REVIEW ARTICLE KERALA MEDICAL JOURNAL

Vitamin D - Current Concepts

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ABSTRACT

Published on 24th December 2018

Vitamin D has important benefits in reducing the risk of many conditions and diseases. In addition to its well-known effects on rickets, osteomalacia and osteoporosis vitamin D influences muscle function, cardiovascular homeostasis, nervous function, and the immune response. Those diseases for which the benefits are well supported and that have large economic effects include many types of cancer, cardiovascular diseases, diabetes mellitus, several bacterial and viral infections, and autoimmune diseases such as multiple sclerosis. The prevalence of vitamin D deficiency/ insufficiency is high throughout the world. The currently recommended daily vitamin D intake of 5–15µg is too low to achieve an adequate vitamin D status in individuals with only moderate skin synthesis. Thus, there is a need to recommend a vitamin D intake that is effective for achieving adequate circulating 25-hydroxyvitamin D concentrations (>75 nmol/L).

Keywords: Diabetes Mellitus, Metabolic Disease, Eldecalcitol, 25-Hydroxyvitamin D, Ultraviolet-B, Vitamin D

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INTRODUCTION

Vitamin D3 was identified in 1919 as the critical factor in resolving the childhood bone disease of rickets.[1] It was not until 50 years later, that it was realized that it acts as a steroid hormone in an endocrine manner.[2] Understanding of vitamin D's role in optimal health has expanded greatly in the past few years. Vitamin D has long been known for its effects on calcium and bone metabolism. Severe vitamin D deficiency causes a lack of bone mineralization, which manifests as rickets in children and osteomalacia in adults. Insufficient vitamin D status also contributes to the osteoporosis. However, it is now becoming increasingly clear that vitamin D has a much broader range of actions in the human body than believed before. Its physiological effects are not only limited to bone. Various other chronic diseases that are frequently observed in modern societies are probably at least in part caused by inadequate vitamin D supply

Metabolism

Active vitamin D is produced from provitamins through conversion steps in the skin, liver, and kidney. The provitamins are ingested from animal fats (ergosterol) or synthesized by the liver (7-dehydrocholesterol),[3] and are converted to calciferol and cholecalciferol by ultraviolet light, a process that occurs in the skin. The compounds are then transported to the liver, where they are converted to 25-hydroxyvitamin D by a specific hydrolase.[4,5] The final conversion occurs in the kidney. In the presence of specific hydrolases and a number of biochemical co-factors, 25-hydroxyvitamin D is converted to either 24, 25-dihydroxyvitamin D or 1, 25-dihydroxyvitamin D. The latter serves as the potent calcium transport promoter.[6] A low serum calcium level and a high PTH level cause conversion to the 1,25 analogue, whereas a high serum calcium level, a higher serum phosphate level, and a low PTH level favour formation of 24,25-dihydroxyvitamin D, which is less potent in activating calcium transport.[7,8] Serum phosphate also plays an important role here,

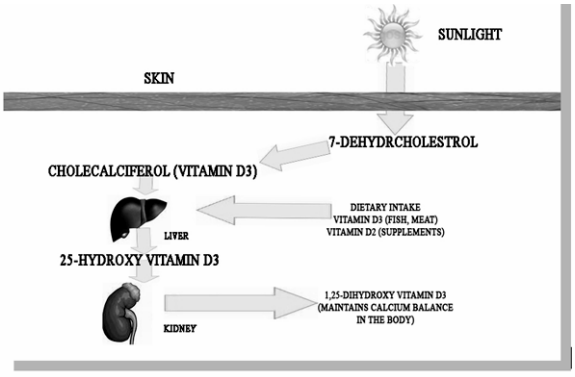

Figure 1. **Vitamin D synthesis**

Cite this article as: Satheesh SK, Fazil VM. Vitamin D - Current Concepts. IMA Kerala Medical Journal. 2018 Dec 24;11(4):105–9.

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because a high concentration of phosphate shunts the 25-hydroxyvitamin D into the 24, 25-dihydroxy form. Although the 24, 25-dihydroxy form is less active in regulating calcium levels, it has an important role in growth-plate chondrocytes.

Sources

There are only a few food sources of vitamin D. Good sources of vitamin D are fortified foods and beverages such as milk, orange juice and margarine. Fish, liver, and egg yolk are the only foods that naturally contain vitamin D. One can obtain vitamin D3 from diet, supplements, and natural and artificial ultraviolet-B (UVB). Cold-water ocean fish is the primary dietary source of dietary vitamin D. Solar UVB is not strong enough to generate vitamin D in the skin in most European countries in winter but can be a good source in summer.[9,10] Sunbeds, which in Europe have UV output similar to that of the Mediterranean midday sun but less UVB, can also generate vitamin D. While both solar and artificial UV entail the risk of skin cancer, the benefits of chronic but moderate UVB irradiance may outweigh the health risks. But the European Commission's Scientific Committee on Consumer Products has warned against use of sunbeds (European Commission, 2006) based on its risk factors.

It appears that cod liver oil may not be a good source of vitamin D now since many forms of cod liver oil sold in the market have too much vitamin A (retinoic acid).[11] The problem with higher intakes of vitamin A is that vitamin A antagonizes the action of vitamin D and its active metabolite.

Vitamin D deficiency

Severe vitamin D deficiency can cause rickets in children and osteomalacia in adults, characterized by impaired bone mineralization.[12,13] Conversely, deficiency / insufficiency of vitamin D causes a decrease in the serum concentration of calcium due to a reduction in intestinal absorption of calcium. This hypocalcaemia stimulates PTH secretion (secondary hyperparathyroidism), resulting in an increase in bone resorption and decrease of bone mineral density (BMD). This may contribute to the pathogenesis of osteoporosis.[14,15] Vitamin D deficiency is also associated with muscle weakness, leading to an increased risk of falling and fractures.[16,12] A significant correlation between the serum concentration of 25(OH) D and falls in elderly people has been reported.[17]

CURRENT CONCEPTS ON VITAMIN D

Muscle Strengthening

Vitamin D deficiency causes reduced aktomyosin content of myofibrils, low calcium content of mitochondria, reduced calcium uptake into the sarcoplasmic reticulum, and low serum levels of muscle enzymes.[18] Daily doses of 17.5 to 20μg supplemental vitamin D are able to prevent falls in elderly adults.[19] It is noteworthy that in elderly people the risk of falling predicts the risk of developing osteoporotic fractures. Therefore, the effects of vitamin D on muscle strength may contribute to the preventive effect of vitamin D on osteoporotic fractures

Infections

There is mounting evidence for a pivotal role of vitamin D in the immune system. Calcitriol is able to induce the differentiation of monocytes into macrophages. In addition, calcitriol increases the activity of macrophages and facilitates their cytotoxic activity. Macrophages represent the first unspecific defence line of the immune system. It is well known that the prevalence of infections such as pneumonia is high in infants with rickets.[18] Studies has demonstrated that patients with tuberculosis have lower circulating 25(OH)D concentrations compared to healthy controls.[20] Some epidemiological data support the assumption that vitamin D may reduce the susceptibility to respiratory tract infections.[21,22] Supplementation with 20μg or 50μg vitamin D daily for three years significantly reduced upper respiratory tract infections compared to placebo.[23]

Allergies

Dendritic cells (DCs) may induce naïve T cells in an immunogenetic direction but also in a tolerogenic direction, depending on the state of their maturation and their cell surface receptor. Tolerogenic DCs generally are semimature. There is accumulating evidence that vitamin D modulates the adaptive immune system.[24] Calcitriol appears to generate tolerogenic DCs in vivo, as demonstrated in models of transplantation and autoimmune disease. DCs appear to be key targets of calcitriol. Calcitriol arrest the differentiation and maturation of DCs, maintaining them in an immature state. Calcitriol is able to enhance the secretion by DCs of the anti inflammatory and anti-allergic cytokine IL-10.

At present, the vitamin D hypothesis of allergies takes two forms: Some argue that vitamin D deficiency may cause allergic reactions whereas others argue that vitamin D excess leads to an increased allergy risk.[25-27] Latter hypothesis is based on the assumption that vitamin D may lead to Th2 predominance and increased IgE production. It is, however, noteworthy that several other epidemiological studies support the vitamin D deficiency hypothesis of allergic reactions.[28,29]

Cancer

Since vitamin D is a key regulator of various cellular metabolic pathways, it is important for cellular maturation, differentiation, and apoptosis.[18] International Agency for Research on cancer[30] that came to the conclusion that there is consistent epidemiological evidence for an inverse association between 25(OH)D and colorectal cancer ,colorectal adenomas, and breast cancer. Gorham et al.[31] have estimated that approximately 32% of colon cancer and approximately 26% of breast cancer can be prevented with 50μg vitamin D daily and 3–10 min daily of noon sunlight seasonality, when weather permits. Such intakes also are expected to reduce case-fatality rates of patients who have breast, colorectal, or prostate cancer by half. Nevertheless, there is also some concern that cancer risk is not only enhanced in individuals with deficient/insufficient vitamin D status, but also if 25(OH)D concentrations rise above 80nmol/L.[32]

Diabetes Mellitus

In vitro and in vivo studies suggest that vitamin D can prevent pancreatic beta-cell destruction and reduces the incidence of autoimmune diabetes. This may at least in part be due to a suppression of proinflammatory cytokines such as tumor necrosis factor (TNF)-α. Incidence rates of type 1 diabetes mellitus were generally higher at higher latitudes and were inversely associated with UVB irradiance, the primary source of circulating vitamin D in humans.[33] Studies show that vitamin D supplementation was associated with a decreased frequency of type 1 diabetes.[34,35]

Evidence from RCTs with vitamin D and/or calcium supplementation suggests that combined vitamin D and calcium supplementation may have a role in the prevention of type 2 diabetes only in populations at high risk (i.e., glucose intolerance). Whereas vitamin D supplementation did not improve glycemic control in diabetic subjects with normal serum 25(OH)D levels.[36] Studies show that administration of 100μg vitamin D3 improved insulin sensitivity in vitamin D deficient and insulin resistant women.[37] Studies have found good observational evidence that low serum 25(OH)D is a risk factor for type 2 diabetes mellitus.[38,39]

Cardiovascular Disease

CVD includes various illnesses such as coronary heart disease (CHD), peripheral arterial disease, cerebrovascular disease such as stroke, and congestive heart failure. There is accumulating evidence that the vitamin D hormone calcitriol exerts important physiological effects in cardiomyocytes, vascular smooth muscle cells, and the vascular endothelium.[40] Several studies have demonstrated that a higher vitamin D status is associated with approximately 50% lower cardiovascular morbidity and mortality risk compared with low vitamin D status.[41,42]

Multiple Sclerosis

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system that is debilitating and can be fatal. In Europe and North America, regions with higher UVB radiation have low rates of MS and vice versa.[18] The prevalence of MS is high in people who were born in a country with low UVB irradiance[43] indicating that vitamin D status during the period of early life is of importance for MS susceptibility. MS disease activity shows inverse fluctuations according to season and vitamin D status.[44,45]

Role of Eldecalcitol

Eldecalcitol (1α, 25-dihydroxy-2β-[3-hydroxypropyloxy] vitamin D3; ED-71) is a new analog of the active form of vitamin D. Eldecalcitol has recently been approved for the treatment of osteoporosis in Japan. In addition to regulation of calcium metabolism carried out by conventional vitamin D analogs, eldecalcitol possesses a strong inhibitory effect on bone resorption and causes a significant increase in bone mineral density. Eldecalcitol has dual effects on the metabolism of bone and calcium and is useful for the treatment of osteoporosis, especially for elderly patients (who frequently suffer from vitamin D deficiency).[46]

Roles of environment and genetics

Individual's responses to vitamin D may depend on personal genetics. For example, dietary factors and smoking may explain 70% of cancer risk in the United States.[47] Polymorphisms of vitamin D receptor alleles affect the action of vitamin D for cancer[48] and autoimmune diseases.[49] Many of the cancers for which diet and smoking are risk factors are also vitamin D sensitive,[50] thus providing an additional way to counter the effects of environment and genetics.

Recommended daily intake

The recommended daily vitamin D intake of 5–15 μg is too low to achieve an adequate vitamin D status in people with only modest UVB exposure. Generally, treating vitamin D deficiency is easy to perform, safe, and inexpensive. Sources of vitamin D could include a combination of food fortification, supplements, and natural and artificial UV-B irradiation, if properly acquired. It has been calculated that 1μg vitamin D increases circulating 25(OH)D levels by approximately 1nmol/L.[51] Thus, a daily intake of approximately 50μg vitamin D would be necessary for increasing the circulating 25(OH)D level from 25nmol/L to 75nmol/L. In order to achieve a 25(OH)D concentration above 75nmol/L in almost all individuals of a group with mean baseline 25(OH)D concentrations of 38nmol/L, daily supplementation with up to 100μg vitamin D is necessary.[52]

Adverse effects of vitamin D supplementation

Another consideration is possible adverse effects from vitamin D supplementation. The primary concern is the risk of hypercalcemia. The toxic signs of hypercalcemia include pain, conjunctivitis, anorexia, fever, chills, thirst, vomiting, and weight loss. However, most cases of vitamin D toxicity occurred at serum 25(OH)D levels >250 ng/mL. There has been concern that higher vitamin D levels might lead to formation of kidney stones (nephrolithiasis). Persons with sarcoidosis or granulomatous disease,[53] or another condition that causes high blood calcium levels should not take vitamin D supplements, which can increase the risk of hypercalcemia.[53] Also, about 10%–20% of those with lymphoma may experience a similar effect.[54]

CONCLUSION

To summarise ,we can well appreciate the association of insufficient vitamin D status with various diseases such as myopathy, cardiovascular disease, cancer, diabetes mellitus, MS, and infections. Meanwhile, evidence has accumulated that vitamin D may indeed play an important role in the etiology of many of these diseases. The most important benefits would come for cancer, cardiovascular disease, diabetes mellitus, allergies, respiratory infections, and multiple sclerosis.

END NOTE

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Conflict of Interest: None declared

REFERENCES

1. Mellanby E. An experimental investigation on rickets.Lancet 1919;1:407-12.
2. Fraser DR, Kodicek E. Unique biosynthesis by kidney of a biological active vitamin D metabolite. Nature 1970;228:764-6.
3. Harmeyer J, DeLuca HF. Calcium-binding protein and calcium absorption after vitamin D administration. Arch Biochem Biophys 1969;133:247.
4. Blunt JW, DeLuca HF. The synthesis of 25-hydroxycholecalciferol: a biologically active metabolite of vitamin D3. Biochemistry 1969;8:671.
5. Jones G, Schnoes HK, DeLuca HF. Isolation and identification of 1,25 dihydroxy vitamin D2. Biochemistry 1975;14:1250.
6. Holick MF, Schnoes HK, DeLuca HF, et al. Isolation and identification of 1,24-dihydroxycholecalciferol: a metabolite of vitamin D active in intestine. Biochemistry 1971;10:2799.
7. Fraser DR, Kodicek E. Regulation of 25-hydroxycholecalciferol-1-hydrolase activity in kidney by parathyroid hormone. Nature 1973;241:163.
8. Rasmussen H, Wong M, Bikle D, et al. Hormonal control of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol. J Clin Invest 1972;51:2502
9. Hypponen, E.Power, C. 2007. Hypovitaminosis D in British adults at age 45 y:nationwide cohort study of dietary and lifestyle predictors. Am J Clin Nutr 85,860-8.
10. Porojnicu, A. C., Dahlback, A., Moan, J. 2008b. Sun exposure and cancer survival in Norway: changes in the risk of death with season of diagnosis and latitude. Adv Exp Med Biol 624, 43-54.
11. Cannell, J. J.et al. 2008. Cod liver oil, vitamin A toxicity,frequent respiratory infections, and the vitamin D deficiency epidemic. Ann Otol Rhinol Laryngol. 117, 864-70
12. Holick MF. Resurrection of vitamin D deficiency and rickets. J Clin Invest. 2006;116(8):2062–2072.
13. Lips P. Vitamin D physiology. Prog Biophys Mol Biol. 2006;92(1): 4–8.
14. Adams JS, Hewison M. Update in vitamin D. J Clin Endocrinol Metab. 2010;95(2):471–478.
15. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Guidelines for preventing and treating vitamin D deficiency and insufficiency revisited. J Clin Endocrinol Metab. 2012;97(4):1153–1158.
16. Janssen HC, Samson MM, Verhaar HJ. Vitamin D deficiency, muscle function, and falls in elderly people. Am J Clin Nutr. 2002;75(4): 611–615
17. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, et al. Effect of Vitamin D on falls: a meta-analysis. JAMA. 2004;291(16): 1999–2006.
18. Zittermann, A. Vitamin D in preventive medicine – are we ignoring the evidence? Br. J. Nutr.2003, 89, 552-572
19. Bischoff-Ferrari, H.A.; Dawson-Hughes, B.; Staehelin, H.B.; Orav, J.E.; Stuck, A.E.; Theiler, R.;Wong, J.B.; Egli, A.; Kiel, D.P.; Henschkowski, J. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. BMJ

2009 Oct 1;339:b3692.doi: 10.1136/bmj.b3692

20. Nnoaham, K.E.; Clarke, A. Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis. Int. J. Epidemiol. 2008, 37, 113-119.
21. Laaksi, I.; Ruohola, J.P.; Tuohimaa, P.; Auvinen, A.; Haataja, R.; Pihlajamäki, H.; Ylikomi, T. An association of serum vitamin D concentrations < 40 nmol/L with acute respiratory tract infection in young Finnish men. Am. J. Clin. Nutr. 2007, 86, 714-717.
22. Ginde, A.A.; Mansbach, J.M.; Camargo, C.A. Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. Arch. Intern. Med. 2009, 169, 384-390.
23. Aloia, J.F.; Talwar, S.A.; Pollack, S.; Yeh, J. A randomized controlled trial of vitamin D3 supplementation in African American women. Arch. Intern. Med. 2005, 165, 1618-1623.
24. Zittermann, A.; Tenderich, G.; Koerfer, R. Vitamin D and the adaptive immune system with special emphasis to allergic reactions and allograft rejection. Inflamm. Allergy Drug Targets 2009,8, 161-168.
25. Wjst, M. Another explanation for the low allergy rate in the rural Alpine foothills. Clin. Mol. Allergy 2005, 3, 7.
26. Hyppönen, E.; Sovio, U.; Wjst, M.; Patel, S.; Pekkanen, J.; Hartikainen, A.L.; Järvelinb, M.R. Infant vitamin d supplementation and allergic conditions in adulthood: northern Finland birth cohort 1966. Ann. N. Y. Acad. Sci. 2004, 1037, 84-95.
27. Bäck, O.; Blomquist, H.K.; Hernell, O.; Stenberg, B. Does vitamin D intake during infancy promote the development of atopic allergy? Acta Derm. Venereol. 2009, 89, 28-32.
28. Zittermann, A.; Dembinski, J.; Stehle, P. Low vitamin D status is associated with low cord blood levels of the immunosuppressive cytokine interleukin 10. Pediatr. Allergy Immu. 2004, 15, 242-246
29. Erkkola, M.et al. Maternal vitamin D intake during pregnancy is inversely associated with asthma and allergic rhinitis in 5-year-old children. Clin. Exp. Allergy 2009, 39, 875-882.
30. World Health Organization. International Agency for Research on Cancer. Vitamin D and cancer. IARC Working Group Reports; WHO Press: Geneva, Switzerland 2008; Volume 5, p. 148.
31. Gorham, E.D.; Mohr, S.B.; Garland, F.C.; Garland, C.F. Vitamin D for Cancer Prevention and Survival. Clin. Rev. Bone Miner Metab. 2009, 7, 159-175.
32. Tuohimaa, P.; Tenkanen, L.; Ahonen, M.; Lumme, S.; Jellum, E.; Hallmans, G.; Stattin, P.; Harvei, S.; Hakulinen, T.; Luostarinen, T.; Dillner, J.; Lehtinen, M.; Hakama, M.. Both high and low levels of blood vitamin D are associated with a higher prostate cancer risk: a longitudinal, nested case-control study in the Nordic countries. Int. J. Cancer 2004, 108,104-108.
33. Mohr, S.B.; Garland, C.F.; Gorham, E.D.; Garland, F.C. The association between ultraviolet B irradiance, vitamin D status and incidence rates of type 1 diabetes in 51 regions worldwide. Diabetologia 2008, 51, 1391-1398.
34. Hyppönen, E.; Läärä, E.; Reunanen, A.; Järvelin, M.R.; Virtanen, S.M. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. Lancet 2001, 358, 1500-1503.
35. Zipitis, C.S.; Akobeng, A.K. Vitamin D supplementation in early childhood and risk of type 1 diabetes: a systematic review and meta-analysis. Arch. Dis. Child. 2008, 93, 512-517.
36. Jorde R, Figenschau Y. Supplementation with cholecalciferol does not improve glycemic control in diabtetic subjects with normal serum 25-hydroxyvitamin D levels. Eur. J. Nutr. 2009, 48, 349-354.
37. von Hurst, P.R.; Stonehouse, W.; Coad, J. Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient – a randomised, placebo-controlled trial. Br. J. Nutr. 2009, 1-7, [Epub ahead of print].
38. Knekt, P., Laaksonen, M., Mattila, C., Harkanen, T., Marniemi, J., Heliovaara, M.,Rissanen, H., Montonen, J., Reunanen, A. 2008. Serum vitamin D and subsequent occurrence of type 2 diabetes. Epidemiology 19, 666-71.
39. Pittas, A. G., Lau, J., Hu, F. B., Dawson-Hughes, B. 2007. The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. J Clin Endocrinol Metab 92, 2017-29.
40. Zittermann, A.; Koerfer R.Vitamin D in the prevention and treatment of coronary heart disease.Curr. Opin. Clin. Nutr. Metab. Care. 2008, 11, 752-757.
41. Pilz, S.; Dobnig, H.; Fischer, J.E.; Wellnitz, B.; Seelhorst, U.; Boehm, B.O.; März, W. Low vitamin D levels predict stroke in patients referred to coronary angiography. Stroke 2008, 39, 2611-2613.
42. Wang, T.J.; Pencina, M.J.; Booth, S.L.; Jacques, P.F.; Ingelsson, E.; Lanier, K.; Benjamin, E.J.;D'Agostino, R.B.; Wolf, M.; Vasan, R.S. Vitamin D deficiency and risk of cardiovascular disease.Circulation 2008, 117, 503-511.
43. Chaudhuri, A. Why we should offer routine vitamin D supplementation in pregnancy and childhood to prevent multiple sclerosis. Med. Hypotheses. 2005, 64, 608-618.
44. Embry, A.F.; Snowdon, L.R.; Vieth R. Vitamin D and seasonal fluctuations of gadoliniumenhancing magnetic resonance imaging lesions in multiple sclerosis. Ann. Neurol. 2000, 48, 271-272.
45. Munger, K.L.; Levin, L.I.; Hollis, B.W.; Howard, N.S.; Ascherio, A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. JAMA 2006, 296, 2832-2838.
46. Noguchi Y, Kawate H, Nomura M, Takayanagi R. Eldecalcitol for the treatment of osteoporosis.Clin Interv Aging. 2013;8:1313-21
47. Doll, R., Peto, R.. 1981. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. J Natl Cancer Inst. 66, 1191-308.
48. Thorne, J., Campbell, M. J. 2008. The vitamin D receptor in cancer. Proc Nutr Soc. 67,115-27.
49. .Ponsonby, A.L.,, Pezic, A., Ellis, J., Morley, R., Cameron, F., Carlin, J., Dwyer, T. 2008.Variation in associations between allelic variants of the vitamin D receptor gene and onset of type 1 diabetes mellitus by ambient winter ultraviolet radiation levels: a meta-regression analysis. Am J Epidemiol. 168, 358-65.
50. Grant, W. B., Garland, C. F. 2006. The association of solar ultraviolet B (UVB) with reducing risk of cancer: multifactorial ecologic analysis of geographic variation in age-adjusted cancer mortality rates. Anticancer Res 26, 2687-99
51. Vieth, R. Vitamin D and cancer mini-symposium: the risk of additional vitamin D. Ann.Epidemiol. 2009, 19, 441-445.
52. Aloia, J,F,; Patel, M.; Dimaano, R.; Li-Ng, M.; Talwar, S.A.; Mikhail, M.; Pollack, S.; Yeh, J.K.Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration. Am. J. Clin. Nutr. 2008, 87, 1952-1958
53. Hewison, M., Burke, F., Evans, K. N., Lammas, D. A., Sansom, D. M., Liu, P., Modlin, R. L., Adams, J. S. 2007. Extra-renal 25-hydroxyvitamin D3-1alpha-hydroxylase in human health and disease. J Steroid Biochem Mol Biol 103, 316-21.
54. Hewison, M., Kantorovich, V., Liker, H. R., Van Herle, A. J., Cohan, P., Zehnder, D. Adams, J. S. 2003. Vitamin D-mediated hypercalcemia in lymphoma: evidence for hormone production by tumor-adjacent macrophages. J Bone Miner Res 18, 579-82.