

Vitamin D and Autoimmune Disease

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ABSTRACT

Vitamin D as a part of the endocrine system is an important component in the interaction between the kidney, bone, parathyroid hormone, and the intestine, which maintains extracellular calcium level within normal limits, in order to keep the vital physiologic process and skeletal integrity. Vitamin D is also associated with hypertension, muscular function, immunity, and ability to encounter infection, autoimmune disease, and cancer. The role of vitamin D in immunity is a feedback reaction of paracrine to eliminate inflammation or to influence CD4 T-cell differentiation and or to increase the function of T suppressor cell or combination between both. The active form of vitamin D produces and maintains self immunologic tolerance, some studies show that 1,25(OH)₂D inhibits induction of disease in autoimmune encephalomyelitis, thyroiditis, type-1 diabetes mellitus, inflammatory bowel disease (IBD), systemic lupus erythematosus, and collagen-induced arthritis and Lyme arthritis.

Key words: vitamin D, autoimmune disease.

INTRODUCTION

Vitamin D is a lipid-soluble vitamin which consists of steroid molecule structure.¹ Vitamin D is not a pure vitamin, because vitamin D requirements are not only fulfilled through consumption of food containing vitamin D but could also be synthesized by the body with the help of sun ray exposure.^{1,2} Currently vitamin D has been considered to be metabolized in the body into steroid hormone metabolites: 1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃] or calcitriol. Several studies focused on interaction between vitamin D metabolites with vitamin D receptors (VDR), as a part of steroid receptor group. The ability of 1,25(OH)₂D₃ in inhibiting growth and stimulating the differentiation of various cell types has opened the possibility of other potentials of vitamin D

in preventing cancer, modulating the immune system, and regulating several endocrine system.¹ This could be proved through previous epidemiological studies that provide proofs on the relationship between vitamin D deficiency with the incidence of cancer, autoimmune diseases, hypertension, and diabetes.¹

Provitamin D is mainly found in animal-based food. Natural vitamin D is found in fish oil, which also serves as sources of vitamin A and D, and vitamin D could also found in eggs, butter, liver, and food made from oily fish such as mackerel, salmon, sardine and herring. At present there are lots of food that already contains vitamin D supplementation, especially dairy products and cereals. Plant-based foods are usually low in vitamin D. This is why a vegetarian should consume around 400 IU daily vitamin D supplementation.^{3,4}

This paper would like to discuss the most current development of vitamin D, especially elements associated with autoimmune disease. Moreover, we would also briefly discuss the latest development of the role of vitamin D as a part of endocrine system including: the mechanism that facilitates the transport of vitamin D metabolites, direct effect of 1,25(OH)₂D₃ that interacts with vitamin D receptor (VDR) and the important function of 1,25(OH)₂D₃ as an autocrine/paracrine gland.⁷

VITAMIN D METABOLISM

Vitamin D requirement is fulfilled through diet and sunlight exposure on the skin.¹ Exposure of sun light to the skin induces photolytic conversion of 7-dehydrocholesterol to previtamin D₃, followed by thermal isomerization of vitamin D₃. It has been proved epidemiologically that vitamin D deficiency mostly affect four-seasons countries especially North America and Europe. This is due to the food deficiency, and furthermore by lack of sun light exposure which at present indicated by the widespread use of sunscreen.^{1,7,8}

Vitamin D is divided into three groups: vitamin D (active and inactive), prodrug or prohormone, and vitamin D analog. Calcitriol [1,25(OH)₂D₃] is the

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active form of vitamin D which functions as endocrine/paracrine gland.⁸ Vitamin D₃ is derived from 7,8-dehydrocholesterol (provitamin D₃), a precursor for cholesterol. When the skin is exposed to sun light or certain artificial light source, ultraviolet radiation will enter the epidermis and cause transformation of 7,8-dehydrocholesterol to vitamin D₃ (cholecalciferol). The wavelength of 290-315 nm is absorbed by C5 and C7-dehydrocholesterol carbon chain to synthesize vitamin D₃ a few hours after the exposure of sun ray.^{1,6-8} (Figure 1)

As age increases, the skin's ability to synthesize vitamin D declines. This ability decreases fourfold over 70 years of age. Factors affecting synthesis of vitamin D₃ are height, geographical location, duration and area of sun exposure.^{1,6,7} Sun exposure causes mild erythema and increases serum vitamin D concentration equals with oral 10.000-25.000 IU consumption (1 IU = 0,025µg). When the sun exposure is not sufficient to fulfill the needs for vitamin D, oral consumptions such as milk are required in order to overcome the deficiency. Vitamin D requirement for age 51-70 years and over 71 years are 400 and 600 IU/day, while children and young adults at least need about 600 IU of vitamin D each day.⁸⁻¹⁰

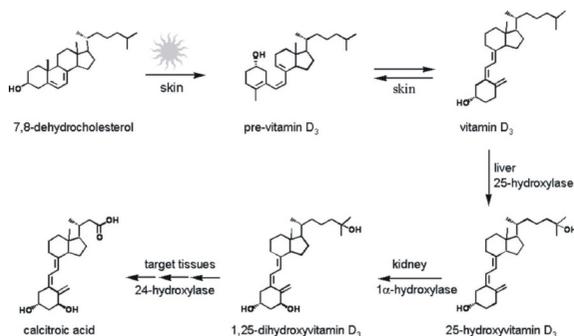


Figure 1. Synthesis, activation, and catabolism of vitamin D. Vitamin D₃ is synthesized on the six through photolytic reaction of 7,8-dehydrocholesterol followed by thermal isomerization. Vitamin D is then transported to the liver by vitamin D binding protein in the serum, then converted to 25-hydroxyvitamin D₃ in the liver, as the main vitamin D₃ metabolite in the circulation. The final phase of activation sequence is the activation of 1β-hydroxylase which is mainly found in the kidney, forming 1,25-dihydroxyvitamin D₃ as the hormonal form of vitamin D. Catabolic inactivation is done by 24-hydroxylase which catalyzes the series of oxidation above as the end of vitamin D passage in the body. (Dusso AS, Brown AJ, Slatopolsky E. *Vitamin D. Am J Physiol Renal Physiol.* Vol 289. July 2005)

In the liver, vitamin D is metabolized to 25(OH)D by the liver cell mitochondria and microsome enzymes with 21-day half time. Serum 25(OH)D concentration varies between 20 to 200 nmol/l (8-80 ng/ml). Individuals exposed greatly to sun rays could show up to 250 nmol/l (100 ng/ml) serum 25 (OH)D concentration. Serum 25(OH)D reflects 25(OH)D₂ and 25(OH)D₃

concentration. Ratio of both types of vitamin D depends on D₂ dan D₃ concentration in the diet and amount of previtamin D₃ from the sun exposure.⁸ Synthesis of 25(OH)D in the liver is regulated by a feed back mechanism, the increased dietary consumption and endogenous production of vitamin D₃. This level could increase up to 500 ng/ml. Serum 25 (OH)D level decreases in severe chronic liver disease.⁶⁻⁹

After being synthesized in the body, vitamin D will be transported to the kidney by vitamin D binding protein and obtain additional C1 and C24. Activity of 25(OH)D in the kidney mitochondria is elevated by increasing the conversion of 25(OH)D to 1,25(OH)₂D. Hypocalcemia does not directly regulate this process. Decrease in serum calcium concentration stimulates secretion of parathyroid hormone (PTH), which will cause secondary hyperparathyroidism.^{8,9}

Synthesis of 1,25(OH)₂D increases the PTH effect in reducing phosphate concentration, especially in the renal cells. 1,25(OH)₂D also limits the activity of 25(OH)D-1β-hydroxylase and increases the conversion of 25(OH)D to 24R,25-dihydroxyvitamin D [24,25(OH)₂D] which serum concentration supposed to be between 0.5-5.0 ng/ml in normal condition. 24,25(OH)₂D is the substrate of 25(OH)D-1β-hydroxylase and converted to 1β,24R,25 trihydroxyvitamin D [1β,24,25(OH)₃D] which metabolizes inactive calcitric acid substances.^{1,6-9}

1,25(OH)₂D is produced in the kidney and placenta, first bound to vitamin D binding protein and transported to various target organs, then the free form will be uptaken by the cells and transported to the special nuclear protein receptor. Vitamin D receptor (VDR) is a family of steroid-retinoid-thyroid hormone-vitamin D receptor group. VDR interacts with the retinoic acid X receptor (RXR) forming a heterodynamic complex form (RXR-VDR) and binds specific DNA and known as vitamin D response element (VDRE).¹

In the intestine, VDR activates the synthesis of calcium binding protein, while in the spine it stimulates the production of osteocalcin, osteopontin, and alkaline phosphatase. 1,25(OH)₂D increases extracellular calcium transport to the intracellular compartment and mobilizes intracellular calcium. Here 1,25(OH)₂D stimulates calcium and phosphate transport from the small intestine lumen into the circulation. 1,25(OH)₂D synergically increases bone resorption with PTH. PTH and 1,25(OH)₂D interacts with the osteoblastic receptor and fibroblast stroma, and stimulates production of RANK ligand on osteoblastic cell surface. RANK ligand interacts through its receptors on the immature osteoclasts, stimulating conversion of immature

osteoclastic precursors to mature osteoclasts. VDR ablation result in compromised intestinal calcium absorption and secondary hypoparathyroidism.^{1,7,8}

During the bioactivation process of vitamin D, the 1,25(OH)₂D form is synthesized from 25(OH)D. In normal physiologic condition, this process is mainly completed in the kidney, however there were some other organs that could also facilitate the conversion, especially in specific conditions (pregnancy, chronic renal disease, sarcoidosis, tuberculosis, granulomatous lesions, and rheumatoid arthritis). However, the extrarenal production of 1,25(OH)₂ is mainly used as autocrine/paracrine gland with specific cell function.¹ Estrogen, prolactine, and growth hormone could alter the 1,25(OH)₂D synthesis. The increase of calcium needs during growth, pregnancy, and lactation increases the absorption of calcium from dairy products and increases the activity of 25(OH)D-1β-hydroxylase.^{1,8} (Figure 2)

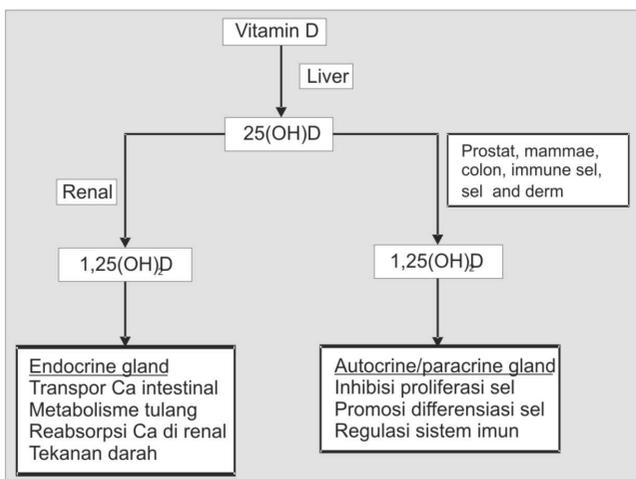


Figure 2. Production of renal and extrarenal 1,25(OH)₂D. (Dusso AS, 2005)

CLASSIC ROLE OF VITAMIN D

Vitamin D as an endocrine system is an important component in the interaction between the kidney, bone, parathyroid hormone, and the intestine, which maintains extracellular calcium concentration within normal limits, so that maintains the vital physiologic process and skeletal integrity.^{1,9} (Figure 3)

In the intestine, the role of vitamin D is vital in the calcium and phosphate absorption process from the food. 1,25(OH)₂D stimulates the uptake and active transport of calcium in the cell.¹ In the skeleton, vitamin D plays a very important role in building and maintaining skeletal mineralization. Bone growth requires calcium and 1,25(OH)₂D to build an optimal osteoblastic bone formation. On the other hand, osteoclastic reabsorption also needs 1,25(OH)₂D and

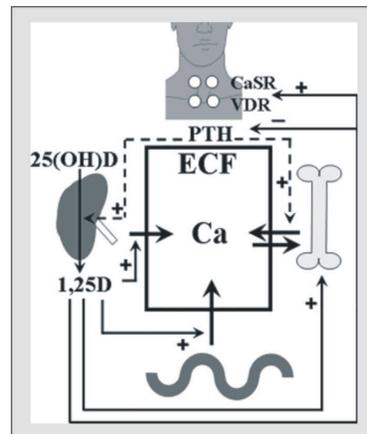


Figure 3. Role of 1,25(OH)₂D in calcium homeostasis. 1,25(OH)₂D is produced in the kidney and influences calcium absorption, bone remodelling control, decreasing PTH function, and calcium reabsorption in order to maintain normal extracellular calcium concentration which is essential for normal cell physiology and skeletal integrity. (Dusso AS, Brown AJ, Slatopolsky E. Vitamin D. Am J Physiol Renal Physiol. Vol 289. July 2005)

VDR. The above components are very essential, so that when any of those are absent, the skeletal balance process will not work properly.^{1,8}

At the parathyroid hormone, vitamin D is a potential endocrine system as a modulator of parathyroid function. Vitamin D deficiency causes parathyroid hyperplasia, which increases the synthesis and secretion of PTH. Administration of 1,25(OH)₂D will inhibit PTH synthesis and growth of parathyroid cells, so that the 1,25(OH)₂D administration serves as therapy for hyperparathyroidism in chronic renal disease patients.^{1,9}

At the kidney, the most important endocrine effect of 1,25(OH)₂D on the kidney is tight control of hemostasis through suppression mechanism of 1β-hydroxylase and stimulation of 24-hydroxylase and through the expression of megalin at the proximal tubule.^{1,16}

NON-CLASSIC ROLE OF VITAMIN D

Various genetic, nutrition, and epidemiologic studies, related vitamin D deficiency not only to calcium hemostasis but also to hypertension, muscular function, immunity and ability to overcome infection, autoimmune disease, and cancer.¹ Below we will discuss about the role of vitamin D other than its classical role to maintain calcium homeostasis and skeletal system.¹

Cell growth suppression. Abe and colleagues found that 1,25(OH)₂D inhibits clonal proliferation of various leukemic cell varieties in human. On the other hand 1,25(OH)₂D also stimulates normal cell differentiation and turns myeloid leukemic cell precursor to be more mature and less aggressive. Result of this study has opened the gate for some other new researches that try to

prove the possibility of calcitriol as therapy for leukemia and myeloproliferative disorders.¹ The protective role of vitamin D to cancer could also be proved with the strong epidemiological relationship between prostate breast, and colon cancer with vitamin D deficiency. Antiproliferative action of vitamin D is more of autocrine nature than endocrine.^{1,16} The underlying mechanism for the hypothesis is by linking $1,25(\text{OH})_2\text{D}$ -VDR system that blocks cancer cell cycle in the transition between G1-G0 through several pathways such as:

1. $1,25(\text{OH})_2\text{D}$ induces cyclin-dependent kinase inhibitor p21 gene transcription in a way that it inhibits cancer cell growth and stimulates monocyte-macrophage cell differentiation.
2. $1,25(\text{OH})_2\text{D}$ induces the synthesis and or stabilization of cyclin-dependent kinase inhibitor p27, which prevents proteosomal degradation.
3. In tumors which growth are regulated by over-expression of TGF- α /EGFR, $1,25(\text{OH})_2\text{D}$ inhibits growth signal of EGFR on the cell membrane and inhibits transactivation of cyclin D1 gene from EGFR at the nucleus. This is the evidence that vitamin D has the potential as therapy for hyperplastic keratinocyte growth in psoriasis patients.
4. In HL60 cell line monocyte and in osteoblast, $1,25(\text{OH})_2\text{D}$ induces the expression of C/EBP β , a protein that is currently believed to have potential as a suppressor of oncogenic-cyclin D1 in epithelial tumor.
5. $1,25(\text{OH})_2\text{D}$ reduces HSPA20 level, a phospho protein that maintains growth and endurance of prolactin-dependent rat Nb2T lymphoma, a tumor that is greatly affected by hormonal factor.

Apoptosis regulation. $1,25(\text{OH})_2\text{D}$ has been proven to be able to induce apoptosis, so that it becomes an important contributor in suppressing excessive growth of the cells. In breast cancer, $1,25(\text{OH})_2\text{D}$ induces apoptosis of cancer cell through reciprocal modulation mechanism of Bcl2 and Bax. This increases intracellular calcium level which will activate calcium-dependent proapoptotic protease, microcalpain and caspase 12. $1,25(\text{OH})_2\text{D}$ also increases proapoptotic and antitumor potential in ionizing radiation in breast cancer. However, the opposite is found on the skin, where $1,25(\text{OH})_2\text{D}$ protects keratinocyte from apoptosis caused by UV light exposure or chemotherapy. Thus the most important thing that could be obtained here is the role of $1,25(\text{OH})_2\text{D}$ as a proapoptotic agent is highly important in controlling the hyperplastic cell growth.^{1, 19-21}

Immune response modulation. Effectivity of vitamin as a part of endocrine system against infection, autoimmune disease, and tolerance to transplantation

is a result of prodifferentiation effect of $1,25(\text{OH})_2\text{D}$ to macrophage-monocyte, antigen presenting cells, dendrite cell (DC) and lymphocyte.¹ This could be proved in vivo in humans and animals that have low VDR function and or vitamin D through in vitro model on regulative function of vitamin D to the immune system.¹⁶

Regulation of skin function and differentiation. Vitamin D has been widely used as a therapy for various types of skin diseases, especially for psoriasis. However, not until the 1980s the true amazing potential of vitamin D in skin protection and therapy for psoriasis was confirmed. This was evidenced through a study that showed dramatic reaction of psoriatic lesions in patients receiveing 1α -hydroxyvitamin D supplementation for severe osteoporosis treatment. As mentioned before, $1,25(\text{OH})_2\text{D}$ is an antiproliferative agent in psoriatic keratinocyte that experiences TGF- α overexpression, which results in the ability of $1,25(\text{OH})_2\text{D}$ to inhibit mitogenic signals of the TGF- α /EGFR growth curve.¹ The immunosuppressive potential of $1,25(\text{OH})_2\text{D}$ in Langerhans cells, antigen-presenting cells of the skin, could also serve as mediator of sterol effect in psoriasis, melanoma, and scleroderma treatment. Not only that, apparently $1,25(\text{OH})_2\text{D}$ is also very important in normal hair and skin growth through keratinocyte differentiation modulation mechanism on the skin.^{1,22}

Regulation of the renin-angiotensin system. The renin-angiotensin system is the main system in regulation of blood pressure, electrolytes, and homeostasis of body fluid volume. Latest clinical and epidemiological studies found significant relationship between inadequate sun exposure or low serum $1,25(\text{OH})_2\text{D}$ concentration with blood pressure and/or the plasma renin activity. This is the evidence of one other role of vitamin D, as negative regulator of the renin-angiotensin system. A study on VDR-null rat found increased plasma renin concentration and increased angiotensin II production, causing hypertension, myocardial hypertension, and increased fluid intake.^{1,25,26}

Regulation of insulin secretion. In an experiment using animals, vitamin D deficiency was related with earlier onset and more aggressive type of diabetes mellitus. This might be in line with the immune function abnormality and disturbance in insulin secretion which are mediated by glucose due to the lack of calcitriol. The currently believed mechanism is by modulating expression of calbindin through VDR that regulates intracellular calcium flow, which results in insulin secretion of the cell.¹ This is proved by $1,25(\text{OH})_2\text{D}$ deficiency in patients with chronic renal failure that always experience disturbance in insulin secretion. Then

the latest study that found 1α -hydroxylase activity in pancreatic cell has increased the possibility of vitamin D potential in regulating vitamin D secretion and preventing the onset of diabetes mellitus.^{1,22,26} This subject needs further study.

Control of muscular function. Muscle weakness and atrophy together with electrophysiological disturbance in muscle contraction and relaxation mechanism often found in patients with vitamin D deficiency, for example in chronic renal failure and long term use of anticonvulsants that could lower serum vitamin D level. Selectively to the cardiac muscles, $1,25(\text{OH})_2\text{D}$ prevents myocardial hypertrophy and facilitates synthesis and release of atrial natriuretic factor. In patients with chronic renal failure, routine supplementation of vitamin D could repair left ventricular function in patients with cardiomyopathy and muscular weakness. The underlying mechanism for this function is not yet clear and still needs further study.^{1,16}

Control of central nervous system. The role of $1,25(\text{OH})_2\text{D}$ to the central nervous system includes induction of VDR (VDR is expressed in the brain and some parts of central and peripheral nervous system) in a way that it helps the effectivity of conduction of motor neuron and synthesis of neurotropic factor (for example nerve growth factor and neurotrophin) that prevents loss of neuron cell.¹ Latest study also found that $1,25(\text{OH})_2\text{D}$ also stimulates expression of neurotropic factor from glia cell line, thus it makes vitamin D a potential candidate for the therapy of Parkinson disease.¹ The close relationship between vitamin D deficiency and abnormal brain growth has made the researchers investigate the possibility of vitamin D as potential therapy for schizophrenia. On the other hand, previous study had found severe motor disturbance in adult rats previously experiencing vitamin D deficiency.^{1,21}

AUTOIMMUNE DISEASE

The etiology and pathogenesis of autoimmune disease is not yet fully understood. However, the formation of autoantibody and T cell activation are based on the same mechanism with immune reaction to foreign materials. When the immune system constantly produce autoantibody (AAB) or active T cell towards endogenous antigen, this will cause tissue or organ damage (autoimmune disease).

Below are several mechanisms considered to be responsible to the occurrence of autoimmune disease:

1. Genetic predisposition caused by several HLA II allele: for example, HLA II DR3+DR4 allele carrier is 500 times more possible to cause type-1 diabetes mellitus compared to DR2 +DR2 carrier.
2. Sex factor especially in autoimmune disease affected

by hormonal factors, for example ratio of systemic lupus erythematosus between female and male is 10:1, and on the opposite in ankylosing spondylitis is 1 : 3.

3. Auto antigen from corresponding area (brain, testicle, uterus) enters systemic circulation (through the vessels, but not through lymphatic system) and interacts with T cell, but this usually does not trigger autoimmune disease, because auto antigen is accompanied by TGF. This is responsible in activation of Th2 cell (other than destruction of Th1 cell). None of these autoantigenic areas cause autoimmune disease, such as myelin-based protein from the brain that causes multiple sclerosis, one of the widely known autoimmune disease. It could be observed on animal trials that myelin production could not be tolerated or T cell anergy, but more to an immunological ignorance; and will become a myelin destruction when specific myelin is present (due to an infection), this is caused by inflammation because the Th1 cell is activated everywhere and then penetrating to the brain. Another example is infertility due to autoantibody to sperm. In normal condition the embryo or fetus that carries a number of paternal foreign antigen is well tolerated, through anergic process from maternal lymphocytes induced by the placenta. When the placenta is unable to tolerate this, abortion will occur.
4. Infection carries a great possibility for autoimmune disease. For example, specific T cell for myelin is activated by the presence of bacteria. This pathogen might trigger costimulatory signals. In addition, the antibody fighting against a few antigens or T cell that cross-reacted with autoantigen, such as antibody to fight against *Streptococcus* with autoantigen from the heart (endocarditis), joint (rheumatoid arthritis), and the kidney (glomerulonephritis)
5. Disturbance in immune system regulation with unknown etiology is probably due to the lack of CD8-containing cells that are supposed to kill CD4-containing cells. Immune mechanism of autoimmune disease is related with type II-V hypersensitivity. One explanation is systemic autoimmune disease event such as systemic lupus erythematosus (type III hypersensitivity) that is considered as organ-specific and tissue-specific autoimmune disease. Another example of type II hypersensitivity is autoimmune hemolytic anemia and Goodpasture syndrome; rheumatoid arthritis, multiple sclerosis, and type I diabetes mellitus (where T cell-CD8 that destructs pancreas B cell) is an example of tipe IV reaction. Example of type V hypersensitivity is activation of hormone receptor (Grave's disease) or hormone receptor block (myasthenia gravis).¹⁷ (Figure 4)

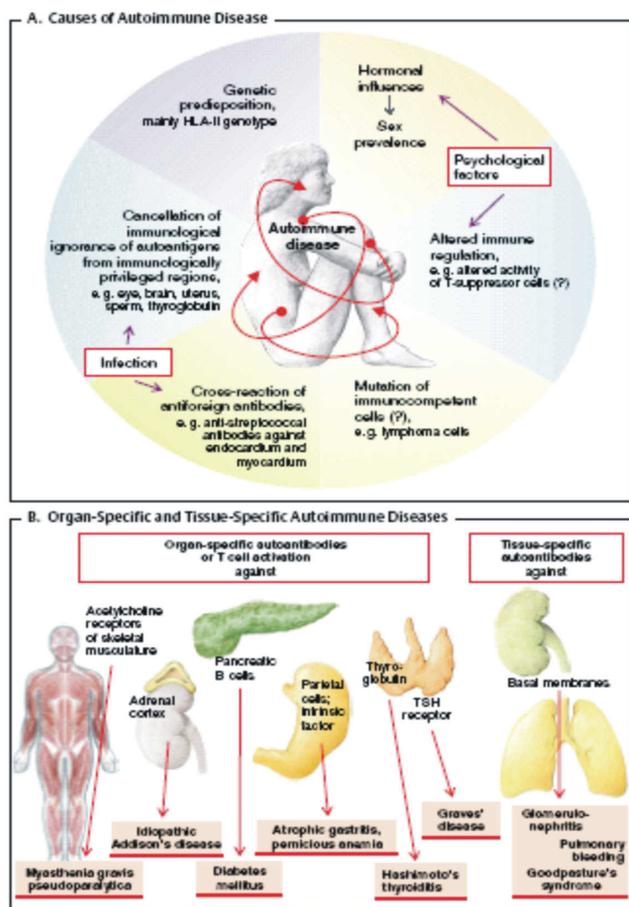


Figure 4. Autoimmune disease. A. Etiology of autoimmune disease is divided to physiologic and infection factor. B. Autoimmune disease could be organ-specific or tissue specific, and both produces antibody. (Silbernagl S, 2000)

ROLE OF VITAMIN D IN THE IMMUNE SYSTEM

Vitamin D as an endocrine system has the ability to control infection, autoimmune disease, and tolerance to organ transplantation. This is based on the ability of $1,25(\text{OH})_2\text{D}$ which shows prodifferentiation effect of monocyte macrophage, antigen presenting cell (APC), dendrite cell (DC), and lymphocyte.¹

There is a cause and effect relationship between $1,25(\text{OH})_2\text{D}$ -VDR function and immunity to infection, where vitamin D-deficient patients often experience reinfection and become worse, for example in Rickets, and compromised immune system in chronic renal failure with vitamin D deficiency. Altered VDR function as a result of certain VDR allele expression, influences the acceptance of mycobacteria or viral infection. $1,25(\text{OH})_2\text{D}$ also function as an adjuvant to vaccine, the mechanism is by $1,25(\text{OH})_2\text{D}$ inducing p21 and C/EBP β that could mediate the increase of macrophage-monocyte immune function. As been mentioned before, $1,25(\text{OH})_2\text{D}$ induces p21 which directly function in the differentiation process of monocyte into mature

macrophage. C/EBP β is an important transcription factor to macrophage which serve as antibacteria, antivirus, and antitumor, and also important in IL-12 synthesis, a cytokine mediating the potential of Th1 function. The fact is, the vital weakness in all of these macrophages is found in rats without C/EBP β . $1,25(\text{OH})_2\text{D}$ induces the expression C/EBP β in the macrophage which contributes to the increase of monocyte differentiation into macrophage which is mediated by $1,25(\text{OH})_2\text{D}$, immune function, and ability to fight against bacteria and tumor cell growth.^{1,17,19}

Local production of $1,25(\text{OH})_2\text{D}$ triggered by bacteria-activated macrophage might provide better explanation on the relationship between vitamin D deficiency and increased infection due to mycobacteria. Latest study has proved that $1,25(\text{OH})_2\text{D}$ production is associated with cytokine regulation in the macrophage. γ -Interferon, increased cytokines related to the severity of tuberculosis in the patient, is a strong inductor of 1α -hydroxylase gene expression which determines the production of $1,25(\text{OH})_2\text{D}$.¹

$1,25(\text{OH})_2\text{D}$ does not only induces macrophage function as antibacteria, but it also work in synergy with the action mediated by Stat1 γ -interferon, the most potent cytokine for macrophage activation. Interaction between $1,25(\text{OH})_2\text{D}$ -VDR complex and Stat1 γ -interferon prevents the deactivation of Stat1, and furthermore prolongs the transactivation of Stat1 from the gene that responds to γ -interferon, including C/EBP β , in a way that it causes significant increase of macrophage immune function. The potential ability of $1,25(\text{OH})_2\text{D}$ -VDR complex in fighting against in vivo mycobacterial infection is contradictive with in vitro data which found that $1,25(\text{OH})_2\text{D}$ has strong suppressive ability towards IL-12 and γ -interferon synthesis, as well as Th1 response. The relationship between VDR and increased Th1 response is proved in *VDR-null* rats that showed failure in the production of Th1 promoting factor IL-18, decrease in Th1 proliferative response to CD3 and CD28 stimulation in the presence of exogenous IL-12, and the decrease of Stat4 expression, a Th1 transcription factor.^{1,24,26}

Contrast with the above mechanism, the stimulation effect to macrophage-monocyte, $1,25(\text{OH})_2\text{D}$ serves as immunosuppressive agent to the lymphocyte. Some cytokines involved in T cell function is the direct target of $1,25(\text{OH})_2\text{D}$ action, including IL-2 which performs suppressive action through $1,25(\text{OH})_2\text{D}$ -VDR complex that weakens the formation of NF-AT complex distal to NF-AT from the IL-2 promotor. $1,25(\text{OH})_2\text{D}$ also supports the development of Th2 cell through the direct effect to original CD4 cell. The most current update from

1,25(OH)₂D is its role in maintaining dendrite cell in immature condition. Dendrite cell is an antigen-presenting cell that could turn T cell into tolerated (immature) condition or immunologic condition, depend on the antigen and the maturity status of dendrite cell. Administration of 1,25(OH)₂D causes decreased expression of costimulatory DC40, DC80, DC86 and IL-12 molecule, and increased level of IL-10. 1,25(OH)₂D also regulates the increase of ILT3 receptor in the dendrite cell, which is associated with tolerance to induction and modulation of chemokine production. Combination of the T cell effect have caused suppression to the T cell.^{1,19,21}

1,25(OH)₂D also prevents rejection to transplantation tissue. Studies on transplantation in rats show that 1,25(OH)₂D is more effective than cyclosporin in maintaining graft without increasing the incidence of fungal and viral infection. This is also found in renal transplantation studies.¹

Overall, the underlying mechanism for 1,25(OH)₂D ability in immunity is a feedback reaction of paracrine gland to minimize inflammation or to stimulate CD4 T cell differentiation and or to increase T suppressor cell function or combination between both.¹

INVOLVEMENT OF VITAMIN D IN AUTOIMMUNE DISEASE

Studies have shown evidences of 1,25(OH)₂D in inhibiting disease induction in autoimmune encephalomyelitis, thyroiditis, type-1 diabetes mellitus, inflammatory bowel disease (IBD), systemic lupus erythematosus, and collagen-induced arthritis and Lyme arthritis, as reported by Hayes et al and Adorini et al. Vitamin D deficiency could accelerate the occurrence of autoimmune encephalomyelitis, but the severity is lower in rats without VDR. In contrast, IBD is more easily found in rats without VDR. This fact has stimulated further study on suspected different autoimmune regulation between the gastrointestinal tract and the central nervous system. Seasonal variation in multiple sclerosis autoimmune disease has proved that the incidence and severity of the disease is affected by serum vitamin D level and sun exposure.^{1,16,21}

From several studies in animals, vitamin D prevents or decreases the intensity of autoimmune diabetes and allergic encephalomyelitis. In human, vitamin D deficiency is one risk factor of type-1 diabetes and multiple sclerosis, however there is still very limited data on this issue.^{1,16}

Kasandra L Munger from Harvard explained that vitamin D has protective effect to multiple sclerosis. Study in 187.500 US nurses proved that women consum-

ing at least 400 IU of vitamin D daily only shows 60% risk of experiencing multiple sclerosis compared to women that only consume less vitamin D. Incidence of multiple sclerosis and other autoimmune disease tends to be more rarely found around the equator with sufficient ultraviolet sun exposure.¹⁶

Cantorna et al studied in animal model about multiple sclerosis, lupus, inflammatory bowel disease, and type-1 diabetes where autoimmune symptoms are suppressed or eliminated after the animals receive 1,25(OH)₂D or the analogue chemical substances. This study also proved that in rats, 1,25(OH)₂D or its analogue could prevent rejection in organ transplantation.¹⁶⁻¹⁹

VDR found in peripheral mononuclear cells has opened wide possibilities for studies on the role of vitamin D as immune system regulator. Currently there are lots of evidences that explain the effect of 1,25(OH)₂D to the immune response. In studies about roles of vitamin D especially in autoimmune disease, Cantrona et al created a model using rats with experimental autoimmune encephalomyelitis (EAE). It could be seen that EAE was mediated by CD4 + T cell (Th1) that recognizes protein in the central nervous system (CNS) through IL-2, γ interferon and TNF- α , while on the other hand Th2 cell mediates IL-10 and IL-4 formation which suppresses EAE in rats. This study proved that normal immune response depends on the balance between Th1 and Th2 cell. One of the causes of autoimmune disease is the domination of immune response by more Th1 and less Th2.²⁴

The study was further elaborated by administration of vitamin D supplement in rats with EAE. In vivo studies has shown that injection of 1,25(OH)₂D could prevent EAE and arthritis, and could delay the onset of type-1 diabetes. In vitro, 1,25(OH)₂D inhibits proliferation of T cell and decreases Th1 production to maintain balance between Th1 and Th2 production. Moreover, 1,25(OH)₂D inhibits Th1 which regulates hypersensitivity response.²⁴ This T cell and balance regulation by 1,25(OH)₂D is currently believed as the underlying mechanism for vitamin D protective action to autoimmune disease. (Figure 5)

At present time, Cantorna and colleagues is focusing their study on the mechanism of benefits of vitamin D to the immune system. Their study indicates that the ability of vitamin in T cell formation affects how mature T cell works. Vitamin D deficiency causes cell to produce more reactive agent than other cells, these cells are produced when T cells grow with excessive level of vitamin D. According to Cantorna, once an autoimmune disease become full-blown, there would be no more chance to alter T cell development.¹⁶

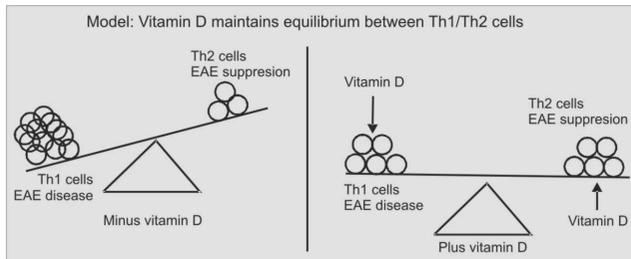


Figure 5. Model illustrating experimental autoimmune encephalomyelitis (EAE) event (left) in vitamin D depletion and in vitamin D sufficient condition (right). It is hypothesized that vitamin D regulates Th cell development by maintaining balance between Th1 and Th2. (Cantorna MT, 2000)

CONCLUSION

Vitamin D as an endocrine system is an essential component in the interaction between the kidney, bone, parathyroid hormone, and the intestine which maintains extracellular calcium level within normal limits at all times in order to sustain vital physiologic process and skeletal integrity. Vitamin D is also related to hypertension, muscular function, immunity, and protection to infection, autoimmune disease, and cancer.

The role of $1,25(\text{OH})_2\text{D}$ in immunity is a feedback mechanism of the paracrine gland in suppressing inflammation or affecting CD4 T cell differentiation and or increasing the function of T suppressor cell or combination of both. Several studies on $1,25(\text{OH})_2\text{D}$ in producing and maintaining self immunologic tolerance show that $1,25(\text{OH})_2\text{D}$ prevents induction of disease in autoimmune encephalomyelitis, thyroiditis, type-1 diabetes mellitus, inflammatory bowel disease (IBD), systemic lupus erythematosus, and also collagen-induced arthritis and *Lyme arthritis*.

$1,25(\text{OH})_2\text{D}$ inhibits T cell proliferation and reduces Th1 production to maintain balance between Th1 and Th2 production. Moreover, $1,25(\text{OH})_2\text{D}$ inhibits Th1 which regulates hypersensitivity response. Regulation of $1,25(\text{OH})_2\text{D}$ to T cell towards balance is currently believed as the underlying mechanism for the protective effect of vitamin D to autoimmune disease. The role of vitamin D in the body, both classic and non-classic, especially its function in immunity and autoimmune disease is not yet clear, and therefore needs further study.

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