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Review article

A review on potential roles of vitamins in incidence, progression, and improvement of multiple sclerosis

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ABSTRACT

Multiple Sclerosis (MS) is an inflammatory and neurodegenerative disease, with unknown etiology. Vitamins, as important micronutrients playing different roles in body, seem to be important in MS pathogenesis. *In vitro*, *in vivo* and human studies, supports the protective role of some vitamins in MS occurrence or progression. Current study reviews recent insights and reports about the importance of vitamins in MS incidence or progression. In accordance, the importance of all water and fat-soluble vitamins in MS pathogenesis based on observational studies in human population and their role in the function of immune system as well as possible therapeutic opportunities are discussed in depth throughout this review.

1. Introduction

Multiple Sclerosis (MS) is an inflammatory and neurodegenerative disease, usually defined by autoimmune responses to myelin sheath in central nervous system (CNS) which causes symptoms such as optic nerve damage, pain, fatigue, and difficulty in movement [1]. Despite all available information about this disease, its etiology is still unknown. However, it is known that MS should be studied as a neuro-inflammatory disease as well as an autoimmune disease at the same time. Different risk factors such as Epstein-Barr virus infection, smoking behavior, season of birth, vitamin D deficiency, and genetic factors are supposed to be involved in MS incidence and occurrence [2]. On the other hand, researchers are focusing on the impact of nutrition on disease prevalence, progression, and improvement [3–5]. Studies are specifically investigating the effect of vitamins on Alzheimer's disease (AD) and Parkinson's disease (PD). A considerable portion of these studies is about the vitamins and their roles. Vitamins are not every-disease-treating elixir, but play important roles in metabolism and in the most of vital pathways.

Vitamins such as vitamin C, vitamin A, and vitamin E act as antioxidant agents and control oxidative stress. Studies suggest that exogenous anti-oxidants (such as vitamin E, vitamin C, carotenoids, and flavonoids) can reduce beta-amyloid toxicity in patients with AD. A combination of these nutrients can have preventative effect on dementia and cognitive impairment [6]. The association of vitamin D and biomarkers of MS (as discussed in detail), amyotrophic lateral sclerosis (ALS), rheumatoid arthritis, PD, and AD has studied extensively. There are evidences to suggest positive effects of high-dose vitamin D3 supplementation in ALS pathophysiology [7].

There are also encouraging evidences for B family vitamins. Restricting effect of cobalamin (vitamin B_{12}) and folate (vitamin B_9) on homocysteine (a neurotoxic metabolite) has made them considerable nutrients. PD patients have lower serum level of cobalamin in their serum (just like MS patients) dietary supplementation of vitamin B_6 have shown to prevent PD development [8]. There is significant association between serum level of thiamine (vitamin B_1) and PD and its supplementation seems to be valuable [9]. Some researchers suggest adequate B vitamins intake should also be a public health priority [10]. However, there are few studies for conclusion and there are conflicting studies, which show no clinical improvement, despite positive

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Table 1
The role of fat-soluble vitamins in multiple sclerosis.

Vitamins	Vitamin serum level in patients	Immune-related role	Neural- or myelin-related role	Clinical remarks	References
Vitamin D	Low	Anti-inflammatory	Improves oxidation in white matter (at high doses)	Risk of hypercalcaemia in the Case of over consumption	[11–16,28,30,33–35,37–40,43,44]
Vitamin A	Low	Anti-inflammatory	Improves astrocytes anti-inflammatory function	Suppresses immune responces improves remyelination	[48–80]
Vitamin E	Low	No evidence	Inhibits necrosis factors improves oligodenrocytes functions	Reduces annual relapses improve remyelination	[81–83,90–98]
Vitamin K	No evidence	No evidence	Effective in oligodendrocyte survival		[99–101]

serological impacts [11]. Future studies should also investigate probable side effects of vitamin therapy such as mortality rate increment [12].

In this paper, we have reviewed the relevant articles in order to clarify the importance of each vitamin in the incidence, progression, and improvement of MS.

2. Fat soluble vitamins

Vitamins D, A, E, and K as fat-soluble vitamins can be stored in a long period of time and travel through the lymphatic system. They can impose a possibility of toxicity, which is discussed separately below. The role of fat-soluble vitamins in MS is summarized in Table 1.

2.1. Vitamin D

Vitamin D is a fat-soluble vitamin and is naturally found rarely in foods. It is usually produced when ultraviolet (UV) ray interacts with 7-dehydrocholesterol in the skin to form pre-vitamin D3. 25-hydroxycholecalciferol (25(OH)D3) is the major circulating metabolite of vitamin D, which is measured to show the vitamin D level of patients [13]. The primary form of vitamin D, known as cholecalciferol (vitamin D3), is available from two sources: skin exposure to UV-B radiation in sunlight [14].Diet can also supply cholecalciferol and ergocalciferol (vitamin D2). In spite of sunlight exposure, diet is a poor source of cholecalciferol, which provides only 40–400 international unit (IU) per food serving [15] in comparison with whole-light-skinned-body exposure for 20 min that produces at least 10,000 IU [16,17]. Although, the best-known function of vitamin D is regulating calcium homeostasis and function, it also has important effects on brain development and function, cell proliferation and apoptosis, regulation of blood pressure, insulin secretion, differentiation of immune cells such as T-helper and dendritic cells, and modulation of immune responses [18–20]. Observational studies, as discussed below, have demonstrated an association between decreased vitamin D level and risk of multiple sclerosis.

2.1.1. Vitamin D and population

Studies show that the frequency of MS incidence increases with increasing latitude, which has strong inverse correlation with duration and intensity of UVB of sunlight and concentrations of vitamin D [21,22]. At high latitudes, the prevalence of MS is lower in populations, consuming vitamin D-rich fatty fish than rest of the population, which emphasizes the positive impact of rich diet on the status of vitamin D [23–26]. Other vitamin D sources may also have the protective role of fatty fish. Accordingly, the risk of MS seems to decrease with migration from higher to lower latitudes [27]. In populations whom reside at higher latitudes, MS is increasingly prevalent. Based on such evidences, sunlight exposure may have protective effect since at higher latitudes lower level of sunlight leads to inadequate levels of vitamin D [28]. It has been shown that the 25(OH)D concentration in black people is lower comparing to white people and they often suffer from vitamin D deficiency due to the fact that melanin pigment in human skin absorbs UVB [29]. In contrast, studies have reported that the risk of MS in black people is less than white people, which is probably due to genetic factors [21,30].

Based on ecologic studies, season of birth has remarkable impact on MS incidence which is consistent with higher risk of MS in the late first trimester of pregnancy due to lower sun exposure or vitamin D intake [31]. Interestingly, analysis of all reported data showed that MS risk is higher in those born in April and lower in those born in October and November [32]. A study have shown that within the patient population of 979 females and 304 males, 62% of patients were born in the spring and summer. Additionally, the individual's risk of having MS and month of birth was highly correlated with April, September, May, and less correlated with November, respectively [33].

Data regarding the relevance of MS with vitamin D is controversial. Van der Mei and colleagues have shown that patients with MS had lower sunlight exposure during their childhood [34]. Other study have also stated that maternal vitamin D deficiency during early pregnancy imposes a nearly 2-fold increase in MS risk in the offspring compared with women with adequate 25(OH)D levels [35]. Accordingly, patients with isolated syndrome had lower level of 25(OH)D3 comparing to healthy controls however no significant difference was observed in the level of 25(OH)D2, vitamin D-binding protein, and also free or bioavailable vitamin D in patients and control groups. Therefore it is suggested that based on lower level of 25(OH)D3 in initial steps of MS and in serious phases, low 25(OH)D3 level can be considered as a risk factor for MS incidence [36]. It is also mentioned that the axonal injury can be decreased by high 25(OH)D levels in MS [37].

2.1.2. Vitamin D and multiple sclerosis

In an investigation on the relevance of circulating plasma carriers of vitamin D, vitamin D binding protein (DBP), and albumin in MS pathogenesis, it has been shown that the plasma level of DBP is significantly higher in patients at remission phases comparing with controls. However, the level of albumin was not significantly different among groups [38].

Despite Smolders and colleagues study which has shown no significant correlation between DBP and relapses, there are multiple other studies suggesting involvement of DBP in the MS pathophysiology [39–42]. Some studies also suggest DBP isoforms in CSF as prognostic biomarker in MS [43]. 1,25(OH)D3, as the active form of vitamin D, has dual effect on immune system by promoting the innate system response and suppressing the adaptive immune activity. T-cells consist of different subgroups such as cytotoxic CD8 + T-cells, CD4 + T-helper cells (Th cells), natural killer T cells (NKT), gamma-delta T-cells, memory, and regulatory T-cells. The effect of 1,25(OH)D3 is well characterized on T-helper cells that their proliferation and cytokine production are under regulation of 1,25(OH)D3 [44]. 1,25(OH)D3 has suppressing effect on producing inflammatory cytokines mediated by type 1 T-helper (Th1) cells. Secretion of IL-2, IL-6, IFN gamma and macrophage colony stimulating factor (M-CSF) are reduced by 1,25(OH)D3. Interestingly, activity of immune responses mediated by Th2 cells including the secretion of IL-3, IL-4, IL-5, IL-10, IL-13 has been enhanced by 1,25(OH)D3. It has been suggested that the positive impact of 1,25(OH)D3 on Th2 responses might suppress the function of Th1 responses. The