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Prevention and Treatment of Vitamin D Deficiency: Current Look at the Issue

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The article presents the current data on the metabolism of vitamin D and its role in the development of bone tissue in children and the further condition thereof. Natural vitamin D sources, as well as the current routine practice of preventing deficiency of this organic substance are unable to fully satisfy a child's demand for this vitamin, which is why recommendations on vitamin D intake ought to be revised. The article details schedules for prescription of vitamin D for preventing and treating the body deficiency thereof based on results of the studies completed in the recent years. The role of the main marker enabling assessing vitamin D concentration in the body – 25(OH)D – the reference values whereof are yet to be commonly established has been analyzed. The article lists recommendations on rickets prevention and treatment in children. The article presents data on the possible mechanisms of development of toxic effects in the setting of vitamin D intake.
Keywords: *vitamin D, cholecalciferol, ergocalciferol, 25(OH)D, 1.25(OH)$_2$D, rickets, osteomalacia, insolation, hypocalcemia, hypercalcemia, hypervitaminosis D, children.*

INTRODUCTION

Vitamin D is a key factor of development and preservation of healthy bone tissue throughout a person's life. It is unique, as it may be generated in the skin due to exposure to sunlight. Rickets is the extreme manifestation of hypovitaminosis D in children, whose epiphyseal plates are still open (late rickets is the manifestation observed in older children and adults). However, months before bones are deformed, some other signs of hypovitaminosis D may occur, such as hypocalcemic spasms, growth retardation, irritability, and torpor [1]. Nowadays, the prevalence of hypovitaminosis D in children and adults is increasing despite the existing opportunities to prevent such hypovitaminosis [1]. Up to 20-35% of formula-fed children and less than 15% of breast-fed and breast- and formula-fed children receive sufficient amounts of this vitamin [2, 3]. Many mothers and even doctors are not aware how much vitamin D a child may receive as a result of spending time in the sun and how much vitamin D is contained in breastmilk and other nutrition. When growing intensively, adolescents need additional vitamin D, but prevention of its deficiency is a rare case. Aside from influencing the human skeleton, one cannot exclude the role of hypovitaminosis D in the development of autoimmune and oncologic diseases, 2nd type diabetes, cardiovascular and infectious pathologies [2, 4].

VITAMIN D METABOLISM

Solar radiation is the primary source of vitamin D. Plasma membrane of epidermal cells or, to be more precise, the basal and spinous layers always contain 7-dehydrocholesterol, i.e. provitamin d_3. Under the influence of ultraviolet radiation with a wavelength of 290 to 315 nm, 7-dehydrocholesterol is transmuted into previtamin d_3, which is then gradually (over several hours) isomerized into vitamin D_3, or cholecalciferol. This process is facilitated by dermal temperature. Vitamin D3 then leaves the cellular membrane [4, 5]. If a person spends too much time in the

sun, vitamin D_3 generated in the skin degrades to lumisterol, tachisterol, and different inactive phosphate products. This is why prolonged exposure to sunlight does not result in vitamin D overdose [3].

Vitamin D_3 is present in nutrition (though only few foods contain it) and pharmaceuticals. Food and pharmaceuticals are the only source of vitamin D_2 (ergocalciferol). Vitamins D_2 and D_3 are absorbed from the intestines and intrude chylomicrons, which are then transported through the lymph tubes and enter the venous circulation. Vitamins D_2 and D_3 from chylomicrons are either bound with the vitamin D–binding protein or deposited in the adipose tissue, where the substances are kept and may be released as needed. They may also go to the liver and undergo further transmutations. Vitamin D_3 generated in the skin enters dermal capillaries. When in the blood stream, it binds with the vitamin D–binding protein like other forms of vitamin D [4].

Vitamin D taken in with food is bound with chylomicrons and is either distributed in the adipose tissue or metabolized in the liver. When taken in as a pharmaceutical, the period of semi-excretion of the micronutrient in the circulation is 4 to 6 hours, whereas in the adipose tissue it may be preserved for up to 2 months [2]. Under normal conditions, less than 10% of vitamin D in the blood circulation comes from food, whereas 90% of it is generated in the skin due to exposure to sunlight [2].

When vitamin D present in the blood circulation together with the vitamin D–binding protein or as a part of chylomicrons enters the liver, it is transmuted into 25(OH)D (25-Hydroxyvitamin D, or calcidiol) under the influence of vitamin D 25-hydroxylase that is a part of microsomal cytochrome P450 2R1(CYP2R1) and mitochondrial cytochrome P450 (CYP27A1). Calcidiol is the primary blood-carried form of vitamin D, which is used to evaluate the vitamin D status of the patient's body. The normal range of 25(OH)D in the blood is 20 to 60 ng/ml or 50 to 150 nmol/L. To convert ng/ml values into the international units, i.e. nmol/L, divide it by 2.5 [5].

Calcidiol is low-active biologically. In the blood, it forms a complex together with the vitamin D–binding protein, and its semi-excretion takes ca. 15 days. Under the physiological conditions, only 2% to 5% of the vitamin D–binding protein is required to be bound with 25(OH)D [2].

The micronutrient is then metabolized in the kidneys. The complex of 25(OH)D and the vitamin D–binding protein is excreted by the kidneys and then reabsorbed in the proximal tubule. There it is transmuted into $1,25(OH)_2D$ or 1,25 dihydroxyvitamin d, or calcitriol. The transmutation process is facilitated by the mitochondrial enzyme 25-hydroxyvitamin d-1alpha hydroxylase (CYP27B1). The concentration of $1,25(OH)_2D$ in the body is under strict control and is approximately thousand times lower than the 25(OH)D concentration. The semi-excretion time for $1,25(OH)_2D$ contained in the blood is 4 to 15 hours. Calcitriol features low affinity to vitamin D–binding protein, but high affinity to vitamin D nuclear receptor present in many tissues and organs; it is also bound with the retinoic acid receptor. The complex of these receptors is the transcription factor that regulates the functioning of almost 2000 target genes, which influence calcium homeostasis and cell differentiation [6].

The primary effect of $1,25(OH)_2D$ is increased absorption of calcium in the small intestine by means of calcium channel activation as well as calbindin, the intracellular calcium carrier, and calcium pumps. These three mechanisms allow transporting calcium against the concentration gradient from enterocytes to blood plasma. Calcitriol increases the absorption of calcium in the small intestine from 10-15% up to 30-40% [7]. Besides, it increases the absorption of phosphorus in the small intestine from 50-60% to 80%. It also increases the reabsorption of phosphorus in the kidneys. Calcitriol stimulates maturation of osteoblasts into osteoclasts. Mature osteoclasts excrete calcium and phosphorus from the bones, thus increasing the calcium and phosphorus concentration in the blood [2].

The enzyme 25-hydroxyvitamin d-1alpha hydroxylase (CYP27B1) is expressed not only in the kidneys, but also in the bones, placenta, prostate, keratinocytes, macrophages, T lymphocytes, dendritic cells and some tumor cells, and parathyroid glands, which enables these cells and tissues to produce $1,25(OH)_2D$, which in this case features autocrine and paracrine properties [2].

VITAMIN D SYNTHESIS REGULATION

The synthesis of calcitriol is stimulated by parathyroid hormone, the concentration of which increases on the top of hypocalcemia and hypophosphatemia. Vice versa, generation of $1,25(OH)_2$ is suppressed when the concentration of calcium and phosphorus is high or when the synthesis of parathormone is suppressed (which causes mediated suppression).

By means of negative feedback, calcitriol suppresses its own synthesis and stimulates its own destruction by inducing renal ferment 25-hydroxyvitamin D-24-hydroxylase (CYP24A1), which transmutes calcidiol and calcitriol into biologically inactive metabolites, including calcitroic acid [4].

EVALUATION OF VITAMIN D LEVEL IN CHILDREN AND ADULTS

The best marker to use when evaluating vitamin D levels is 25(OH)D in the blood [3]. Evaluation of $1,25(OH)_2D$ level may be ambiguous, as the concentration of calcitriol may be within the normal range or increased on the top of hypovitaminosis D, the reason for which is secondary hyperparathyroidism [4].

There are many controversies in relation to the reference range of 25(OH)D in the blood. There is a risk that when the level of 25(OH)D goes downward, hypovitaminosis D signs may occur, yet there are many cases when an extremely low 25(OH)D level is not accompanied by any signs of rickets [2].

When the concentration of 25(OH)D is below 25 nmol/L, it is believed to be a sign of apparent hypovitaminosis D. The range believed to be normal is 50 to 150 nmol/L [3].

If 25(OH)D is less than 50 nmol/L in a child, the concentration of alkaline phosphatase is increased. If less than 40 nmol/L, X-ray signs of rickets may occur [4]. Judging by the level of parathormone that reversely correlates to the concentration of 25(OH)D in adults, we may notice that the synthesis of parathormone is suppressed to a maximal extent when the level of 25(OH)D is 20 to 110 nmol/L. In children, however, this relation is not that apparent [8]. The absorption of calcium in adults is not decreased unless 25(OH)D falls below 10 nmol/L [1].

Studies carried out in the U.S., Canada, India, Africa, Australia, Brazil, Central Asia, Mongolia, and New Zealand indicate that 30% to 50% of children and adults (and up to 98% in some countries) have < 50 nmol/L of 25(OH)D [25]. According to a study conducted in the U.S., ca. 16-54% of adolescents have < 50 nmol/L of 25(OH)D. A study carried out in Finland has shown that the mineral density of bone tissue is decreased in girls that have < 25 nmol/L of 25(OH)D in the puberty [1].

Hypovitaminosis D pathophysiology. Clinical signs of rickets

Insufficient production of vitamin D and insufficient intake thereof with food leads to a decrease in the level of 25(OH)D, which may result in hypocalcemia. However, the level of phosphorus stays within the normal range, and the level of $1,25(OH)_2D$ may be within the normal range or even increased [3].

If the level of calcidiol continues to decrease, parathyroid hormone is produced to keep calcium concentration in the blood within the normal range. The hormone increases calcium concentration by means of bone demineralization. Calcium level is then normalized. However, parathyroid hormone reduces the phosphorus reabsorption in the kidneys, which is why phosphorus level in the blood is decreased [1-4]. At this stage, the concentration of alkaline phosphatase in the blood may be increased, as this enzyme is produced by active osteoblasts [9].

Severe 25(OH)D deficiency leads to decompensation of the mechanisms that keep the calcium concentration in the blood within the normal range [4]. Doctors then note hypocalcemia, hypophosphatemia, a significantly increased blood concentration of alkaline phosphatase, and signs of bone demineralization [10]. As a result, forming bone tissue is not mineralized adequately. It is the osteoid that is not mineralized, which leads to late rickets. Enchondral calcification of epiphyseal plate may be decreased or even nullified, which results in a

deformation of this plate [1]. In children, such a condition is manifested with dwarfism and bone deformation characteristic of rickets. In adults, the manifestation is late rickets, which disrupts the supporting function of the bones and increases the risk of bone fracture [11]. Bone manifestations of rickets include enlarged anterior fontanel, outstanding frontal eminences, craniotabes (craniomalacia), Garrison's groove, rachitic beads, and enlarged wrists and ankles. A saber-shaped deformation of long tubular bones may take place under load. As a rule, rickets-affected children also suffer locomotor retardation; they learn to walk later. There may also be hyperreflexia, muscular and bone pains. These manifestations are accompanied by delayed teething and enamel pathology [1-6].

SOURCES OF VITAMIN D

The production of vitamin D in the skin depends on the intensity of solar radiation, and therefore, on the latitude, the season, the time of day, the cloud cover, and the level of air pollution [2]. The production of vitamin D in the skin peaks when the sun is at the zenith. If a person has spent some time in the sun and received an erythema dose, i.e. a minimum solar radiation dose required for dermal erythema to appear in 24 hours after exposure, the amount of vitamin D produced in the skin will then be equal to an oral intake of 10,000 to 25,000 IU of vitamin D_2 [12]. Fair-skinned people who evolved in the areas of reduced UV radiation have better capacities to produce vitamin D, as melanin serves as a barrier to sunlight [2]. To receive a minimum erythema dose in southern areas of the Northern hemisphere, fair-skinned people need to spend 4-10 minutes in the sun at the meridian, whereas black people need to spend 60-80 minutes. In the winter, solar radiation in the areas of 33° or greater latitude results in almost no vitamin D_3 production in the skin [2].

An interesting study carried out in Cincinnati, south-western Ohio (38° north latitude), showed that 20 minutes of exposure of uncovered face and hands to sunlight per day allows for production of the sufficient amount of vitamin D. In Beijing (40° north latitude), a person needs to spend 2 hours in the sun to achieve normal synthesis of vitamin D in September or October. A child that wears only a diaper needs four times less time in the sun than a fully-clad child to produce an equal amount of vitamin D. For calcidiol concentration to reach 27.5 nmol/L, a breast-fed child needs to spend 30 minutes per week in the sun wearing only a diaper, or 2 hours per week when fully-clad, but with the face uncovered. Sunscreen with SPF = 8 or more reduces the dermal synthesis of vitamin D by 95% [4]. It ought not to be ignored that the American Academy of Pediatrics does not recommend direct exposure of children under 6 months of age to sunlight.

There are only few foods that contain a sufficient amount of vitamin D_3. Those include cod liver oil (400 to 1000 IU per teaspoon), oily fish (mackerel, salmon, sardine, and tuna contain ca. 250 to 300 IU per 100 g), yolk (20 IU in one yolk), and beef liver. Vitamin D_2 is present in mushrooms (100 IU per 100 g of fresh mushrooms), yeast, and UV-exposed herbs. There are also vitamin D-enriched foods like formulas, milk, yoghurts, butter, cheese, bread, cereals, and even beer [2]. It is interesting to note that although vitamin D is a fat-soluble vitamin, the fat content of food enriched with this micronutrient does not affect its bioavailability [14].

When the amount of vitamin D in the body exceeds the need therefor, the redundant vitamin D is deposited in adipose tissue, where it may be preserved for several months. This is a fundamental principle of hypovitaminosis D prevention and treatment, when a large dose of vitamin D is administered once a week, a month, or even once in six months. Vitamin D can also be accumulated by means of exposure to sunlight. For instance, people who are directly exposed to sunlight during the summer months produce a sufficient amount of vitamin D to survive several winter months [2].

DRUG-BASED PREVENTION OF HYPOVITAMINOSIS D

All infants shall receive 400 IU, or 10 μg, of vitamin D per day with food or as a pharmaceutical immediately from the moment of birth [1]. To convert IU to μg, divide it by 40.

In Russia, there are capsules D_3VIT Baby available for neonates. Each capsule contains 200 IU, or 5 μg, of vitamin D_3. There is also Vigantol, an oily solution that contains 20,000 IU of vitamin D_3 per ml, and Aquadetrim, an ethanol-water solution that contains 15,000 IU of vitamin D_3 per ml. Besides, there is Vitamin D_3 BON, an oily solution for oral and intramuscular administration; it contains 20,000 IU per ml. Therefore, Aquadetrim, available in Russia, contains 500 IU per drop, and Vigantol contains ca. 667 IU per drop. A more convenient pharmaceutical is D_3VIT Baby gelatin capsules, which contain 200 IU per capsule and ensure precise dosage. 200 IU is half a daily dose for infants. The special gelatin shell allows producing this pharmaceutical without using any preservatives and keeping it in a fridge. Besides, one may open a gelatin capsule to administer the drug in the drop form immediately from the infant's birth.

Vitamin D is fat-soluble and is absorbed in the small intestine like other fats. In the small intestine, vitamin D is aggregated with salts of bile acids and forms micelles, which transport the micronutrient to the enterocyte membrane. It enters enterocytes by means of passive diffusion. In theory, other lipids shall be there for vitamin D to be absorbed effectively, as fats stimulate secretion of bile. Several studies on vitamin D bioavailability have shown the similarity of different vitamin D pharmaceutical forms (oily or ethanol solution or powder). What is more, patients suffering malabsorption syndrome, e.g. those with cystic fibrosis, absorb oily vitamin D solution less effectively as compared to powder or ethanol solution. There may exist a carrier protein that facilitates vitamin D absorption alongside with passive diffusion [15].

Breastmilk contains 22 IU per liter (15 to 50 IU per liter), which does not meet the infant's needs [16]. That is why 400 IU shall be administered to breast-fed and breast- and formula-fed children from the first days of life. On the other hand, the American Academy of Pediatrics states that nursing mothers may take increased doses of vitamin D (4,000 to 6,400 IU), as it increases the concentration of vitamin D in breastmilk to 873 IU per liter. Mothers do not suffer any toxic effects.

Formulas contain 40 to 100 IU of vitamin D per 100 kcal, i.e. ca. 400 IU per liter. Thus, if an infant consumes less than a liter of formula per day, 400 IU of vitamin D shall be administered thereto [1, 3].

Over-1 children and adults ought to take 600 IU of vitamin D per day, and over-70 persons should take 800 IU per day [3].

It ought to be noted that previous recommendations stated a smaller dose for infants (200 IU per day). However, unlike 400 IU a day, this dose does not allow keeping the level of 25(OH)D at 50 nmol/L [1].

The Endocrine Society recommends higher prophylaxis dosage of vitamin D, which allows reaching 75 nmol/L. To do so, infants should take 400-1,000 IU per day (it is safe to take in up to 2,000 IU), 1-18-year-old children and adolescents should take 600-1,000 IU per day (it is safe to take in up to 4,000 IU), and adults should take 1,500-2,000 IU per day (it is safe to take in up to 10,000 IU) [12].

Most premature infants need at least 400 IU of vitamin D per day, as they do not receive sufficient amounts of the micronutrient via the placenta, and often have feeding issues and an accompanying hepatic and renal pathology [3].

Pregnant women may need at least 1,000 IU of vitamin D per day [1, 3]. If a pregnant woman suffers hypovitaminosis D, her child will not avoid it. A study carried out in the UK in the 1990s has shown that if a pregnant woman has vitamin D concentrations within the normal range, it is associated with a better condition of bone tissue in her children at the age of 9 [17].

Patients suffering malabsorption syndrome, obesity, or taking glucocorticosteroids, anticonvulsants, rifampicin, or undergoing antiretroviral therapy, may require an increased dosage. In such cases, the dose of vitamin D shall be adjusted by controlling the levels of 25(OH)D and parathyroid hormone as well as the bone mineralization status. When prescribing vitamin D to such children, it is recommended to measure 25(OH)D level once a quarter until it reaches the normal range. The level of parathormone and the bone mineral status shall be evaluated every 6 months until normalized [2].

A study carried out in Turkey (38° north latitude) has shown that hypovitaminosis D is identified in 80.9% of 4-month-old children that are breast-fed and take 40 IU of vitamin D per day during the winter, and in 45.5% of such children during the summer months. The normal range was considered to be ≥ 75 nmol/L of 25(OH)D [18]. Given that Russia is situated in the North, e.g. Moscow is at 55° north latitude, it is recommended to continue prophylaxis-aimed administration of vitamin D regardless of the season.

TREATMENT OF HYPOVITAMINOSIS D-ASSOCIATED RICKETS

For such treatment, both vitamin D_3 and vitamin D_2 drugs may be used as their effect is very similar [3].

According to the British National Formulary for Children 2013, UK, children under 6 months of age shall take 3,000 IU of vitamin D per day. For children aged from 6 months to 12 years, the dose is 6,000 IU per day; from 12 years to 18 years – 10,000 IU per day. Given that 12-18-year-old adolescents may take the drug irregularly, a single oral administration of 300,000 IU is recommended. This dose may be divided into two administrations with a 12-hour-long interval. After 8 to 12 weeks of treatment, it is replaced with prophylaxis-aimed dosage of vitamin D. Such dosage is taken until the child's linear growth is completed. It is recommended to control blood calcium level once or twice a week at the initial stages of treatment, as well as in case of emesis or nausea, in all the children receiving therapeutic dosage of vitamin D [19].

The Endocrine Society recommends all under-18 children to take a therapeutic dose of 2,000 IU per day or 50,000 IU per week for 6 weeks; after that, patients start taking a prophylactic dose of 400 IU per day for infants / 600 IU per day for children aged from 1 to 18 years [12].

Patients suffering obesity and malabsorption syndrome and taking medicines that may influence vitamin D metabolism shall take doubled or tripled dosage, i.e. at least 6,000 to 10,000 IU per day, to treat hypovitaminosis D. The subsequent maintenance dose is 3,000 to 6,000 IU per day [2, 12].

The treatment strategy that prescribes 50,000 IU of vitamin D twice a month does not have toxic effects; this is proved by a 6-year-long experience [20].

When patient's compliance is in doubt, it is recommended to prescribe 100,000-600,000 IU of vitamin D over 1-5 days to children over 1 month of age and continue with maintenance dosage thereafter. According to a large-scale meta-analysis, hypercalcemia and hypercalciuria are not caused by loading doses of up to 300,000 IU, e.g. 2 x 15 ml vials of Aquadetrim, which contain 15,000 IU of vitamin D per ml. The risk of these adverse effects becomes high if the dose exceeds 400,000 IU [21].

Caution is advised when taking large doses of ergocalciferol, as it contains propylene glycol [3].

When treating rickets, calcium drugs shall be administered alongside with vitamin D to prevent hypocalcemia, even if serum calcium concentration is not reduced. Hypocalcemia may emerge when parathyroid hormone is normalized and the bones are re-mineralized, which is referred to as hungry bone syndrome. It is especially important when using treatment patterns with vitamin D doses of 50,000 to 600,000 IU. It is recommended to prescribe 75 mg/kg of elemental calcium per day. The daily dose may be divided into several administrations [1].

When treating rickets, the clinical signs (pain) submerge within 2 weeks, expansion of distal long bones subsides within 6 months, and X-shaped and O-shaped lower limb deformation may be corrected within 2 years. Residual deformities of the skeleton may persist in adolescents [4].

Intramuscular administration of vitamin D is not recommended [3].

Alpha-hydroxylated drugs, such as calcitriol or alphacalcidol, shall not be used to treat hypovitaminosis D-associated rickets. They are intended to treat hypophosphatemic rickets with FGF23 increase or some other vitamin D metabolism defects [3].

VITAMIN D OVERDOSE AND TOXICITY

Vitamin D overdose with the development of toxic effects is an extremely rare case, as the level of 25(OH)D in the blood has to exceed 25 nmol/L (or even 500 to 750 nmol/L, according to some data) for toxic responses to develop [22].

The primary toxic effect of vitamin D is hypercalcemia. Manifestations of hypervitaminosis D are as follows: loss of weight, loss of appetite, abdominal pain, emesis, fecal retention, polyuria, polydipsia, arterial hypertension, arrhythmia, nephrolithiasis, and renal failure [22-24].

The level of $1,25(OH)_2D_3$ may remain unincreased even on the top of toxic responses [23, 24]. Vitamin D overdose increases the level of calcidiol to such an extent that vitamin D–binding protein is no longer able to bind all of the 25(OH)D. As a result, calcidiol remains unbound and is seemingly able to affect vitamin D receptors in target cells. The levels of vitamin D dihydroxy metabolites, such as $24,25(OH)_2D_3$, $25,26(OH)_2D_3$, and $25(OH)D_3$-26,23-lactone, also become higher. These metabolites may also stimulate gene transcription.

The risk of toxic effects of vitamin D intake is high under certain conditions, e.g., in case of granulomatosis, genetic disorders, rare polymorphisms of enzymes taking part in vitamin D metabolism [22]. Vitamin D may become toxic due to sarcoidosis, when the concentration of 25(OH)D is within the normal range, but the expression of extrarenal CYP27B1 is excessive. Idiopathic infantile hypercalcemia is accompanied by CYP24A1 mutation. Therefore, 25 hydroxyvitamin d3-24-hydroxylase, the key enzyme for $1,25(OH)_2D_3$ degradation, is absent. Even a prophylactic dose of vitamin D may lead to a hypercalcemic crisis in such a child.

CONCLUSION

As of now, hypovitaminosis D is identified in 30% to 50% of children and adults. It is especially frequent in breast-fed children, black-skinned people, those who live far from the Equator, as well as in patients with an accompanying renal and hepatic pathology, patients with malabsorption syndrome, or those who undergo anticonvulsant or antiretroviral therapy. The contemporary therapeutic patterns provided in the article are based on the results of recent large-scale studies. It is evident that the current rickets prevention practice does not meet vitamin D needs of pediatric patients and should be reviewed.

CONFLICT OF INTEREST

The author has indicated she has no financial support / conflict of interest relevant to this article to disclose.

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