

The Impact of Vitamin D on The Development of Multiple Sclerosis (Review article)

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Abstract:

Multiple Sclerosis is a harmful disease causes severe and painful symptoms. In the recent period, researchers have tended to study the effect of vitamin D deficiency on general health. Several studies have reported that there is a relation between vitamin D levels and MS disease progression. Epidemiological testimony

and reports have recorded that there are an association between the decrement in plasma vitamin D levels and the incidence of MS also with the disease development; and it has seen that when take vitamin D as supplement may protect the MS patients against disease development. Despite clear evidence of the correlation between disease progression and vitamin D deficiency but the mechanism yet unclear.

Key words: vitamin D deficiency, multiple sclerosis, metabolism.

تأثير فيتامين د على تطور مرض التصلب المتعدد

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الخلاصة:

التصلب اللويحي مرض ضار يسبب أعراضاً شديدة ومؤلمة. اتجه الباحثون في الفترة الأخيرة إلى دراسة تأثير نقص فيتامين د على الصحة العامة. أفادت العديد من الدراسات أن هناك علاقة بين مستويات فيتامين (د) وتطور مرض التصلب العصبي المتعدد. سجلت الشهادات والتقارير الوبائية أن هناك علاقة بين انخفاض مستويات فيتامين (د) في البلازما والإصابة بمرض التصلب العصبي المتعدد أيضاً مع تطور المرض ؛ وقد لوحظ أنه عند تناول فيتامين د كمكمل قد يحمي مرضى التصلب المتعدد من تطور المرض. على الرغم من وجود دليل واضح على العلاقة بين تطور المرض ونقص فيتامين (د) إلا أن الآلية غير واضحة حتى الآن.

الكلمات المفتاحية: نقص فيتامين دي، مرض التصلب العصبي، الايض.

Introduction:

The knowledge of the fact that the impact of vitamin D on growth and development, bone, muscles, immune and nerve system function has focused for 3 decades. The increment in the vitamin D levels is related to slow the severity of multiple sclerosis (MS) development, and with decrease the

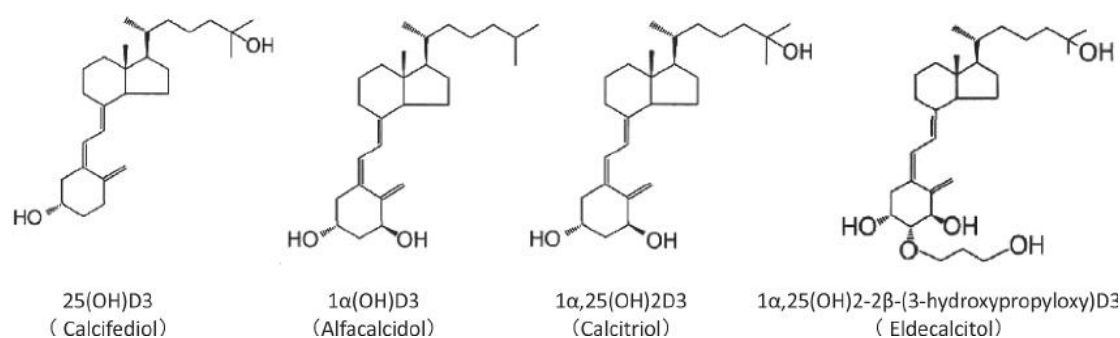
clinical MS activity which include lowering the risk of relapse and disease progression by decrease the disease activity on brain MRI ^[1]. Usually in general population, the taken of vitamin D as supplement may reduce the risk of MS, and also in babies of women who supplemented Vitamin D before and

during pregnancy ^[2]. Present review article will summarize the online studies on vitamin D's deficiency as risk for onset and development of MS.

Structure and synthesis of vitamin D:

Vitamin D is one of the lipid-soluble vitamins, also known as 'hormone' (like testosterone, estrogen, and cortisol) and not acts as a vitamin. Vitamin D is an

important molecule, not synthesized in the body so it must be taken from external source, vitamin D produced by the body by inter-conversion from inactive to the active form ^[3]. The active form of vitamin D, 1,25-dihydroxyvitamin D (1,25[OH]₂VD) which is called as calcitriol has structurally like several hormones such as aldosterone and cortisol ^[4].



Structure (1): Vitamin D forms.

Sunlight is the major source of vitamin D, also may be taken from diet and supplementation. UVB can form Vitamin D under skin were found as inactive form in the 290–315-nm range photolysis 7-dehydrocholesterol, which then isomerizes to vitamin D₃ or cholecalciferol. Fatty fish as salmon and mackerel, egg yolk, liver oil act as a rich source for Vitamin D. Vitamin D₂ or ergocalciferol is the plant form of vitamin D, these forms also found in fortified foods (such as milk and its derivatives) ^[5].

Vitamin D absorption:

When compared with concentrations obtained from vitamin D at exposure for sunlight, food is a bad source of vitamin D where it provides 40 to 400 IU of full dietary meal while sun exposure for 20 minutes can generate 10,000 IU of vit D ^[6]. Sunlight exposure and vitamin D synthesis in the skin may be affected by the differences in skin pigmentation, sun block using, age and other factors ^[7].

There are two inactive forms of vitamin D (colocalciferol and ergocalciferol), transport to the liver to convert them into 25 (OH) D (calcidiol). Enhancing PTH (parathyroid hormone), the 25 (OH) D

undergoes another hydroxylation process but at the kidneys or other tissues to 1,25 (OH)₂VD, which are considered the active form ^[8]. The active form (1,25 (OH)₂VD) has a short half-life (few hours), but 25 (OH) D has a long lifespan (15-65 days). It's important to note that most assays evaluating 25 (OH) D do not distinguish between the two vitamin D forms (vitamin D₃ or D₂). However, the component because the natural sources of ergocalciferol are scarce, and ergocalciferol is much faster metabolized than cholecalciferol ^[9]. The active form 1,25(OH)₂VD is secreted in circulation and transported in the bloodstream. The active form of vitamin D is bound with its binding protein in circulation. 1,25(OH)₂VD changes its biological activity by binding to vitamin D receptor [VDR], which then enhanced the transcriptional complex formation which binds to the elements of vitamin D ^[10]. This binding controlling about 500 genes expression that regulate several physical functions ^[11]. Vitamin D receptor is located in many tissues, its effect is not limited to functions known as bone, kidney and gut. The non-classic effect for vitamin D receptors can act as controlling factor

for three main locations: hormone secretion, immune function and cellular proliferation and differentiation^[12].

Since ancient times in the year 1900, hypotheses have been linked the lack of vitamin D and rickets, which was very common among children, since the recommendations required exposure to the sun as a source of vitamin D for the prevention of rickets^[13]. Other musculoskeletal conditions of the deficiency of vitamin D consist of secondary hyperparathyroidism which raised the bone turnover rate, bone loss, and increase risk of low-trauma fractures. Now a day, beyond studies we note that VDR is widely distributed in the tissues of the body and has several biological functions. Vitamin D deficiency is associated with many diseases such as cancers, infectious diseases, cardiovascular diseases, diabetes mellitus, autoimmune disorders and mental disorders^[14]. However, now we understand that autoimmunity may be association with vitamin D deficiency, and that increase the risk of autoimmune diseases.

Vitamin D metabolism

The general metabolic pathways for vitamin D are (shown in Figure 1). The major step in this pathway is that; the conversion of 7-dehydrocholesterol to cholecalciferol (vitamin D₃) which occur under the skin by the effect of ultraviolet B from the sun or also after vitamin D supplementation, the first step is hydroxylation occur in liver enhanced by enzyme (vitamin D-25-hydroxylase), the start by CYP2R1^[15]; this produced in 25-OH-D; the intermediate which determined in blood to assess the vitamin D levels^[16]. Then, the hydroxylation process also occurs but in the proximal tubule of the

kidney, by the effect of enzyme 1 α -hydroxylase (CYP27B1)^[15], produce 1,25-OH-2D (calcitriol), which consider as the active metabolite of vitamin D. The decrement in calcium intake and the levels of parathyroid hormone (PTH) enhanced the hydroxylation which occur in kidney and elevated the serum calcitriol concentration, but the phosphaturic hormone fibroblast growth factor 23 (FGF23) and rise the concentration of calcitriol hormone having opposite action. The vitamin D 24-hydroxylase (an enzyme found in kidney and encoding by the CYP24A1 gene) can stimulate an inactivating process for vitamin D metabolism. it is under control of FGF23 and the concentration of calcitriol. The role of this process has been well known in the studies which suggested that the CYP24A1 gene mutations enhanced many neonatal hypercalcemia^[16]. Vitamin D and its derivatives, such as calcitriol, are carried in circulation by the vitamin D-binding protein (DBP) (which is a plasma globulin in general its synthesis occur in the liver) and to a lesser extent by albumin. The calcitriol dissociation from DBP when reach a target cell and first joining to vitamin D receptor (VDR) in the cytoplasm, as illustrated in Figure 1^[17], after that the complex formed a heterodimer when arrived to nucleus by binding to the retinoid X receptor (RXR). Finally, this complex (calcitriol-VDR-RXR) binding to vitamin D-responsive elements (VDREs), which encoding in a specific sequence in DNA, about 5–10% of the genome as shown in Figure 1. Thus, calcitriol, secreted in circulation by kidney and appear its effect in several tissues by joining to its receptor, so its act as a hormone^[18].

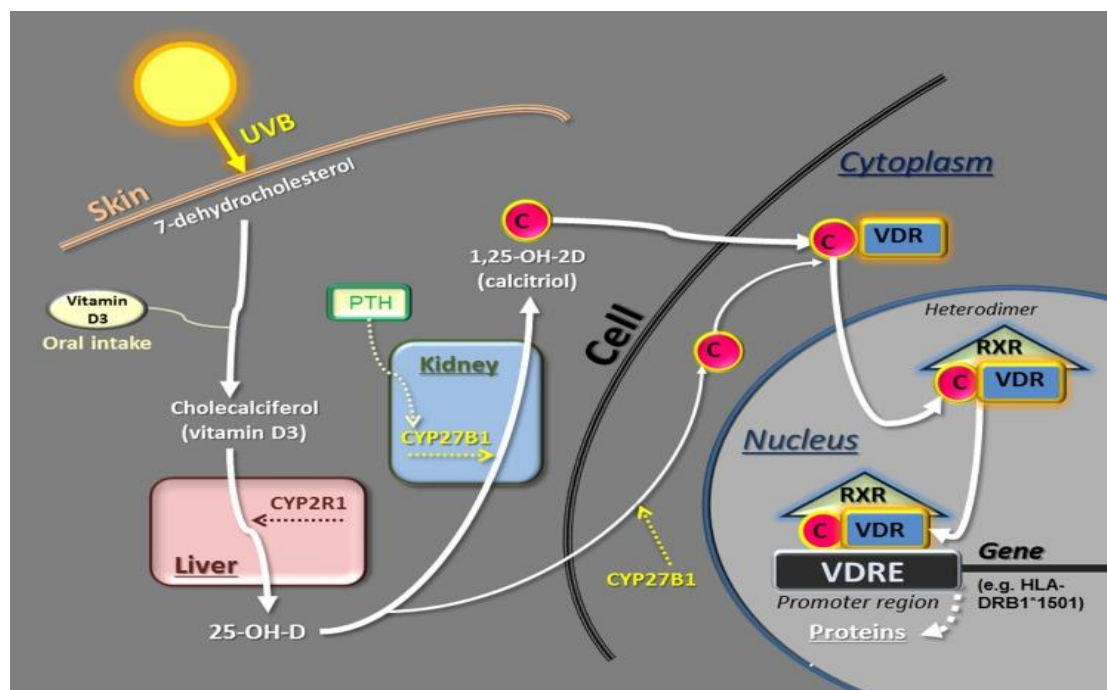


Figure (1): Vitamin D metabolism [3]

Vitamin D actions

Vitamin D receptors are distributed to different areas of different tissues and cells (such as immune system cells: monocytes, macrophages, DC cells, lymphocytes B and T, [19], CNS (including neurons and astrocytes, oligodendrocytes [20]. These different cells express the CYP27B1 enzyme and within its host convert 25-OH-D in situ to calcitriol where the effect of intracrine and paracrine between these cells and nearby tissue to their class in the process of balancing calcium levels maintain the bone components, also have a function Other Escherichia, including the protection of cardiovascular and anti-growth and proliferation of cancer cells, and anti-inflammatory process, and this role is useful in tying the risk of type 1 diabetes, which is an autoimmune disease and other immune diseases such as MS, Crohn's disease, and rheumatoid arthritis. The expected function of calcitriol in the cells of the central nervous system is its effects on the protection of the nervous system as well as in the innate and adaptive immunity of the central nervous system by invasive lymphocytes. The

presence of vitamin D and CYP27B1 receptors in neuron and immune cells is a clear evidence of a relationship between vitamin D and neurodegenerative diseases, such as MS. The illustrated of the immune functions for vitamin D on immunity, appears to be very important for understanding and explaining the effect of vitamin D in the deterioration of MS development [21].

The effect of vitamin D on immune system in relation to autoimmune diseases

A recent study suggested that the autoimmune encephalomyelitis (EAE) act as a better animal choice for MS experiments, whereas the evolution of vitamin D must be done routinely in this disease, and that's studied from long time about more than 20 years. Calciferol has a protective and treated effect for EAE, especially in the presence of VDR. However, the studies of the effect of vitamin D deficiency on the EAE development are contradictory. If vitamin D3 supplement is used, the benefit role is appeared in women, likely a potentiation

by oestrogens. There is different mechanism were suggested to illustrated the vitamin D and calcitriol effects: an anti-inflammatory effect, affected on macrophages^[22], its effect on several kinds

of cytokines^[23], its effect on controlling the action of lymphocyte T helper 1 (Th1), T lymphocyte cells (Tregs), Th17 and Th2 and invariant natural killer T-cells (iNKTs)^[23].

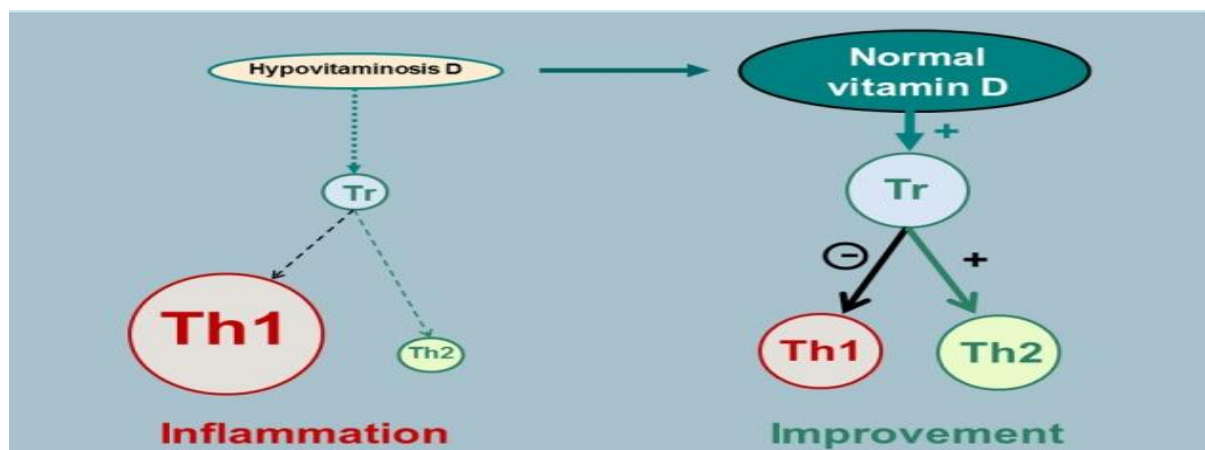


Figure (2): The hypothetical immunomodulatory effects of vitamin D^[36].

Roles of Vitamin D in Immunity

Vitamin D plays major roles on calcium and bone balance. The expressions of VDR on immune cells (e.g. antigen presenting cells, T & B cells) and these immunologic cells are all association with the vitamin D conversion to its active metabolite, vitamin D has an important role in an autocrine system (consider as a hormone) and also has an immunologic action. Vitamin D also change the innate and adaptive immune system. Deficiency in vitamin D is related with elevated autoimmunity and raised infection susceptibility. The immune cells during autoimmune diseases are illustrated the ameliorative action of vitamin D, the good effects of vitamin D supplementation in patients with autoimmune disease may appear as its effects on bone health and calcium levels^[24]:

- Macrophages and dendritic cells (DCs) mainly express vitamin D receptors; so, the expression of VDR gene in T cells is controlling after activation.
- In macrophages and monocytes, the active metabolite of vitamin D positively

correlated with VDR expression and the cytochrome P450 protein, CYP27B1.

- The 1,25(OH)₂VD enhanced monocyte proliferation and IL-1 expression and cathelicidin by macrophages, participate in the innate immune as a response to microorganisms.
- 1,25(OH)₂VD reduce DC maturation, inhibiting controlling the expression of class II from MHC, CD 40, 80 and m86. As well as, it lowering IL-12 release by DCs but enhancing the secretion of IL-10.
- In T cells, vitamin D reduced the secretion of Interleukins 2 & 7 and interferon- γ (IFN γ) and also decrease the cytotoxic activity and proliferation of CD4⁺ and CD8⁺ T cells.
- 1,25(OH)₂VD enhanced the evolution of forkhead box protein 3 (FOXP3) + regulatory T (T_{Reg}) cells and TR1 cells.

The impact of vitamin D on multiple sclerosis.

In recent days, it has been documented that multiple sclerosis is a multi-disorders disease that affects people who have a genetic predisposition and are exposed to environmental triggers^[25].

Genetic risk factors in multiple sclerosis and vitamin D

It was found that in those families who having more than one patient with MS will be more likely that their siblings will be affected with the disease ^[26]. A previous study determined that a change in more than one gene was found in patients with neurodegeneration, which is equivalent to one percent of the genes responsible for multiple sclerosis, also share immune disorders as T-cell differentiation, B-cell regulation and cytokine pathways ^[27].

Human Leukocyte antigen system and vitamin D

The Human Leukocyte antigen system (HLA system) has several immune responses. In another study it was suggested that the HLA-DRB1 * 1501 allele, found in nearly a quarter of the population, is closely associated with the risk of developing MS, which accounts for 11% of the total encoding gene, but the remaining HLA alleles have less effect. Meanwhile HLA-A * 0201 can be protective. As the risk of multiple sclerosis with one or more HLA-DRB1 * 15 alleles is increased, it is necessary to indicate the relationship of vitamin D with MS. For MS where in the main haplotype DR2 associated with MS which carries HLA-DRB1 * 15 allele and is not generally preserved among the individual patterns associated with non-MS ^[28]. The authors recorded that a decrease in the vitamin D in early age I children can affect the expression of HLA-DRB1 in the thymus and effected on elevated the risk of autoimmunity in other stage in the life ^[29]. Other studies suggested that the probability of the MS- highly associated with HLA-DRB1*1501 allele and the frequency increase in white persons when compare to other race, this is why the prevalence of MS is relatively low in black people who live in hot countries, regardless of their vitamin D status ^[30]. Furthermore, Women are more likely to carry HLA-DRB1 * 15 than men and are therefore more likely to

develop MS. The effect of calcitriol on the expression of HLA-DRB1 * 15 is likely to decrease the incidence of MS in women with high levels of vitamin D (25); HLA-DRB1*04, *07 and *09 alleles, which express the 'nonresponsive' VDRE motif, were related to decrease the risk of MS variables associated with VDR can affect the risk of MS conferred by HLA-DRB1 * 1501, and in a group of MS patients (ie, a community with a specific genetic risk for MS), VDREs do not appear to play a role. Important in the DRB1 promoter area in exposure to MS ^[30].

Environmental factors and multiple sclerosis

In addition to genetic risk factors, a recent study suggested that there are three main environmental risk factors for MS have been identified which including old infection with Epstein-Barr virus (EBV), vitamin D deficiency and smoking ^[31].

Vitamin D insufficiency and MS

Although scientific studies documenting the direct relationship of vitamin D deficiency to MS and being considered a direct infection factor are few and limited ^[32]. In a study that gathered 52 diverse studies, there was a very important link ($p < 10^{-8}$) between the prevalence of MS and the amount of sun exposure each year. In France, sunlight maps show large climatic zones similar to those of the main areas of MS prevalence. Identified by farmers ^[33]. Moreover, in another study, there was an inverse correlation between the incidence of the disease versus the amount of solar radiation obtained in some of the French regions included in the study ^[34], with increase the association between UV and MS prevalence than for that between MS prevalence and the latitude of the area ^[34]. Results increased in women than men (men) ^[35]. The relationship between MS, UVB and vitamin D mechanisms is a key point. Several studies have recorded that the protection / risk of these environmental factors may occur at different periods

during the first part of life until early adulthood. In some studies, vitamin D supplements were found to be associated with a lower risk of multiple sclerosis, but other protective factors could not be excluded in these studies ^[36]. Of great importance, since it was based on the level of vitamin D serum itself, it was a study of young American soldiers who gave at least two serum samples a few years before any neurological symptoms appeared during their military service. White soldiers with vitamin D levels in the top quintile (between 99 and 152 nmol / L) had significantly lower risk of MS than those with the lowest vitamin D levels between 15 and 63 nmol / L) ($p < 0.01$). Furthermore, in a recent Swedish case control study, an association was found between relatively high levels of serum OH-D (n75 nmol / L) during the years before the onset of the disease and a lower risk of MS ^[37].

Conclusion:

As a conclusion, maintaining vitamin D levels is considered one of the most important steps in the treatment and follow-up of MS patients

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