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*Mini Review*

# Vitamin D, Vitamin B12, Folate, Iron and Creatine Kinase in Multiple Sclerotic Patients Who Smoke

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**Abstract**

It was aimed to investigate how vitamin D, B12, Folate, Iron and Creatine Kinase levels may change in patients with multiple sclerosis who smoke. For this purpose, the importance of vitamin D, B12, folate and iron in Multiple Sclerosis patients will be emphasized, and the contribution of the changes in the amount of these substances to the pathogenesis of the disease will be discussed. Multiple Sclerosis is a multi-factor autoimmune disease with a long and costly treatment process that seriously reduces the quality of life. Smoking, an important pathogen, is a preventable cause of death. Vitamin D is an important vitamin hormone that regulates calcium metabolism. Vitamin B12 and Folate are essential molecules for cognitive functions as well as nucleotide metabolism. Iron, which creates anemia in its deficiency and toxic effect by accumulating in excess, is one of the essential elements for human health. Creatine kinase is an enzyme found in many tissues that provides a practical way of energy reserve and utilization. As a result, we think that smoking may contribute negatively to the formation of Multiple Sclerosis and the disease process, with its effect of both initiating and increasing inflammation and reducing anti-inflammatory.

*Keywords:* Multiple Sclerosis; Smoking; Vitamins; Iron; Creatine Kinase.

## 1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease characterized by autoimmune destruction of myelin sheaths and subsequent neuronal death, characterized by multifocal and temporarily dispersed central nervous system damage leading to axonal damage. MS, which is one of the leading causes of neurological deficiency in young adults, is not known exactly, but extensive epidemiological data reveal that it is a complex disease affected by genetic and environmental factors [1-2].

Epidemiological data reveal that environmental factors play an important role in the pathogenesis of MS. One of the main environmental risk factors for MS is smoking. Both active smoking and passive smoke exposure have been found to be associated with the risk of developing MS, disease progression, and clinical disability. Smokers have a higher risk of developing MS than non-smokers. Unlike other MS risk factors, smoking increases the risk of MS regardless of age of exposure, both duration and intensity of smoking independently contribute to an increased risk of MS. Interestingly, the effect of smoking on MS risk persists until five years after quitting and is reversed ten years after quitting. However, although it is difficult to associate a heterogeneous compound such as cigarette smoke with certain mechanisms of action, lung irritation from burnt tobacco products appears to alter the risk of MS and possibly cause local oxidative stress and pro-inflammatory response, unlike systemic nicotine [2].

It is useful to highlight inflammation as the primary goal to be addressed in order to improve the course of the disease. It should be noted that there is a direct link between MS, including human dietary behavior, gut microbiota, amounts of vitamin D, B12, folate, iron, CK, and other inflammatory neurological disorders, and that these substances can be effective tools to suppress low-grade inflammation [3].

## 2. Potential of Vitamin D, Vitamin B12, Folate, Iron and Creatine Kinase

Many studies have been carried out that prove that vitamin D has an important key role in immune system

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functions and further shows that it is in an opposite relationship with MS, and it has been found that this vitamin has an immunodilator effect that prevents the formation of MS [4]. Mechanisms associated with vitamin D (Figure 1) and smoking negatively affect the course of multiple sclerosis [5].

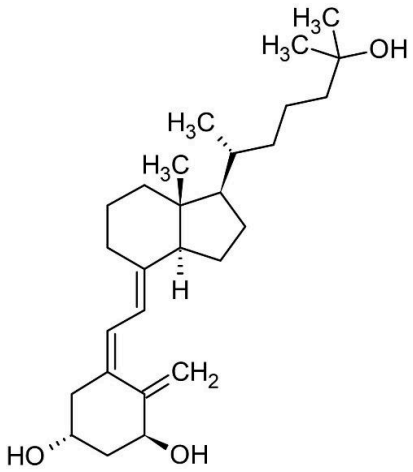


**Figure 1.** Calcitriol; most active form of vitamin D.

Many studies in recent years have explained that vitamin D abnormalities in MS patients are associated with disease risk [6]. It is noted that most recent studies report lower serum vitamin D among current smokers than non-smokers [7].

Vitamin D has hormone-like functions. By demonstrating the presence of 1α-hydroxylase in the human brain, it has been suggested that the active form of the central nervous system can be synthesized from the inactive form of vitamin D. As a result of epidemiological studies, the prevalence of MS increased from the equator to the poles and this raised the question mark that it might be related to vitamin D. Vitamin D deficiency is thought to be effective in determining the remission and attacks of Multiple Sclerosis [4].

Many studies have been conducted that prove that vitamin D has an important key role in immune system functions and further shows that it is in an opposite relationship with MS. It has been found that this vitamin has an immunodilator effect preventing the formation of MS. There are also studies showing that vitamin D supplements to be taken before MS diagnosis will reduce the activity of the disease and slow its course [4].

Many studies indicate that vitamin D levels are low in MS patients due to physical inactivity and inability to benefit from sunlight. The course of vitamin D levels and vitamin D supplementation are thought to play an important role in the clinical treatment of these patients. As a result of the studies carried out, it is obvious that vitamin D cannot be considered as an ordinary vitamin and has positive effects on cognitive function, brain and autoimmune system. While there is a risk of malnutrition in patients with multiple sclerosis, most studies related to nutritional therapy mainly focus on unsaturated fatty acids and vitamin D. However, their validity in treatment has not been proven yet, and their role in reducing symptoms, slowing the course of the disease and preventing the disease has been emphasized [4].

1.25 (OH) 2D has been shown to inhibit the production of inflammatory cytokines in response to a variety of inflammatory and / or infectious stimuli. In addition to these anti-inflammatory effects, 1,25 (OH) 2D can enhance antibacterial defense by stimulating phagocytosis and increasing the production of reactive oxygen species and antimicrobial peptides, both of which are important. Cigarette smoke is crucial in initiating the inflammatory response by the release of inflammatory cytokines such as alveolar macrophages, IL-8 and MCP-1, and it enhances the inflammatory response by attracting additional inflammatory cells, including monocytes and neutrophils, into the lungs. Cigarette smoke has been shown to impair the antibacterial activity of important resident phagocytes in the lung and alveolar macrophages that contribute to the clearance of infections. Given the anti-inflammatory and anti-bacterial functions of 1,25 (OH) 2D, it may be tempting to guess that cigarette smoke can prevent these effects. However, few studies have shown that cigarette smoke can affect vitamin D metabolism by increasing the catabolizing enzyme that disrupts CYP24A1 (24-hydroxylase, 1.25 (OH) 2D) or by decreasing CYP27B1 (1α-hydroxylase, which causes the formation of the enzyme). But also because the vitamin D receptor (VDR) is expressed locally in the lungs, as in alveolar macrophages, these effects of cigarette smoke on vitamin D metabolism could potentially limit the immunomodulatory effects of vitamin D in the airway [8].

Vitamin B12 and folate deficiency has been associated with cognitive dysfunction in MS patients [9]. There is evidence that vitamin B12 is important for myelin synthesis and integrity. MS is usually clinically and pathologically distinguishable from vitamin B12 deficiency, but demyelination is a prominent feature of both conditions [10].

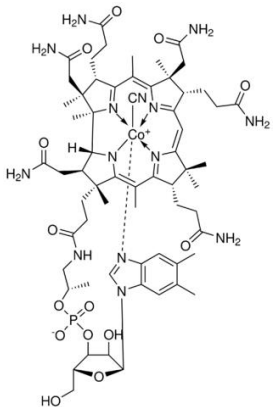


**Figure 2.** Vitamin B12; α-(5,6-Dimethylbenzimid-azolyl)cyanocobamide.

Vitamin B12 is produced by bacteria in people's large intestines. The most important sources of Vitamin B12 for humans are animal proteins. For children up to 18 years of age, the recommended daily amount of Vitamin B12 for adult non-pregnant women and men is 2 µg and for pregnant women and breastfeeding women 3 µg Vitamin B12 acts as a cofactor for homocysteine remethylation catalyzed by the enzyme methionine synthase. This reaction has the potential to affect cognition by regeneration of the active form of tetrahydrofolate (Figure 3), a compound required for DNA replication. In addition, the reaction can also cause adult neurogenesis in the hippocampus, an area of the brain necessary for memory and learning but highly susceptible to the negative effects of aging. It is also likely to lead to a reduction in homocysteine, which is neurotoxic and can result in atherosclerosis. A decrease in Vitamin B12 can cause abnormal fatty acids to accumulate in neural tissue membranes. Studies conducted in MS patients revealed that the disease is associated with low vitamin B12 levels [11].

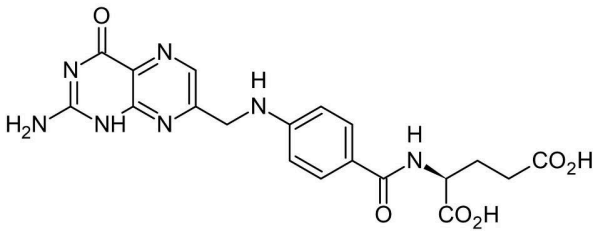


**Figure 3.** Folic acid (Folate), vitamin B9.

Smoking can alter appetite and consequently affect nutrient intake and serum micronutrients. It has been suggested that cigarette smoke negatively affects vitamin B12 metabolism and converts it into inactive forms. In a study conducted, while the serum level of vitamin B12 did not differ significantly between the smoker and non-smoker groups, it was reported that the active form of vitamin B12 was significantly lower in the smoker group compared to the non-smoker group [12].

Vitamin B12 deficiency should always be investigated in MS. Deficiency can aggravate MS or impair healing. There is evidence that vitamin B12 is important for myelin synthesis and integrity [10]. In a study to evaluate the effects of smoking on folate and vitamin B12 concentrations in circulating and tissues directly exposed to cigarette smoke, it was shown that smokers had significantly lower plasma red blood cell, folate, and vitamin B12 concentrations when compared to smokers and non-smokers [13].

Iron is an element that has an important role in maintaining many neurobiological activities. Oxidative phosphorylation is necessary in enzymatic reactions such as electron transfer, neurotransmitter synthesis as well as myelin production. Iron is transported in the brain through axons, depending on its ferritin. If this transport is interrupted due to axonal damage or normal aging process, oxidative cell damage and neurodegeneration due to iron accumulation in the brain occur. Studies conducted in recent years; It supports iron accumulation in MS and emphasizes its role in pathogenesis [14]. Iron accumulation in cerebral dark gray matter has been recognized as a global marker for MS neurodegeneration [15]. In a study, it was reported that there was a significant relationship between decreased signal intensity and increased pathological iron accumulation in MS patients [14].

Damage after smoking is associated with exposure to the particulate fraction of cigarette smoke. These particles alter iron homeostasis, triggering lung, liver, and systemic metal deposition. This change in iron homeostasis affects oxidative stress and inflammation [16].

While the amount of serum iron and ferritin has been reported to increase in smokers [16], another study shows that aqueous extracts of cigarette smoke cause iron reduction and release from ferritin in mice [17].

Iron may contribute to the pathogenesis and progression of multiple sclerosis as it accumulates in the human brain with age [18]. The localization of iron accumulation in the brains of patients with MS indicates that iron may increase oxidative damage in these disease states [19]. After disrupting iron homeostasis (both in the lungs and systemically) by cigarette smoke particles, it triggers the tissue damage mechanism. The accumulated iron then catalyzes oxidative stress and biological action [16].

Serum creatine kinase (CK) has proven valuable in the diagnosis of myopathy and myocardial infarction. The brain as well as muscle tissue has been shown to contain high concentrations of CK. The role of the enzyme in the brain was recognized by Mcllwain (1963) as maintaining the level of adenosine-triphosphate (ATP). The significance of CK is its relationship to the movement of carbohydrates and ions across the nerve cell membrane [20].

Astrocytes in the white matter prolong the fine processes in contact with axons at Ranvier nodes, which are thought to be involved in the regulation of homeostatic and metabolic functions necessary for a proper activity of axons. These astrocytic end legs are too thin to contain mitochondria and energy metabolism is locally achieved by glycolysis, glycogenolysis and phosphocreatine (PCr) degradation. Free creatine (Cr), which is formed by removing phosphate from PCr, then diffuses back to the mitochondria for phosphorylation [21]. In the study conducted by Steen et al. (2010), CK-B levels were investigated in the white matter of 17 progressive MS (9 primary and 8 secondary), 9 benign MS and 10 healthy control groups. In the study, it was reported that CK-B levels were lower in MS subjects compared to the control group. PCr metabolism in the white matter, which appears to be normal in MS, is impaired due to decreased CK-BB levels. A defective PCr metabolism in astrocytes contributes to the degeneration of oligodendrocytes and axons in MS [21]. It is known that smoking causes free radical-mediated lipid

peroxidation that causes increased membrane permeability. Cellular damage in the heart and brain causes CK to be released into the circulation [22].

Smoking is seen as an important risk factor in the development of cardiovascular and cerebrovascular diseases. Creatine kinase (CK) and its isoforms (CK-MM, CK-MB, CK-BB) have been advocated as sensitive markers in the assessment of cardiac and cerebral injury. In a study, a significant increase in serum CK activity was observed in the heart and brains of rats exposed to cigarette smoke. In addition, exposure to cigarette smoke resulted in a significant increase in all three isoforms in serum [22].

## 3. Conclusion

Evidence continues to grow that environmental factors play an important role in the development of multiple sclerosis. However, few environmental factors have consistently been associated with multiple sclerosis in epidemiological studies. Smoking is one of these factors. Compared to nonsmokers, previous studies have shown that smokers have a 40–80% increased risk of multiple sclerosis [23].

As a result, we think that smoking may contribute negatively to the development of MS and the disease process with its effect of both initiating and increasing inflammation and reducing anti-inflammatory.

## Conflict of Interest

The authors declare no conflict of interest.

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