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Review of Recommendations for Supplementation of Vitamin D in Children and Adolescents

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The aim of this paper was a comprehensive review of recent guidelines and recommendations for supplementation of vitamin D in children and adolescents. Vitamin D deficiency is commonly reported among healthy infants, children and adolescents in Europe, particularly in certain risk groups, such as breastfed infants of non-compliant parents, darker skin children and adolescents, and those living in the northern hemisphere. Furthermore, a deficiency occurs in children who are rarely exposed to sunlight, obese children, in chronic renal, liver or intestinal diseases and in those using anticonvulsants and systemic glucocorticoids. Guidelines drawn up by ESPGHAN, the American Society of Pediatrics, the Institute of Medicine, Endocrine Society, Vitamin D opinion leaders (EVIDAS) and a global consensus of 11 organizations are concordant in recommending that all infants should receive 400 IU (10 µg) of vitamin D per day, and children after the first year of life (1-18 y) should receive 600 IU (15 µg) per day. Promotion of this public health measure is the duty of pediatricians and other health professionals. There are several guidelines published on prevention and therapy of vitamin D deficiency which will be presented in this review. **Conclusion** – There is a high level of concordance in the recommendations presented in selected guidelines and position papers for a daily dosage of vitamin D in infancy, childhood and adolescence.

Introduction

The term vitamin D (calciferol) refers to a group of lipid soluble secosteroids with endocrine function. Two basic forms of vitamin D are D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). Vitamins D_2 and D_3 are formed by photolysis caused by UV-B rays (wavelengths 280-315 nm) from their sterol precursors. Certain plants and fungi synthesize vitamin D_2, while vitamin D_3 synthesis occurs in animals (fish, birds, vertebrates) and human skin. Vitamins D_2 and D_3 from food, supplements and drugs are absorbed in the small intestine, and the degree of absorption depends on the presence of fat from foods that stimulate the production of pancreatic lipase and bile salts as well as other factors.

Vitamins D_2 and D_3 are inactive prohormones that bind to vitamin D-binding proteins and transport them to the liver where they are converted into 25-hydroxy vitamin D

(25(OH)D) with the aid of the 25-hydroxylase enzyme. Another hydroxylation occurs in the kidney with the help of 1α-hydroxylase, when vitamin D is converted to its active form of 1,25-dihydroxy vitamin D (1,25(OH)D). This hydroxylation is also regulated by the concentration of calcium and phosphate by parathyroid hormone (PTH). 1,25(OH)D as an active metabolite is involved in numerous physiological processes, especially in calcium and phosphorus metabolism (1).

Although the physiological role of vitamin D is largely related to maintaining the musculoskeletal system, the biological properties of this relatively simple compound go much further than the maintenance of calcium and phosphate homeostasis, therefore, vitamin D is considered a pleiotropic molecule with many extra-skeletal effects.

Inadequate intake of vitamin D in childhood can lead to development of rickets and osteomalacia. Vitamin D in childhood also plays a role in the prevention of autoimmune diseases (asthma, diabetes type 1), infectious diseases (respiratory infections, influenza) and cardiovascular diseases (2, 3). Clinical research has shown that many human cell types carry the vitamin D receptor (VDR), therefore VDR and vitamin D play a role in regulation of cell proliferation and differentiation, e.g. in cells of the immune system (T-cells, macrophages, monocytes) and epidermal cells (2). Several professional organizations and expert groups have formulated and published guidelines for supplementation of vitamin D in pregnant and lactating women, infants, children and adolescents.

In this review we will present the relevant recommendations published by various authorities on this subject.

The Prevalence of Inadequate Vitamin D Intake in Infants and Children in Europe

The European Food Safety Authority (EFSA) Panel on Nutrition, Novel Foods and Food Allergens provided an overview of vitamin D intake in infants and children (4). The results show that vitamin D intake is insufficient, also taking the dietary supplements into account. Furthermore, the prevalence of vitamin D deficiency in infants and young children in Europe ranges from 10 to 30%, even in the population with a higher intake of vitamin D in the form of dietary supplements, suggesting that endogenous vitamin D synthesis cannot compensate for intake through diet and dietary supplements. The Panel concluded that the total supply of vitamin D derived from food and endogenous synthesis, depending on the time of the year, is insufficient for most infants and children across Europe (4).

Risk groups for the development of deficiency are the following: a) Children with dark skin; b) Children who are insufficiently exposed to sunlight (inadequate sun exposure involves frequent use of sunscreen with high sun protection factor, staying indoors most of the day, wearing clothes that cover most of the skin, and staying in the area of the northern latitudes during the winter months); c) Children suffering from chronic liver diseases, chronic intestinal disease and chronic renal diseases; d) Children on therapy with certain drugs such as antiepileptics (phenytoin, carbamazepine) and systemic glucocorticoids; e) Obese children.

In obese children, adolescents and adults, lower serum 25(OH) vitamin D concentrations were found compared to people with normal body mass index. The reason for this may be sequestration of vitamin D in the excess adipose tissue (2). However, there are several other hypotheses proposed as explanations of the mechanisms of low vitamin D status in obese individuals. Some of them are volumetric dilution or negative feedback mechanisms from increased circulating 1,25(OH)D. Furthermore, some authors consider that obese individuals spend less

time outdoors, they often cover-up and wear more clothing, thus they reduce their sun exposure and endogenous synthesis of vitamin D in the skin (5). As a result, obese children and adolescents may require higher doses of vitamin D (usually two to three times more vitamin D for their age group) to achieve a normal serum concentration of 25(OH)D. Lifestyle could be another factor that affects the relationship between obesity and the concentration of 25(OH)D in the blood. There is currently no evidence that vitamin D deficiency, associated with obesity, has negative consequences on bone mineral density in the pediatric population (2). In some, but not all studies, BMI and adiposity have been negatively associated with the change in vitamin D status after vitamin D therapy (5).

Diagnosis of Deficiency

The concentration of 25(OH) D in the blood is considered the best indicator of vitamin D status, and this concentration is a reflection of dietary intake and vitamin D synthesis in the skin. Although 1,25(OH)D is an active form, this molecule is not a useful marker of synthesis in the skin and dietary intake, and does not correlate well with health effects. The main reasons for this are its short half-life and the fact that 1,25(OH)D is not regulated by vitamin D intake but by other factors, such as PTH. Therefore, the concentration of 1,25(OH)D in the blood may be normal or even elevated as a result of secondary hyperparathyroidism.

Measurement of 25(OH)D is automated and affordable, commercial methods are based on the principle of the ligand method (the reaction mixture contains an antibody to a part of the molecule 25(OH)D). The gold standard method is liquid chromatography and tandem mass spectrometry (liquid tandem mass spectrometry chromatography - LCMS) (6). Vitamin D deficiency is considered to be present in children with a blood concentration of 25(OH)D <50 nmol/L, while severe vitamin D deficiency is found in children <25 nmol/L. There are also other approaches that classify the deficiency as a 25(OH)D blood concentration of 20-37 nmol/L, but there is more and more research that suggests higher cutoff values (50 nmol/L).

For scientific and clinical purposes, the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) Nutrition Board recommends the pragmatic application of a 25(OH)D cutoff serum value of >50 nmol/L indicating an adequate status, and 25(OH)D blood concentration <25 nmol/L indicating severe vitamin D deficiency (2). According to the American Academy of Pediatrics, serum 25(OH)D concentrations in infants and children should be ≥50 nmol/L, but there is still controversy as to whether there are specific health benefits to a higher cutoff value, such as 75 nmol/L or even higher, for healthy children (7).

Guidelines for Supplementation

The American Academy of Pediatrics (AAP) guidelines, published in 2014 (7), as well as the position of the Institute of Medicine (IOM) published in 2011 (8), do not recommend reliance on sunlight exposure in order to receive the recommended allowance of vitamin D, therefore, supplementation is required and should be advised. Regarding the form of vitamin D supplement, a recent meta-analysis showed that vitamin D3 is more efficacious at raising serum 25(OH)D concentrations in comparison with vitamin D2. Therefore, vitamin D3 could be considered the preferred form of vitamin D supplement (9).

There are several guidelines across the globe published by distinguished professional associations and expert groups that define the recommended preventive and therapeutic dosages of vitamin D in order to reach

Table 1. Vitamin D supplementation: daily dosage guidelines according to selected authorities

Organization	Children				Women	
	Age (year)					
	<1	1-3	4-8	9-18	Breastfeeding	Lactating
ESPGHAN (2)	400 IU or 10 µg	600 IU or 15 µg	600 IU or 15 µg	600 IU or 15 µg	-	-
American Society of Pediatrics (7)	400 IU or 10 µg	600 IU or 15 µg	600 IU or 15 µg	600 IU or 15µg	-	-
French Society of Pediatrics (10)	1000 - 1200 IU or 25 - 30 µg*; 600 - 800 IU or 15 - 20 µg†	Two doses of 80.000 to 100 000 IU or 2000 - 2500 µg every winter (Nov and Feb)‡		-	-	-
Institute of Medicine (8, 11)	400 IU or 10 µg	600 IU or 15 µg	600 IU or 15 µg	600 IU or 15 µg	600 IU or 15 µg	600 IU or 15µg
Endocrine Society (12)	400 – 1000 IU or 10 – 25 µg	600 – 1000 IU or 15 - 25 µg	600 – 1000 IU or 15 - 25 µg	600 – 1000 IU or 15 – 25 µg	1500 – 2000 IU or 37,5 – 50 µg	1500 – 2000 IU or 37,5 – 50 µg
Vitamin D opinion leaders (EVIDAS) (13)	400 – 600 IU or 10 – 15 µg	600 – 1000 IU or 15 – 25 µg	600 – 1000 IU or 15 – 25 µg	600 – 1000 IU or 15 – 25 µg	Women (16-45 y): 1500 – 2000 IU or 37,5 - 50 µg§	
Consensus of 11 organizations (global) (14)	400 IU or 10 µg	600 IU or 15 µg	600 IU or 15µg	600 IU or 15µg	600 IU or 15 µg	600 IU or 15 µg

*Infants up to 18 months of age either breast fed or fed on unfortified milk; †Infants up to 18 months of age fed on fortified milk; ‡Children aged 18 months to 5 y; §For prevention of complications of pregnancy and fetal development.

the adequate levels of serum vitamin D in infancy, childhood and throughout life. The guidelines are shown in Table 1.

Several clinical situations may require therapeutic doses of vitamin D, mainly in children with chronic fat malabsorption, and those chronically taking anti-seizure medications, antifungals or long-term high dosages of systemic glucocorticoids. Higher dosages of vitamin D supplementation may be necessary to achieve adequate vitamin D status in children at risk, and this status should be determined using laboratory tests (e.g. serum 25(OH)D, PTH concentrations and indicators of bone-mineral status). After a vitamin D supplement is prescribed, 25(OH)D levels should be repeatedly tested at 3 month intervals until normal levels have been achieved. PTH and bone mineral status should be monitored every 6 months until they have normalized (6). Munns et al., in the consensus document of 11 organizations, recommend 2000 – 6000 IU (50 – 150 µg) of vitamin D for treatment of rickets, depending on age (14).

For patients with a serologically confirmed vitamin D deficiency (25(OH)D < 50 nmol/L), a therapeutic dosage of vitamin D should be introduced, with a preferable treatment period of 1–3 months. Control laboratory measurement of 25(OH)D concentration should not be earlier than 8–12 weeks after the beginning of therapy (12, 13,15). The recommended dosages are as follows: for neonates (younger than one month) 1000 IU/day (25 µg/day); for infants older than 1 month and toddlers 2000–3000 IU/day (50–75 µg/day); for children and adolescents aged 1–18 years 3000–5000 IU/day (75–125 µg/day) (13, 15). For patients with intestinal malabsorption, vitamin D should be administered in larger oral doses up to

50,000 IU/2–3 times a week, or parenteral or intramuscular doses of vitamin D, if available (13, 15).

In certain clinical situations, the use of vitamin D_3 is ineffective and an active form calcitriol is recommended. The use of active vitamin D metabolites or vitamin D analogs is recommended in these situations:

- In patients with renal failure (nephrotic syndrome and chronic kidney failure),
- In patients with severe liver failure,
- In patients with inherited metabolic diseases (hereditary resistance to vitamin D),
- In severe forms of malabsorption (short bowel syndrome, lymphangiectasia),
- In patients after bariatric surgery, and
- In patients with long-term glucocorticoid use (6).

Vitamin D Toxicity and Upper Level of Intake

Many studies are showing that vitamin D is probably one of the least toxic fat-soluble vitamins. It is widely accepted that a serum 25(OH)D concentration of up to 250 nmol/L is safe for children and adults, with the exception of those who have hypersensitivity to vitamin D (15). Hypersensitivity is related to children and adults with idiopathic infantile hypercalcemia (15, 17), Williams-Beuren syndrome (18), granulomatous disorders and some lymphomas (19, 20). Genetic susceptibility and metabolic differences probably modulate the threshold of vitamin D toxicity, therefore respect for recommended dosages in a prerequisite in terms of vitamin D supplementation (21). Contraindications for vitamin D supplementation are hypercalcaemia, hypervitaminosis D or renal osteodystrophy with hyperphosphatemia. Some of the symptoms of vitamin D toxicity are: vomiting, decreased appetite, dehydration, muscle weakness, irritability, constipation and fatigue (22).

The Endocrine Society guidelines concluded that vitamin D toxicity is not only extremely rare, but a 25(OH)D concentration of at least 375 nmol/L (150 ng/mL) is required before there would be any concern of vitamin D toxicity (12). The IOM set tolerable upper limits of daily vitamin D supplementation at 1000 IU/day (25 μg) in infants younger than 6 months, 1500 IU/day (37,5 μg) in older infants, 2000 IU (50 μg) per day in toddlers, 2500 IU/day (62,5 μg) in children 4–8 y of age and 3000 IU (75 μg) in older children and adults (8). The upper levels of intake set by the EFSA are: for infants at 1000 IU/day (25 μg) and for young children 2000/day (50 μg), based on data relating high vitamin D intakes to impaired growth and hypercalcemia (4, 20). The EFSA set the upper level (UL) of intake for adults, including pregnant and lactating women, at 4000 IU/day (100 μg). Despite the paucity of data for high vitamin D intake in children and adolescents, the UL for children and adolescents aged 11-17 years was set at 4000 IU/day (100 μg), since owing to the phases of rapid bone formation and growth, this age group is unlikely to have a lower tolerance for vitamin D compared to adults (23, 24). Still, there are many unsolved issues and debates regarding vitamin D supplementation and screening, therefore an individual anamnestic approach is always recommended (25).

Conclusion

Healthy children and adolescents should be advised to follow a healthy lifestyle including a balanced diet with foods high in vitamin D content, together with appropriate outdoor activities associated with responsible sun exposure. All the relevant guidelines are concordant in recommending that all infants should receive oral supplementation of 400 IU/day (10 μg) of vitamin D. For healthy children,

but also especially for children in high-risk groups, oral supplementation should be considered beyond 1 year of age (at least 600 IU (15 μg)). Seasonal variations in sunlight efficacy in vitamin D synthesis should be taken into consideration when planning supplementation. Pediatricians, dietitians and other health care professionals should try to make vitamin D supplements readily available for all children, especially for those children at risk of vitamin D deficiency.

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References

1. Soltirovska Salamon A, Paro – Panjan D. The impact of vitamin D: From a fetus to an infant. Central Eur J Paed. 2018;14(1):27-36.
2. Braegger C, Campoy C, Colomb V, Decsi T, Domellof M, Fewtrell M, et al. ESPGHAN Committee on Nutrition. Vitamin D in the healthy European paediatric population. J Pediatr Gastroenterol Nutr. 2013;56(6):692-701.
3. Grossman Z, Hadjipanayis A, Stiris T, Del Torso S, Mercier JC, Valiulis A, et al. Vitamin D in European children-statement from the European Academy of Paediatrics (EAP). Eur J Pediatr. 2017;176(6):829-31.
4. European Food Safety Authority (EFSA). Scientific Opinion on nutrient requirements and dietary intakes of infants and young children in the European. EFSA Journal. 2013;11(10):3408.
5. Pourshahidi LK. Vitamin D and obesity: current perspectives and future directions. Proc Nutr Soc. 2015;74(2):115-24.
6. Vranešić Bender D, Giljević Z, Kušec V, Laktašić Žerjavić N, Bošnjak Pašić M, Vrdoljak E, et al. Guidelines for the prevention, detection and therapy of vitamin D deficiency in adults. Lijec Vjesn. 2016;138(5-6):121-32.
7. Golden NH, Abrams SA; Committee on Nutrition. Optimizing bone health in children and adolescents. Pediatrics. 2014;134(4):e1229-43.
8. Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. In: Ross AC, Taylor CL, Yaktine AL, et al., editors. Dietary Reference Intakes for Calcium and Vitamin D.Washington (DC): National Academies Press (US); 2011.
9. Tripkovic L, Lambert H, Hart K, Smith CP, Bucca G, Penson S, et al. Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis. Am J Clin Nutr. 2012;95(6):1357-64.
10. Vidailhet M, Mallet E, Bocquet A, Bresson JL, Briend A, Chouraqui JP, et al. Vitamin D: still a topical matter in children and adolescents. A position paper by the Committee on Nutrition of the French Society of Paediatrics. Arch Pediatr. 2012;19:316-28.
11. Ross AC, Manson JE, Abrams SA, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know? J Clin Endocrinol Metab. 2011;96:53-58.
12. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2011;96:1911-30.
13. Pludowski P, Karczmarewicz E, Bayer M, Carter G, Chlebna-Sokol D, Czech-Kowalska J, et al., Practical guidelines for the supplementation of vitamin D and the treatment of deficits in Central Europe – recommended vitamin D intakes in the general population and groups at risk of vitamin D deficiency. Endokrynol. Pol. 2013:64(4):319-27.
14. Munns CF, Shaw N, Kiely M, Specker BL, Thacher TD, Ozono K, et al. Global Consensus Recommendations on Prevention and Management of Nutritional Rickets. J Clin Endocrinol Metab. 2016;101(2):394-15.
15. Pludowski P, Holick MF, Grant WB, Konstantynowicz J, Mascarenhas MR, Haq A, et al. Vitamin D supplementation guidelines. J Steroid Biochem Mol Biol. 2018;175:125-35.
16. M. Gigante, L. Santangelo, S. Diella, G. Caridi, L. Argentiero, M.M. D'Alessandro, et al. Mutational spectrum of CYP24A1 gene in a cohort of italian

patients with idiopathic infantile hypercalcemia, Nephron. 2016;133(3):193-204.

17. Schlingmann KP, Kaufmann M, Weber S, Irwin A, Goos C, John U, et al. Mutations in CYP24A1 and idiopathic infantile hypercalcemia. N Engl J Med. 20114;365(5):410-21.
18. Pober BR. Williams-Beuren syndrome. N Engl J Med. 2010;21;362(3):239-52.
19. Holick MF. Vitamin D update 2015: what we need to know about its health benefits and potential for toxicity? Standardy Medyczne Pediatria. 2015;12(5):759-65.
20. Holick MF. Vitamin D is not as toxic as was once thought: a historical and an up-to-date perspective. Mayo Clin. Proc. 2015;90(5):561-64.
21. Hmami F, Oulmaati A, Amarti A, Kottler ML, Bouharrou A. Overdose or hypersensitivity to vitamin D?. Arch Pediatr. 2014;21(10):1115-19.
22. Eevgen Benedik E, Fidler Mis N. New recommendations for vitamin D intake. Zdrav Vestn. 2013;82(Suppl 1):I-145-51.
23. European Food Safety Authority (EFSA), Parma, Italy, EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) Scientific Opinion on the Tolerable Upper Intake Level of vitamin D. EFSA Journal. 2012;10(7):2813.
24. Kucan R, Soltirovska Šalamon A, Andronikov D, Benedik E. Dietary Sources of Vitamin D, Vitamin D Supplementation, and Its Bio-Viability. Central Eur J Paed. 2018;14(2):115-22.
25. Minisola S, Pepe J, Donato P, Vigna E, Occhiuto M, Ferrone F, et al. Replenishment of vitamin D status: theoretical and practical considerations. Hormones (Athens). 2018 (in press) doi: 10.1007/s42000-018-0040-6.