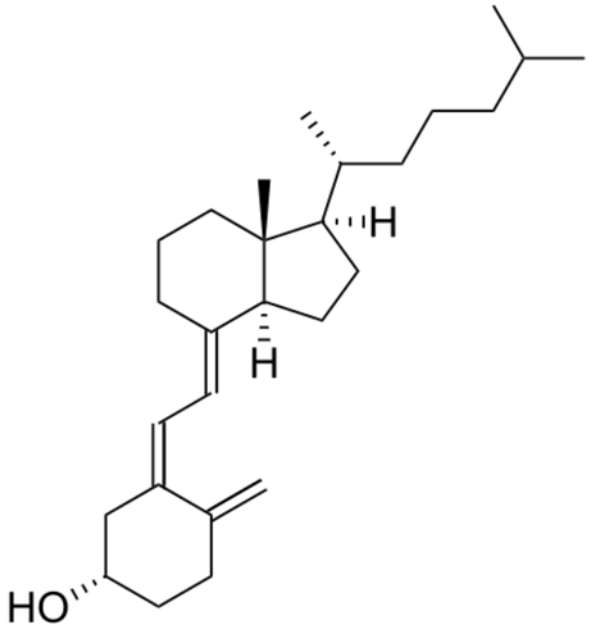
Hypervitaminosis D

From Wikipedia, the free encyclopedia

Hypervitaminosis D is a state of vitamin D toxicity. The normal range for blood concentration is 30.0 to 74.0 nanograms per milliliter (ng/mL).[1]

Contents

Hypervitaminosis D



Cholecalciferol (shown above) and ergocalciferol are the two major forms of Vitamin D.

Classification and external resources

Specialty	endocrinology
ICD-10	E67.3 (http://apps.who.int/classifications/icd10/browse/2016/en#/E67.3)
ICD-9-CM	278.4 (http://www.icd9data.com/getICD9Code.ashx?icd9=278.4)
DiseasesDB	13939 (http://www.diseasesdatabase.com/ddb13939.htm)
MedlinePlus	001594 (https://medlineplus.gov/ency/article/001594.htm)

Signs and symptoms

Symptoms of vitamin D toxicity may include the following:

- Dehydration
- Vomiting
- Decreased appetite
- Irritability
- Constipation
- Fatigue
- Muscle weakness
- Metastatic calcification of the soft tissues[2]

An excess of vitamin D causes abnormally high blood concentrations of calcium, which can cause overcalcification of the bones, soft tissues, heart and kidneys. In addition, hypertension can result.[3]

Hypervitaminosis D symptoms appear several months after excessive doses of vitamin D are administered. In almost every case, a low-calcium diet combined with corticosteroid drugs will allow for a full recovery within a month. Vitamin D toxicity is closely related to a depletion of Vitamin K[4] and that repletion of Vitamin K allows individuals to supplement with higher doses of Vitamin D without the negative calcium-related side effects.

Recommended supplement limits

The U.S Institute of Medicine has established a Tolerable Upper Intake Level (UIL) to protect against vitamin D toxicity. These levels in microgram (mcg or µg) and International Units (IU) for male and female are: (Conversion : 1 µg = 40 IU and 0.025 µg = 1 IU.[5])

- 0–6 months: 25 µg (1000 IU)
- 7–12 months: 38 µg (1500 IU)
- 1–3 years: 63 µg (2500 IU)
- 4–8 years:75 µg (3000 IU)
- 9+ years:100 µg (4000 IU)
- Pregnant and Lactating: 100 µg (4000 IU)

The recommended daily allowance is 15 µg/d (600 IU per day). Overdose has been observed at 1,925 µg/d (77,000 IU per day). Acute overdose requires between 15,000 µg/d (600,000 IU per day) and 42,000 µg/d (1,680,000 IU per day) over a period of several days to months, with a safe intake level being 250 µg/d (10,000 IU per day).[6] Foods contain low levels, and have not been known to cause overdose.

Suggested tolerable upper intake level (UL)

Based on risk assessment, a safe upper intake level of 250 µg (10,000 IU) per day in healthy adult has been suggested.[6][7]

Long-term effects of supplementary oral intake

Excessive exposure to sunlight poses no risk in vitamin D toxicity through overproduction of vitamin D precursor, cholecalciferol, regulating vitamin D production. During ultraviolet exposure, the concentration of vitamin D precursors produced in the skin reach an equilibrium, and any further vitamin D that is produced is degraded.[8] This process is less efficient with increased melanin pigmentation in the skin. Endogenous production with full body exposure to sunlight is comparable to taking an oral dose between 250 µg and 625 µg (10,000 IU and 25,000 IU) per day.[8]

Vitamin D oral supplementation and skin synthesis have a different effect on the transport form of vitamin D, plasma calcifediol concentrations. Endogenously synthesized vitamin D_3 travels mainly with vitamin D-binding protein, which slows hepatic delivery of vitamin D and the availability in the plasma.[9]

Orally administered vitamin D produces rapid hepatic delivery of vitamin D and increases plasma calcifediol.[9] One of the richest food sources of vitamin D — wild salmon — would require 35 ounces (1 kg) to provide 10,000 IU.[10] It has been argued that ingestion of vitamin D in large amounts was achieved in the process of grooming by furry human ancestors and that from UV-exposed human skin secretions early humans ingested vitamin D by licking the skin; however, this putative ingestion of vitamin D by early humans is not quantified.[11] A study found 34% of its sample of healthy western Canadians to be under 40nmol/L at some point and 97% to be under 80nmol/L at least once.[12]

It has been questioned whether to ascribe a state of sub-optimal vitamin D status when the annual variation in ultraviolet will naturally produce a period of falling levels, and such a seasonal decline has been a part of Europeans' adaptive environment for 1000 generations.[13][14] Still more contentious is recommending

supplementation when those supposedly in need of it are labeled healthy and serious doubts exist as to the long-term effect of attaining and maintaining serum 25(OH)D of at least 80nmol/L by supplementation.[15]

Current theories of the mechanism behind vitamin D toxicity propose that:

- Intake of vitamin D raises calcitriol concentrations in the plasma and cell
- Intake of vitamin D raises plasma calcifediol concentrations which exceed the binding capacity of the DBP, and free calcifediol enters the cell
- Intake of vitamin D raises the concentration of vitamin D metabolites which exceed DBP binding capacity and free calcitriol enters the cell

All of which affect gene transcription and overwhelm the vitamin D signal transduction process, leading to vitamin D toxicity.[16]

Cardiovascular disease

Evidence suggests that dietary vitamin D may be carried by lipoprotein particles into cells of the artery wall and atherosclerotic plaque, where it may be converted to active form by monocyte-macrophages.[9][17][18] This raises questions regarding the effects of vitamin D intake on atherosclerotic calcification and cardiovascular risk as it may be causing vascular calcification.[19] Calcifediol is implicated in the etiology of atherosclerosis, especially in non-Caucasians.[20][21][22]

The levels of the active form of vitamin D, calcitriol, are inversely correlated with coronary calcification[23] Moreover, the active vitamin D analog, alfacalcidol, seems to protect patients from developing vascular calcification.[24][25] Serum vitamin D has been found to correlate with calcified atherosclerotic plaque in African Americans as they have higher active serum vitamin D levels compared to Euro-Americans.[22][26] [27][28] Higher levels of calcidiol positively correlate with aorta and carotid calcified atherosclerotic plaque in African Americans but not with coronary plaque, whereas individuals of European descent have an opposite, negative association.[22] There are racial differences in the association of coronary calcified plaque in that there is less calcified atherosclerotic plaque in the coronary arteries of African-Americans than in whites.[29]

A case control study on a population in southern India found that more than 50% of patients with ischaemic heart disease had serum levels of vitamin D higher than 222.5 nmol/L, but the study did not evaluate causation.[21]

Among descent groups with heavy sun exposure during their evolution, taking supplemental vitamin D to attain the 25(OH)D level associated with optimal health in studies done with mainly European populations may have deleterious outcomes.[15] Despite abundant sunshine in India, vitamin D status in Indians are low and suggests a public health need to fortify Indian foods with vitamin D. However, the levels found in India are consistent with many other studies of tropical populations which have found that even an extreme amount of sun exposure, does not raise 25(OH)D levels to the levels typically found in Europeans.[30][31][32][33]

Recommendations stemming for a single standard for optimal serum 25(OH)D concentrations ignores the differing genetically mediated determinates of serum 25(OH)D and may result in ethnic minorities in Western countries having the results of studies done with subjects not representative of ethnic diversity applied to them. Vitamin D levels vary for genetically mediated reasons as well as environmental ones.[34][35][36][37]

Ethnic differences

Possible ethnic differences in physiological pathways for ingested vitamin D, such as the Inuit, may confound across the board recommendations for vitamin D levels. Inuit compensate for lower production of vitamin D by converting more of this vitamin to its most active form.[38] The Inuit have relatively high rates of esophageal cancer and there are ethnic differences in the metabolism of vitamin D between Caucasians and Inuit.[38][39]

A Toronto study of young Canadians of diverse ancestry applied a standard of serum 25(OH)D levels that was significantly higher than official recommendations.[40][41] These levels were described to be 75 nmol/L as "optimal", between 75 nmol/L and 50 nmol/L as "insufficient" and < 50 nmol/L as "deficient". 22% of individuals of European ancestry had 25(OH)D levels less than the 40 nmol/L cutoff, comparable to the values observed in previous studies (40nmol/L is 15 ng/mL). 78% of individuals of East Asian ancestry and 77% of individuals of South Asian ancestry had 25(OH)D concentrations lower than 40 nmol/L. The East Asians in the Toronto sample had low 25(OH)D levels when compared to whites. Vitamin D deficiency is highly prevalent in China and occurred in more than 40% of adolescent girls in winter.[31] In a Chinese population at particular risk for esophageal cancer and with the high serum 25(OH)D concentrations have a significantly increased risk of the precursor lesion.[12]

Studies on the South Asians population uniformly point to low 25(OH)D levels, despite abundant sunshine.[42] Rural men around Delhi average 44nmol/L. Healthy Indians seem have low 25(OH)D levels which are not very different from healthy South Asians living in Canada. South Indian patients with ischemic heart disease have serum 25-hydroxyvitamin D_3 levels which are above 222.5 nmol/l and considered extremely high.[21] Measuring melanin content to assess skin pigmentation showed an inverse relationship with serum 25(OH)D.[40] The uniform occurrence of very low serum 25(OH)D in Indians living in India and Chinese in China does not support the hypothesis that the low levels seen in the more pigmented are due to lack of synthesis from the sun at higher latitudes. A study of French Canadians found that a significant minority did not maximize ingested serum 25(OH)D for genetic reasons; vitamin D-binding protein polymorphisms explained as much of the variation in circulating 25(OH)D as did total ingestion of vitamin D.[43][44] Oral vitamin D intake is lower in Europe than both North America and Scandinavia.[9][45]

Premature aging

Complex regulatory mechanisms control metabolism. Recent epidemiologic evidence suggests that there is a narrow range of vitamin D levels in which vascular function is optimized. Levels above or below this natural homeostasis of vitamin D increase mortality.[17] Overall, excess or deficiency in the calcipherol system appear to cause abnormal functioning and premature aging.[46][47][48]

See also

- Hypervitaminosis

References

1. MedlinePlus Encyclopedia *25-hydroxy vitamin D test (https://medlineplus.gov/ency/article/003569.htm)*
2. Black AS, Kanat IO (1985). "A review of soft tissue calcifications". *The Journal of Foot Surgery*. **24** (4): 243–50. PMID 4045112.
3. Dionne JM, Abitbol CL, Flynn JT (January 2012). "Hypertension in infancy: diagnosis, management and outcome". *Pediatric Nephrology*. **27** (1): 17–32. doi:10.1007/s00467-010-1755-z. PMID 21258818.

4. Masterjohn C (2007). "Vitamin D toxicity redefined: vitamin K and the molecular mechanism". *Medical Hypotheses*. **68** (5): 1026–34. doi:10.1016/j.mehy.2006.09.051. PMID 17145139.
5. "Dietary Reference Intakes Tables [Health Canada, 2005]". Retrieved 21 July 2011.
6. Hathcock JN, Shao A, Vieth R, Heaney R (January 2007). "Risk assessment for vitamin D". *The American Journal of Clinical Nutrition*. **85** (1): 6–18. PMID 17209171.
7. Vieth R (December 2007). "Vitamin D toxicity, policy, and science". *Journal of Bone and Mineral Research*. 22 Suppl 2: V64–8. doi:10.1359/jbmr.07s221. PMID 18290725.
8. Holick MF (March 1995). "Environmental factors that influence the cutaneous production of vitamin D". *The American Journal of Clinical Nutrition*. **61** (3 Suppl): 638S–645S. PMID 7879731.
9. Haddad JG, Matsuoka LY, Hollis BW, Hu YZ, Wortsman J (June 1993). "Human plasma transport of vitamin D after its endogenous synthesis". *The Journal of Clinical Investigation*. **91** (6): 2552–5. doi:10.1172/JCI116492. PMC 443317. PMID 8390483.
10. Lu Z, Chen TC, Zhang A, Persons KS, Kohn N, Berkowitz R, Martinello S, Holick MF (March 2007). "An evaluation of the vitamin D3 content in fish: Is the vitamin D content adequate to satisfy the dietary requirement for vitamin D?". *The Journal of Steroid Biochemistry and Molecular Biology*. **103** (3-5): 642–4. doi:10.1016/j.jsbmb.2006.12.010. PMC 2698592. PMID 17267210.
11. [Effects Of Vitamin D and the Natural selection of skin colour:how much vitamin D nutrition are we talking about http://www.direct-ms.org /pdf/VitDVieth /Vieth%20Anthropology%20vit%20D.pdf]
12. Abnet CC, Chen W, Dawsey SM, Wei WQ, Roth MJ, Liu B, Lu N, Taylor PR, Qiao YL (September 2007). "Serum 25(OH)-vitamin D concentration and risk of esophageal squamous dysplasia". *Cancer Epidemiology, Biomarkers & Prevention*. **16** (9): 1889–93. doi:10.1158/1055-9965.EPI-07-0461. PMC 2812415. PMID 17855710.
13. Kull M, Kallikorm R, Tamm A, Lember M (January 2009). "Seasonal variance of 25-(OH) vitamin D in the general population of Estonia, a Northern European country". *BMC Public Health*. **9**: 22. doi:10.1186/1471-2458-9-22. PMC 2632995. PMID 19152676.
14. Hoffecker JF (September 2009). "Out of Africa: modern human origins special feature: the spread of modern humans in Europe". *Proceedings of the National Academy of Sciences of the United States of America*. **106** (38): 16040–5. Bibcode:2009PNAS..10616040H. doi:10.1073/pnas.0903446106. JSTOR 40485016. PMC 2752585. PMID 19571003.
15. Tseng, Lisa (2003). "Controversies in Vitamin D Supplementation". *Nutrition Bytes*. **9** (1).
16. Jones G (August 2008). "Pharmacokinetics of vitamin D toxicity". *The American Journal of Clinical Nutrition*. **88** (2): 582S–586S. PMID 18689406.
17. Hsu JJ, Tintut Y, Demer LL (September 2008). "Vitamin D and osteogenic differentiation in the artery wall". *Clinical Journal of the American Society of Nephrology*. **3** (5): 1542–7. doi:10.2215/CJN.01220308. PMC 4571147. PMID 18562594.
18. Speeckaert MM, Taes YE, De Buyzere ML, Christophe AB, Kaufman JM, Delanghe JR (March 2010). "Investigation of the potential association of vitamin D binding protein with lipoproteins". *Annals of Clinical Biochemistry*. **47** (Pt 2): 143–50. doi:10.1258/acb.2009.009018. PMID 20144976.
19. Demer LL, Tintut Y (June 2008). "Vascular calcification: pathobiology of a multifaceted disease". *Circulation*. **117** (22): 2938–48. doi:10.1161/CIRCULATIONAHA.107.743161. PMC 4431628. PMID 18519861.
20. Fraser DR (April 1983). "The physiological economy of vitamin D". *Lancet*. **1** (8331): 969–72. doi:10.1016/S0140-6736(83)92090-1. PMID 6132277.
21. Rajasree S, Rajpal K, Kartha CC, Sarma PS, Kutty VR, Iyer CS, Girija G (2001). "Serum 25-hydroxyvitamin D3 levels are elevated in South Indian patients with ischemic heart disease". *European Journal of Epidemiology*. **17** (6): 567–71. doi:10.1023/A:1014559600042. PMID 11949730.
22. Freedman BI, Wagenknecht LE, Hairston KG, Bowden DW, Carr JJ, Hightower RC, Gordon EJ, Xu J, Langefeld CD, Divers J (March 2010). "Vitamin d, adiposity, and calcified atherosclerotic plaque in african-americans". *The Journal of Clinical Endocrinology and Metabolism*. **95** (3): 1076–83. doi:10.1210/jc.2009-1797. PMC 2841532. PMID 20061416.
23. Watson KE, Abrolat ML, Malone LL, Hoeg JM, Doherty T, Detrano R, Demer LL (September 1997). "Active serum vitamin D levels are inversely correlated with coronary calcification". *Circulation*. **96** (6): 1755–60. doi:10.1161/01.cir.96.6.1755. PMID 9323058.

24. Brandi L (November 2008). "1alpha(OH)D3 One-alpha-hydroxy-cholecalciferol--an active vitamin D analog. Clinical studies on prophylaxis and treatment of secondary hyperparathyroidism in uremic patients on chronic dialysis". *Danish Medical Bulletin*. **55** (4): 186–210. PMID 19232159.
25. Ogawa T, Ishida H, Akamatsu M, Matsuda N, Fujiu A, Ito K, Ando Y, Nitta K (January 2010). "Relation of oral 1alpha-hydroxy vitamin D3 to the progression of aortic arch calcification in hemodialysis patients". *Heart and Vessels*. **25** (1): 1–6. doi:10.1007/s00380-009-1151-4. PMID 20091391.
26. Bell NH, Greene A, Epstein S, Oexmann MJ, Shaw S, Shary J (August 1985). "Evidence for alteration of the vitamin D-endocrine system in blacks". *The Journal of Clinical Investigation*. **76** (2): 470–3. doi:10.1172/JCI111995. PMC 423843. PMID 3839801.
27. Cosman F, Nieves J, Dempster D, Lindsay R (December 2007). "Vitamin D economy in blacks". *Journal of Bone and Mineral Research*. 22 Suppl 2: V34–8. doi:10.1359/jbmr.07s220. PMID 18290719.
28. Dawson-Hughes B (December 2004). "Racial/ethnic considerations in making recommendations for vitamin D for adult and elderly men and women". *The American Journal of Clinical Nutrition*. **80** (6 Suppl): 1763S–6S. PMID 15585802.
29. Tang W, Arnett DK, Province MA, Lewis CE, North K, Carr JJ, Pankow JS, Hopkins PN, Devereux RB, Wilk JB, Wagenknecht L (May 2006). "Racial differences in the association of coronary calcified plaque with left ventricular hypertrophy: the National Heart, Lung, and Blood Institute Family Heart Study and Hypertension Genetic Epidemiology Network". *The American Journal of Cardiology*. **97** (10): 1441–8. doi:10.1016/j.amjcard.2005.11.076. PMID 16679080.
30. Goswami R, Kochupillai N, Gupta N, Goswami D, Singh N, Dudha A (October 2008). "Presence of 25(OH) D deficiency in a rural North Indian village despite abundant sunshine". *The Journal of the Association of Physicians of India*. **56**: 755–7. PMID 19263699.
31. Lips P (July 2010). "Worldwide status of vitamin D nutrition". *The Journal of Steroid Biochemistry and Molecular Biology*. **121** (1-2): 297–300. doi:10.1016/j.jsbmb.2010.02.021. PMID 20197091.
32. Schoenmakers I, Goldberg GR, Prentice A (June 2008). "Abundant sunshine and vitamin D deficiency". *The British Journal of Nutrition*. **99** (6): 1171–3. doi:10.1017/S0007114508898662. PMID 18234141.
33. Hagenau T, Vest R, Gissel TN, Poulsen CS, Erlandsen M, Mosekilde L, Vestergaard P (January 2009). "Global vitamin D levels in relation to age, gender, skin pigmentation and latitude: an ecologic meta-regression analysis". *Osteoporosis International*. **20** (1): 133–40. doi:10.1007/s00198-008-0626-y. PMID 18458986.
34. Engelman CD, Fingerlin TE, Langefeld CD, Hicks PJ, Rich SS, Wagenknecht LE, Bowden DW, Norris JM (September 2008). "Genetic and environmental determinants of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels in Hispanic and African Americans". *The Journal of Clinical Endocrinology and Metabolism*. **93** (9): 3381–8. doi:10.1210/jc.2007-2702. PMC 2567851. PMID 18593774.
35. Creemers PC, Du Toit ED, Kriel J (December 1995). "DBP (vitamin D binding protein) and BF (properdin factor B) allele distribution in Namibian San and Khoi and in other South African populations". *Gene Geography*. **9** (3): 185–9. PMID 8740896.
36. Lips P (March 2007). "Vitamin D status and nutrition in Europe and Asia". *The Journal of Steroid Biochemistry and Molecular Biology*. **103** (3-5): 620–5. doi:10.1016/j.jsbmb.2006.12.076. PMID 17287117.
37. Borges CR, Rehder DS, Jarvis JW, Schaab MR, Oran PE, Nelson RW (February 2010). "Full-length characterization of proteins in human populations". *Clinical Chemistry*. **56** (2): 202–11. doi:10.1373/clinchem.2009.134858. PMID 19926773.
38. Rejnmark L, Jørgensen ME, Pedersen MB, Hansen JC, Heickendorff L, Lauridsen AL, Mulvad G, Siggaard C, Skjoldborg H, Sørensen TB, Pedersen EB, Mosekilde L (March 2004). "Vitamin D insufficiency in Greenlanders on a westernized fare: ethnic differences in calcitropic hormones between Greenlanders and Danes". *Calcified Tissue International*. **74** (3): 255–63. doi:10.1007/s00223-003-0110-9. PMID 14708040.
39. Friborg JT, Melbye M (September 2008). "Cancer patterns in Inuit populations". *The Lancet. Oncology*. **9** (9): 892–900. doi:10.1016/S1470-2045(08)70231-6. PMID 18760245.
40. Gozdzik A, Barta JL, Wu H, Wagner D, Cole DE, Vieth R, Whiting S, Parra EJ (September 2008). "Low wintertime vitamin D levels in a sample of healthy young adults of diverse ancestry living in the Toronto area: associations with vitamin D intake and skin pigmentation". *BMC Public Health*. **8**: 336. doi:10.1186/1471-2458-8-336. PMID 18817578.

41. Scientific Advisory Committee on Nutrition (2007) Update on Vitamin D Position Statement by the Scientific Advisory Committee on Nutrition 2007 ISBN 978-0-11-243114-5
42. Harinarayan Vitamin D Status in India – Its Implications and Remedial Measures (2009) [cite http://www.japi.org/january_2009/R-1.html]a review of over 50 studies of 25(OH)D
43. Sinotte M, Diorio C, Bérubé S, Pollak M, Brisson J (February 2009). "Genetic polymorphisms of the vitamin D binding protein and plasma concentrations of 25-hydroxyvitamin D in premenopausal women". *The American Journal of Clinical Nutrition*. **89** (2): 634–40. doi:10.3945/ajcn.2008.26445. PMID 19116321.
44. Labuda M, Labuda D, Korab-Laskowska M, Cole DE, Zietkiewicz E, Weissenbach J, Popowska E, Pronicka E, Root AW, Glorieux FH (September 1996). "Linkage disequilibrium analysis in young populations: pseudo-vitamin D-deficiency rickets and the founder effect in French Canadians". *American Journal of Human Genetics*. **59** (3): 633–43. PMC 1914903. PMID 8751865.
45. McKenna MJ (July 1992). "Differences in vitamin D status between countries in young adults and the elderly". *The American Journal of Medicine*. **93** (1): 69–77. doi:10.1016/0002-9343(92)90682-2. PMID 1385673.
46. Tuohimaa P (March 2009). "Vitamin D and aging". *The Journal of Steroid Biochemistry and Molecular Biology*. **114** (1-2): 78–84. doi:10.1016/j.jsbmb.2008.12.020. PMID 19444937.
47. Keisala T, Minasyan A, Lou YR, Zou J, Kalueff AV, Pyykkö I, Tuohimaa P (July 2009). "Premature aging in vitamin D receptor mutant mice". *The Journal of Steroid Biochemistry and Molecular Biology*. **115** (3-5): 91–7. doi:10.1016/j.jsbmb.2009.03.007. PMID 19500727.
48. Tuohimaa P, Keisala T, Minasyan A, Cachat J, Kalueff A (December 2009). "Vitamin D, nervous system and aging". *Psychoneuroendocrinology*. 34 Suppl 1: S278–86. doi:10.1016/j.psyneuen.2009.07.003. PMID 19660871.

Categories: Vitamin D | Effects of external causes | Hypervitaminosis