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Special Article - Vitamin D Deficiency

Vitamin D Deficiency

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Abstract

Vitamin D is a key regulator of calcium and bone homeostasis. Beside gut, bone and kidney, many other tissues possess vitamin D receptors, suggesting that the hormone exerts pleiotropic effects. Severe vitamin D deficiency is expressed clinically as rickets in children and osteomalacia in adults. Minimal 25OHD level needed to prevent these severe nutritional complications in most individuals is of 30nmol/l or 12ng/ml, but the actual threshold for minimizing bone loss, risk of falls, fracture risk or other non-calcemic diseases supposedly related to vitamin D insufficiency is currently ill defined and much debated. Most experts agree, however, that vitamin D daily supplements of 800-1600 IU (20-40 micrograms) and 25OHD levels above 50nmol/l (20ng/ml) are sufficient to prevent bone-related complications of vitamin D deficiency. Vitamin D excess could lead to intoxication, with severe complications, such as hypercalcemia, bone demineralization and soft tissue calcifications.

The Role of Vitamin D in Health

Vitamin D is considered, together with Parathyroid Hormone (PTH) and Fibroblast Growth Factor 23 (FGF23), a main regulator of phosphocalcic and bone metabolism [1]. Vitamin D is synthesized in the skin from its precursor 7-dehydrocholesterol under the influence of ultraviolet light, therefore it is considered" the sunshine vitamin" [2]. Vitamin D can also have dietary origins (animal - vitamin D3, or vegetal - vitamin D2), which become more important when sunlight exposure is diminished [2]. Once in the bloodstream, the bulk of vitamin D gets hydroxylated in the position 25 after a single passage in the liver, leading to 25 Hydroxyvtamin D (25OHD) which is the most abundant vitamin D metabolite, best reflecting vitamin D status [3]. 25OHD is bound in the circulation mainly by a specific transporter named vitamin D Binding Protein (DBP) and the free (unbound) 25OHD is in equilibrium with bound 25OHD [4]. A second hydroxylation taking place in the kidney in the position 1 alpha under the action of 1 alpha hydroxylase (CYP27B1) transforms the 25OHD precursor into the active D metabolite, 1,25(OH)2D which specifically binds to the nuclear Vitamin D Receptor (VDR) and activates it [5]. Circulating 1,25(OH)2D is 1000 fold lower than 25OHD [1,5]. The major source of circulating 1,25(OH)2D is the kidney, therefore kidney 1 alpha hydroxylation is considered a fine tuning step of vitamin D activation [5]. Other tissues have, however, the capacity to locally activate vitamin D through 1 alpha hydroxylation in a paracrine manner [6]. VDRs are found in classical vitamin D targets (gut, bone, kidney and parathyroid glands), but also in many other tissues (central nervous system, immune system, endocrine pancreas, skin, skeletal muscle, cardiovascular system, various cancer cells), suggesting that vitamin D may have pleiotropic roles, independent of calcium and bone metabolism [7]. Probably the main role of vitamin D in health is the stimulation of active calcium absorption in the gut, which becomes important for the maintenance of circulating calcium levels (also a resource for bone mineralization) in the condition of low calcium intake [8]. 1,25(OH)2D has direct effects also on kidney, stimulating calcium reabsorption in the distal tubules [9] and on bone, where it differentiates chondroblasts monocytic precursors into osteoclasts, stimulates osteoblastic activity and increases osteoprotegerin expression, thereby decreasing osteoclast activation [8,10]. These effects are however less important for bone health than vitamin D stimulation of active gut calcium absorption, since diet calcium supplementation can by itself revert the deleterious effects of severe vitamin D deficiency or resistance on bone [11].

The description of VDRs in many other tissues rose the suspicion that vitamin D status may influence the onset and evolution of other diseases, such as autoimmunity (diabetes, multiple sclerosis) [12,13], muscular contractility and the risk of falls associated with frailty fractures [14], various forms of cancer [15], but also cardiovascular diseases [16] and even overall mortality [17]. Many of these pathological situations are indeed frequently associated with D hypovitaminosis, but decreased vitamin D levels may be a consequence of decreased sunlight exposure due to the disease rather than directly influence disease onset or severity [18]. Moreover, no clear Randomized Clinical Trials (RCTs) could find a direct relationship between the repletion of vitamin D reserves and a better disease outcome [19,20].

Vitamin D Deficiency: Rickets and Osteomalacia, Osteoporosis

Low sunlight exposure combined with low dietary intake and aggravated by racial differences in skin pigmentation caused an epidemic of severe nutritional vitamin D deficiency and rickets in children for centuries [21]. Rickets is an invalidating skeleton disease, comprising bone and joint deformities, frail bones and short stature [22]. Although easily preventable with food vitamin D supplementation, nutritional rickets is still endemic in certain regions of the world [23]. The rare forms of genetic rickets, due to inactivating mutations of 1 alpha hydroxylase or of the VDR may have normal or even increased levels of 25OHD and cannot be treated with vitamin D [24], but are not the subject of this minireview.

Severe vitamin D deficiency may also occur in adult life, either in persons with important ultraviolet light deprivations or with severe malabsorption. Growth plates are closed in adults, but severe vitamin

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D deficiency leads to osteomalacia - a delay in bone mineralization with osteoid abundance, bone frailty and fractures [23].

Less severe vitamin D deficiency is associated with osteoporosis and increased fracture risk especially at advanced ages. D hypovitaminosis causes a reactive increase in PTH secretion generating high turnover bone loss [25]. Several nutritional studies demonstrated that vitamin D supplementation is beneficial for bone mass and may decrease fracture risk [26-30]. The serum concentration of 25OHD needed to be reached for decreasing fracture risk, as well as the vitamin D type, dosage and sequence of administration are however still controversial [10] (see below).

Vitamin D Deficiency - Definition and Evaluation

Freshly synthesized vitamin D does not last long enough in the circulation, because it is hydroxylated in the liver after just one passage. Vitamin D itself is therefore not a good parameter for reflecting an optimal vitamin D repletion status [10,31].

Since 1,25(OH)2D is the active vitamin D metabolite, directly stimulating the VDR, one would expect that 1,25(OH)2D circulating levels may efficiently mirror vitamin D sufficiency. The level of circulating 1,25(OH)2D is, however, 1000 fold lower than that of 25(OH)D [31]. It is therefore not unexpected to observe 1,25(OH)2D levels still within the normal range (20 to 45 pg/ml) in the majority of patients having low or even very low 25OHD3 levels [32]. Secondly, VDRs have isoforms with different affinities for 1,25(OH)2D binding, which are expressed in various proportions in individuals [33], therefore a certain 1,25(OH)2D concentration may be sufficient for an individual but insufficient for another. Thirdly, 1,25(OH)2D synthesis is tightly regulated and the active hormone has a short half-life, therefore it does not accurately reflect vitamin D nutritional status [31]. Finally, circulating 1,25(OH)2D reflects only kidney vitamin D activation, whereas other tissues also possess the capacity to activate 25OHD into 1,25(OH)2D through local 1 alpha hydroxylation, the active hormone acting locally, in a paracrine way [6,32].

The evaluation of circulating 25OHD, precursor of active 1,25(OH)2D and most represented vitamin D metabolite in the general circulation, is considered to give a better image of the organism's vitamin D repletion [34,35]. The main problem remains to define thresholds of this metabolite below which a high risk of clinically relevant hypovitaminosis-related bone disease may appear [10]. It was initially arbitrarily considered that 25OHD levels lower than 75nmol/l (30ng/ml) were in the range of "vitamin D insufficiency" and accompanied by an increased risk of complications, such as bone frailty, propensity toward infections, cardiovascular disease, autoimmunity or even cancer [19]. Recent epidemiological studies proved, however, that the majority of the actual population has 25OHD levels between 50 and 75nmol/l (20-30 ng/ml), mainly due to modern life-related lower sunlight exposure, despite the absence of significant modifications in the incidence of the above-mentioned diseases [19,36]. The "disease threshold" of circulating 25OHD should be therefore lower than 50nmol/l (20ng/ml). Indeed, mean 25OHD levels in children suffering of clinically relevant nutritional rickets or adults suffering of osteomalacia are much lower in different studies, ranging between 8 and 30nmol/l (3 and 12 ng/ml) [10]. Vitamin D repletion can, furthermore, slip back the evolution of rickets when a 25OHD threshold of 30nmol/l (12ng/ml) is attained [22,37]. Below this level, active intestinal calcium absorption may decrease up to severe consequences such as hypocalcemia, reactive hyperparathyroidism and disturbances in the calcification of new bone. A logical conclusion should be that 25OHD levels above 30nmol/l will prevent nutritional rickets or osteomalacia, whereas 25OHD levels below 30nmol/l could be considered in the range of "severe vitamin D deficiency" [10,22,37].

It is known that age is an independent risk factor for osteoporosis and frailty fractures. Many third age patients, more so the institutionalized, have decreased sunlight exposure, which, together with calcium and vitamin D nutritional deficiencies and a certain degree of malabsorption, contribute to D hypovitaminosis, hypocalcemia and reactive hyperparathyroidism. This biological spectrum contributes, together with various degrees of hypogonadism, to significant bone loss [25]. Observational studies clearly demonstrated that vitamin D supplementation in the elderly with 25OHD levels below 50nmol/l (20ng/ml) can normalize serum PTH levels in the majority of patients, therefore the 25OHD threshold of 50nmol/l may be used to define "vitamin D deficiency" [25,32,38].

Most of the experts agree that, for bone health reasons, 25OHD should be above 50nmol/l. The Institute of Medicine considers that 25OHD levels below 30nmol/l are certainly deficient for the completely American population, while levels above 40nmol/l may be sufficient for half the adult population and values above 50nmol/l are sufficient for more than 97% of the population [39]. A significant expert minority argues that even higher 25OHD thresholds, of 75 or even 125nmol/l may be accompanied by wider benefits with respect to the prevention of other diseases [40]. These speculations are, however, not supported by RCTs and may even encourage vitamin D over-dosage and intoxication.

An important debate also argues whether free (biologically available) 25OHD may be a more reliable parameter than total 25OHD for defining vitamin D nutritional status [4].

Vitamin D Supplementation for the Prevention of Bone Disease

Historical experience showed that nutritional rickets could be prevented and cured with the administration of one daily teaspoon of cod liver oil, containing about 400IU of vitamin D3 [41]. This is the present daily recommended dose for the prevention of rickets in infants and children [42].

Some interventional studies in third age patients using vitamin D supplementation until above the deficiency threshold with/without calcium showed an increase in bone mass [26-29] or an arrest of bone mass loss [30]. The observed increase was generally modest [26,27], but more important when basal 25OHD was lower [28,29]. Several RCTs and their meta-analyses [7] showed divergent outcomes of vitamin D supplementation on the prevention of fractures: clear beneficial effects, borderline positive effects [10,28] and no effects [43]. It is, however, a general consensus that vitamin D supplementation should be done at persons at risk for osteoporosis or established osteoporosis in association to antiresorbtive therapy, with a minimal daily dose of 800IU/day of vitamin D and adequate calcium intake from food

or supplements (>1g/day). Recent interventional studies showed that 800IU/day of vitamin D can increase 25OHD levels above 50nmol/l in only 89% elderly patients with D hypovitaminosis, whereas a daily dose of 1600IU normalizes 25OHD levels in 97.5% of patients, without risk of vitamin D intoxication [44].

Most guidelines advise a bone health threshold of 50nmol/l of 25OHD. However, certain experts argue in favor of higher threshold levels which could be attained only with higher daily vitamin D doses [45,46]. Higher daily supplement doses or the alternate high dose periodical vitamin D administration (e.g. 300000 to 500000 IU/month) may not be advisable despite rapid increase of 25OHD levels [47], because a level of 25OHD above 125nmol/l was associated with a paradoxical effect of increased risk of falls and fractures [47,48]. The administration of active 1 alpha hydroxylated forms of vitamin D for the prophylaxis of osteoporosis is again not advisable, because this type of therapy cannot be controlled with 25OHD measurement, efficient doses may greatly vary from one individual to another and at the same dose certain patients may be more at risk for vitamin D toxicity, which should be systematically checked. This type of therapy should be kept for patients with 1 alpha hydroxylation deficiency [49].

Vitamin D Intoxication

Vitamin D excess, with 25OHD way beyond 250nmol/l (100ng/ml) produces severe complications caused by high intestinal absorption and kidney reabsorption of calcium, as well as high osteoclastic activity with bone demineralization [50]. Intoxicated patients develop severe hypercalcemia and/or hypercalciuria, extensive bone demineralization with pathological fractures, renal lithiasis, nephrocalcinosis, and ectopic calcifications of soft tissues with important cardiovascular impact [51]. Although some authors consider daily administration of up to 10 000IU of vitamin D to be safe, literature data is limited due to small patient number and short follow up [52]. Most guidelines consider, however, a daily intake of 4000IU to be the highest acceptable dose for adults without the risk of vitamin D intoxication [53,54].

Concluding Remarks

1. Vitamin D is one of the main regulating hormones of calcium and bone metabolism and is important for bone health. Its central action is exerted on the active intestinal absorption of calcium. Vitamin D deficiency is related to bone disease, such as rickets, osteomalacia or third age osteoporosis.

2. Beside its classical effects, vitamin D may also have other pleiotropic, non-calcemic roles. It is not clear whether D hypovitaminosis is a consequence of diminished sunlight exposure of diseased patients or may be directly involved in disease pathogenesis. There is no clinical proof that vitamin D supplementation may improve the evolution of other diseases and it should not be used for other purposes than bone pathology.

3. Circulating 25OHD is the best indicator of vitamin D reserve. The definition of vitamin D deficiency is not unanimously accepted, but severe vitamin D deficiency could be considered at 25OHD values below 30nmol/l (12ng/ml), at high risk for rickets or osteomalacia. Milder vitamin D deficiency could be defined by the cut point of 50nmol/l (20ng/ml), at which many third age patients develop secondary hyperparathyroidism, involved in high turnover loss of bone mass.

4. Persons at risk to develop vitamin D deficiency are infants and growing children, third age population, persons with insufficient sunlight exposure and/or with important skin pigmentation and persons suffering of different types of malabsorption. Rickets prophylaxis implies daily vitamin D supplementation (400IU) in infants and small children. Prophylaxis of third age osteoporosis implies daily supplementation with vitamin D (a minimum of 800IU up to 1600IU) and calcium (1000mg). Patients with established osteoporosis and treated with antiresorptive drugs should ingest vitamin D supplements.

5. Higher vitamin D doses given daily or intermittently are not proven to have supplementary benefits and may even lead to vitamin D intoxication or other unwanted effects. Active vitamin D metabolites should be used mainly for treating patients having deficiencies in 1 alpha hydroxylation and less for preventing osteoporosis.

References

1. Goltzman D, Mannstadt M, Marcocci C. Physiology of the Calcium-Parathyroid Hormone-Vitamin D Axis. Front Horm Res. 2018; 50: 1-13.
2. Bouillon R. Comparative analysis of nutritional guidelines for vitamin D. Nat Rev Endocrinol. 2017; 13: 466-479.
3. Bouillon R, Carmeliet G. Vitamin D insufficiency: Definition, diagnosis and management. Best Pract Res Clin Endocrinol Metab. 2018; 32: 669-684.
4. Bikle D, Bouillon R, Thadhani R, Schoenmakers I. Vitamin D metabolites in captivity? Should we measure free or total 25(OH)D to assess vitamin D status? J Steroid Biochem Mol Biol. 2017; 173: 105-116.
5. Christakos S. In search of regulatory circuits that control the biological activity of vitamin D. J Biol Chem. 2017; 292: 17559-17560.
6. Bikle DD, Patzek S, Wang Y. Physiologic and pathophysiologic roles of extra renal CYP27b1: Case report and review. Bone Rep. 2018; 8: 255-267.
7. Bouillon R, Marcocci C, Carmeliet G, Bikle D, White JH, Dawson-Hughes B, et al. Skeletal and Extraskeletal Actions of Vitamin D: Current Evidence and Outstanding Questions. Endocr Rev. 2019; 40: 1109-1151.
8. Carmeliet G, Dermauw V, Bouillon R. Vitamin D signaling in calcium and bone homeostasis: a delicate balance. Best Pract Res Clin Endocrinol Metab. 2015; 29: 621-631.
9. Blaine J, Chonchol M, Levi M. Renal control of calcium, phosphate, and magnesium homeostasis. Clin J Am Soc Nephrol. 2015; 10: 1257-1272.
10. Masuyama R, Stockmans I, Torrekens S, Van Looveren R, Maes C, Carmeliet P, et al. Vitamin D receptor in chondrocytes promotes osteoclastogenesis and regulates FGF23 production in osteoblasts. J Clin Invest. 2006; 116: 3150-3159.
11. Christakos S, Li S, De La Cruz J, Bikle DD. New developments in our understanding of vitamin metabolism, action and treatment. Metabolism. 2019; 98: 112-120.
12. Takiishi T, Gysemans C, Bouillon R, Mathieu C. Vitamin D and diabetes. Endocrinol Metab Clin North Am. 2010; 39: 419-446.
13. Brănişteanu DD. The immune modulating effects of vitamin D: how far are we from clinical applications? Acta Endocrinologica (Buc). 2006; II: 437-455.
14. Girgis CM, Clifton-Bligh RJ, Hamrick MW, Holick MF, Gunton JE. The roles of vitamin D in skeletal muscle: form, function, and metabolism. Endocr Rev. 2013; 34: 33-83.
15. Mondul AM, Weinstein SJ, Layne TM, Albanes D. Vitamin D and Cancer Risk and Mortality: State of the Science, Gaps, and Challenges. Epidemiol Rev. 2017; 39: 28-48.

16. Bouillon R. Vitamin D and cardiovascular disorders. Osteoporos Int. 2019.

17. Pilz S, Grübler M, Gaksch M, Schwetz V, Trummer C, Hartaigh BÓ, et al. Vitamin D and Mortality. Anticancer Res. 2016; 36: 1379-1387.

18. Scaranti M, Júnior Gde C, Hoff AO. Vitamin D and cancer: does it really matter? Curr Opin Oncol. 2016; 28: 205-209.

19. Heaney RP. What is vitamin D insufficiency? and does it matter? Calcif Tissue Int. 2013; 92: 177-183.

20. van Daele PLA. Vitamin D, many associations but few that seem to matter. Neth J Med. 2017; 75: 178.

21. Holick MF. Resurrection of vitamin D deficiency and rickets. J Clin Invest. 2006; 116: 2062-2072.

22. Elder CJ, Bishop NJ. Rickets. Lancet. 2014; 383: 1665-1676.

23. Uday S, Högler W. Nutritional Rickets and Osteomalacia in the Twenty-first Century: Revised Concepts, Public Health, and Prevention Strategies. Curr Osteoporos Rep. 2017; 15: 293-302.

24. Acar S, Demir K, Shi Y. Genetic Causes of Rickets. J Clin Res Pediatr Endocrinol. 2017; 9: 88-105.

25. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. Endocr Rev. 2001; 22: 477-501.

26. Bischoff-Ferrari HA, Dietrich T, Orav EJ, Dawson-Hughes B. Positive association between 25-hydroxy vitamin D levels and bone mineral density: a population-based study of younger and older adults. Am J Med. 2004; 116: 634-639.

27. Kuchuk NO, Pluijm SM, van Schoor NM, Looman CW, Smit JH, Lips P. Relationships of serum 25-hydroxyvitamin D to bone mineral density and serum parathyroid hormone and markers of bone turnover in older persons. J Clin Endocrinol Metab. 2009; 94: 1244-1250.

28. Lips P, van Schoor NM. The effect of vitamin D on bone and osteoporosis. Best Pract Res Clin Endocrinol Metab. 2011; 25: 585-591.

29. Ooms ME, Lips P, Roos JC, van der Vijgh WJ, Popp-Snijders C, Bezemer PD, et al. Vitamin D status and sex hormone binding globulin: determinants of bone turnover and bone mineral density in elderly women. J Bone Miner Res. 1995; 10: 1177-1184.

30. Reid IR, Horne AM, Mihov B, Gamble GD, Al-Abuwsi F, Singh M, et al. Effect of monthly high-dose vitamin D on bone density in community-dwelling older adults substudy of a randomized controlled trial. J Intern Med. 2017; 282: 452-460.

31. Lips P. Vitamin D physiology. Prog Biophys Mol Biol. 2006; 92: 4-8.

32. Brănişteanu DD, Bottermann P, Zbranca E, Mogoş V. Sunlight exposure and vitamin D supplementation at the institutionalized elderly - effects on calcium and bone metabolism. Acta Endocrinologica (Buc). 2007; III: 169-178.

33. Van Etten E, Verlinden L, Giulietti A, Ramos Lopez E, Brănişteanu DD, Bomfim Ferreira G, et al. The vitamin D receptor gene FokI polymorphism: functional impact on the immune system. Eur J Immunol 2007; 37: 395-405.

34. Atef SH. Vitamin D assays in clinical laboratory: Past, present and future challenges. J Steroid Biochem Mol Biol. 2018; 175: 136-137.

35. Herrmann M, Farrell CL, Pusceddu I, Fabregat-Cabello N, Cavalier E. Assessment of vitamin D status - a changing landscape. Clin Chem Lab Med. 2017; 55: 3-26.

36. LeBlanc ES, Zakher B, Daeges M, Pappas M, Chou R. Screening for vitamin D deficiency: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2015; 162: 109-122.

37. Carpenter TO, Shaw NJ, Portale AA, Ward LM, Abrams SA, Pettifor JM. Rickets. Nat Rev Dis Primers. 2017; 3: 17101.

38. Bouillon R, Van Schoor NM, Gielen E, Boonen S, Mathieu C, Vanderschueren D, et al. Optimal vitamin D status: a critical analysis on the basis of evidence-based medicine. J Clin Endocrinol Metab. 2013; 98: E1283-1304.

39. Manson JE, Brannon PM, Rosen CJ, Taylor CL. Vitamin D Deficiency - Is There Really a Pandemic? N Engl J Med. 2016; 375: 1817-1820.

40. Wacker M, Holick MF. Sunlight and Vitamin D: A global perspective for health. Dermatoendocrinol. 2013; 5: 51-108.

41. Hess AF, Unger IJ. Prophylactic therapy for rickets in a Negro community. JAMA. 1917; 69: 1583.

42. Shaw NJ. Prevention and treatment of nutritional rickets. J Steroid Biochem Mol Biol. 2016; 164: 145-147.

43. Zhao JG, Zeng XT, Wang J, Liu L. Association Between Calcium or Vitamin D Supplementation and Fracture Incidence in Community-Dwelling Older Adults: A Systematic Review and Meta-analysis. JAMA. 2017; 318: 2466-2482.

44. Cashman KD, Ritz C, Kiely M, Odin Collaborators. Improved Dietary Guidelines for Vitamin D: Application of Individual Participant Data (IPD)-Level Meta-Regression Analyses. Nutrients. 2017; 9.

45. 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: 1911-1930.

46. Dawson-Hughes B, Mithal A, Bonjour JP, Boonen S, Burckhardt P, Fuleihan GE, et al. IOF position statement: vitamin D recommendations for older adults. Osteoporos Int. 2010; 21: 1151-1154.

47. Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, Staehelin HB, Meyer OW, Theiler R, et al. Monthly High-Dose Vitamin D Treatment for the Prevention of Functional Decline: A Randomized Clinical Trial. JAMA Intern Med. 2016; 176: 175-183.

48. Sanders KM, Seibel MJ. Therapy: New findings on vitamin D3 supplementation and falls - when more is perhaps not better. Nat Rev Endocrinol. 2016; 12: 190-191.

49. Brandi ML. Indications on the use of vitamin D and vitamin D metabolites in clinical phenotypes. Clin Cases Miner Bone Metab. 2010; 7: 243-250.

50. Wani M, Wani I, Banday K, Ashraf M. The other side of vitamin D therapy: a case series of acute kidney injury due to malpractice-related vitamin D intoxication. Clin Nephrol. 2016; 86: 236-241.

51. Galior K, Grebe S, Singh R. Development of Vitamin D Toxicity from Overcorrection of Vitamin D Deficiency: A Review of Case Reports. Nutrients. 2018; 10. pii: E953.

52. McNally JD, Iliriani K, Pojsupap S, Sampson M, O'Hearn K, McIntyre L, et al. Rapid normalization of vitamin D levels: a meta-analysis. Pediatrics. 2015; 135: e152-166.

53. EFSA NDA Panel (EFSA Panel of Dietetic Products NaA). Scientific opinion on dietary reference values for vitamin D. EFSA J. 2016; 179.

54. Bouillon R, Rosen C. The IOM - endocrine society controversy on recommended vitamin D targets: in support of the IOM position. Feldman D, Pike JW, Bouillon R, editors. In: Vitamin D. 4th edition. London: Elsevier. 2018; 1065-1089.