

What is the Real Fate of Vitamin D in Multiple Sclerosis?

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ABSTRACT

Multiple sclerosis (MS) is a multifactorial disease (caused by both environmental and genetic features) that could result from a demyelination of the myelin sheath. Subsequently, it leads to many scars or lesions in different places within the central nervous system. The symptoms that occur depend on the site and rigorosity of the lesions and this is why people with MS experience different symptoms. Although, it is not clearly known that why people develop MS, research suggests that vitamin D plays a key role in preventing or repairing the damaged myelin. Previous studies have shown that vitamin D is a potent natural immune-regulator and has an anti-inflammatory action. Increased exposure to vitamin D may result in changed immunologic profiles or commotion that donates to MS risk. Vitamin D deficiency is caused by insufficient sunlight exposure or low dietary vitamin D₃ intake. Recent studies have also indicated that, there are several polymorphisms for vitamin D receptor (VDR) gene, but the effect of VDR gene polymorphisms on protein function of VDR and how exerts second signaling pathways in cells is still unknown. Therefore, this review focuses on vitamin D metabolism and genetic polymorphisms related to VDR and MS to better understand of discrepancies among patients.

Keywords: Multiple sclerosis, polymorphism, vitamin D receptor

INTRODUCTION

Previous publication reported that low-levels of vitamin D are associated with multiple sclerosis (MS). MS is a continual inflammatory demyelinating disorder of the central nervous system (CNS), with extremely inconstant medical sequence that classically exhibited a relapsing-remitting (RR) configuration. This continual halting ailment typically pursues a polishing and fading route in excess of several years prior to development of disability. Pathologically, there are scraps of swelling (plaques) inside the CNS with demyelination of axons and oligodendrocyte defeat. Axon defeat is current untimely in the illness route, but turn into the major characteristic as the illness expands eventually. It is hypothesized that loss of axons is the main mechanism underlying progressive disability.^[1-9] The prevalence of MS changes deeply related to different population. Due to personality changeability the sorts of sickness incidence, its'

influence, conditions and outcome are complex and difficult to investigate. The dominance is eminent by foremost incongruity, which is judged by inherited, biological, and demographic features. In Isfahan/Iran an augment in frequency and occurrence numbers of MS was accounted. It has been confirmed that Isfahan city could be reflected as the vicinities with the highest frequency of MS in Asia and Oceania.^[10-18] Previous published data also suggested that there are two leading categories of threat characteristics for MS such as; environmental and genetic factors. Aptitude of individual to catch MS might be indicated with complicated connections among these two factors. Subsequently, due to inter- or intra- individual variability in MS patients, the final clinical outcome could be harmful or defensive. Previous reports recommended that there is a strong correlation of vitamin D status in the pathogenesis of autoimmune diseases. It seems that a level of 50 nm of vitamin D could fragment the deterioration threat in RR MS. Vitamin D deficit could be identified once the level is <20 ng/mL.^[19-30] The fortitude of this structured review is to display the evidence related to the metabolism and genetic polymorphism of vitamin D receptor (VDR) in the treatment of MS.

JUSTIFICATION

THE FATE OF VITAMIN D

Metabolism

Intestinal calcium insertion is one of the oldest and best recognized proceedings of vitamin D that was initially explained by Schachter and Rosen in 1959 (*in vitro*) and Wasserman *et al.* in 1961 (*in vivo*). It seems that integration of calcium from the luminal contents of the intestine follow both Trans and Para cellular patterns. Abolition of calcium must work beside this gradient, and potency seems mandatory. The primary tread, could be calcium entrance across the brush border membrane that is conveyed by modification in the fat composition of the membrane as well as an augment in linoleic and arachidonic acid and an increase in the phosphatidylcholine: phosphatidylethanolamine ratio.^[31,32] These alterations are connected with augmented membrane fluidity, which could be disclosed as an outcome in improved calcium flux. Without troublemaking related to the task of the

cell, calcium that enters to the brush border must be inspired into the cytoplasm. In lower level of vitamin D in body the accumulation of calcium next to the inside surface of the plasma membrane of the microvilli might be observed. Therefore, for absorption of calcium and phosphate into gut lumen, a cluster of fat-soluble secosteroids identified as vitamin D seems important. It could be used as vitamin D₂ and D₃ or ergocalciferol and cholecalciferol with the analogous dynamic metabolites respectively. Vitamin D₂ encloses a double bond and an extra methyl set. Cholecalciferol generated in the skin metabolized to be active.^[1,2,29-32] One of the main calcium binding protein in the microvillus is calmodulin that acts a key function in calcium transfer inside the microvillus. The concentration of calmodulin could be increased by vitamin D.^[32-35] It is metabolized trough a sequence of hydroxylation feedbacks in the skin, liver, and the kidneys to the active metabolite calcitriol, which has a half-life of some hours. Cytochrome P2R1 and cytochrome P27B1 are the key enzymes accountable for the metabolism of vitamin D. CYP27B1 encrypts the vitamin D-activating 1- α hydroxylase enzyme. Vitamin D is passed from bloodstream to the liver, where it is changed to the prohormone calcidiol. Subsequently, calcidiol in kidneys or immune system (by monocytes-macrophages) changes to dynamic form of vitamin D, calciteriol. Calciteriol could proceed as cytokine once produced by monocytes-macrophages that protecting the body opposed to microbial attacker. Calciteriol is released into blood the place, which could binds to its specific binding protein receptor. The inference of oral vitamin D with chylomicrons and lipoproteins could be documented by an extra speedy hepatic distribution [Figure 1].^[1-37]

Vitamin D receptor and its' polymorphism

Published literature indicates that more than 50 genomic regions have been connected with MS vulnerability. One of the mainly significant tasks of vitamin D is raising calcium absorption in the intestines.^[1,31-41] Lv *et al.* in 2013 mentioned that vitamin D and VDR could be assumed as environmental and genetic factors in neurodegenerative ailments including MS, Alzheimer disease, and Parkinson disease.^[42] Smolders *et al.* in 2013, reported that in primary human astrocytes *in vitro*, the dynamic formula of vitamin D, could be induced by

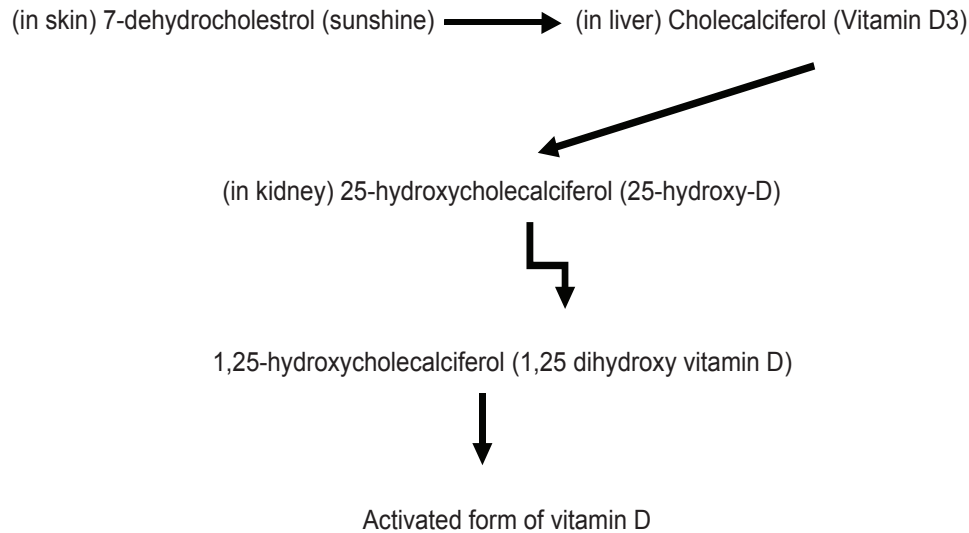


Figure 1: Fate of vitamin D from skin to blood circulation^[1-37]

up-regulation of VDR and CYP24A1.^[43] Calcitriol arbitrates its property by binding to the VDR, which is predominantly situated in the nuclei of purpose cells. The binding of calcitriol to the VDR allows the VDR to act as a transcription factor that modulates the gene expression of transport proteins, which are involved in calcium absorption in the intestine.^[1-43] The association among the existence of Bsm1 constraint splinter distance polymorphism of VDR and bone loss in ambulatory patients with MS has been reported by Lambrinouadaki *et al.* in the 2012. They confirmed that VDR's Bsm1 polymorphism is linked with a trivial outcome in younger patients with MS.^[44] VDR belongs to the nuclear receptor superfamily of steroid/thyroid hormone receptors, and VDR are expressed by cells in most organs, including, the brain, heart, skin, gonads, prostate, breast, CNS, microglia, activated monocytes and B and T lymphocytes. Vitamin D increases expression of the tyrosine hydroxylase gene in adrenal medullary cells. It is also involved in the biosynthesis of neurotrophic factors, synthesis of nitric oxide synthase, and increased glutathione levels. The VDR is known to be involved in cell proliferation and differentiation. Vitamin D also affects the immune system, and VDR are expressed in several white blood cells, including monocytes and activated T and B cells.^[1-51]

Protective duty of vitamin D

Previous publications reported that vitamin D has been connected with metabolic and immunological procedures, which recognized its character as a vital element linked to strength and protection.^[52,53] As a

protective agent to prevent degeneration connected to different part of CNS, two mechanism of action could be considered for vitamin D. Firstly, 25(OH) D bound to its binding protein which called VDBP. The complex of vitamin D-VDBP could pass through cell membrane. In the next step, it is changed to 1,25(OH) 2D in the mitochondria and subsequently bind to the VDR. In this stage, it could be relevant to genomic properties. Secondly, 1,25(OH) 2D as free form binds to its' receptor for both genomic and non-genomic effects. A number of these genomic properties proceed to adjust the metabolism of vitamin D, but also involve location of genes connected to cellular propagation/delineation and the immune system, including cytokines and cytokine receptors. Ramagopalan *et al.* demonstrated that the strongest MS genetic vulnerability area, the human leukocyte antigen-*DRB1* (*HLA-DRB1*) allele of the *HLA-DR* gene, is up-regulated by 1,25(OH) 2D via a highly potted vitamin D responsive elements. Another protective role of vitamin D is the existence of an inverse correlation with Epstein Barr virus DNA load in patients with MS.^[1,54] It seems that inflammation reaction due to infection, could targeted oligodendrocytes and myelin. It is reported that sun exposure and vitamin D could increase the levels of interleukine 10. The production of viral analog of human interlukine 10 may interfere with normal pathway that is produced by immune cells. Cigarette smoking and latitude could also raise the risk of MS.

Using foods rich in vitamin D seems important in prevention of disease.^[28,29] Steffensen *et al.* in

2013 mentioned that MS patients who have no sun exposure and low dietary vitamin D intake during the winter months should be recommended to take vitamin D supplements to achieve serum vitamin D levels of at least 50 nmol/l.^[55] Holmøy *et al.* in 2012 recommended that MS patients should be supplemented with 800 IU of vitamin D at least from autumn to spring.^[22] The mainly documented function is in calcium homeostasis, where vitamin D and parathyroid hormone-proceed to continue steady serum calcium concentrations through their exploit on bone, intestinal calcium absorption and renal calcium excretion. On the other hand, details carry a task for vitamin D in brain upgrading and connotation, cardiovascular health, and musculoskeletal health. In addition, vitamin D is considered to have anti-neoplastic possessions, control insulin assembly and have wide immunomodulatory properties. In the endocrine system, vitamin D is wrought in the kidneys by the exploit of the 1 α hydroxylase enzyme programmed by the cytochrom P27B1 located on the chromosome.^[12] Of careful significance to MS, is that 1 α hydroxylase is existing in the mitochondria of numerous cell categories of neuronal and glial cells of the CNS. There is a durable opposite association between period and strength of sunshine and the amount of vitamin D in body fluids.^[1-57]

CONCLUSIONS

In agreement with previous publications,^[1-57] we conclude that the cumulative occurrence of MS in Isfahan/Iran,^[3,8,9,14,17,18] could be evaluated related to the critical role of biological and daily life threat issues. Geographic models of incidence, altering sex ratio and rising occurrence summit to a main part for environmental and genetic factors. VDR and its' polymorphism could support a reasonable pathogenic link to MS. Therefore, as a natural immune modulators (vitamin D) hypovitaminose D could be linked with both metabolic and immunological processes. Further studies in this direction related to genetic variation of VDR could be useful in Iranian population.

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