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Review

Vitamin D Deficiency and Toxicity

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Abstract

In this review, it is aimed to investigate the risk of Vitamin D deficiency, diseases caused by the deficiency of Vitamin D in addition to classical effects and toxicity risks due to excessive Vitamin D intake. As is known, Vitamin D is becoming more and more understandable every day, and new studies are needed. However, as a result of the literature reviews done in this study, it was investigated the cause-and-effect relationship of toxicities risks, diseases determined due to Vitamin D insufficiency or Vitamin D deficiency, determination of treatment doses, and health policy applied to prevent Vitamin D insufficiency and toxicity, it is seen that it is important to use standard methods enriched with controlled studies.

Keywords: Chronic diseases, Vitamin D deficiency, Vitamin D toxicity, Vitamin D

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Vitamin D deficiency, especially seen in Western populations, can lead to serious health problems. Vitamin D is a group of steroids that are hormones and hormone precursors because they can be synthesized in the appropriate biological conditions which is one of the vitamins that are soluble in fat.[1–3] The main task of Vitamin D is to provide the mineral balance in our bodies. It regulates the metabolism and absorption of minerals and determines serum calcium and phosphorus levels. The target organs that vitamin D affects are the kidneys, small intestines, and bone. In these organs, the effect is caused by the active form of calcitriol. Vitamin D deficiency causes rickets disease in children and osteoporosis in adults.[4, 5]

Vitamin D Resources and Metabolism

Vitamin D has two sources, cholecalciferol (Vitamin D_3) and ergocalciferol (Vitamin D_2). Cholecalciferol is derived from 7-dehydrocholesterol by the action of sun (UV) rays and is the main source of Vitamin D.[6–8] Ergocalciferol, which we call Vitamin D_2, is derived from foods. Since they have similar metabolisms, they are both called D vitamins.[6, 9]

Dietary uptake of vitamin D_2 is limited. Vitamin D in foods is mostly found in fatty fish species such as salmon (salmon fish), mackerel, tuna fish, sardine and also in nutrients such as egg yolk, milk, broccoli, green onion, parsley water terrace. But no food contains vitamin D until it supplies the daily vitamin D requirement. In the breast milk there is vitamin D of 10-60 IU/L.[10–12] In America and some European countries, milk, yogurt, orange juice, and cereals are enriched with Vitamin D.[13, 14] Dietary or endogenously synthesized Vitamin D_2 or D_3 is stored in fat cells and circulated if necessary.[10, 15]

Vitamin D is converted to 25-hydroxyvitamin D_2 (25(OH) D) by the 25-hydroxylase enzyme in the liver. Parathyroid hormone is involved in the mechanism of the conversion of 25 (OH) D to 1.25(OH)2D. In the absence of this hormone, 1.25(OH)2D cannot occur.[8, 16]

Vitamin D is an important vitamin and its deficiency in our lives in terms of our health cause many health problems.

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Recenntly scientific researches show that vitamin D has different effects besides the known classical effects. The active form of Vitamin D, the cholecalciferol (Vitamin D_3) receptor, has been found in many tissues and cells of the human body. Many important diseases such as cancer, autoimmune diseases, and diabetes mellitus (DM) have been suggested to be related to Vitamin D.[10]

Inadequate sunlight intake, such as long-term stay in indoor environments such as home and office, clothing style, use of sun protection creams with high protection factor, and seasonal changes cause Vitamin D insufficiency to occurs more frequently.[17] Studies conducted in different countries show that Vitamin D deficiency is a worldwide problem and this is a major health problem.[18, 19] Mortality due to fragile fractures due to insufficient 25(OH)D, especially hip fracture, is common.[20, 21]

Vitamin D is derived skin and diet and is carried through the circulation of Vitamin D by binding to the vitamin D binding protein (DVBP). It is converted to 25(OH)D) by 25-hydroxylase enzyme in the liver.[22, 23] Vitamin D deficiency occurs when 25 (OH) D level is <20 ng/mL and vitamin D is 25 (OH) D level >30 ng/mL. 25(OH)D levelvitamin D intoxication occurs when 25 (OH) D level >150mL.[24] Active Vitamin D plays a role in the maintenance of normal bone mineral balance and insulin secretion and, at the same time, inhibits parathyroid hormone (PTH) synthesis and secretion, leading to the proliferation of parathyroid glands. [23, 25] Vitamin D deficiency, impaired calcium balance and secondary hyperparathyroidism.[26]

Cardiovascular diseases are one of the most important causes of death in patients with end-stage renal disease (ESRD). Vitamin D deficiency is an independent factor for the development of ESRD. In hemodialysis patients, it has been shown that there is an association between insufficient Vitamin D status and endothelial dysfunction.[27]

Vitamin D is suggested to be a potential regulator in the prevention of diabetes.[28, 29] Although Vitamin D is shown to be effective in the prevention of type 1 DM, the mechanism is not fully explained. The hypotheses put forward in this regard are that active Vitamin D improves beta-cell function, increases insulin sensitivity in target cells, and protects beta-cells from harmful immunological damage. It is thought that Vitamin D has a direct or indirect protective effect on the immune response.[30] As is known, type 2 DM develops in the form of complete insulin deficiency due to damage of pancreatic beta cells. Unlike type 1 DM, the function of pancreatic beta-cells is impaired, insulin resistance and inflammation are common.[31] Vitamin D is associated with type 1 DM, as is the effect on type 2 DM.

Some studies show that there is a relationship between Vitamin D and obesity, but it is being debated whether if vitamin deficiencies are caused by obesity or obesity causes Vitamin D deficiency. The causes of Vitamin D deficiency in obese patients have been investigated and realized that they have been avoiding open-air activities due to limited mobility and socialization. They have been feeding with missing foods due to Vitamin D, having more closed clothing choices than weaker ones, lack of basic dietary habits, (OH)$2D_3$ levels increased due to increased PTH level, suppression of 25(OH)D_3 synthesis in the liver, and increased levels of PTH in the body, resulting in decreased bioavailability due to adherence to adipose tissue, reduction of liver synthesisic 25(OH) D_3 synthesis due to hepatic steatoz as been reported as the major factors.[32–34] Prospective studies investigating the relationship between Vitamin D and obesity and determination of the relationship by reference methods is required.

It has also been reported in a study that there is a negative correlation between antenatal Vitamin D supplementation and bilirubin levels in newborns during pregnancy.[35] As the need for Vitamin D increases during pregnancy, the risk of Vitamin D deficiency in pregnancies is also increasing. D vitamins can pass placentally through the mother to the fetus.[36, 37] In the absence of Vitamin D, both mother and fetus can be affected. These effects include low birth weight infant, growth retardation, retardation (congenital rickets, craniotabes, wide fontanelle, decrease in bone mineral density, and ossification), neonatal hypocalcemic seizure, enamel hypoplasia in the teeth, and calcium balance disorders in the development of bone tissue.[38, 39] The lack of vitamin D deficiency during pregnancy increases the risk for infants fed breastfeeding.[40–44] The World Health Organization states that in pre-pregnancy, pregnancy, and lactation periods, women are exposed to iron, zinc, folic acid, iodine, and Vitamin A supplementation, and it is emphasized that the evaluation of pregnancies with respect to Vitamins D in terms of maternal and infant health is important in the tests performed.[45]

Clinical data show that Vitamin D is associated with neuronal differentiation, axonal attachment, dopaminotagenosis, brain structure, and function. The lack of Vitamin D in fetal life and childhood is associated with autistic spectrum disorder and schizophrenia also stresses the importance of Vitamin D deficiency.[46] However, there is a need to study more so that these mechanisms can be fully explained.[47]

Recent epidemiological studies have reported that some psychiatric disorders (such as depression and Alzheimer's) that are not associated with brain anomalies are associated with Vitamin D levels. Detection and treatment of Vitamin D deficiency with tests to be performed in depression

and other mental disorders increase the quality of life of patients as well as being a cheap, easy, and effective treatment for patients.[47]

Vitamin D Toxicity

Vitamin D deficiency can lead to many health problems, and excessive intake also causes toxicity. Vitamin D deficiency treatment is performed in two phases. In the first stage, the acute deficiency is treated in the patient, and the second phase is the filling of the body reserves. The upper limit for children younger than 1 year has been reported to be 1000 IU/day for long-term Vitamin D therapy, and 2000 IU/day for children over 1 year.[48–50] Pediatric toxic threshold doses are not clearly defined and serum 25(OH) D concentration is up to 140 ng/it is considered harmful if it is low. Depending on the variations in the calcic response to Vitamin D in the treatments administered, there may be individual responses at specific doses. Failure to determine appropriate doses in long-term treatments, age inappropriate doses, and variable response to contraindication may result in toxicity.[51, 52]

Elevated levels of Vitamin D emphasize hypercalcemic response. In vivo studies suggest that 25(OH)D is responsible for 1.25(OH)2D rather than toxic by binding competitively to Vitamin D receptors.[53]

Vitamin D increases calcium absorption from the gastrointestinal tract. Vitamin intoxication is secondary to high doses of Vitamin D intake. Reported toxicity is associated with overdosage of prescribed Vitamin D in cases of exposure, or consumption of over-the-counter supplements containing Vitamin D.[54, 55] In our country, an excess of Vitamin D is generally reported to be associated with unnecessary or inappropriate doses of Vitamin D and long-term outpatient prescribing.

Vitamin D toxicity may indicate symptoms such as hypercalcemia, hypercalciuria, renal calculus, hyperphosphatemia, polyuria, polydipsia, ectopic calcification of soft tissues (kidney and lung), nausea, and vomiting.[56, 57] Loss of appetite, vomiting, constipation, growth retardation, polyuria, dehydration and the indication of vitamin D poisoning such as fever develops as hypercarbia secondary. Vitamin D is characterized by hypercalciuria and hypocalcemia-associated nephrocalcinosis and 25(OH)D vitamin (>150 ng/mL) parathyroid hormone suppression.[58]

In the treatment of Vitamin D poisoning, external Vitamin D intake is discontinued and intravenous fluid therapy, loop diuretics, glucocorticoids, and calcium-restricted diet are administered. In addition to treatment, calcitonin and bisphosphonates (pamidronate) are used in severe cases.

In the United States, it has been reported that Vitamin D supplementation in foods and beverages from 1930 to 1950 led to Vitamin D toxicity.[59]

In Turkey since 2005, according to the recommendations of the Ministry of Health, free Vitamin D supplements (400 IU/day) are regularly given to infants to reduce the prevalence of nutritional risk.[60]

Conclusion

The figures for Vitamin D used in food supplements may be misleading and should not be used unless credibility is proved. Again multivitamins should not be preferred for Vitamin D treatment. It has been reported that unnecessary treated patients should be evaluated for signs of hypervitaminosis. The use of Vitamin D in the form of prescription and unconsciousness can cause health problems. Vitamin D levels should be controlled at regular intervals and the deficiency or excess of Vitamin D to be detected by standard tests should be resolved by appropriate treatments. Clinical trials evaluating the metabolism of Vitamin D and its relationship to chronic diseases are needed.

Disclosures

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References

1. Champe PC, Harvey RA, Ferrier DR. Vitamins Biochemistry. 3rd ed. New York: Lippincott Williams and Wilkins; 2005. p. 371–93.
2. Bringhurst FR, Demay MB, Krane SM, Kronenberg HM. Disorders of bone and mineral metabolism. In: Harrison's Principles of İnternal Medicine. New York: McGraw-Hill; 2002.
3. Fidan F, Alkan BM, Tosun A. Çağın pandemisi: D Vitamini eksikliği ve yetersizliği. Türk Osteoporoz Derg 2014;20:71–4.
4. Wranicz J, Szostak-Węgierek D. Health outcomes of Vitamin D. Part I. Characteristics and classic role. Rocz Panstw Zakl Hig 2014;65:179–84.
5. Genç A, Sevim D, G Özen AT, Yılmaz GD. D Vitamininin Çeşitli hastalıklardaki nadir kullanım alanları. Ankara Üniv Fak Mecm 2015;68. DOI: 10.1501/Tıpfak_000000890.
6. Guyton AC, Hall JE. Bölüm 79: Paratiroid hormonu, kalsitonin, kalsiyum ve fosfat mekanizması, D Vitamini, kemik ve dişler. In: Çavuşoğlu H, Yeğen BC, editors. Tıbbi Fizyoloji. Vol. 11. İstanbul: Nobel Tıp Kitabevleri; 2007. p. 978–94.
7. Vitamin D and Cancer Prevention: Strengths and Limits of the Evidence. National Cancer Institute. Available at: http://www.cancer.gov/cancertopics/factsheet/prevention/vitamin-D. Accessed Dec 24, 2018.
8. Açıkgöz A, Günay T, Uçku R. Gebelikte D Vitamini gereksinimi ve desteklenmesi. TAF Prev Med Bull 2013;12:595–608.
9. O'Riordan JL, Bijvoet OL. Rickets before the discovery of Vita-

min D. Bonekey Rep 2014;3:478. [CrossRef]
10. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266–81.
11. Henderson A. Vitamin D and the breastfed infant. J Obstet G necol Neonatal Nurs 2005;34:367–72. [CrossRef]
12. Ataş A, Çakmak A, Soran M. D Vitamin metabolizması ve rikets hastalığı. Bakırköy Tıp Derg 2008;4:1–7.
13. Baysal AA. Beslenme. Vol. 14. Ankara: Hatipoğlu Yayınları; 2012. p. 176–83.
14. Ersoy N, Ersoy G. D Vitamini yetersizliği ve depresyon: Ne yapabiliriz. Hacettepe Üniv Sağlık Bilimler Fakültesi Derg 2017;4:1–14.
15. Özçelik DC, Koçer H, Kasım İ, Şencan İ, Kahveci R, Özkara A. D Vitamini. Turk Med J 2012;6.
16. World Health Organization. Food and Agriculture Organization. Guidelines on Food Fortification with Micronutrients. Geneva: World Health Organization; 2006.
17. Öğüş E, Sürer H, Kılınç A, Fidancı V, Yılmaz G, Dindar N, et al. D Vitamini düzeylerinin aylara, cinsiyete ve yaşa göre değerlendirilmesi. Ankara Med J 2014;15:1–5.
18. Mithal A, Wahl DA, Bonjour JP, Burckhardt P, Dawson-Hughes B, Eisman JA, et al. Global Vitamin D status and determinants of hypovitaminosis D. Osteoporos Int 2009;20:1807–20. [CrossRef]
19. Kurt M, Cmertoğlu İ, Yalın P, Diner G. Osteoporozlu hastalarda D Vitamini dzeyleri. Turk J Osteoporos 2011;17:68–70.
20. Gallagher JC, Sai AJ. Vitamin D insufficiency, deficiency, and bone health. J Clin Endocrinol Metab 2010;95:2630–3. [CrossRef]
21. Kuroda T, Shiraki M, Tanaka S, Ohta H. Contributions of 25-hydroxy Vitamin D, co-morbidities and bone mass to mortality in Japanese postmenopausal women. Bone 2009;44:168–72.
22. Sözen T. D hormon: Güncel gelişmeler. Hacettepe Tıp Derg 2011;42:14–27.
23. Kıdır V. D Vitamininin kardiyovasküler ve metabolik etkileri. J Clin Exp Investig 2013;4:398–404. [CrossRef]
24. Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R, et al. Estimates of optimal Vitamin D status. Osteoporos Int 2005;16:713–6. [CrossRef]
25. Bikle D. Nonclassic actions of Vitamin D. J Clin Endocrinol Metab 2009;94:26–34. [CrossRef]
26. London GM, Guérin AP, Verbeke FH, Pannier B, Boutouyrie P, Marchais SJ, et al. Mineral metabolism and arterial functions in end-stage renal disease: Potential role of 25-hydroxy Vitamin D deficiency. J Am Soc Nephrol 2007;18:613–20. [CrossRef]
27. Pilz S, Tomaschitz A, Drechsler C, de Boer RA. Vitamin D deficiencyand heart disease. Kidney Int Suppl 2011;1:111–5.
28. Danescu LG, Levy S, Levy J. Vitamin D and diabetes mellitus. Endocrine 2009;35:11–7. [CrossRef]
29. Bolluk S, Akbulut G. D Vitamini ve diabetes mellitus. Turk Klin J Endocrinol 2013;8:65–72.
30. Takiishi T, Gysemans C, Bouillon R, Mathieu C. Vitamin D and diabetes. Rheum Dis Clin 2012;38:179–206. [CrossRef]
31. Chagas CE, Borges MC, Martini LA, Rogero MM. Focus on Vitamin D, inflammation and Type 2 diabetes. Nutrients 2012;4:52–67. [CrossRef]
32. Targher G, Bertolini L, Scala L, Cigolini M, Zenari L, Falezza G, et al. Associations between serum 25-hydroxyvitamin D3 concentrations and liver histology in patients with non-alcoholic fatty liver disease. Nutr Metab Cardiovasc Dis 2007;17:517–24.
33. Daniel D, Hardigan P, Bray N, Penzell D, Savu C. The incidence of Vitamin D deficiency in the obese: A retrospective chart review. J Community Hosp Intern Med Perspect 2015;5:26069.
34. Çimen MB, Çimen ÖB. Obezite ve D Vitamini. Mersin Üniv Sağlık Bilimleri Derg 2016;9:102–12.
35. Akbulut H. D Vitamininin Yenidoğan Hiperbilirubinemisi Üzerine Etkisi (Doctoral Dissertation. Konya: Selçuk Üniversitesi Tıp Fakültesi; 2016.
36. Pettifor JM. Nutritional rickets: Deficiency of Vitamin D, calcium, or both? Am J Clin Nutr 2004;80:1725S–9S. [CrossRef]
37. Finer S, Khan KS, Hitman GA, Griffiths C, Martineau A, Meads C. Inadequate Vitamin D status in pregnancy: Evidence for supplementation. Acta Obstet Gynecol Scand 2012;91:159–63.
38. Pérez-López FR. Low maternal vitamin D status during pregnancy requires appropriate therapeutic intervention. Int J Gynaecol Obstet 2012;116:4–5. [CrossRef]
39. Inuit FN. Métis health committee canadian paediatric society (CPS), Vitamin D supplementation: Recommendations for Canadian mothers and infants. Paediatr Child Health 2007;12:583–9. [CrossRef]
40. Prentice A. Micronutrients and the bone mineral content of the mother, fetus and newborn. J Nutr 2003;133:1693S-1699S.
41. Hatun Ş, Bereket A, Çalıkoğlu AS, Özkan B. Günümüzde D Vitamini yetersizliği ve nütrisyonel rikets. Çocuk Sağlığı ve Hastalık Derg 2003;46:224–41.
42. Erol M, İşman F, Kucur M, Hacıbekiroğlu M. Annede D Vitamini eksikliğinin değerlendirilmesi Orijinal Araştırma. Türk Pediatri Arşivi 2007;42:1–9.
43. Pehlivan İ, Hatun Ş, Aydoğan M, Babaoğlu K, Türker G, Gökalp AS. Maternal serum Vitamin D levels in the third trimester of pregnancy. Turk J Med Sci 2002;32:237–41.
44. Daaboul J, Sanderson S, Kristensen K, Kitson H. Vitamin D deficiency in pregnant and breast-feeding women and their infants. J Perinatol 1997;17:10–4.
45. World Health Organization. Making Pregnancy Safer. WHO Technical Consultation on the Prevention and Management of Pre-Eclampsia/Eclampsia and Calcium and Vitamin D Supplementation for Women during Pregnancy; 2011. Available at: http://www.who.int/nutrition/events/2011_consultation_prevention_preandeclampsia_Ca_VAD_pregn ancy/en. Accessed Aug 9, 2012.
46. Eyles DW, Burne TH, McGrath JJ. Vitamin D, effects on brain development, adult brain function and the links between low levels of Vitamin D and neuropsychiatric disease. Front Neuroendocrinol 2013;34:47–64. [CrossRef]

47. Humble MB. Vitamin D, light and mental health. J Photochem Photobiol B 2010;101:142–9. [CrossRef]
48. Wagner CL, Greer FR, American Academy of Pediatrics Section on Breastfeeding, American Academy of Pediatrics Committee on Nutrition. Prevention of rickets and Vitamin D deficiency in infants, children, and adolescents. Pediatrics 2008;122:1142–52.
49. Greenbaum LA. In: Nelson Textbook of Pediatrics. Kliegman RM, Stanton BF, Geme JW, Schor NF, Behrman RE, editors. Philadelphia, PA: Elsevier Saunders; 2011. p. 208–9.
50. Nimesh M, Singh P, Jhamb U, Dubey A P. An unsuspected pharmacological Vitamin D toxicity in a child and its brief review of literature. Toxicol İnt 2015;22:167. [CrossRef]
51. Araki T, Holick MF, Alfonso BD, Charlap E, Romero CM, Rizk D, et al. Vitamin D intoxication with severe hypercalcemia due to manufacturing and labeling errors of two dietary supplements made in the United States. J Clin Endocrinol Metab 2011;96:3603–8. [CrossRef]
52. Adams JS, Lee G. Gains in bone mineral density with resolution of Vitamin D intoxication. Ann Intern Med 1997;127:203–6.
53. Deluca HF, Prahl JM, Plum LA 1,25-dihydroxy Vitamin D is not responsible for toxicity caused by Vitamin D or 25-hydroxy Vitamin D. Arch Biochem Biophys 2011;505:226–30. [CrossRef]
54. Sezer RG, Guran T, Paketçi C, Seren LP, Bozaykut A, Bereket A, et al. Comparison of oral alendronate versus prednisolone in treatment of infants with Vitamin D intoxication. Acta Paediatr 2012;101:e122–5. [CrossRef]
55. Anık A, Çatlı G, Abacı A, Dizdarer C, Böber E. Acute Vitamin D intoxication possibly due to faulty production of a multivitamin preparation. J Clin Res Pediatr Endocrinol 2013;5:136–9.
56. Bonillon R. Vitamin D: From photosynthesis, metabolism, and action to clinical application. In: Endocrinology. 6th ed. 2010. p1089–110.
57. Maji D. Vitamin D toxicity. Indian J Endocrinol Metab 2012;16:295–6. [CrossRef]
58. Whayne TF Jr. Vitamin D: Popular cardiovascular supplement but benefit must be evaluated. Int J Angiol 2011;20:63–72.
59. Alshahrani F, Aljohani N. Vitamin D: Deficiency, sufficiency and toxicity. Nutrients 2013;5:3605–16. [CrossRef]
60. Hatun Ş, Ozkan B, Bereket A. Vitamin D deficiency and prevention: Turkish experience. Acta Paediatr 2011;100:1195–9. [CrossRef]