania, where the highest concentrations of 25(OH)D were in people under 10 years of age. This is because vitamin D is essential for the proper development and prevention of rickets, so more attention is paid to its supplementation in the paediatric population than in the adult group (12). Consider a family that overdosed on vitamin D after eating food cooked in peanut oil that contained 5 million units of vitamin D3/mL. Vitamin D plasma levels were 55 and 60 IU/mL in the father and mother, respectively, and 9.6 IU/mL in their 11-month-old infant (normal range, 0--1.6 IU/mL) (23).

3.4 Organ symptoms resulting from toxic vitamin D levels

Long-term administration of high doses of vitamin D to a child may lead to the appearance of side effects. It should be emphasized that most of the symptoms of VDT are due to concomitant hypercalcemia. Hypercalcemia is defined as a serum calcium concentration that is greater than two standard deviations above the normal mean, which in children can vary according to age and sex, reflecting changes in normal physiology at each stage of development. Hypercalcemic disorders in children can be manifested by hypotonia, poor feeding, vomiting, constipation, abdominal pain, lethargy, polyuria, dehydration, lack of development and seizures. In severe cases, renal failure, pancreatitis and reduced consciousness may occur, and older children and adolescents may present with neuropsychiatric symptoms such as difficulty concentrating and learning, apathy, mood disorders, drowsiness or headaches, and in extreme cases even coma (14). It is also worth paying attention to gastrointestinal disorders, which can often be underestimated in children or explained by other causes. These are abdominal pain, constipation, reluctance to eat, weight loss, vomiting, which result in water and electrolyte disorders. Predisposed people may develop gastric ulcers or pancreatitis (1) Another example of adverse effects of vitamin D may be cardiac arrhythmias, ECG abnormalities in the form of QT shortening and ST segment elevation, and the development of hypertension. Patients with hypervitaminosis D require special nephrological observation, because hypercalcemia will appear along with hypercalcemia. This means an increased tendency to calcium oxalate deposits in the kidneys, the formation of kidney stones and the development of nephrocalcinosis (4). Severe hypercalcemia can lead to acute renal failure requiring haemodialysis (3) Although permanent kidney damage in children is rare, it is reasonable to point out that vitamin D, which has so many health-promoting effects that guarantee normal child growth, can also have toxic properties in excess, disrupting the functioning of many systems and organs.

Treatment of vitamin D poisoning consists of: discontinuation of intake, restriction of calcium and phosphorus in the diet, intravenous saline hydration, loop diuretics, glucocorticoids, calcitonin and bisphosphonates (21).

3.5 Vitamin D supplementation

Vitamin D deficiency in infants is common. Most pediatric professional associations recommend routine vitamin D prophylaxis for infants. However, the optimal dosage and duration of supplementation are still up for debate. Oral vitamin D supplementation is the current standard of care for exclusively breastfed infants. Most professional pediatric associations recommend 400 IU/d of oral vitamin D supplementation for breastfed infants. However, studies around the world have shown that this dose may be insufficient to maintain adequate serum 25(OH)D levels and bone mineral content in healthy infants. Therefore, professional associations from countries such as France and Finland recommend routine supplementation of more than 1000 IU/d of oral vitamin D for healthy infants (15). Vitamin D deficiency has been reported to be independently associated with stunted growth, obesity, and early activation of the hypothalamic-pituitary-gonadal axis. Randomized phase 3 clinical trials to investigate the effects of long-term vitamin D replacement on the growth, body composition, and puberty development of school-age children with vitamin D deficiency are lacking (16).

When vitamin D poisoning occurs, hypercalcemia usually persists for more than a few months. Therefore, we are clinically trying to use short-acting active vitamin D (1alpha-OHD(3) and 1,25-(OH)(2)D(3)). Recently, analogues of 1,25-(OH) (2)D(3) have been developed with a strong stimulating effect on keratinocyte differentiation, but insufficient activity increasing serum calcium (22).

3.6 Vitamin D in children with chronic kidney disease

Government organizations in Europe and North America agree on the minimum serum vitamin D concentration (10ng/mL), but the discussion about the optimal upper limit is still ongoing. In children with chronic kidney disease, the target concentration of 25(OH)D is 30 ng/mL - these are the recommendations of the European Society of Paediatric Nephrology. It is also suspected that patients with chronic kidney disease need higher doses of supplementation to achieve the expected serum concentration. Pay attention to the case of children with associated proteinuria. In this case, the dose of vitamin D should also be increased due to the loss of 25(OH)D-binding proteins (17).

4. A global trend for vitamin D

According to many studies, over the past years, and especially in the post-COVID-19 period, a reduced percentage of vitamin D hypovitaminosis has been noted, with a shift towards increasingly frequent cases of hypervitaminosis. This trend is most likely due to increased population awareness of the significant impact of low vitamin D levels on the body's homeostasis. Which at first glance could be a positive measure, but unfortunately too little is still said about excessive vitamin D concentration and its negative impact. The growing popularity of over-the-counter preparations is not conducive to this situation. Very often, parents worried about their children give them supplements without monitoring its level in the serum. In the end, it can have a very unpleasant effect. Empirical, unmonitored, long-term supplementation of vitamin D with the use of non-recommended supraphysiological doses, especially when administered intramuscularly, should be discouraged. It is very important to take into account the age of the child, and in the case of adults, their body weight. Educating parents about the properties of vitamin D and constantly emphasising that there is a risk of overdose in the event of oversupply is also crucial (24).

5. Summary

Due to its broad therapeutic index, vitamin D toxicity is rare, but is possible with excessive doses or long-term use beyond medical control. Parents should be made aware of the potential dangers of non-compliance, and every child with hypercalcemia should be diagnosed for VDT. Physicians should take a thorough history with parents before starting vitamin D supplementation in pediatric patients, excluding the prior administration of over-the-counter preparations. Children receiving high doses should have continuously monitored serum 25(OH)D levels, and hypercalcemia, family history of VDT, and nephrolithiasis should be an alarm signal and indicate for 25(OH)D determination for dose adjustment. A daily supply of smaller than periodically higher doses is preferred (6-9).

Attention should also be paid to errors in the production of dietary supplements that can cause vitamin D hypervitaminosis in children. Physicians should be aware of this possibility in unexplained cases and repeatedly emphasize the risks and make recommendations to families regarding the use of dietary supplements. To prevent such unwanted situations from occurring, all manufacturers should always monitor the ingredient levels of their products, and all this should be supervised by government regulatory agencies, as is the case in the pharmaceutical industry (20).

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