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MULTIPLE SCLEROSIS AND VITAMIN D: A COMPREHENSIVE REVIEW

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ABSTRACT

Multiple sclerosis (MS) is characterized by inflammation, demyelination, axonal or neuronal loss, and astrocytic gliosis in the central nervous system (CNS), which can result in varying levels of disability. The major risk factors of MS identified include hypovitaminosis D while environmental protective factors include allele HLA DRB11501, obesity, Epstein-Barr virus infection, sexual hormones, and smoking. From different risk factors contributing to the development of MS, Vitamin D status is of particular interest since it is not only a modifiable risk factor but is also associated with MS disease activity. MS patients with lower serum vitamin D concentrations were shown to have higher disease activity. In the following article, we will briefly review the effects of vitamin D on MS by outlining its effects on the immune and nervous system and by reviewing the association between vitamin D and MS risk as well as MS disease activity. We will also review the effects of vitamin D supplementation on MS risk.

INTRODUCTION

Multiple sclerosis (MS) is a constant multifactorial and polygenic immune system sickness of the focal sensory system (CNS), influencing overwhelmingly youthful to moderately aged grown-ups, particularly females. In any case, no single quality or environmental component has been unambiguously distinguished as the causative specialist, and almost certainly, the aggregate impacts of a few qualities and natural variables lead to sickness beginning. Until now, the specific reason for this incapacitating neurocoherent sickness stays tangled. Epidemiological and exploratory information recommend low vitamin D levels to be related with illness inclination in malignant growth, schizophrenia, cardiovascular afflictions, rheumatoid joint pain, and immune system sicknesses, for example, fundamental lupus erythematosus, type 1 diabetes, and MS. The point of this part is to investigate the relationship between lack of vitamin D and MS risk, and to introduce the most recent information and improvements on the job of vitamin D as a gamble factor for MS. MS is a chronic, progressive disease that causes autoimmune inflammation and demyelination of the central nervous system (CNS) with subsequent axonal damage [1]. It can present as acute optic neuritis (most common), brainstem/cerebellar syndrome, pyramidal tract demyelination, and/or spinal cord syndromes. MS is depicted by inflammation with demyelination, extensive immune infiltration, damage to oligodendrocytes, and axonal loss, supposedly autoimmune in nature. Deficiency of vitamin D is also common in temperate areas due to a lack of sunlight and altered

lifestyles. Both sun exposure and vitamin D level, independent of serum levels, are linked to multiple sclerosis. Sufficient vitamin D levels have decreased the prevalence and progression of MS. The role of vitamin D in the pathogenesis of MS is not entirely understood; however, some genetic studies have shown that various immunomodulators associated with MS are linked to vitamin D-associated regulation of gene expression. This article aims to assess the correlation between the clinical efficacy of vitamin D supplementation and symptom control in patients with MS.

Pathophysiology:

MS refers to the plaques that form in the CNS combined with inflammation, demyelination, axonal injury and axonal loss. These plaques are found in the brain and spinal cord, essentially in the white matter around the ventricles, optic nerves and tracts, corpus callosum, cerebellar peduncles, long tracts and subpial region of the spinal cord and brainstem, but also in the grey matter. They are expressed in all forms of MS but vary over time quantitatively and qualitatively showing a profound heterogeneity in the structure and immunopathological patterns of demyelination and oligodendrocyte pathology between relapsing remitting course and progressive forms of disease. During the early stages of the relapsing remitting course, the pathology is marked by important demyelination and a variable degree of axonal loss and reactive gliosis. Patients in general, present with focal inflammatory plaques that contain demyelinated axons, reduced number of oligodendrocytes, astrocyte proliferation with subsequent gliosis, transected axons, and perivenular as well as parenchymal infiltrates of lymphocytes and macrophages. In the progressive course, MS is dominated by diffuse grey and white matter atrophy and characterized by low-grade inflammation and microglial activation at the plaque borders combined with diffuse injury of the normal-appearing white matter outside the plaque[1]. Inflammation, microglial activation, axonal and myelin injury occurring during this course are followed by secondary demyelination [2]. In general, the patterns of tissue injured in patients presented with primary or secondary progressive course of MS are homogeneous. They showed oligodendrocyte loss, preferential destruction of small-caliber axons, astrocytic gliosis, and demyelination that consists of the essential criteria [3]. Demyelination and subsequent neurodegeneration associated with different forms of MS involved various components of adaptive and innate immunity [4]. Myelin sheaths are particularly vulnerable to non-specific products, such as cytotoxic cytokines, excitotoxins, reactive oxygen or nitric oxide species, which are released by activated macrophages and microglia [5]. However, the most commonly observed patterns of demyelination are antibody and complement-associated changes, as well as hypoxia-like tissue injury, in which the initiation of demyelination is attributed to the degeneration of distal oligodendrocyte processes and apoptosis of oligocytes, while the loss of polarity by astrocytes leads to the disturbance of the structural organizational of the perivascular glia limitans [6]. Classically, MS is regarded as a T cell-mediated autoimmune disorder with a predominance of $CD8^+$ cells compared with other T-cell subsets, B cells or plasma cells. It is believed that this disease begins in inflammatory-induced lesions consisting mainly of $CD8^+$ T cells, and $CD4^+$ T cells, and activate microglia/macrophages [7]. Evidence of the suppression of function that restricts $CD4^+$ T-cell responses and the tissue-damaging role of $CD8^+$ T cells reported to co-localize with axonal pathology have been observed [8]. Indeed, the specific interaction of $CD8^+$ T cells with target cells requires MHC-I expression which is tightly regulated in neurons and MHC-I molecules only in response to strong danger signals such as proinflammatory cytokines IFN-γ or TNF-α [9]. Molecular mimicry, T cell co-expression, or bystander activation of T cells have all been proposed as possible inciting events. The activated B cells and monocytes reach the CNS by crossing the blood-brain barrier or blood

CSF barrier via the choroid plexus and propagate inflammation there. This model is also used to study MS-like diseases by introducing activated cells into the CNS of animals, thus kick-starting the disease. The hallmarks of MS lesions include axonal loss, astrocytic gliosis, demyelination, and plaque formation. Axonal loss is thought to be due to inflammatory mediators, such as reactive oxygen species (ROS) and NO, released from activated inflammatory cells, ultimately leading to mitochondrial dysfunction. This further propagates ROS generation and contributes to demyelination. Clinically, these disease processes have wide-ranging implications. Moreover, demyelinated axons may become hyper-excitable, thus being responsible for the positive symptoms that occur; or on the other hand, demyelination may slow conduction and cause ectopic signals.[10] With respect to vitamin D, there are strong indicators of it having a critical role to play in immunomodulation. Higher levels of vitamin D, irrespective of dietary intake, seem to predict a lower risk of MS. Moreover, children born with low vitamin D levels and insufficient vitamin D levels during pregnancy are both associated with higher risks of MS.

Overview of vitamin D synthesis, intake, and activation:

Vitamin D as a nutrient is that it can be synthesized by the human body through the action of sunlight. Vitamin D is a prohormone also known as calciferol, comprises a group of fat-soluble seco-sterols. The two major forms are vitamin D_2 and vitamin D_3. Vitamin D_2 (ergocalciferol) is largely human-made and added to foods, whereas vitamin D_3 (cholecalciferol) is synthesized in the skin of humans from 7-dehydrocholesterol and is also consumed in the diet via the intake of animal-based foods. The D_2 and D_3 forms differ only in their side chain structure. The differences do not affect metabolism (i.e., activation), and both forms function as prohormones. When activated, the D_2 and D_3 forms have been reported to exhibit identical responses in the body, and the potency related to the ability to cure vitamin D–deficiency rickets is the same. Experimental animal studies have indicated that vitamin D_2 is less toxic than vitamin D_3, but this has not been demonstrated in humans. The activation steps involved in converting vitamin D from the diet and cutaneous synthesis are illustrated in Figure-1. Vitamin D, in either the D_2 or D_3 form, is considered biologically inactive until it undergoes two enzymatic hydroxylation reactions. The first reaction takes place in the liver, mediated by the 25-hydroxylase (most likely cytochrome P450 2R1 [CYP2R1]) which forms 25-hydroxyvitamin D (hereafter referred to as 25OHD). The second reaction takes place in the kidney, mediated by 1α-hydroxylase (CYP27B1), which converts 25OHD to the biologically active hormone, calcitriol (1,25-dihydroxyvitamin D). The 1α-hydroxylase gene is also expressed in several extra-renal tissues, but its contribution to calcitriol formation in these tissues is unknown. 25OHD, the precursor of calcitriol, is the major circulating form of vitamin D; it circulates and bounds to a specific plasma carrier protein, vitamin D binding protein (DBP). DBP also transports vitamin D and calcitriol.

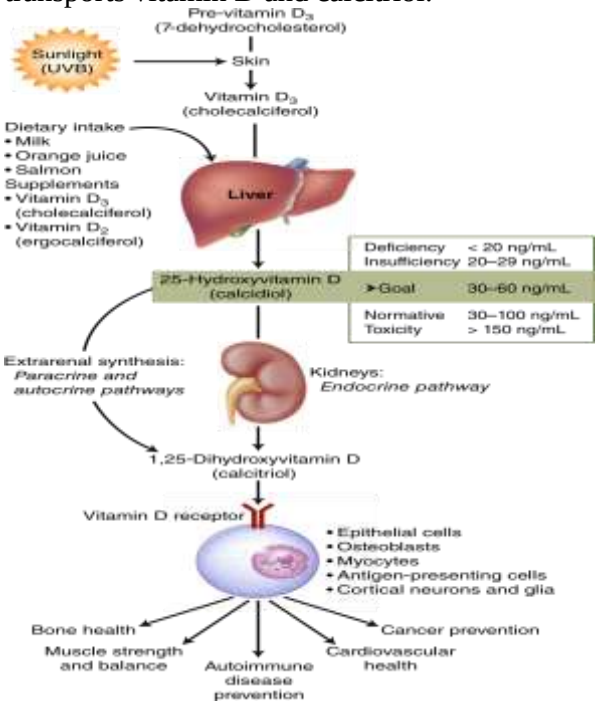

Figure 1: Overview of vitamin D synthesis

Effect of Vitamin D on the Innate and the Adaptive Immune System:

Not only MS but also several other autoimmune disorders are associated with vitamin D deficiency. Accordingly, studies performed *in vitro* and *in vivo* have shown that 1,25(OH)2D3 has anti-inflammatory effects by suppressing the innate as well as the adaptive immune system[11] Regarding the innate immune system, after phagocytosis of microbes through macrophages, Toll-like receptors are activated, resulting in an up-regulation of VDR and CYP27B1 expression in macrophages and monocytes[12]. In macrophages, 1,25(OH)2D3 then activates cathelicidins, which are antimicrobial peptides[13].

Another anti-inflammatory mechanism of action of 1,25(OH)2D3 is exerted through its various effects on glucocorticoids, including an increased stimulation of monocytes by glucocorticoids to produce mitogen-activated kinase phosphatase 1, which reduces the pro-inflammatory activity of mitogen-activated protein kinases[14]. Addressing immune cells, which are part of the innate and the adaptive immune system, 1,25(OH)2D3 increases the differentiation of hematopoietic stem cells into natural killer cells and inhibits the function of the dendritic cell line[15]. Regarding the dendritic cell line, 1,25(OH)2D3 inhibits the differentiation of monocytes into dendritic cells, the maturation of dendritic cells, the production of proinflammatory cytokine IL-12, the expression of the major histocompatibility complex class II, and the presentation of antigens[16]. Furthermore, dendritic cells are induced to undergo apoptosis. Mediated by its effects on dendritic cells, 1,25(OH)2D3's influence on the adaptive immune system has been attributed to its various effects on T cells, including the altered production of cytokines and selective induction of T cells into apoptosis[17]. In vitro, B cell proliferation and B cell differentiation into plasma cells are inhibited and B cell apoptosis is induced, resulting in the reduced production of antibodies [18]. In a study of 40 MS patients, however, immunoglobulin G (IgG) concentrations and 25(OH)D concentrations did not significantly correlate in CSF or serum. This could be another indicator that the response of MS patients to vitamin D is reduced as shown by Bhargava et al[19].

VITAMIN D AS AN IMMUNOMODULATOR [20,21]:

Vitamin D role in innate immune response:

Immunomodulatory effects of vitamin D occurs through the regulation of nuclear transcription factors, NF-AT and NF-kappa, or direct binding to the vitamin D responsive elements in the promoters of cytokines' genes. Vitamin D inhibits the expression of interferon and proinflammatory cytokines in monocytes (IL-1, IL-6, TNF-α, IL-8 and IL-12). The gene for TNF-α has VDR responsive elements in its promoter, while the gene for IFN-γ has a negative transcriptional regulatory element for vitamin D. The regulation of granulocyte-macrophage colony stimulating factor is regulated by VDR monomers, which bind to the repressive complex in the promoter of this gene, competing with the nuclear factor AT1. Vitamin D blocks the activation of NF-kB by increasing the expression of IκBα and interfering with binding of NF-kB to the genes it regulates (IL-8, IL-12, etc.). The effect of vitamin D has been particularly investigated on the maturation, differentiation and migration of antigen presenting dendritic cells (DC). Vitamin D and its analogues inhibit the differentiation and maturation of DC, although these cells alone express CYP27A1 and are capable of creating 25OH-vitamin D. In vitro treatment of DC with calcitriol leads to downregulation of CD40, CD80 and CD86 co-stimulatory molecules expression and decreased production of IL-12, while IL-10 production is increased. This contributes to the reduction of T cell activation level, in other words, vitamin D acts in creating a tolerogenic type of DCs.

Vitamin D role in adaptive immune response: Immunomodulatory effects of vitamin D in the acquired immune system are the result of its direct effect on cell proliferation, differentiation, and apoptosis of T lymphocytes (especially T-helper) and B-

lymphocytes. Vitamin D inhibits proliferation and cytokine response of Th1 and Th17 cells, induces the formation of regulatory T-cells (Treg or Th3) and the production of IL-4. Differentiation and maturation of B cells is inhibited by the use of 1,25(OH)2D3. Also, by slowing the maturation of DC and inhibiting the expression of MHC II molecules and co-stimulating molecules on antigen presenting cells, vitamin D reduces the ability of these cells to present antigens and activate T cells. In addition, vitamin D modulates the expression of cytokines in DC, inhibiting the production of key cytokines of Th1 and Th17 differentiation (IL-12 and IL-23), but enhancing the release of IL-10, and chemokines MIP-3a (CCL22) involved in the recruitment of regulatory CCR4+ T cells. Treatment of dendritic cells with vitamin D may induce a formation of CD4+/CD25+ suppressor T cells, due to reduced expression of co-stimulatory molecules and production of IL-10. These cells inhibit Th1 cell responses and are critical in the regulation of immune tolerance. Ability of VDR agonists to enhance Treg activation in vitro was observed in several studies. In addition, VDR agonists enhance the suppressive capacity of Treg cells. It has been shown that vitamin D regulates a set of genes in the DC cells, which increases the potential of these cells to induce Treg cells, independently of vitamin D effect on DC differentiation and maturation. However, the role of tolerogenic DC does not seem to prerequisite the Treg cells induction with vitamin D, as evidenced by the very action of vitamin D, or in combination with dexamethasone, for the creation of IL-10 producing Treg cells in in vitro system, in the absence of antigen presenting cells.

Effect of vitamin D on autoimmune diseases: Although there are still no large-scale prospective studies, the results of epidemiological studies suggest an association between a number of diseases with a concentration of vitamin D in the blood. Due to the ability to induce innate and suppress acquired immune response, vitamin D has a beneficial role in the prevention and treatment of various autoimmune diseases, and the prevention of transplant rejection. There is an inverse correlation between serum vitamin D concentration and the incidence and severity of autoimmune diseases, such as type 1 diabetes mellitus (DM), systemic lupus erythematosus, multiple sclerosis (MS), inflammatory bowel disease (IBD), rheumatoid arthritis, psoriasis, fibromyalgia and other. In contrast, vitamin D does not exhibit the same beneficial effects in several diseases in which the immune system plays a key role, such as asthma and infection. Some authors draw attention to vitamin D enriched foods, which seems to cause a higher incidence of allergic diseases.

Vitamin D Status and Its Association with MS Risk: An important clinical association between MS and vitamin D is that populations located farther from the equator and, therefore, receiving less exposure to UVB radiation face more frequently vitamin D deficiency and simultaneously a higher risk of MS. In observational studies, the distinction of the effects of UVB radiation and the effects of vitamin D on MS risk is only insufficiently adjusted. However, since Ramagopalan et al. found the MS susceptibility gene HLA-DRB1∗ 1501 to be regulated by a vitamin D dependent promotor, a clinically relevant UVB independent effect of vitamin D on MS risk appears feasible. To attempt to answer the question whether low 25(OH)D causes MS or MS causes low 25(OH)D, different research groups performed Mendelian randomization studies. Concordantly, these studies found a higher likelihood of developing MS if patients' genes predetermined them to have lower 25(OH)D concentrations leading to the conclusion that 25(OH)D concentrations indeed influence MS risk.

Diagnostic and treatment protocols currently in use for multiple sclerosis (MS): There is no single diagnostic test for MS. The diagnosis is based on evidence of (1) at least two different lesions (plaques or scars) in the white matter of the CNS (the space dissemination criterion); (2) at least two different episodes in the disease course (the time dissemination criterion); and (3) chronic

inflammation of the CNS, as determined by analysis of the CSF (the inflammatory criterion). The presence of one or more of these criteria allows a general diagnosis of MS, which may be refined according to the subsequent course of the disease. An international panel on the diagnosis of MS suggested that the time dissemination criterion should be confirmed by clinical signs on MRI at least 3 months after the previous clinical episode or on a previous MRI. The panel also suggested that the inflammatory criterion could replace the space dissemination criterion when the latter is missing at the clinical and paraclinical levels. To make a diagnosis of MS, the physician must:

- Find evidence of damage in at least two separate areas of the CNS, which includes the brain, spinal cord, and optic nerves.
- Determine that the damaged areas developed at least 1 month apart.
- Exclude all other possible diagnoses.
- Observe that the symptoms last for more than 24 hours and occur as distinct episodes separated by 1 month or more.
- Perform an MRI (the most sensitive imaging test for MS)
- Perform a spinal tap and examination for oligoclonal bands.

At autopsy, multiple, discrete pink or gray areas that have a hard, rubbery texture are identified within the white matter. The lesions are composed of areas of myelin and oligodendrocyte loss along with infiltrates of inflammatory cells, including lymphocytes and macrophages. The relative preservation of axons and neurons within these lesions helps to differentiate MS from other destructive pathological processes that are accompanied by focal inflammation [22]. More than 30% of MS patients have moderate-to-severe spasticity, mostly in the legs. Initial clinical findings in MS patients are often sensory disturbances, the most common of which are paresthesias (numbness and tingling), dysesthesias (burning and "pins and needles"), diplopia, ataxia, vertigo, and bladder (urinary sphincter) disturbances. A common manifestation of MS is unilateral numbness affecting one leg that spreads to involve the other leg and rises to the pelvis, abdomen, or thorax. Sensory disturbances usually resolve but sometimes evolve into chronic neuropathic pain. Trigeminal neuralgia also occurs. Another common presenting sign of MS is optic neuritis, highlighted by complete or partial loss of vision. Bladder dysfunction occurs in more than 90% of MS patients and results in weekly or more frequent episodes of incontinence in one-third of patients. At least 30% of patients experience constipation. Fatigue occurs in 90% of patients and is the most common work-related disability associated with MS. Sexual problems are often experienced as well.[21]

Treatment of multiple sclerosis:

The goal is to begin treatment as soon as possible in order to treat the first exacerbation, prevent future exacerbations, and slow the development of the illness. For acute exacerbation, high-dose intravenous glucocorticoids are the first line of therapy (methylprednisolone). Plasmapheresis is the second line of treatment. Patients who do not react to or tolerate corticosteroid medication may benefit from the use of adrenocorticotropic hormone (ACTH) gel as an alternative treatment. Through the melanocortin system, the melanocortin peptide ACTH has direct anti-inflammatory and immune-modulatory actions, while also indirectly increasing cortisol production through the adrenal cortex. ACTH has deleterious effects that are similar to those of corticosteroids, but it may be less destructive to bone and may be associated with a lower incidence of avascular necrosis (AVN). While the management of an acute exacerbation of multiple sclerosis is rather simple, the therapy of multiple sclerosis over the long term is dependent on the kind of MS that the patient is experiencing. Primary progressive MS (PP-MS) is the most severe of the four types of MS that have been identified: Clinically isolated syndrome (CIS), relapsing-remitting MS (RR-MS), secondary progressive MS (SP-MS), and

secondary remitting MS (RS-MS). People having their first episode of MS who are at high risk of acquiring MS, as well as those that have been diagnosed with RR-MS, should be treated as a matter of urgency. Rather than using high-dose interferon-beta-1a and glatiramer acetate as first-line therapies for the majority of individuals with active MS, it is now advised that they utilize highly effective disease-modifying medications. In contrast to the traditional "treat to target" approach, in which therapy of modest or moderate effectiveness would be initially used and advanced to a more effective agent when breakthrough disease (as determined clinically or by MRI) occurs, the new recommended approach makes use of treatment of high effectiveness from the beginning of the treatment process. Observational studies have shown that initiating high-efficacy therapy early in the course of the disease improves long-term outcomes in the patient. In the vast majority of cases, we suggest beginning therapy with ocrelizumab or another anti-CD20 drug, or with natalizumab in individuals who do not have the John Cunningham virus, before moving on to other options. Therapy with anti-CD20 antibodies is a potential treatment option because of their high degree of efficacy, low frequency of infusions or injections, favourable safety profile, and absence of rebound following treatment discontinuation. Individuals who have new or growing MRI lesions as a result of progressive therapy multiple sclerosis (PPMS) may also be considered for ocrelizumab treatment. The following situations may necessitate a change in therapy: suboptimal response, having experienced more than one relapse with active MRI scans in the prior year while on treatment, and safety concerns, such as the development of persistent high-titer neutralizing antibodies in patients receiving IFN-b therapy, among others. In the event of significant side effects that may be related to the medication, as well as in the case of women who get pregnant while undergoing treatment, many disease-modifying therapies necessitate the cessation of therapy. Only glatiramer acetate, which can be taken continuously throughout pregnancy, and in some cases previous use of ocrelizumab, alemtuzumab, and cladribine, which all have long-lasting pharmacodynamic effects that persist after the medication has been discontinued, are exempt from this restriction. Glatiramer acetate is a medication that can be taken continuously throughout pregnancy.

CONCLUSION:

Vitamin D is essential for the prevention and management of MS. The strong relationship between vitamin D and MS is a primary indication of the vital step of supplementation in preventing and managing MS. Environmental factors related to vitamin D deficiency have proven to be central in triggering the onset and prognosis of the disease. Current treatment strategies for MS include steroids and plasmapheresis. The principal approach to MS, according to our review, must be to integrate dietary measures in the treatment protocols. A combination of drugs and physical, speech, and occupational therapies, exercise, rest and healthful nutrition may relieve symptoms and promote a satisfactory quality of life.

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