Review

Vitamin D and the Immune System

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ABSTRACT. Evidence of the role of vitamin D in the regulation of T and B cells, macrophages, dendritic cells, and keratinocytes continues to accumulate and provides a link between vitamin D and many autoimmune diseases, including Crohn's disease, juvenile diabetes mellitus, multiple sclerosis, asthma, and rheumatoid arthritis. Considering the influence of vitamin D on the immune system, it may have potential as a treatment for immune-mediated diseases, even if additional research is required to better quantify dosage. But the biggest obstacle to its clinical use is its potent hypercalcemic effect. The calcium status of the host may influence the effect of vitamin D on immunity. (First Release Jan 15 2010; J Rheumatol 2010;37:491–5; doi:10.3899/jrheum.090797)

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AUTOIMMUNITY   VITAMIN D   B LYMPHOCYTES   T LYMPHOCYTES

Vitamin D is a seco-steroid, that is, a steroid characterized by the breaking of 1 of the bonds in the steroid rings. Vitamin D acts on target cells in a steroid hormone-like manner, by binding to a specific nuclear receptor called the vitamin D receptor (VDR), which functions as a heterodimer, generally with the retinoid X receptor. This ligand-receptor complex interacts with a specific vitamin D responsive element, i.e., a DNA sequence involved in initiating transcription of messenger RNA coding for calcium-transporting proteins and growth factors responsible for calcium-phosphate metabolism and other cellular actions[1].

Because of differences in its side chain, vitamin D is distinguished by 2 biological forms, called ergocalciferol (vitamin D_2), present in some vegetable and fungal sources, and cholecalciferol (vitamin D_3), produced in the skin after ultraviolet B radiation exposure. Each form, to be biologically active, must be converted to 25 hydroxyvitamin D_3 ($25OHD_3$) by hydroxylation in position 25 by the enzyme 25-hydroxylase, mostly but not exclusively found in the liver[2,3]. Further, to be completely active, $25OHD_3$ is additionally hydroxylated in position 1 by the enzyme 1-alpha-hydroxylase, mainly present in the proximal renal tubule. The enzyme 1-alpha-hydroxylase has also been described in immune cells, bone, epithelia, and parathyroid glands[4]. In the proximal renal tubule, parathyroid hormone (PTH) is capable of stimulating 1-alpha-hydroxylase, while fibroblast growth factor-23 is involved in 1-alpha-hydroxy-

lase inhibition[5,6]. In macrophages and keratinocytes the main role in 1-alpha-hydroxylase regulation is played by Toll-like receptor (TLR) activation and by the availability of vitamin D[7,8]. Moreover, in keratinocytes, $1,25(OH)_2D_3$ production is increased by tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ)[9,10]. Both the proximal renal tubule cells and keratinocytes may express 25-hydroxyvitamin D_3-24-hydroxylase, a mitochondrial P450 enzyme that catabolizes both $1,25(OH)_2D_3$ and 25OHD[11,12]. A nonfunctional alternatively spliced form of 25-hydroxyvitamin D_3-24-hydroxylase has been seen in the cytoplasm of macrophages that may be responsible for impeding substrate access to the mitochondrial 25-hydroxyvitamin D_3-24-hydroxylase[13].

Moreover, even if the activity of 1-alpha-hydroxylase is mainly regulated by calcium-phosphorus blood levels, vitamin C may also be involved in the transformation of vitamin D into the active metabolite by influencing 1-alpha-hydroxylase[14].

Role of Vitamin D in Immune System Regulation

The primary role of vitamin D is the regulation of bone mineral homeostasis; however, its importance in the regulation of the immune system has emerged in the last 30 years. In 1983 it was demonstrated that macrophages were involved in vitamin D production and that VDR were isolated in activated human inflammatory cells[15,16]. In 1984, Rigby, *et al*[17] found that vitamin D may inhibit T cell proliferation. Evidence grew of the role of vitamin D in the regulation of the immune system.

It has been shown that the enzyme 1-alpha-hydroxylase is present not only in renal tissues but also in activated macrophages and dendritic cells[18,19], even if PTH inhibition has been seen only in renal tissues. In murine macrophages, 1-alpha-hydroxylase may be regulated by other mediators, such as IFN-γ[20].

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Vitamin D plays a role in T and B cell regulation. Indeed, VDR overexpression in active CD4+ T cells and $1,25(OH)_2D_3$ inhibition of T cell proliferation have been demonstrated[21,22]. Mahon, *et al*[22], using microarray technology, identified over 102 genes that were targets of $1,25(OH)_2D_3$ in CD4+ T cells. Of the 102 genes, 57 genes were downregulated and 45 were upregulated by $1,25(OH)_2D_3$. Some of the identified targets were regulators of nuclear factor-kB; others were genes for interleukin 2 (IL-2) receptor ß and for IgE binding factor. In addition, $1,25(OH)_2D_3$ is responsible for preventing supplementary recruitment of T cell and antigen presentation by downregulation of CD4+ T cell production of IL-2 and IFN-γ, respectively[23,24]. Moreover, $1,25(OH)_2D_3$ increases the production of the T helper 2 cell-associated cytokines IL-4 and IL-5[22]. To investigate the relationship between $1,25(OH)_2D_3$ and T CD4+ cells, Froicu, *et al*[25] examined CD4+ T cells from VDR knockout (KO) mice. In those mice, CD4+ T cells produced more IFN-γ and less IL-2, IL-4, and IL-5 than did CD4+ T cells from wild-type (WT) mice. Moreover, VDR KO mice were characterized by an amplified antigen-specific IFN-γ response and an increased mixed lymphocyte reaction[25]. These data suggest that WT mice, which can respond to vitamin D, produce less IFN-γ, which is a T helper 1 cell-associated cytokine, and more IL-4 and IL-5, which are T helper 2 cell-associated cytokines. Further, $1,25(OH)_2D_3$ has an inhibitory effect on T helper 1, by suppressing IL-12 synthesis, and on T helper 17, by suppressing IL-6 and IL-23 production[26]. Using an *in vivo* model of T helper 1-mediated colitis in mice, Daniel, *et al*[26] demonstrated that $1,25(OH)_2D_3$ may upregulate IL-4 and downregulate IL-6 and IL-17, as well as IL-12p70 and IL23p19, two dendritic cell mediators responsible for the induction of a proinflammatory differentiation of naive T cells toward T helper 1 and T helper 17, respectively.

Recently, $1,25(OH)_2D_3$ inhibition of T helper 17 has been demonstrated in mice at several levels, including a direct reduction of dendritic cell ability to activate T helper 17, a reduced ability to support T helper 17 polarization of naive CD4+ T cells, and an inhibition of T helper 17-related IL-17 production[27]. As demonstrated in a murine experimental autoimmune uveitis model, $1,25(OH)_2D_3$ oral administration prevented and partially reversed disease and suppressed immunological response, shown by reduction of both ROR-gamma-t (retinoic acid receptor-related orphan receptor gamma t) and IL-17 in CD4+ T cells, 2 indicators of T helper 17 cell function. By contrast, *in vitro*, $1,25(OH)_2D_3$ inhibited IL-17 expression in naive CD4+ T cells purified from these mice, without suppressing T helper 17 cell function, as reflected by unaltered ROR-gamma-t, STAT3, and FoxP3 expression. Moreover, $1,25(OH)_2D_3$ inhibited bone marrow-derived dendritic cell ability to influence T helper 17 polarization of naive CD4+ T cells[27].

Regarding B cell regulation, $1,25(OH)_2D_3$ is involved in the suppression of immunoglobulin production and B cell proliferation and differentiation[28]. Because patients with systemic lupus erythematosus (SLE), particularly those with antinuclear autoantibodies and amplified disease activity, had reduced $1,25(OH)_2D_3$ levels, suggesting that vitamin D might be involved in the regulation of autoantibody expression, Chen, *et al*[28] studied the effects of $1,25(OH)_2D_3$ on B cells from patients with SLE. That study showed that $1,25(OH)_2D_3$ has a direct effect on B cells, including an inhibitory effect on proliferation, on generation of class-switched memory B cells, on plasma cell differentiation, and on immunoglobulin production[28].

Vitamin D also plays a role in macrophage regulation. Indeed, $1,25(OH)_2D_3$ is responsible for monocytes developing into "resident" tissue macrophages, and influences their cytokine expression. It stimulates macrophages to produce prostaglandin E_2, which is involved in the inflammatory process and inhibits the expression of granulocyte-macrophage colony-stimulating factor. Moreover, $1,25(OH)_2D_3$ reduces MHC II antigen expression on the cell membrane surface and induces macrophages and epithelial cells to produce cathelicidin, a peptide involved in antimicrobial action[29-31]. Cathelicidin is responsible for activating the innate immune response by binding to its transmembrane receptor and is correlated to higher levels of the enzyme 1-alpha-hydroxylase in macrophages and keratinocytes[7,8]. The enzyme 1-alpha-hydroxylase further increases the production of cathelicidin through the production of $1,25(OH)_2D_3$.

Further, $1,25(OH)_2D_3$ is responsible for inhibiting the differentiation of monocytes into dendritic cells and inhibits the differentiation, maturation, activation, and survival of dendritic cells, leading to reduced dendritic cell stimulatory activity on T cells, as demonstrated in studies on human and murine monocyte-derived dendritic cell cultures exposed to $1,25(OH)_2D_3$[32-36].

Recently, $1,25(OH)_2D_3$ has been regarded as important for the interaction of monocytes with T cells, because $1,25(OH)_2D_3$ reduced both the CD40L-related production of proinflammatory cytokines, including IL-1 and TNF-α, and the expression of surface costimulatory molecules, such as CD80 and CD86. Under the influence of $1,25(OH)_2D_3$ and CD40L, monocytes reduce T cell proliferation and IFN-γ production, and amplify IL-10 synthesis[37]. Moreover, $1,25(OH)_2D_3$-related reduction of CD40, CD80, and CD86 expression in antigen-presenting cells, such as dendritic cells, is responsible for reduced T cell activation[38].

As shown in a recent study[26], $1,25(OH)_2D_3$ can also promote dendritic cells to induce CD4+/CD25+ regulatory T cells (T reg). The study used mice with a reporter for augmented FoxP3 expression and IL-10 production, which are decisive for T reg development. Moreover, Gregori, *et al*[39] found in transplanted mice that $1,25(OH)_2D_3$ induces dendritic cells with a tolerogenic phenotype and an augmented

percentage of CD4+/CD25+ T reg in the spleen and in the transplant-draining lymph nodes. These regulatory T cells are responsible for an increased tolerance and for a transfer of transplantation tolerance.

Vitamin D and Autoimmunity

Many autoimmune diseases are linked to vitamin D deficiency, including Crohn's disease, juvenile diabetes mellitus, multiple sclerosis (MS), asthma, and rheumatoid arthritis (RA)[29,40-44]. It has been suggested that $1,25(OH)_2D_3$ is responsible for suppression of autoimmune diseases by decreasing IL-2 and IFN-γ production, and increasing IL-4 expression, as has been demonstrated in mice[24,45,46]. Nevertheless, the role of $1,25(OH)_2D_3$ in IL-4 expression is controversial. On one hand, $1,25(OH)_2D_3$ is responsible for inhibition of IL-4 production from murine T helper 1 and T helper 2 cells[47]. On the other hand, Cantorna, *et al*[48] and Boonstra, *et al*[21] have demonstrated that $1,25(OH)_2D_3$ is involved in increasing IL-4 production through murine T helper 2 cell stimulation.

Administration of an analog of $1,25(OH)_2D_3$ to diabetic mice reduces IL-12 and IFN-γ expression and prevents dendritic cell maturation and T helper 1 cell infiltration of the pancreatic islets and inhibits diabetes progression[49]. CD4+/CD25+ T reg are probably involved in the protection of mice from diabetes because under $1,25(OH)_2D_3$ treatment, the number of CD4+/CD25+ T reg in the pancreatic lymph nodes is increased[49].

Numerous studies have demonstrated that serum levels of $25(OH)D_3$ are significantly lower in many cases of autoimmune diseases, including SLE, RA, and insulin-dependent diabetes mellitus, than in the healthy population[40,50-53]. Moreover, in RA, lower $25(OH)D_3$ serum levels were directly correlated to higher disease activity[52]. A recent study has shown lower $25(OH)D_3$ serum levels in patients with undifferentiated connective tissue disease than in controls. The study suggested that in some of these patients, vitamin D insufficiency plays a role in the successive development of a well established autoimmune disease, such as RA, SLE, mixed connective tissue disease, Sjögren's syndrome, systemic vasculitis, and antiphospholipid syndrome[54].

Additional evidence of the role of vitamin D in autoimmunity is the demonstration of genetic polymorphisms for the VDR gene in patients with autoimmune conditions such as inflammatory bowel diseases, RA, MS, and juvenile diabetes mellitus[55-58].

In vivo studies using murine models, however, suggest that not only vitamin D but also an adequate calcium intake plays a role in regulation of the autoimmune response in the gastrointestinal tract and the central nervous system. A reduced inclination toward inflammatory bowel diseases such as ulcerative colitis and Crohn's disease has been associated with calcium intake coupled to vitamin D treatment[59]. Moreover, dietary calcium doses are directly linked to vitamin D effectiveness in preventing experimental T helper cell-dependent autoimmune diseases such as experimental autoimmune encephalomyelitis. The observation that vitamin D may reduce the incidence of this autoimmune disease only if associated with adequate calcium intake underlines the importance of serum calcium in regulation of autoimmune response. Even hypercalcemic doses of vitamin D fail in preventing experimental autoimmune encephalomyelitis if not associated with adequate calcium intake. However,

Table 1. The influence of 1,25 $(OH)_2D_3$ in the regulation of mediators produced by immune cells.

Action of 1,25 $(OH)_2D_3$ on Immune Mediators	Producing Cells	1,25 $(OH)_2D_3$ Effects	References
↓ IL-1	Dendritic cells, macrophages	↓ Flogosis	37
↓ IL-2	T helper 1 cells	↓ T cells	23
		↓ Antigen presentation	
↑ IL-4	T helper 2 cells	↑ T helper 2 cell	22, 25
↑ IL-5	T helper 2 cells	↑ B cell, ↑ eosinophil	22, 25
↓ IL-6	T cells, macrophages	↓ T helper 17	26
↑ IL-10	Dendritic cells	↑ T reg activation	26, 37
↓ IL-12	Dendritic cells, macrophages	↓ T helper 1	26
↓ IL-17	T helper 17 cells	↓ Immunological response	27
↓ IL-23	Macrophages	↓ T helper 17	26
↓ Immunoglobulins	B cells	↓ Immunological response	28
↓ TNF-α	Macrophages	↓ Flogosis	37
↓ IFN-γ	T helper 1 cells	↓ T cells	24, 25
		↓ Antigen presentation	
↓ CD40	Antigen-presenting cells	↓ T cell activation	38
↓ CD80	Antigen-presenting cells	↓ T cells activation	38
↓ CD86	Antigen-presenting cells	↓ T cell activation	38
↑ FoxP3	Dendritic cells	↓ T reg activation	26

T reg: CD4+/CD25+ regulatory T cells; TNF: tumor necrosis factor; IFN: interferon.

vitamin D doses that do not cause hypercalcemia may reduce the incidence of experimental autoimmune encephalomyelitis, probably because the function of vitamin D may be both calcium-dependent and calcium-independent[60].

Although the real mechanism responsible for the role of calcium in autoimmune response is unknown, it may involve intracellular mechanisms, considering that calcium is an important intracellular messenger. However, the relationship of dietary calcium and intracellular calcium is still unidentified.

Conclusions

We have reported a link between vitamin D and the immune system (Table 1). It is suspected that vitamin D exerts immunoregulatory activities because it is produced by numerous cells of the immune system and VDR are expressed by many of these cells, and because vitamin D has a role in the inhibition of T helper 1, T helper 17, and dendritic cell differentiation, and in the induction of T reg.

Considering the influence of vitamin D on the immune system, it is suggested that vitamin D can be used in the treatment of immune-mediated diseases. The incidence and severity of autoimmune diseases, including RA, juvenile diabetes mellitus, inflammatory bowel disease, and MS may be reduced by increasing vitamin D intake[29].

Another question is how much vitamin D is needed to affect autoimmune response. Studies showed that a high pharmacologic dosage of vitamin D, regardless of sunlight exposure, is required to play a role in the regulation of autoimmune response, even if additional research is required to better quantify how much vitamin D intake is needed[29,61]. The most significant obstacle blocking its clinical use is its potent hypercalcemic effect, even though the calcium status of the host may influence the effect of vitamin D on immunity[59,60].

REFERENCES

1. Jones G, Hogan DB, Yendt E, Hanley DA. Vitamin D metabolites and analogs in the treatment of osteoporosis. Can Med Assoc J 1996;155:955-61.
2. Saarem K, Pedersen JI. 25-Hydroxylation of 1 alpha-hydroxyvitamin D-3 in rat and human liver. Biochim Biophys Acta 1985;840:117-26.
3. Tokar EJ, Webber MM. Chemoprevention of prostate cancer by cholecalciferol (vitamin D3): 25-hydroxylase (CYP27A1) in human prostate epithelial cells. Clin Exp Metastasis 2005;22:265-73.
4. Hewison M, Burke F, Evans KN, Lammas DA, Sansom DM, Liu P, et al. Extra-renal 25-hydroxyvitamin D3-1 alpha-hydroxylase in human health and disease. J Steroid Biochem Mol Biol 2007;103:316-21.
5. Perwad F, Zhang MY, Tenenhouse HS, Portale AA. Fibroblast growth factor 23 impairs phosphorus and vitamin D metabolism in vivo and suppresses 25-hydroxyvitamin D-1 alpha-hydroxylase expression in vitro. Am J Physiol Renal Physiol 2007;293:F1577-83.
6. Bajwa A, Forster MN, Maiti A, Woolbright BL, Beckman MJ. Specific regulation of CYP27B1 and VDR in proximal versus distal renal cells. Arch Biochem Biophys 2008;477:33-42.
7. Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science 2006;311:1770-3.
8. Schauber J, Dorschner RA, Coda AB, Buchau AS, Liu PT, Kiken D, et al. Injury enhances TLR2 function and antimicrobial peptide expression through a vitamin D-dependent mechanism. J Clin Invest 2007;117:803-11.
9. Bikle DD, Pillai S, Gee E, Hincenbergs M. Regulation of 1,25-dihydroxyvitamin D production in human keratinocytes by interferon-gamma. Endocrinology 1989;124:655-60.
10. Bikle DD, Pillai S, Gee E, Hincenbergs M. Tumor necrosis factor-alpha regulation of 1,25-dihydroxyvitamin D production by human keratinocytes. Endocrinology 1991;129:33-8.
11. Zierold C, Darwish HM, De Luca HF. Two vitamin D response elements function in the rat 1,25-dihydroxyvitamin D 24-hydroxylase promoter. J Biol Chem 1995;270:1675-8.
12. Xie Z, Munson SJ, Huang N, Portale AA, Miller WL, Bikle DD. The mechanism of 1,25-dihydroxyvitamin D(3) autoregulation in keratinocytes. J Biol Chem 2002;277:36987-90.
13. Ren S, Nguyen L, Wu S, Encinas C, Adams JS, Hewison M. Alternative splicing of vitamin D-24-hydroxylase: a novel mechanism for the regulation of extrarenal 1,25-dihydroxyvitamin D synthesis. J Biol Chem 2005;280:20604-11.
14. Cantatore FP, Loperfido MC, Magli DM, Mancini L, Carrozzo M. The importance of vitamin C for hydroxylation of vitamin D3 to 1.25(OH)2D3 in man. Clin Rheumatol 1991;10:162-7.
15. Adams JS, Sharma OP, Gacad MA, Singer FR. Metabolism of 25-hydroxyvitamin D3 by cultured pulmonary alveolar macrophages in sarcoidosis. J Clin Invest 1983;72:1856-60.
16. Provvedini DM, Tsoukas CD, Deftos LJ, Manolagas SC. 1,25-dihydroxyvitamin D3 receptors in human leukocytes. Science 1983;221:1181-3.
17. Rigby WF, Stacy T, Fanger MW. Inhibition of T lymphocyte mitogenesis by 1,25-dihydroxyvitamin D3 (calcitriol). J Clin Invest 1984;74:1451-5.
18. Monkawa T, Yoshida T, Hayashi M, Saruta T. Identification of 25-hydroxyvitamin D3 1 alpha-hydroxylase gene expression in macrophages. Kidney Int 2000;58:559-68.
19. Fritsche J, Mandal K, Ehrnsperger A, Andreesen R, Kreutz M. Regulation of 25-hydroxyvitamin D3- 1 alpha-hydroxylase and production of 1 alpha, 25-hydroxyvitamin D3 by human dendritic cells. Blood 2003;102:3314-6.
20. Overbergh L, Decallonne B, Valckx D, Verstuyf A, Depovere J, Laureys J, et al. Identification and immune regulation of 25-hydroxyvitamin D 1-alpha hydroxylase in murine macrophages. Clin Exp Immunol 2000;120:139-46.
21. Boonstra A, Barrat FJ, Crain C, Heath VL, Savelkoul HF, O'Garra A. 1 alpha, 25-dihydroxyvitamin D3 has a direct effect on naïve CD4(+) T cells to enhance the development of Th2 cells. J Immunol 2001;167:4974-80.
22. Mahon BD, Wittke A, Weaver V, Cantorna MT. The targets of vitamin D depend on the differentiation and activation status of CD4 positive T cells. J Cell Biochem 2003;89:922-32.
23. Lemire JM, Archer DC, Beck L, Spiegelberg HL. Immunosuppressive actions of 1,25-dihydroxyvitamin D3: preferential inhibition of Th1 functions. J Nutr 1995;125:1704S-8S.
24. Cantorna MT. Vitamin D and autoimmunity: is vitamin D status an environmental factor affecting autoimmune disease prevalence? Proc Soc Exp Biol Med 2000;223:230-3.
25. Froicu M, Weaver V, Wynn TA, McDowell MA, Welsh JE, Cantorna MT. A crucial role for the vitamin D receptor in experimental inflammatory bowel diseases. Mol Endocrinol 2003;17:2386–92.
26. Daniel C, Sartory NA, Zahn N, Radeke HH, Stein JM. Immune modulatory treatment of trinitrobenzene sulfonic acid colitis with

calcitriol is associated with a change of a T helper (Th) 1/Th17 to a Th2 and regulatory T cell profile. J Pharmacol Exp Ther 2008;324:23-33.

27. Tang J, Zhou R, Luger D, Zhu W, Silver PB, Grajewski RS, et al. Calcitriol suppresses antiretinal autoimmunity through inhibitory effects on the Th17 effector response. J Immunol 2009;182:4624-32.

28. Chen S, Sims GP, Chen XX, Gu YY, Chen S, Lipsky PE. Modulatory effects of 1,25-dihydroxyvitamin D3 on human B cell differentiation. J Immunol 2007;179:1634-47.

29. Cantorna MT, Mahon BD. Mounting evidence for vitamin D as an environmental factor affecting autoimmune disease prevalence. Exp Biol Med 2004;229:1136-42.

30. Wang TT, Nestel FP, Bourdeau V, Nagai Y, Wang Q, Liao J, et al. Cutting edge: 1,25-dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression. J Immunol 2004;173:2909-12.

31. Gombart AF, Borregaard N, Koeffler HP. Human cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the vitamin D receptor and is strongly upregulated in myeloid cells by 1,25-dihydroxyvitamin D3. Faseb J 2005;19:1067-77.

32. Berer A, Stockl J, Majdic O, Wagner T, Kollars M, Lechner K, et al. 1,25-dihydroxyvitamin D(3) inhibits dendritic cell differentiation and maturation in vitro. Exp Hematol 2000;28:575-83.

33. Griffin MD, Lutz WH, Phan VA, Bachman LA, McKean DJ, Kumar R. Potent inhibition of dendritic cell differentiation and maturation by vitamin D analogs. Biochem Biophys Res Commun 2000;270:701-8.

34. Penna G, Adorini L. 1 Alpha,25-dihydroxyvitamin D3 inhibits differentiation, maturation, activation, and survival of dendritic cells leading to impaired alloreactive T cell activation. J Immunol 2000;164:2405-11.

35. Piemonti L, Monti P, Sironi M, Fraticelli P, Leone BE, Dal Cin E, et al. Vitamin D3 affects differentiation, maturation, and function of human monocyte-derived dendritic cells. J Immunol 2000;164:4443-51.

36. Canning MO, Grotenhuis K, de Wit H, Ruwhof C, Drexhage HA. 1-alpha,25-dihydroxyvitamin D3 (1,25(OH)(2)D(3)) hampers the maturation of fully active immature dendritic cells from monocytes. Eur J Endocrinol 2001;145:351-7.

37. Almerighi C, Sinistro A, Cavazza A, Ciaprini C, Rocchi G, Bergamini A. 1a,25-dihydroxyvitamin D3 inhibits CD40L-induced pro-inflammatory and immunomodulatory activity in human monocytes. Cytokine 2009;45:190-7.

38. van Etten E, Mathieu C. Immunoregulation by 1,25-dihydroxyvitamin D3: basic concepts. J Steroid Biochem Mol Biol 2005;97:93-101.

39. Gregori S, Casorati M, Amuchastegui S, Smiroldo S, Davalli AM, Adorini L. Regulatory T cells induced by 1 alpha, 25-dihydroxyvitamin D3 and mycophenolate mofetil treatment mediate transplantation tolerance. J Immunol 2001;167:1945-53.

40. Ponsonby AL, McMichael A, van der Mei I. Ultraviolet radiation and autoimmune disease: insights from epidemiological research. Toxicology 2002;181-182:71-8.

41. Hypponen E, Laara E, Reunanen A, Jarvelin MR, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. Lancet 2001;358:1500-3.

42. Holick MF. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. Am J Clin Nutr 2004;79:362-71.

43. Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. JAMA 2006;296:2832-8.

44. Litonjua AA, Weiss ST. Is vitamin D deficiency to blame for the asthma epidemic? J Allergy Clin Immunol 2007;120:1031-5.

45. Cantorna MT, Humpal-Winter J, DeLuca HF. In vivo upregulation of interleukin-4 is one mechanism underlying the immunoregulatory effects of 1,25-dihydroxyvitamin D3. Arch Biochem Biophys 2000;377:135-8.

46. Bemiss CJ, Mahon BD, Henry A, Weaver V, Cantorna MT. Interleukin-2 is one of the targets of 1,25-dihydroxyvitamin D3 in the immune system. Arch Biochem Biophys 2002;402:249-54.

47. Staeva-Vieira TP, Freedman LP. 1,25-dihydroxyvitamin D3 inhibits IFN-gamma and IL-4 levels during in vitro polarization of primary murine CD4+ T cells. J Immunol 2002;168:1181-9.

48. Cantorna MT, Woodward WD, Hayes CE, DeLuca HF. 1,25-dihydroxyvitamin D3 is a positive regulator for the two antiencephalitogenic cytokines TGF-beta 1 and IL-4. J Immunol 1998;160:5314-9.

49. Gregori S, Giarratana N, Smiroldo S, Uskokovic M, Adorini L. A 1alpha,25-dihydroxyvitamin D(3) analog enhances regulatory T-cells and arrests autoimmune diabetes in NOD mice. Diabetes 2002;51:1367-74.

50. Kamen DL, Cooper GS, Bouali H, Shaftman SR, Hollis BW, Gilkeson GS. Vitamin D deficiency in systemic lupus erythematosus. Autoimmun Rev 2006;5:114-7.

51. Littorin B, Blom P, Scholin A, Arnqvist HJ, Blohme G, Bolinder J, et al. Lower levels of plasma 25-hydroxyvitamin D among young adults at diagnosis of autoimmune type 1 diabetes compared with control subjects: results from the nationwide Diabetes Incidence Study in Sweden (DISS). Diabetologia 2006;49:2847-52.

52. Patel S, Farragher T, Berry J, Bunn D, Silman A, Symmons D. Association between serum vitamin D metabolite levels and disease activity in patients with early inflammatory polyarthritis. Arthritis Rheum 2007;56:2143-9.

53. Ruiz-Irastorza G, Egurbide MV, Olivares N, Martinez-Berriotxoa A, Aguirre C. Vitamin D deficiency in systemic lupus erythematosus: prevalence, predictors and clinical consequences. Rheumatology 2008;47:920-3.

54. Zold E, Szodoray P, Gaal J, Kappelmayer J, Csathy L, Gyimesi E, et al. Vitamin D deficiency in undifferentiated connective tissue disease. Arthritis Res Ther 2008;10:R123.

55. Fukazawa T, Yabe I, Kikuchi S, Sasaki H, Hamada T, Miyasaka K, et al. Association of vitamin D receptor gene polymorphism with multiple sclerosis in Japanese. J Neurol Sci 1999;166:47-52.

56. Simmons JD, Mullighan C, Welsh KI, Jewell DP. Vitamin D receptor gene polymorphism: association with Crohn's disease susceptibility. Gut 2000;47:211-4.

57. Garcia-Lozano JR, Gonzalez-Escribano MF, Valenzuela A, Garcia A, Nunez-Roldan A. Association of vitamin D receptor genotypes with early onset rheumatoid arthritis. Eur J Immunogenet 2001;28:89-93.

58. Motohashi Y, Yamada S, Yanagawa T, Maruyama T, Suzuki R, Niino M, et al. Vitamin D receptor gene polymorphism affects onset pattern of type 1 diabetes. J Clin Endocrinol Metab 2003;88:3137-40.

59. Cantorna MT, Munsick C, Bemiss C, Mahon BD. 1,25-Dihydroxycholecalciferol prevents and ameliorates symptoms of experimental murine inflammatory bowel disease. J Nutr 2000;130:2648-52.

60. Cantorna MT, Humpal-Winter J, DeLuca HF. Dietary calcium is a major factor in 1,25-dihydroxycholecalciferol suppression of experimental autoimmune encephalomyelitis in mice. J Nutr 1999;129:1966-71.

61. May E, Asadullah K, Zügel U. Immunoregulation through 1,25-dihydroxyvitamin D3 and its analogs. Curr Drug Targets Inflamm Allergy 2004;3:377-93.