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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

development of regulatory T-cells is induced by 1,25(OH)D3 which leads to the elevated level of IL-10 and TGF-beta. Additionally, 1,25(OH)D3 suppresses IL-17 secretion from Th17 cells. Collectively, 1,25(OH)D3 suppresses the responses of Th1 and Th17 and induces the responses of regulatory T-cell (Treg). It also regulates the proliferation and localization of Th cells. 1,25(OH)D3 can also target CD8 + T-cells and invariant natural killer T (iNKT) cells. *In vitro* evidences shows that the proliferation of CD8 + T cells are inhibited by 1,25(OH)D3 and the proliferation of vitamin D Receptor (VDR) knockout CD8 + T-cells are occurred independent of antigen stimulation due to over-production of IL-2 [44–46]. Based on multiple evidences, vitamin D can have immune regulatory role, which is crucial for suppressing inflammation that is dominant in MS pathophysiology.

The maturation of human dendritic cell (DC) can be regulated by 1,25(OH)D3 and VDR. Following exposure of differentiating human and mouse monocytes to 1,25(OH)D3, expression of molecules responsible for antigen capture is increased and DC differentiation and maturation is inhibited that leads to the insufficient stimulatory capacity of CD8 + T-cells specific antigen. Furthermore, the number of Treg cells will be increased that promotes IL-10 up-regulation from CD4 + T-cells and decreasing the level of tumor necrosis factors (TNF) and interferons (IFN). Such molecules might have effect on suppression and interaction of DCs and T-cells in mice and humans. 1,25(OH)D3 can be synthesized by immune cells including macrophages, DCs and T-cells and can have contribution to immune responses regulation. While 1,25(OH)D3 activates VDR and 25-hydroxylase through intrinsic pathways, the maturation of DCs will be arrested. Such inductions have shown suspension in DCs maturation and have made them immature phenotypically and functionally [47].

#### 2.1.3. Vitamin D and treatment

Based on multiple evidences, boosting the serum level of vitamin D can be an advantage for treating and preventing MS since vitamin D supplements are cheap, convenient and safe for taking [48]. It is estimated that taking enough vitamin D can help to prevent more than 110,000 deaths per year [49]. However, the so-far performed interventional trials were not able to clearly support the hypothesis that vitamin D consumption can control the disease outcome [48]. Moreover, excess of vitamin D level in serum might lead to life-threatening hypercalcaemia, which has been reported in some case-control studies. It has been shown that treatment with high doses of vitamin D derivatives such as cholecalciferol or ergocalciferol is more safe than calcitriol (1,25(OH)D3) in case of inducing symptomatic hypercalcaemia [50,51].

### 2.2. Vitamin A

Vitamin A known as retinol, retinal and retinoic acid is categorized as a fat-soluble vitamin which is involved in various number of physiological functions including growth, development, immune functions and vision. Vitamin A deficiency is associated with risk of infections and can impose considerable risk of mortality and morbidity worldwide. Roles of vitamin A in immune system functions are documented in a large scale. On the other hand, its roles in brain development and activity is elicited [52].

#### 2.2.1. Vitamin A and population

It has been shown that the low level of vitamin A might be associated with the risk of MS [53]. Also, level of neutrophilic glutathione peroxidase (GSH-Px), vitamin A, and vitamin E are reported to be lower in serum of MS patients [54].

A study contributing 88 relapse-remitting MS patients reported a negatively associated level of serum retinol and magnetic resonance imaging (MRI) output [55]. Additionally, the retinol plasma level of MS patients under IFN-beta1a therapy is reported to be higher comparing to untreated groups, and also an expression of retinoid receptor subtypes is observed in mentioned patients which further emphasized on the association of retinol plasma level and activity of specific retinoid receptor subtypes [56]. Vitamin A inhibits differentiation of Th17 and promotes Treg differentiation so it may be involved in disease course of MS. Some studies have reported no correlation between vitamin A serum level and relapse rate. However, they have reported a positive correlation between vitamin A and vitamin D serum level, which might be due to the patients' diet. Accordingly, it has been suggested that retinoic acid has tissue specific manner and its local production in CNS might cause relapse courses [57,58]. Based on these population studies, vitamin A can be considered as a significant micronutrient in pathophysiology of the disease more extended studies are needed for a strong conclusion.

#### 2.2.2. Vitamin A and multiple sclerosis

Astrocyte derived retinoic acid (RA) plays considerable role in development and formation of blood-brain barrier (BBB) [59]. It has been shown that the expression of retinaldehyde dehydrogenase 2 (RALDH2) as a critical enzyme for the synthesis of RA is enhanced in reactive astrocytes in MS lesions. Additionally, over-expression of RALDH2 and higher levels of RA improve the restoration of the BBB integrity after its disruption due to such inflammatory factors as TNF in MS patients. It has been suggested that antioxidant transcription factor nuclear E2-related factor (Nrf2) is involved in protective role of RA and attenuates reactive oxygen species (ROS) levels in BBB lesions [60]. Accordingly, RA reduces the expression of IL-6, chemokine C—C motif ligand 2 (CCL2), and vascular cell adhesion molecule (VCAM-1) in brain endothelium which is increased under the inflammation state. Therefore, RA might serve as a potential therapeutic agent to reduce neuro-inflammatory diseases consequences. Moreover, Retinoid x receptor gamma (RXR-γ) has positive effect on oligodendrocyte differentiation and stimulates remyelination of injured CNS, positively [61]. Furthermore, there is evidence that RA receptors and vitamin D in heterodimerisation with RXR are able to bind hormone response elements and stimulate or repress transcription of certain target genes. However the pattern of their combination determines their effect on gene expressions [62]. Studies have shown that the circulatory level of RA and expression of RA-related genes can be influenced by external light in animal models [63,64].

Retinoid-related orphan receptor gamma (RORγ) is responsible for survival of immune cells such as Th17 in experimental autoimmune encephalomyelitis (EAE) model and is stimulated by melatonin following light exposure. RORγ is negatively activated by all-trans-retinoic acid. Therefore, the number of Th17 and IL17 level can be regulated by light dependent vitamin A [65]. As a result of supplementation with vitamin A, down-regulation of RAR-alpha [66] and IL-17 and ROR-gamma in peripheral mononuclear cells derived from the patients' blood [67] has been reported.

Retinoid molecules including all-trans-retinoic acid have been shown to suppress demyelination of CNS in EAE models which is associated with decreased IFN-gamma and TNF-alpha mRNA expression level and increased IL-4 and decreased IL-2 production by immune cells [68–70]. Deficiency of vitamin A is associated with decreased production of IL-4 and IL-10 and enhanced production of IFN-gamma [71–75]. The effect of vitamin A on IL-10 secretion from Th2 cells has been mentioned by many studies. It has been shown that the synthesis of IL-2 as an inflammatory cytokine by Th1 cells is inhibited by IL-10. Additionally, the level of IL-10 secretion from B-cells derived from MS patients were enhanced by RA administration and treating B-cells of MS patients by glatiramer acetate or IFN-beta-1b is able to retain this effect. Accordingly, RA affects positively IgG secretion and proliferation of B-cells in MS patients under stimulation by TLR9/RP105 [76].

#### 2.2.3. Vitamin A and treatment

IFN-beta-1a and b are the most used treatments against MS, which reduces the frequency of MS attacks and disease burden. In order to

determine the possible role of RA as a booster for IFN-beta, it has been shown that RA alone is able to reduce the count of IFN-gamma secreting cells but it has no effect on proliferation of T-cells. Additionally, RA in combination with IFN-beta-1b can potentiate the restoration of defective T-suppressor cell function [77]. Studies have shown that supplementation with retinyl palmitate, a retinol ester that can be converted to retinol [78], reduces myelin oligodendrocyte protein (MOG)-induced proliferation of T-cells derived from MS patients *in vitro*. This effect can be a result of reduction in production of IL-2 [79,80]. IL-10 has been also shown to be involved in suppressing T-cell mediated autoimmunity in EAE [81].

In another study, the effect of vitamin A on disease progression of 101 patients with MS is evaluated. The results shows that vitamin A, administered as retinyl palmitate, suppresses the progression of upper limbs and cognitive disabilities but not those of the lower limbs in MS patients. These results were achieved by comparing multiple sclerosis functional composite (MSFC) and expanded disability status scale (EDSS) scores. MSFC score, an index for physical functioning, was improved in treated group but no significant difference in EDSS score, and index of disabilities, was observed. There were also no significant changes in white matter lesions and relapse rates. The authors suggested that vitamin A may have better effect on neurodegenerative features rather than inflammatory features of MS [82]. A synthetic retinoid, Etretinate, has also been shown to potentiate the effect of IFN-beta-1b on cell function suppression [83]. It is suggested that vitamin A supplementation can be beneficial to relief inflammation and useful for protecting the brain. Although, we may see this benefit in patients in degenerative phase and further, vitamin A supplementation is recommended to be a part of MS therapeutic program [84]. Despite these findings, an extensive cohort study on the relevance of receiving carotenoids, vitamins C and E, and the risk of MS have shown no noticeable reduction in the risk due to vitamin-rich diet [85]. It is north worthy that ingestion of different preparations of vitamin A and different length of consumption can lead to significant variable plasma level of vitamin A in healthy subjects and may interfere the conclusions [86,87]. Based on these findings, vitamin A seems to be valuable in suppressing neurodegenerative or inflammatory conditions of MS patients but more studies under controlled situations with stronger methodology are needed for a trustable conclusion.

### 2.3. Vitamin E

Vitamin E belongs to the family of tocopherols and tocotrienols and has distinctive antioxidant activities in body. Additionally, it has been shown that vitamin E is involved in regulation of gene expression, activity of immune system and modulating cell signaling.

#### 2.3.1. Vitamin E and population

Comparing CSF and serum levels of vitamin E in 36 Patients of MS and 32 matched control, has shown that the serum vitamin E and vitamin E/cholesterol ratio were significantly lower in patients. However, the mean CSF vitamin E levels and the CSF/serum vitamin E ratio did not vary significantly between the two study groups [88]. These findings were supported by two other studies reporting a decrease level of vitamin E in the body in patients with multiple sclerosis [89,90]. Furthermore, it is observed that the ratio of plasma vitamin E to cholesterol and triglyceride are decreased during MS exacerbation and increased during treatment with IFN-beta [91]. It is shown that this increment is not a direct result of IFN-beta treatment [92] so it might be due to disease suppression and suggests an overproduction of free radicals during the active phase of the disease. Consequently, consumption of antioxidant molecules such as alpha-tocopherol can relief the adverse effects. There are evidence that the levels of alpha-tocopherol and glutathione are decreased in demyelinating plaques of patients with multiple sclerosis [93].

Seemingly, natural doses of vitamin E does not have significant protective roles and studies have failed to show MS risk improvement by dietary intakes of vitamins E and C [94,95]. A prospective study among two large cohorts of women did not find any association between higher intakes of vitamin E and reduced risk of MS [85,96].

Increasing serum concentrations of alpha-tocopherol has been associated with reduced odds for simultaneous and subsequent MRI disease activity in relapsing-remitting MS patients during IFN-beta treatment [97]. In a clinical study, a mixture of several polyunsaturated fatty acids (PUFAs), mono unsaturated fatty acids (MUFAs), saturated fatty acids along with vitamins E and A, significantly reduced annual relapse rate, and the risk of sustained disability progression compared to control. Vitamin E was reported to be a necessary component of this mixture but it did not decrease annual relapse rate meaningfully while administered alone [98].

#### 2.3.2. Vitamin E and multiple sclerosis

In animal models, the effect of vitamin E on the state of myelin has been investigated. Vitamin E in conjunction with Ebselen, both having antioxidant properties, protects against ethidium bromide induced demyelination and interferes with the cholinergic neurotransmission by altering acetylcholine esterase activity in various brain regions and in the erythrocytes [99]. Also, it is reported that vitamin E increases endogenous remyelination of hippocampus in addition to reducing the damage caused by ethidium bromide in rats [100].

Studies on therapeutic effects of tocopherol derivative, TFA-12, in EAE mice models revealed that TFA-12 promotes oligodendrocyte regeneration and remyelination and reduces inflammation, astrogliosis, and myelin loss. In addition, TFA-12 induces the oligodendrocyte precursor cells differentiation into mature oligodendrocytes by inhibiting of the Notch/Jagged1 signaling pathway [101].

Several studies have stated that vitamin E can inhibit NF-kB, a transcription factor involved in cell apoptosis and proliferation, in different cell types [102–104]. NF-kB is reported to be induced in the spinal cord of EAE rat models and its activation is persistent throughout the disease period and decreases during the recovery phase. *In vivo* inhibition of NF-kB activation by pyrrolidine diticarbomate results in attenuation of EAE clinical symptoms [105]. In light of these findings, it is conceivable that vitamin E by inhibiting NF-kB could have therapeutic importance in MS.

### 2.4. Vitamin K

No observational study was found regarding vitamin K deficiency and MS pathogenesis, which might be due to the fact that vitamin K deficiency is uncommon. However two studies have mentioned the importance of growth arrest specific gene 6 (Gas6) which is a vitamin K-dependent gene having role in MS progression [106,107]. This vitamin K-dependent gene is believed to play role in survival of oligodendrocytes and as the result improvement of myelination in the CNS. Gas6 is also an important factor in sphingolipid synthesis which seems to be important in remyelination [108]. However, no study was found to report observations based on EAE or any intervention and clinical trial on individuals and further investigations are required to clarify the possible correlation of vitamin K in pathophysiology of MS.

## 3. Water soluble vitamins

Vitamins C, $B_1$, $B_3$, $B_6$, $B_9$, and $B_{12}$ are water-soluble vitamins, which are believed to play considerable role in incidence, progression, or treatment of multiple sclerosis. The role of water-soluble vitamins in MS is summarized in Table 2.

### 3.1. Vitamin C

Ascorbate plays a role in synthesis of collagen which itself is associated with myelin formation. Study has shown that intra-hippocampal

**Table 2**
The role of water-soluble vitamins in multiple sclerosis.

| Vitamins | Vitamin serum level in patients | Immune-related role | Neural- or myelin-related role | Clinical remarks | References |
|---|---|---|---|---|---|
| Vitamin C | High | No evidence | Effective in dendritic cell maturation | Not suggested | [102,105–109] |
| Vitamin B9, B12 | Low | Immune regulator | Effective in homocystein uptake effective in myelin synthesization | Improves EDSS reduces relapses | [110–115,117–127] |
| Vitamin B6 | Controversial | No evidence | Effective in myelin synthesization | Reduces the risk of myelin damage | [129,130] |
| Vitamin B3 | Controversial | No evidence | Reduces inflammation | Improves EDSS | [135–137] |
| Vitamin B1 | Controversial | No evidence | Increases T-cell proliferation | Reduces fatigue | [138–140] |

injection of vitamin C improves memory for passive avoidance learning in Wistar rats [109]. This finding is important as more than 65% of patients with MS show signs of cognitive impairment and usually their ability to recall previously learned information reduces [110]. Epidemiological studies have found no reduction in MS risk with the intake of antioxidant vitamins such as vitamin C [111]. A study on the potential importance of uric acid has revealed that it has a remarkable effect on preventing the development of EAE symptoms or reducing them in comparison with ascorbic acid [112]. Additionally, high levels of vitamin C can be potentially harmful for patients due to promoting Fenton's reaction, a reaction that produces hydroxyl radicals in iron-rich tissues such as brain or spinal cord white matter. As the reduced form of iron ion, ferrous, is a part of this reaction, high concentrations of anti-oxidants such as vitamin C can promote it and as the result, may worsen inflammatory state due to radical production [113–115]. As a result, using vitamin C in therapeutic doses may worsen inflammatory diseases such as MS by promoting the Fenton's reaction [116]. It is reported that administration of vitamin C, not only shows no protective role against EAE development, but also worsens lipid peroxidation both *in vivo* and *in vitro* in the presence of $Fe^{3+}$ [112].

### 3.2. Vitamin $B_9$ and $B_{12}$

Folate (vitamin $B_9$) and cobalamin (vitamin $B_{12}$) are known as two key micronutrients in individuals. These two vitamins are considered as important cofactors in methylation reactions that makes them crucial for DNA synthesis and repair, metabolism of fatty acids and some amino acids, and also normal functioning of nervous system [117]. These two vitamins are also important cofactors for metabolism of homocysteine to methionine. Deficiency of cobalamin and folate is one of the most commonly seen deficiencies in patient suffering from MS and in most of the cases, high levels of homocysteine is observed. Homocysteine is a neurotoxic substance that cellular studies [118–120] as well as epidemiological studies [121,122] suggest that it can be harmful for the CNS as an inflammatory and a neurodegenerative agent. Folate and cobalamin are known as important cofactors for homocysteine uptake [123].

Evidences show that serum levels of cobalamin and folate is decreased in relapsing-remitting patients in comparison with control group. Increased level of homocysteine is also observed in mentioned patients [124]. Another study has also shown that some patients with multiple sclerosis are also suffering from megaloblastic anemia or macrocytosis as a sign of $B_{12}$ deficiency [125]. There are also other studies, which have reported mild macrocytosis or borderline low serum $B_{12}$ concentration in MS patients [126,127] and others have reported high levels of homocysteine in serum of MS patients [128,129]. A meta-analysis [130] also supports this observations and claims that $B_{12}$ and folate are in low levels in MS patients and homocysteine level is higher than healthy people.

$B_{12}$ also is an important cofactor in formation of myelin sheath [131]. It also incorporates in the modulation of immune system by having role in modulation of cytokines TNF-gamma activity so that cobalamin deficiency may worsen the inflammations that might be seen in MS [132].

In contrast, some studies have reported no correlation between folate or cobalamin and MS [90] but some have mentioned that in spite of normal $B_{12}$ serum level in these cases, the unsaturated $B_{12}$ binding capacity was higher that can be considered as a sign for body demand [133]. Multiple treatments with cobalamin and folate have also been reported with improvements in EDSS scores or decrease relapse risk [133,134].

### 3.3. Vitamin $B_6$

Vitamin $B_6$ and its active form, pyridoxal 5′-phosphate (PLP) play key roles in metabolism of amino acids, sugars, and lipids. As its significant functions, involvement in neurotransmitter synthesis, gene expression, or transamination can be mentioned [135].

Few studies were found on the correlation of $B_6$ vitamin and MS. There is controversy in studies as normal or higher than normal serum levels of vitamin $B_6$ is reported, and in contrast other studies have reported decreased serum levels of $B_6$ in comparison with control group have reported that $B_6$ serum level was normal in MS patients or higher than control group in some cases [90,136]. However, $B_6$ seems to play important roles in synthesizing sphingomyelins such as myelin sheath [137]. $B_6$ is one of the cofactors in homocysteine uptake which has neurotoxic and neuroinflammatory roles as discussed above [136]. However, as $B_6$ is not the main cofactor comparing with $B_9$ and $B_{12}$, and a study have reported no significant correlation between $B_6$ and homocysteine serum level [138], homocysteine uptake from $B_6$-dependent pathway leads to cysteine which is an amino-acid having role in myelin formation. It is suggested that nitric-oxide produces peroxinitrate which is a highly active radical and consuming $B_6$ vitamin daily during adolescence may reduce the risk of myelin damage [139].

### 3.4. Vitamin $B_3$

Vitamin $B_3$ also known as nicotinic acid or niacin is another water-soluble micronutrient, which plays essential roles as nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) as two important coenzymes in hydrogen transferring processes. Investigations have shown the role of niacin deficiency in cardiovascular diseases [140] as well as its active forms, NAD and NADP, roles in neural mechanisms such as lipid metabolism or DNA repair [141].

Few studies are devoted to determine the relevance of nicotinic acid and MS. Offermanns and Schwaninger have mentioned that ketone bodies, dimethyl fumarate (DMF), and nicotinic acid involving hydroxycarboxylic acid 2 receptors can reduce inflammation in neural system [142]. It has reported that rats with nicotinic-acid deficiency had less long-chain fatty acid than those favoring $B_3$-rich diet [143]. Treating patients with cytoflavin, a combination of nicotinamide and riboflavin (vitamin $B_2$), is reported to cause improvement in EDSS score, which might be another evidence for vitamin $B_3$ value for clinical purposes [144].

### 3.5. Vitamin $B_1$

Vitamin $B_1$ is not considered as much as other vitamins regarding MS pathogenesis but there are studies suggesting that thiamine has important roles in nervous system [145,146]. Thiamine deficiency causes increased C−C chemokine ligand 2 (CCL2) expression in spinal cord and T-cell proliferation in EAE mice model, which worsens the symptoms [147]. Human study also reports that MS patients intervened by thiamine, experienced improvement in their fatigue which might be due to the $B_1$ role in oxidative phosphorylation in mitochondria [148]. However, there are few studies in this field to make a strong conclusion whether thiamine is valuable for MS patients or not.

## 4. Conclusion

In this review, we tried to clarify the role of vitamins in MS. Vitamins are important micronutrients that play different roles in our body. As discussed above, evidences strongly suggest that vitamins D, $B_{12}$, and $B_9$ can have considerable roles in MS pathogenesis. On the other side, supplementation of vitamins A, E, and $B_1$ can also be beneficial in order to decelerate MS progression or improve unfavorable conditions such as fatigue and cognitive impairments. Vitamin C supplimentation, despite its antioxidant roles, may worsen patients conditions by stimulation Fenton's reaction in the CNS white matter, as mentioned.

The relevance of vitamins in MS pathophysiology have been explored extensively. However, the exact role of each vitamin is required to be investigated in MS. Evidences on the effect of some vitamins and their possible roles are lacking. More trials in order to establish new treatment approaches based on vitamins are recommended due to unknown etiology of MS which might open up new opportunities to develop more efficient therapeutic strategies.

## Conflict of interests

Authors have no conflict of interest.

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