Critical Reviews in Food Science and Nutrition
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/bfsn20

Vitamin D and Multiple Sclerosis
Swui-Ling Ho \(^a\), Lini Alappat \(^a\) & Atif B. Awad \(^a\)
\(^a\) Department of Exercise and Nutrition Science, School of Public Health and Health Professions, University at Buffalo, Buffalo, NY
Accepted author version posted online: 20 Sep 2011.

To cite this article: Swui-Ling Ho, Lini Alappat & Atif B. Awad (2012): Vitamin D and Multiple Sclerosis, Critical Reviews in Food Science and Nutrition, 52:11, 980-987
To link to this article: http://dx.doi.org/10.1080/10408398.2010.516034

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.tandfonline.com/page/terms-and-conditions

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae, and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand, or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.
Vitamin D and Multiple Sclerosis

SWUI-LING HO, LINI ALAPPAT, and ATIF B. AWAD
Department of Exercise and Nutrition Science, School of Public Health and Health Professions, University at Buffalo, Buffalo, NY

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system and characterized by neurological and cognitive manifestations. The disease is more common in populations living in high altitudes with low sun exposure, women more than men, and certain ethnic backgrounds more than others. The etiology of MS is yet unknown, although several factors have been implicated in its development. These include genetic factors and environmental factors as well as dietary components and their interactions. Among the dietary components that have recently attracted the attention is vitamin D. This mini-review summarizes current knowledge on the potential use of vitamin D in the protection and treatment of MS. In addition, the mechanism(s) by which vitamin D plays a role in the development and/or protection from MS are discussed.

Keywords immune cells, genetics, environment, diet, mechanism

INTRODUCTION

Multiple sclerosis is characterized by neurological and cognitive manifestations including visual impairment, tremors, sensory disturbance, ataxia, and sexual dysfunction (Sharrack and Hughes, 1996). Based on the clinical manifestations and prognosis of the disease, MS can be presented as relapsing-remitting (most common), primary progressive, and secondary progressive forms (Noseworthy, 1999). These diverse clinical manifestations of MS imply the involvement of several immunological and chronic inflammatory processes in its pathogenesis (Lucchinetti et al., 1996; Trapp et al., 1999). Scattered demyelination of the white matter in the central nervous system, perivascular inflammation, axonal damage, and destruction of oligodendroglia with disintegrated blood brain barrier are the hallmarks of MS pathology (Trapp et al., 1999). Although the etiology of MS is not known, evidence suggests that its development is associated with genetic, environmental, nutritional, and immunological factors. In the following sections, we will review the available evidence for the role of these factors in the development of MS.

GENETIC FACTORS AND MS

Studies conducted on the relationship between high latitude and incidence of MS suggests a role for genetics in the development of the disease. While MS is more prevalent in higher latitudes with high dairy and animal meat consumption, the Sami population (indigenous group in Northern Scandinavia and Russia) was found to be resistant to MS (Willer et al., 2005). Evidence suggests that the lower incidence of MS in this high latitude population could be due to their high lactose intolerance (Smith et al., 2009).

Researchers have identified some genes that modulate the occurrence and clinical course of MS in the HLA and non-HLA regions. In the indigenous Sami people, MS-related haplotypes are less frequently observed compared to the non-Sami Norwegian population (Harbo et al., 2007). Re-combinations of different haplotypes may offer a protective genetic effect against MS and could be the reason behind the lower than expected prevalence of MS in Europe (Goldacre et al., 2004; Landtblom et al., 2005; Pugliatti et al., 2006). Genome-wide association studies have provided new insights into the MS pathophysiology (Baranzini et al., 2009; Hafler et al., 2007). Other than HLA and non-HLA regions, epigenetic factors such as hormones and gender-related genetic expressions also could alter the presentations of MS and this could explain, at least in part, the higher prevalence of MS in females than males (Kampman and Brustad, 2008). Genetic studies with MS patients from different regions of the world also revealed HLA allelic heterogeneity (Dyment et al., 2005; Fogdell et al., 1995; Marrosu et al., 1997; Ramagopalan et al., 2009; 2007).

ENVIRONMENTAL FACTORS AND MS

Given the worldwide occurrence of MS, there are high, medium, and low frequency zones (Kurtzke et al., 2000). The
high frequency areas are found mainly in Europe while the low frequency zones are in parts of Asia and Africa (Kurtzke et al., 2000). Though countries located far away from the Equator were considered to be high frequency areas for MS, emerging evidence shows this trend to be diminishing (Alonso and Hernan, 2008). Studies conducted in France and Australia indicated that UV exposure is closely associated with MS prevalence (van der Mei et al., 2001; Vukusic et al., 2007). In Tasmania, an island located south of Australia, higher UV exposure in adolescents decreased the incidence of MS (van der Mei et al., 2003). Similar results were also obtained in studies conducted in the Arctic circle of Norway, where adequate outdoor activity accompanied with sun exposure lowered the risk of MS development (Kampman et al., 2007). Decreased incidence of skin cancer in MS victims is another indirect evidence for the protective effect of sun exposure in MS (Goldacre et al., 2004). Two theories have been put forward to explain this effect; one is the immunosuppressive effect of UV radiation and the other is the subcutaneous vitamin D production with sunlight exposure (Kampman and Brustad, 2008).

Besides sunlight exposure, the inflammatory responses triggered by latent viruses such as Epstein-Bar virus, human herpes virus, and retrovirus are also proposed as risk factors for MS (Goldacre et al., 2004; Haahr and Munch, 2000; Perron et al., 1993). Furthermore, interactions between certain viruses and environmental factors have also been proposed. For example, studies have demonstrated that vitamin D could modulate the immune responses to Epstein-Barr infection (Holmoy, 2008). MS patients are more frequently inflicted by infectious mononucleosis before the onset of the disease (Pugliatti et al., 2008). Moreover, patients with infectious mononucleosis also reported lower level of outdoor activities (Kampman et al., 2007). Thus environmental factors play a critical role in the development of MS (Wallin et al., 2004; Hammond et al., 1988).

**GENETICS-ENVIRONMENT INTERACTIONS IN MS**

Regarding prevalence of MS, the disparity noticed between genders suggests that genetic as well as environmental factors might be involved in the disease pathogenesis (VanAmerongen et al., 2004). The unusually high prevalence of MS in early age groups in Sardinia suggests the same (Cocco et al., 2009; Pugliatti et al., 2005).

Interactions between genetic and environmental factors in MS have also been proposed. For example, sun and UV exposure can provide selective protection against MS in females (Kampman et al., 2007; Islam et al., 2007). Animal studies illustrated the protective effect of vitamin D3 in autoimmune encephalitis, although observed only in female mice (Smolders et al., 2008).

**NUTRITIONAL FACTORS AND MS**

People living in high latitudes are more vulnerable to MS. However, studies conducted in Norway, illustrated a low incidence of MS in coastal fishing areas compared to inland areas where intake of animal milk is more common (Swank et al., 1952). The protein or fat coming from surf instead of turf is thought to be responsible for the low prevalence of MS in coastal areas of Norway (Swank et al., 1952). This negative correlation between fish consumption and MS incidence has also been observed in USA and other countries (Agranoff and Goldberg, 1974). Kampman et al. (2007) found that Norwegians who consumed fish more than three times a week had adequate protection against MS (Kampman et al., 2007). Similar results have also been obtained from Canada (Ghadirian et al., 1998).

In Japan and Greenland where there is a higher than average fish consumption, there is extremely low prevalence of MS (Kira, 2003; Kurtzke, 1975).

**VITAMIN D AND MS**

A. Vitamin D metabolism:

Vitamin D is synthesized in the skin from 7-dehydrocholesterol by the action of UV and to a limited extent from diet. Fortified milk and milk products are among the few foods considered to be good sources of vitamin D (Calvo et al., 2004). The activation of the vitamin takes place initially in the liver (25-hydroxy vitamin D) and later on in the kidney to form 1,25-dihydroxyvitamin D3 (vitamin D3), the most active form of the vitamin (vandenBerg, 1997; Akeno et al., 1997). Excess vitamin D can be stored in the liver and muscles (Akeno et al., 1997).

Perhaps the most well known function of vitamin D is its role in calcium and phosphorus homeostasis which contributes to bone and muscle health (Cherniack et al., 2008; Pittas et al., 2005). Vitamin D also actively participates in gene regulation and immunological functions (Pittas et al., 2005) and could therefore be involved in the pathogenesis of cancer (Tuohimaa et al., 2007), MS (Cantorna, 2008; MacLean, and Freedman, 2009) and cardiovascular diseases (Kendrick et al., 2009). Since the main focus of this mini-review is on the role of vitamin D in MS, the following sections will discuss the current knowledge in this area.

B. Vitamin D in tissues of interest to MS:

The immuno-biological effects of vitamin D are mediated through a vitamin D receptor (VDR) through a ligand-activated transcription factor binding with vitamin D response element (Carleberg et al., 2001). Both 1α-hydroxylase and 24-hydroxylase that are required for vitamin D metabolism are expressed in the cells of the central nervous system (Overbergh et al., 2000; Zehnder et al., 2001), and the induction of the transcription of VDR and nerve growth factor (NGF) by 1,25 (OH)2D suggests a biological need for vitamin D in the CNS (Garcion et al., 2002;
Neveu et al., 1994). Expression of VDR in monocytes, antigen presenting cells (APCs), and activated T lymphocytes, add more support to the theory of the role for vitamin D in immune function (Provedini et al., 1983; Veldman et al., 2000). This has been well-documented by studies showing VDR’s role in the transcription, proliferation, and differentiation of immune cells such as B lymphocytes and dendritic cells (Dong et al., 2005; Muthian et al., 2006).

Animal studies have found that enzymes responsible for the synthesis of active vitamin D are present in cerebral cortex, brain stem, and cerebellum (Zehnder et al., 2001). Although the exact mechanisms are not fully elucidated, it appears that 1,25(OH)2vitamin D exerts protective effects on neurons, oligodendrocytes, and astrocytes (Garcion et al., 2002).

C. Vitamin D and MS: The evidence

One of the major functions of vitamin D is immunoregulation (Gregori et al., 2001; Griffin et al., 2001). The animal model of human MS, experimental autoimmune encephalopathy (EAE), is characterized by T-lymphocytes infiltration and peri-vascular inflammatory cell infiltration (Van Eten et al., 2003). In EAE, the major immune elements involved are T helper cells (Th1), interferon-γ (IFN-γ), and macrophages. Macrophages are considered to be critical in the development of EAE since the depletion of macrophages eliminates the signs of EAE in susceptible animals (Tran et al., 1998). In the EAE model, mice exposed to UV radiation before being immunized with myelin or myelin components were found to be effectively protected from EAE development. Neither modifying the ongoing nor preventing the relapse of EAE was observed; however, when the UV radiation treatment was initiated after immunization (Hauser et al., 1984). Another study showed that treating mice with 1,25(OH)2vitamin D during the EAE induction can reduce the severity of EAE presentations (Cantorna et al., 1996). Feeding a vitamin D deficient diet to mice not only resulted in an increase in the susceptibility to EAE but also accelerated and aggravated the EAE symptoms (Cantorna et al., 1996).

Moreover, concomitant supply with 1,25(OH)2vitamin D and immuno-suppressive agents such as cyclosporine, sirolimus, or calcium can prevent the presence of signs of EAE (Branisteanu et al., 1995; Cantorna et al., 1999). This result can further illustrate the concerted interactions between 1,25(OH)2vitamin D, immuno-suppressive agents and calcium in the prevention of EAE. Low calcium intake will lead to secondary hyperparathyroidism, and increases vitamin D turnover. This may result in vitamin D deficiency, and thus result in the aggravation of EAE symptoms and signs (Lips, 2001).

Since macrophages play a critical role in MS progression, it is plausible that oxidative stress and reactive oxygen species (ROS) produced in these cells are also part of the pathogenesis of MS (Gilgun-Sherki et al., 2004). Some encouraging findings have demonstrated the effectiveness of antioxidants in reducing the incidence, severity, and duration of EAE (Gilgun-Sherki et al., 2004). However, the role for vitamin D in modulating oxidative stress and reducing free radicals has not been elucidated yet.

VITAMIN D AFFECTS SPECIFIC IMMUNE CELLS

Several studies have investigated the role of vitamin D in the function of some immune cells like microglial and dendritic cells, lymphocytes, macrophages, and monocytes.

A. Vitamin D and APC-microglial and dendritic cells

After in vitro exposure to 1,25(OH)2 vitamin D, the expression of MHC-class II molecules with reduced IL-12 and increased IL-10 secrections were observed in CNS dendritic cells (Griffin et al., 2001; Maynard and Weaver, 2008). Interleukin-12 (IL-12), the pro-inflammatory cytokine produced by antigen presenting cells (APC), can shift the immune profile toward Th1 cells and then activate inflammatory responses (VanAmerongen et al., 2004). Proliferation and maturation of APC in CNS, including microglial and dendritic cells, were inhibited by the presence of 1,25(OH)2 vitamin D (Smolders et al., 2008). Furthermore, the pro-inflammatory cytokine IL-12 was down regulated by dendritic cells while the anti-inflammatory cytokine IL-10 produced by regulatory T cell (Tr) was up-regulated (Griffin et al., 2001; Maynard and Weaver, 2008). Dendritic cells also indirectly inhibited the Th cell proliferation and IFN-γ production (VanAmerongen et al., 2004).

B. Vitamin D and T-lymphocytes (CD4+ and CD8+ cells)

In vivo and in vitro animal studies demonstrated cell cycle arrest and apoptosis of activated T-lymphocytes after the exposure to vitamin D (Cippitelli et al., 2002; Decallonne et al., 2005). Pro-inflammatory cytokines including interleukin-2 (IL-2), IL-6, interferon-γ (IFN-γ), granulocyte-macrophage colony-stimulating factors (GM-CSF) that activate macrophages and MHC expression induced by T helper 1 cells (Th-1 cells) are all inhibited by 1,25(OH)2 vitamin D in vitro (Muller et al., 1993; Towers and Freedman, 1998). 1,25(OH)2 vitamin D has been shown to inhibit the T helper (Th) cell and myelin binding peptide (MBP) specific T-cell proliferation in vitro (Correale et al., 2009). In contrast, the absence of inhibitory activity on T-cell proliferation was observed in the presence of 24,25(OH)2 vitamin D or 25,26(OH)2 vitamin D, the inactive forms of vitamin D3 (Correale et al., 2009). VDR expression was significantly increased in the presence of 1,25(OH)2 vitamin D in CD4+ T-cells, MBP specific T-cell, and T-lymphocytes without being previously stimulated (Correale et al., 2009). Up-regulation of 1-α hydroxylase in the presence of 1-α hydroxylase mRNA in T-lymphocytes is responsible for the production 1,25(OH)2 vitamin D from 25(OH) vitamin D which resulted in T-cell function inhibition (Correale et al., 2009). These authors concluded that
vitamin D may play a role in T-cell homeostasis in MS and could offer a treatment modality.

C. Vitamin D and B lymphocytes

VDRs are expressed in activated B cells (Veldman et al., 2000; Chen et al., 2007). The exposure of 1,25 (OH)₂vitamin D to B lymphocytes resulted in decreased B cell proliferation, immunoglobulin production, and apoptosis (Chen et al., 2007). The possible mechanisms of vitamin D action on B lymphocyte functions are still unknown; however, its effects are thought to be mediated by monocytes and macrophages (Chen et al., 2007).

D. Vitamin D and macrophages and monocytes

It has been known for quite some time that 1,25 (OH)₂vitamin D could induce a pro-monocyte into a macrophage (Koeffler et al., 1984). Vitamin D could also enhance the antigen-presenting and phagocytic activities of macrophages (Perkins et al., 1995).

MECHANISM OF ACTION OF VITAMIN D

A. Vitamin D and cytokines:

Due to its effect on immune cells and APCs, it is conceivable that vitamin D can regulate cytokine production in those cells. The production of pro-inflammatory cytokines, including IL-2, IFN-γ, TNF-α can be decreased by the presence of 1,25 (OH)₂vitamin D (D’Ambrosio et al., 1998; Lemire and Adams, 1992; Lemire et al., 1994; Reichel et al., 1989; Cantorna et al., 1998); while the production of anti-inflammatory cytokines, IL-4 and tumor growth factor-β (TGF-β), can be enhanced (Cantorna et al., 1998). The production of pro-inflammatory cytokines (e.g., IL-12) from APCs can be suppressed by vitamin D, and the anti-inflammatory cytokine (e.g., IL-10) production can be increased (Penna and Adorini, 2000).

Vitamin D may influence the release of other cytokines, such as osteopontin, that in turn may influence the cytokines mentioned above. Osteopontin, a pro-inflammatory cytokine exerts both inhibitory and stimulatory effects like increased macrophage IL-12 production, IFN-γ and TNF expression, and decreased regulatory T-cell and IL-10 production (Stromnes and Goverman, 2007). The expression of osteopontin is up-regulated in the brain cells of MS patients (Chabas et al., 2001).

Prenatal vitamin D deficiency may contribute to decreased transcription of calcineurin and FK506 binding protein, and thus impaired T cell activation (Eyles et al., 2007). Both calcineurin and FK506 are immuno-suppressive. The transcription of other proteins, including catalase and heat stroke proteins (HSP) were altered in prenatal vitamin D-deficient animal studies (Almeras et al., 2007).

B. Vitamin D and nitric oxide (NO)

Although 1,25(OH)₂vitamin D is required for the production of inducible nitric oxide synthase (iNOS) in macrophages, the role for NO in MS is still controversial (Rockett et al., 1998). While some studies reported a reduction in brain NO of MS patients with vitamin D, others found the opposite (Cross et al., 2000; Willenborg et al., 1999; Zhao et al., 1996). Garcia et al. (1997) demonstrated the inhibitory effect of the iNOS by vitamin D in rats (Garcia et al.). This could partially illustrate its role in MS since iNOS has been shown to be up-regulated in neurons of neuro-degenerative patients (Garcia et al., 1998).

C. Vitamin D and the Blood-brain barrier

There is no direct evidence to indicate an effect of 1,25 (OH)₂vitamin D on the integrity of blood-brain barrier; however, a reduction in macrophage infiltration noticed in EAE rats after vitamin D exposure may imply its suppressive effect on trans-endothelial migration of monocytes (Nashold et al., 2000; Nataf et al., 1996).

D. Vitamin D and genetic factors of MS

Since vitamin D and genetic factors are associated with the susceptibility to MS, it is plausible that vitamin D receptor gene (VDRG) polymorphism might also be responsible for the development or modulation of MS (Fukazawa et al., 1999; Niino et al., 2000; Uitterlinden et al., 2004; Zmuda et al., 2000). Furthermore, the VDRG polymorphisms are not universal (e.g., Fok-I in UK, Apa-I in Japanese and Australian MS population) with marked disparity in different geographic regions (Fukazawa et al., 1999; Niino et al., 2000; Tajouri et al., 2005). Only Fok-I polymorphism located on the exon of VDRG was found to be involved in the modulation of immune function (Partridge et al., 2004). Ramagopalan et al. (2009) demonstrated that vitamin D can directly regulate the expression of HLA-DRB1*1501 that determines the susceptibility to MS (Neveu et al., 1994).

VITAMIN D AND THE MANAGEMENT OF MS

The therapeutic effects of vitamin D on MS based on large scale, randomized control trials are still lacking. A large scale observation study conducted in the U.S. showed that vitamin D supplementation proved to be beneficial in MS subjects; however, some weak points of the study design made the results inconclusive (Munger et al., 2004). Several small studies illustrated that the supplementation with vitamin D could increase the plasma 25(OH) vitamin D and cytokine TNF-β levels while decreasing the IL-2 mRNA levels (Mahon et al., 2003). In a clinical study of 12 subjects, vitamin D decreased the number of MS lesions present in the magnetic resonance image (MRI) (Kimball et al., 2007). Serum anti-inflammatory cytokine-TGF-β1 levels can significantly increase after vitamin D supplementation for 6 months, as shown in a clinical trial (Kimball et al., 2007). Randomized clinical trials are required for further evaluating the effectiveness of vitamin D in the treatment of MS.

Synergistic effects have been observed by combining 1,25 (OH)₂vitamin D and immunosuppressive agents such as cyclosporine, sirolimus, or minerals like calcium in treating MS (Stromnes and Goverman, 2007; Chabas et al., 2001).
Hyperparathyroidism caused by reduced calcium intake results in increased vitamin D turnover and thereby decreased VDR expression (Issa et al., 1998). A combination of 1,25 (OH)2 vitamin D with lymphocyte proliferation inhibitor mycophenolate mofetil (MMF) could lead to the generation of CD4 expression (Issa et al., 1998). A combination of 1,25 (OH)2 vitamin D/MMF with the suppression of natural immune function can effectively decrease the immune reactions in completely mismatched organ transplant animals (Griffin et al., 2001). Whether or not this combination could effectively ameliorate the EAE presentation needs to be elucidated by further investigation.

The possible side effect caused by vitamin D supplementation is a concern for the treatment of MS. High dose of 1,25 (OH)2 vitamin D may increase plasma calcium levels and possibly lead to tissue calcifications which could lead to renal or heart failure (VanAmerongen et al., 2004). A recently published study, however, did not find any significant increase in the serum calcium levels of MS patients taking high dosages of vitamin D supplements (Burton et al., 2010). Patients with sarcoidosis, mycobacterium infection, or use of thiazide diuretics are vulnerable to hypercalcemia and hypervitaminosis D (Hathcock et al., 2007). Use of 1,25 (OH)2 vitamin D analogues without hypercalcemic effect—by adding a benzene ring or modifying the side chain of vitamin D—might provide a solution for those adverse effects (Bouillon et al., 1995). Although more than 270 analogues have been developed, so far no evidence of clinical effectiveness of 1,25 (OH)2 vitamin D analogues on decreasing MRI lesions in MS patients have been reported (37).

**CONCLUSION**

There are many in vitro and in vivo studies supporting the immuno-modulative effects of vitamin D in the treatment of MS. The effect of vitamin D on several functions of the immune cells, especially Th1 and regulatory T cells, has been surveyed in this review. More research is needed to expand our knowledge in these areas. For example, the role of vitamin D in influencing the oxidative stress associated with MS needs further elucidation. In addition, well-designed randomized clinical trials to test the effectiveness of vitamin D and its analogues in MS patients are still needed.

**REFERENCES**


