Multiple Sclerosis and Evaluation of Vitamin D Effect :A Review Study

ABSTRACT

Multiple sclerosis is an autoimmune disease of the central nervous system with symptoms of neurodegenerative diseases. The symptoms vary depending on damage location. Some of the symptoms include cognitive disorders, anxiety and depression, visual impairment, respiratory, speech and swallowing disorders, muscle spasm and fatigue.

Due to the lack of a definitive treatment method, various therapeutic approaches are proposed to control the disease. Drugs are classified into attack control drugs, complication control drugs and disease-modifying drugs. Vitamin D is a hormone-like steroidal compound with immune modulatory and anti-inflammatory properties. Vitamin D deficiency is associated with a variety of inflammatory, neurologic and autoimmune diseases.

Many studies on patients as well as experimental autoimmune encephalomyelitis studies have shown that the administration of vitamin D reduces inflammation in inflammatory diseases of the central nervous system. As argued, vitamin D level was significantly lower in MS compared to healthy subjects as controls. Also, a higher level of vitamin D is reported in relapsing-remitting MS patients compared to patients with progressive MS. It is observed that higher serum levels of vitamin D can reduce the severity of symptoms, progress, and also delays the relapses. Few studies considered vitamin D to be ineffective in stopping or inhibition the disease. Despite the controversies concerning the role of vitamin D in MS progress, there is a lot of interest in further research in this regard with the hope of reaching a common ground. Therefore, frequent reviews of past and recent studies are essential to achieve the same results.

Keywords: Multiple sclerosis; Demyelinating Diseases; Neurodegeneration; Vitamin D.

***Abbreviations*:** MS=Multiple sclerosis; CNS=central nervous system; EAE= experimental autoimmune encephalomyelitis; VDR= Vitamin D receptor

Introduction

MS is a neurodegenerative and demyelinating disease. It is one of the most debilitating neurodegenerative diseases among the youth which are prevalent in 20 to 40-year-olds and in women two times more than men. But with therapeutic methods, the disease side-effects can be controlled to a degree (1).

MS symptoms are unpredictable and vary depending on severity, type, and location of the damage and the occurrence of all symptoms in one patient are very unlikely. A complete or partial remission of symptoms occurs in approximately 70% of patients in the early stages of the disease. Among the symptoms of MS, as a multi-symptom disorder, are visual impairment and walking as well as bladder difficulties. Fatigue and cognitive decline can occur due to pain, infection and depression (2).

Psychological and cognitive disorders, anxiety and depression

Anxiety, anger, despair, lack of communication, lack of courage, disability, self-accusation, difficulty in remembering, concentration, and inability to comprehend are among the psychological and cognitive disorders in MS

patients(3). Research also suggests mania, depression and hallucinations as other MS symptoms. Depression is the most common psychiatric symptom and a major cause of mortality in MS patients. As a major significant symptom, depression in MS affects patients' quality of life (QoL) and may cause fatigue, which results in non-compliance of medication. Restless legs syndrome (RLS) can be a cause of MS-related fatigue compared to a healthy control group. Moreover, neural studies indicate that 40-65% of MS patients suffer from advanced cognitive impairment, short-term memory capacity disorder and/or severe disorders such as dementia (4).

Visual impairment

Visual impairment is a major clinical symptom in MS occurring in about 70% of patients. Blurred vision or diplopia and temporary complete loss of vision in one or both eyes are among the symptoms usually accompanied by mild or severe pain in the eyes. Sometimes it is a visual impairment from red to orange, or red to silver**.** Visual impairment can be due to inflammation in the retina. Following the inflammation, a lymphocytic infiltration occurs, which is due to the brain demyelinating lesion (2,5).

Optic neuritis is one of the most common symptoms of MS, but depending on the location of the damage, the symptoms differ and occurs in 70% of the patients. Optic radiation lesions is one of the side-effects of MS in which the occipital gray matter area is attacked. Some research report damage to outer-retina in MS patients. Another side-effect of MS is ocular motility disorder in which the type of ocular motility depends on the location and severity of damage (5)**.**

Muscle spasm, stiffness and Fatigue

Muscles are antagonistic pairs which means when a muscle contracts, the other pair relaxes making it possible to perform various moves. In the event of muscle spasm or stiffness, both muscles contract at the same time. These impulsive contractions disrupt movement and can be painful and debilitating.

Painful muscle spasms are a common symptom in MS disease. The attacks take less than 2 minutes, but may occur multiple times in an hour. Tension, pulling, or heaviness associated with physical pain is common in MS which occur due to demyelinated lesion and damage to the axons. During the recovery phase, weakness, numbness and visual disorders may eliminate, but the hands and feet will continue to be impaired, and with relapse of the disease, symptoms may reappear and may even aggravate (6).

Respiratory, speech and swallowing disorders

MS is associated with impaired breathing and swallowing, as well as speech disorders, which may be exacerbated by progression of the disease. In coughing, adequate strength of the respiratory muscles is necessary to produce the required pressure and airway clearance. Respiratory muscular weakness increases the risk of respiratory failure as one of the main causes of the patients ' disability or death. However, exercise can increase the airway clearance capacity and cough strength. Swallowing disorder may not be detected at the early or even in middle stages of the disease, but many patients experience it. In MS, coordination of swallowing may be impaired as the result of demyelination of the cortico-bulbar region, the cerebellum, or the brainstem, which weakens the muscles fundamental for swallowing. Consequently, this causes malnutrition, dehydration and lung infection. With disease progression, swallowing problems can ultimately endanger patients 'lives. Interrupted speech, inability to make sentences, slowing or altering speech and swallowing disorder may be other MS symptoms (7).

Incontinence of excretion

One of the possible problems for patients with MS is intestinal and bladder disorders which affects their QoL. Constipation and fecal incontinence occur in 41% to 93% of MS patients. Frequent urinary incontinence occur in about one-third of the patients, and half the patients complain about its impact on their QoL(8).

Sexual disorders

Sexual disorder, including loss or lack of sexual desire and erectile dysfunction, is one of the most common symptoms reported by MS patients. It affects 40-80% of women and 50-90% of men. There is little information on sexual disorders faced by MS patients from the psychological aspect, the disorder causes depression. The severity of symptoms associated with sexual disorder increases significantly over time. Prognostic factors are the aggravation of sexual disorders, the level of physical inability, fatigue and depression, as well as individual sex. Primary sexual dysfunction is caused through neurological damage to the brain and spinal cord, which leads to reduced lubrication and ejaculatory dysfunction. Secondary sexual dysfunction is followed by MS-related problems (such as bladder dysfunction). Tertiary sexual dysfunction occurs under psychosocial effects such as poor body image or low self-esteem (9).

Cerebellar, balance and motor problems

The cerebellar disorders in relapsing-remitting MS and progressive MS cause neurological symptoms, physical impairments, and concentration (10). Cerebellum and its neurological pathways are usually affected by MS, and

cerebellar ataxia, especially in progressive MS, is seen in 80% of the cases. These patients either suffer from acute cerebellar disorder or have chronic cerebrovascular problems. During the relapse, the brainstem and cerebellum are damaged. A study of approximately 15,000 patients who had experienced approximately 50,000 relapse sessions showed that 10% of the relapses were cerebellar. These were more common in men and those patients who had a longer history of illness. Cerebellar and brainstem damage is also associated with poor reconstruction. MS-related tremor seems to be due to the involvement of cerebellum or thalamic disease. Tremor may affect the body, vocal cords, head or limbs. While severe tremor in MS is highly debilitating, it is reported in a study that it occurs in only 3% of patients (2). Tremor's pathophysiology in MS is complicated and is probably due to a disorder in cerebellar connections and or basal ganglia connections and cortical. Equilibrium dysfunction and dizziness, walking difficulty, disorder of movement coordination and paralysis of the organs are among the MS symptoms, and gait ataxia seems to be due to anterior lobe injury in the cerebellum. Cerebellar dysarthria is unusual in the early stages of the disease but occurs at the stage of the secondary progressive disease normally. Damage to the cerebellum for any reason, leads to disorder in verbal fluency, concentration and memory, and ultimately in daily life. A volume decrease in the posterior-inferior cerebellum causes diagnostic disorders in the patient, while reducing the size of the anterior cerebellum leads to movement disorders in patients (11) .

MS Types

MS has different types, each with its own characteristics. It can generally be categorized into four groups. However, regardless of the type of disease, some patients only experience a mild type throughout their life, and in a number of types, the symptoms emerge and progress quickly. But in general, there is a type between the two extremes. In all MS types, there are two phases known as relapsing and remitting phases. Forty five percent of patients have relapsing-remitting MS (RR MS), 20% suffer from primary progressive MS (PP MS), and 45% suffer from secondary progressive MS (SP MS) (12).

MS type is hard to detect and types are transformable. The disease relapses with the appearance of new symptoms or the return of old symptoms for 24 hours or more without altering the internal temperature of the body or infection. Relapse occurs when inflammatory and immune cells attack the nerve myelin and disrupt the normal function of the nerve. Usually, symptoms of relapse appear after a few days and can last for days, weeks (most commonly) or months leading to mild to severe symptoms. Remitting occurs when inflammation in nerve cells is reduced and the attack on these cells, and thus demyelination, is also reduced. Depending on the severity of inflammation and

demyelination and the rate of remyelination, remitting may be minor or major. The extent of demyelination is related to meningeal inflammation which is a base for identification (13).

MS relapse is generally unpredictable and can occur with no special symptoms. Some of the factors that affect the relapse of the disease include: The effect of seasons; relapses occur in the spring and summer more than autumn and winter. Infections: Like colds and influenza that increase the risk of relapse. Emotional and physical stresses and the incidence of any severe illness can be a factor in the relapse of the disease. Increasing the temperature in some patients causes the relapse of the disease. For this reason, it is recommended that patients avoid showering with hot water, saunas and spending hours in open air during hot days (14).

Scientists have categorized MS types as follows:

1- Relapsing remitting MS (RR MS)

Between 65% to 85% of the patients initially face this type of MS as the most common type. In this type of MS, patients experience a series of attacks, followed by remitting or recovery, and symptoms generally or partially disappear before another attack (relapse). Attacks can remit after a few weeks to several years.

In the early stages of RRMS, symptoms of the disease disappear completely during recovery, but after several relapses, it is possible that part of the myelin injury will persist, leading to a relative improvement. The probability of women having this type of MS is two times that of men, which in Iran increases by three times (15).

2- Progressive-Relapsing MS (PRMS)

A rare form of MS that occurs in less than 5% of patients. In this type, the disease progresses continuously and there is no remit or recovery in patients, and relapses or attacks occur occasionally. There have been numerous advancements in MS treatment. For relapsing type, there are more than 10 correctional treatments that target the damages caused by T-cells or B-cells(16).

3- Primary-Progressive MS (PPMS)

This type of MS is relatively unusual, affecting between 10% and 20% of the patients. In this type, gradual decline in an individual's physical ability is observed from the very beginning of the disease and deterioration is a continuous process. This type of MS is usually diagnosed in older people over 40 years of age. Unlike relapsing-remitting MS, men and women are equally at risk for this type of MS (15).

4- Secondary-Progressive MS (SPMS)

Most patients undergoing relapsing-remitting clinical procedures (RR) are likely to enter the secondary progressive (SP) phase. In this phase, attacks rarely occur but cause more disability in patients (15). In this type of MS, the symptoms created after the relapse of the disease are not completely eliminated, and disability always increases. In order to diagnose the progression of relapsing-remitting (RR) compared to this type of MS, the patient needs to undergo continuous deterioration for at least 6 months. On average, 50% of RRMS patients develop SPMS within 10 years of diagnosis. Some researchers argue that MS often involves younger adults and women. The course of the disease is usually relapsing-remitting for 10 years and then goes into the secondary progressive phase (15).

The four MS types presented are the main ones. But there are also MS types that are mild and are recognized after many years known as benign MS. In this type of MS, a complete or partial recovery occurs after the appearance of the symptoms, which is why it can be detected several years after contracting the disease. The necessary condition for diagnosis of benign MS is that no progress is observed 10 to 20 years after the disease and it does not cause any disabilities. It should be noted that the benignity of this type of MS does not mean that no complications occur to patients, but after years relapse might occur. There is a type of malignant MS that progresses very rapidly and sometimes is fatal but it rarely happens (15). However, despite the development of drug research in the field of treatment, there is no consensus on drug therapy of progressive MS patients. In the progressive phase, the gray matter atrophy is so progressive that its pathology can be distinguished from the pathology of white matter damage (17). Also, progressive patients have more cortical atrophy than RRMS patients, which is the cause of severe cognitive dysfunction in progressive patients. At present, the severity of gray matter atrophy and its symptoms and its association with cortical demyelination is still unknown and requires further in vivo studies(18).

MS Pathology

The name of multiple sclerosis refers to numerous plaques, especially in the white matter of the brain and the spinal cord, which is generally made up of white myelin. Myelin contains blood vessels that supply oxygen and nutrition to the nervous system. In MS, inflammation generally occurs in myelin. In this

case, the lymphocytes T- cells and B-cells with an important role in the immune system, similar to an invasive agent, attack myelin by crossing the blood-brain barrier. This phenomenon leads to more inflammation and the stimulation of other cells and immune factors such as cytokines and antibodies. Further leak in the blood-brain barrier leads to swelling, activation of macrophages, and more activity of cytokines and malignant proteins. And finally, demyelination occurs (18).

Symptoms of MS are due to the development of new lesions and the progression of old lesions in myelin. The release of inflammatory cells, especially those with monocytes origins, causes ulcers resulting from the removal of myelin. These cells remove myelin through phagocytosis. A number of monocyte activation markers include LFA-1, MHC Class II, and MAC-1 (19).

In the early stages of the disease, a regenerative process called remyelination occurs to compensate for damage to myelin by regeneration and repair. This is why most patients experience a symptom relief after an MS attack or relapse. However, myelin is inflamed again and oligodendrocytes cells are not able to rebuild cells 'myelinated sheaths completely. Frequent attacks result in a reduction in the efficacy of remyelination, leading into a hardened plaque around the damaged axon (18). As the result of damages to myelin, wounds are created which are referred to as lesion, plaque or sclerosis. Damage to myelin leads to a reduction in the transmission speed of messages along the nerves, and sometimes disruptions in the transmission of messages occur such that the transmission of the message from one nerve axon to another, due to damage, does not occur. In addition, the nerves themselves are destroyed (18). Although MS is defined as a brain white matter and spinal cord disease, the pathology of gray matter was presented in the early 19th century and stated that in 26% of patients gray matter lesions are in the cortical and subcortical regions, proved today through immunohistochemistry techniques and MRI.

In this disease, several pathophysiologic mechanisms are involved which include: oxidative stress, inflammation, demyelination, axonal injury, gliosis, remyelination, changes in the immune system, and brain dysfunction. The evaluation of biological markers, immunologic responses, signs of response to therapeutic interventions to control the patient's disability has an important role in improving the quality of life (QoL) of patients (20).

In the early stages of the disease, myelin destruction occurs due to the presence of microglia and activated astrocytes, and with progression of the

disease, axon is degenerated, which is a reason of major damage in patients. The neurological disorder in RR-MS patients is due to myelinating inflammation, while axonal degeneration plays a major role in the SP-MS type (19). In general, pathology of the progressive MS includes the loss of myelin, oligodendrocytes and axonal degeneration .Pathophysiological processes can be unique to each patient. In addition, a wide range of genes involved in the incidence of MS and progression of the disease, as well as genes associated with the disease-protection mechanism, are reported in the research(21).

MS diagnosis

Due to the wide variety of symptoms, MS may not be detected months to years after contracting the disease. Physicians, especially neurologists, perform full physical and neurological examinations. As some of the MS symptoms are shared with other diseases, doctors use tests such as blood tests and internal ear tests to check the body balance to exclude other diseases. In the past, MS was only confirmed when MS symptoms occurred at least twice, and each involved different parts of the CNS. But now MS in the patient is confirmed only with the occurrence of one neurological symptom and provided there is evidence of an MRI scan confirming plaque production in the brain and spinal cord (21) .

The most common MS diagnostic methods

1- Neurological examination and patient history

The first step is to investigate a patient's history of disorders. Then, movements of joints and muscles, involuntary movements and visual sensations of the patient are examined, which include changes in vision, eye movement, coordination of the arms and legs, balance, senses, speech, or reflexive movements, as well as any weakness. So far, there is the possibility of MS confirmation, but its definitive diagnosis is done by performing more tests (22).

2-Magnetic Resonance Imaging (MRI)

MRI is a useful tool for diagnosing the disease and monitoring the treatment process that can show the presence and severity of the disease. The role of MRI is to indicate the demyelination and atrophy regions in the brain (22). The diagnostic quality by MRI is enhanced with contrast of gadolinium with high-resolution images in which gadolinium venous injection (Gd 64) is used and provides a complete image of the brain and spinal cord (23).

In 95% of the patients, it is possible to determine the exact location and size of brain lesions. More advanced MRI technologies, like the 3-T MRI, show the presence of gray matter ulcers and brain atrophy. Gray matter atrophy seems to occur in the early stages of the disease, even at the stage before the onset of MS symptoms. The use of in-vivo 7-T MRI to show cortical damage in patients shows the relationship between cortical pathology and the duration of the disease (24).

3. Electrophysiological test (Evoked Potential)

In this test, the movement of neural massages throughout the nerves is examined to determine whether it is normal or slow. To this end, small electrodes are placed on the head, and then the brain waves and the brain's response to visual or auditory messages are checked. If the messages are slow and responses are slowly transmitted, myelin damage has occurred and the risk of contracting MS is increased (25).

4. Lumbar puncture test

Cerebrospinal fluid is a clear, colorless fluid circulating around the brain and the spinal cord through the ventricular system. This test is done with local anesthetic and the cerebrospinal fluid is extracted by a syringe from the lower part of the waist. The cerebrospinal fluid in MS patients often consists of a type of abnormal antibody indicating that the immune system is involved. As a result of testing, oligoclonal bands are seen. The test was done frequently in the past, but now it is only used if MS diagnosis is not confirmed by other methods. The method causes headache in patients post-sampling (26).

Treatment of MS

So far, no definitive treatment is found for MS. However, there are different treatments for controlling the disease. Treatment method depends on a variety of factors, such as patients ’condition, type of disease, severity, and the degree of disability in a patient. Slowing down progression of the disease, reducing the number of attacks, increasing the recovery speed and relieving the problems caused by dysfunctioning organs, are the goals pursued in the treatment of MS. One of the methods is drug therapy. Medications are categorized into three main groups: drugs for the treatment of attacks, drugs for controlling disease symptoms and medications for slowing the disease progression. For example, Slowdown drugs for the progression of the disease are interferons, Glatiramer

acetate (Copaxone) and Novantron. Drugs to reduce the severity and duration of attacks are corticosteroids. Corticosteroids such as Pronozone and Dexamethasone, either orally or intravenously, have side effects including stomach ulcers, mood changes, fatigue and overweight. In the long run, corticosteroids might impair the immune system, and increase the risk of infection and acute diabetes. A bout drugs controlling the symptoms of the disease for muscle spasm, for example, baclofen and diazepam are used to relax muscles. Ritalin, a CNS stimulant, is used in patients with severe fatigue (27).

Vitamin D

Vitamin D is a steroidal and lipid-soluble compound with the same function as steroid hormones that has been shown to play an immune modulatory and anti-inflammatory role in *in vivo* and *in vitro* studies(28)**.** UVB in sunlight is the most important biological agent for producing DNA damage which acts as a source of vitamin D production in the skin. This vitamin is present in two biological forms. Vitamin D2 (Ergo Calciferol) and Vitamin D3 (Cholecalciferol). UVB radiation to the skin converts dehydrogenated cholesterol to cholecalciferol (29).

According to Mealy et al., the administration of vitamin D reduces inflammation in diseases of the CNS (30). Through the comparison of vitamin D2 with D3, some studies found that the capability of vitamin D2 to add a serum level of 25(OH)D is only 30% of vitamin D3 (31). Some other researchers, however, state that there is no difference between the effectiveness of these two forms of vitamin D (32). Minimal Erythema Dose (MED) describes the amount of exposure to sunlight in vitamin D production. A MED is equivalent to 6,000 to 10,000 IU of vitamin D3. To produce 10000 IU to 15,000 IU vitamin D in the body, about 15 minutes of sunlight is sufficient. But the amount of vitamin D depends on several factors, including the amount of skin coverage, the amount of skin melanin, the latitude of the place of residence, the season, and the use of sunscreens (33).

Different amounts of 25(OH)D in serum

The main form of vitamin D in the bloodstream is 25-hydroxyvitamin D [25(OH) D]. Due to the relatively long half-life of the compound (15 days) in the serum, it is used to measure the amount of vitamin D in the body. The standard levels of serum vitamin D (25(OH) D) are determined on the basis of the report:

Toxic range of vitamin D (80-150ng/ml) 200-374nmol/l, Optimal vitamin D level: (25-80ng/ml)62-200nmol/l, Inadequate vitamin D level: (20-29ng/ml) 52-72nmol/l, Vitamin D deficiency: (20-25ng/ml) 50-62nmol/l and less (33).

In examining the serum level of vitamin D in 1163 people with an average age of 60 years, it was shown that vitamin D level in 40.8% of the respondents is in the range of ≤ 50nmol/l ,which suffers vitamin D deficiency. Also, 79.8% of the respondents have vitamin D levels lower than 75 nmol/L, which is considered to be the upper limit for vitamin D deficiency. Since the above mentioned amounts are the minimum standards determined, the prevalence of vitamin D deficiency is alarming (34).

Vitamin D and MS Disease

The effects of vitamin D and its analogues are known. The most important role of this vitamin is calcium homeostasis through absorption of calcium from the intestine, its reabsorption from the kidneys and its sedimentation in the bones and teeth (33). Scientists stated that there is a strong correlation between the amount of UV light and the incidence of autoimmune diseases, including MS (35). According to several studies, a pattern of high MS prevalence is observed in regions with less radiation intensity, which decreases the amount of vitamin D synthesis in the skin. Studies have shown that vitamin D deficiency associated with multiple autoimmune diseases, such as cardiovascular disease, cancer, type-1 diabetes, inflammatory bowel disease, rheumatoid arthritis and multiple sclerosis(36).

Unfortunately, because vitamin D is difficult to eat and most people intake vitamin D from their exposure to sunlight UVB light, people with UVB deficiency in their places usually suffer from a lack of vitamin D.Many studies have suggested that this vitamin may affect the pathogenesis and multiplicity of MS. According to J. Smolders et al, Vitamin D deficiency is one of the causes of MS. Boontanrart et al, have demonstrated the synthesis of active vitamin D3 (1, 25-$(OH)_2$ D) in the CNS.Vitamin D enhancement is effective in reducing the risk of disease. Based on the difference in metabolism of this vitamin in men and women, it is believed that women may benefit from the effects of vitamin D immunization more than men (37, 38).

Vitamin D and genetic factors effective in MS

Calcitriol [$1,25(OH)_2D$] help to regulate about 200 genes and is effective in angiogenesis, differentiation and cell death (33). Among the genetic factors

affecting MS in relation to vitamin D, is the CYP27B1 gene encoding the 1-α-hydroxylase enzyme, which converts 25(OH)D into active forms of vitamin [1,25$(OH)_2$D]. Two variants of this gene have been identified. In people with a loss of GYP27B1 gene, the risk of MS is increased (33).

The CYP24A1 gene is capable of encoding the 24-hydroxylase and degradation of 25(OH)D and so its active form that is [1,25$(OH)_2$D]. The GWAS research center identified and studied the CYP24A1 gene to investigate the genetic factors affecting 25(OH) D (39). Vitamin D receptor (VDR) is 1, 25$(OH)_2$D receptor in the cell. To regulate the transcription of the gene, the calcitriol joins VDR and the retinoid X receptor. In a study on the Australian population, it was found that VDR polymorphism could be a risk factor for MS disease (40). Several animal, human and *in vitro* studies confirm the effects of vitamin D on the expression of genes associated with immune regulation. Vitamin D acts by regulating the gene transcription rate. After the connection of 1, 25$(OH)_2$ D to VDR, it is transferred to the nucleus. Another genetic factor affecting MS is the presence of VDR binding sites (VDREs) on DNA. Vitamin D forms a complex with the retinoic acid x receptor at the DNA level before binding to VDERs. At this stage, vitamin D has an effect on the rate of gene transcription. In a study, the effect of enrichment of VDREs on autoimmune diseases was investigated. The levels of VDERs in the DNA of the immune cells are greater than the non-immune cells found in genomic regions associated with MS disease (41, 42).

MS, Vitamin D and immunological effects

Some researchers argued that 1,25$(OH)_2$D play an effective role in regulating the immune system and it was later found that VDR exists in many tissues, including immune cells.

All immune cells, including T-cells, express VDR. A research has shown that vitamin D affects the level of cellular immunity (43). Boontanrart et al stated that, high levels of vitamin D reduce the risk of progression to a number of neurological diseases, such as MS or Parkinson's disease, by regulating the immune system. In autoimmune diseases such as MS, the natural defense mechanisms of the body, where there are autoimmune agents, are activated and attack tissues and cells of the body. This means that the immune system, which is constantly activated and fought against the virus and bacteria, in autoimmune diseases, is confused, attacks and exterminates internal tissues (38).

Many studies are done on the immunology of MS and its pathology, including myelin damage, plaque formation, disruption of axon, and remyelination. If an internal or external antigen is present on T-cells (CD8+ or CD4+), T-cells are activated and a series of immunologic cascades occur in which anti-myelin antibodies, macrophages, types of interleukins (IL-2s) and cytokines are involved. Evidence suggests that vitamin D with immunomodulatory effects has an impact on MS through influencing the activity of B-cells and T-cells and regulating interleukins (44). The accumulation of inflammatory cells with MS ulcers provides the circumstances for degradation of active tissues, which can be created by activating microglia and astrocytes and by inflammatory cytokines of the immune system. Microglia is activated during infections or diseases of the CNS. The mechanisms regulated by the activated microglia for controlling immune damage are not well known and it is estimated that vitamin D has regulatory effects on the immune system and controlling the diseases of CNS(38).

In MS, symptoms of depression occur due to high pro-inflammatory cytokines activity. These include cytokine tumor necrosis factor alpha (TNFα) derived from monocytes and macrophages and interleukins 1 and 6 (IL-1 and IL-6) found in the bloodstream and cerebrospinal fluid (CSF). In antidepressant treatment, the level of these cytokines is reduced (45).

Vitamin D reduces the production of pro-inflammatory cytokines and increases the production of anti-inflammatory cytokines. This vitamin is expected to act as inhibitor or at least modulator of the symptoms of inflammation and, consequently, depression in MS patients. However, some studies do not confirm this role of vitamin D (45). Linda Rolf et al. in a study on MS patients examined the TNFα / IL-10 ratio and pro-inflammatory / anti-inflammatory cytokine ratio before and after administering vitamin D3. Despite their anticipation, they did not see a change in the pro- and anti-inflammatory cytokine, as well as in the TNFα / IL-10 ratio. According to their study, the effect of vitamin D3 on inflammatory biomarkers in MS was not confirmed (46). Vitamin D is effective on the path to an inflammatory cascade and can alter the cellular response, which acts as a sterol hormone. After the genome effect of vitamin D, myeloid cells, including monocytes, dendritic cells and macrophages, produce less pro-inflammatory cytokines (such as IL-12, TNF, IL1) and more IL-10. (This path leads to T_{reg} cellular differentiation). CD4+T lymphocytes are also affected by vitamin D and yield the same results. Scientist showed T_{Regs} migrate to the CNS and suppress immune responses (47). The use

of 1,25 $(OH)_2D$ as skin ointment and so UV light on mice stimulates the T_{Reg} differentiation(48). The delivery of antigens to T-cells initiating or promoting immunologic reactions is done by dendritic cells, which is related to foreign or self-antigens. In vitro experiments showed that after vitamin D intake, the differentiation of dendritic cells is decreased (47). Through CD_4T-cell, as well as through the proliferation of Transforming Growth Factor (TGF), IL-4 and IL-10, vitamin D decreases secretion of interferon-gamma (IFN-γ) , IL-2 and IL-5. These result in the displacement of the immune response from a T-helper1 (Th1) to T-helper2 (Th2). Therefore, MS is referred to as Th1-dominant auto immune disease (49).

Through multiple activity, increasing the bactericidal activity of macrophages and inhibiting macrophage and antigenic antigen confrontation with dendritic cells, 1,25 $(OH)_2D$ inhibits immune-related diseases, such as MS. Moreover, by inhibiting the MHCPR expression (Major Histo Compatibility complex II) on the cell surface, 1,25 $(OH)_2D$ inhibits the antigen-presenting capacity of macrophages and lymphocytes. For vitamin D, there is a cellular pathway associated with the 1-α-hydroxylase activity in cells, which is related to epithelial cells, neutrophils and macrophages. Parathyroid hormone (PTH) does not affect this extra-renal enzyme. Macrophages and dendritic cells activated by the production of 1-α-hydroxylase convert vitamin D3 to calcitriol [1, 25$(OH)_2$ D], which is the active metabolite of vitamin D3. This enzyme is regulated by immune factors such as interferon gamma (ɣ-IFN) (50). Anti-proliferative and anti-inflammatory effects of vitamin D on MS in vivo on CD8+ Tcells, CD4+ Tcells and antigen presenting cells obtained from peripheral blood and CNS is confirmed (51).

Vitamin D has a mitigating effect on the production of pro-inflammatory cytokines (e.g., monocyte / macrophage derived cytokines, tumor necrosis factor alpha (TNFα), interleukin (IL-1 and IL- 6) and has an incremental effect on the production of anti-inflammatory cytokines (such as IL-10). Also, administering a high dose of vitamin D for 12 weeks reduces the production of IFNγ (interferon-γ) through stimulation of T-cells (52). Panitch et al., in a study of 18 MS patients treated with IFNγ, confirmed the malignant effects of IFNγ on worsening of the disease in 7 patients out of 18 patients (53). On the other hand, some studies have shown significant changes in serum cytokines after vitamin D administration. Sotirchos et al. found contradictory results. Since the sampling method is effective in controlling the level of serum cytokines, it may be possible to answer the contradictory results (54).

The effects of Vitamin D on MS

To determine the optimum level of vitamin D, the maximum tolerable absorption, the maximum vitamin supplement and the identification of acceptable levels of vitamin D in vitamin D-deficiency-related diseases, the Institute of Medicines and Food Board (FNB) was established. The institute announced that Adequate Intake (AI) levels of vitamin D to maintain bone health include: For people over the age of one year, the maximum daily intake is 2000 IU, for people aged 50 and above, it is 200 IU per day, for individuals aged 51-70, 400 IU daily, and for people over 70 years of age, it is 600IU daily (55).

A number of studies suggest that maintaining serum level of Vitamin D in the range of 75-110 nmol/L, daily intake of 500 IU to 800 IU of vitamin D is necessary (56). Wingerchuk and Burton's research showed that the consumption of about 20,000 IU of cholecalciferol per week increased the amount of 25(OH)D by 50 nm /L (57, 58). The FNB Institute declared that the daily intake of 1000 IU of vitamin D increases the serum level of this vitamin by 25 nmol/L and recommends continuous and daily intake of 800 IU to maintain normal levels of vitamin D (56). Some studies have shown that maintaining a serum level of 70 nmol/L of vitamin D, intaking at least 500IU is necessary daily (59).

Researchers reported that in patients with MS, the level of vitamin D was lower and the lower level of vitamin D is associated with an increase in the incidence and relapse (60). Also, some reported that adding vitamin D has an ameliorative effect on the course of the disease. Scientists were studied the effect of Vitamin D on the course of MS disease. In a study, 16 MS patients received 5000IU vitamin D, 16 mg / kg of calcium and 10 mg / kg of magnesium per day for 11 to 24 months. It was found that the number of attacks by patients was decreased with respect to the expected number of attacks (14 Attack vs. 32 expected attacks, $P < 0.005$) However, these results did not indicate whether the desired outcome was the result of vitamin D intake or one of the compounds taken with vitamin D (61).

Ashton writes that there is a direct association between high levels of 25(OH)D and fewer MS plaques and it is estimated that vitamin D nutrition may have a significant immune effect on inflammation of the CNS system (62). Several studies have suggested that high levels of vitamin D are associated with a reduced risk of MS disease. The researchers report that 25(OH)D serum increase by 50 nmol /L reduces the risk of active ulcers by 57% (63). Pedersen

et al., in EAE studies, showed that vitamin D intake decreases inflammation in the CNS (64).

Some studies have suggested that a low level of 25(OH)D is related to the increased risk of progressive MS disease .Christina Hartl et al. stated that seasonal changes are inversely related with 25(OH) D serum levels in MS patients (65). In a study of people who had little sunlight exposure, researchers concluded that the cause behind the prevalence of vitamin D related chronic diseases in these individuals is due to the fact that the reported AI in 1997 was insufficient (56).

Numerous researches are conducted on the appropriate level of vitamin D uptake such that it does not increase the toxicity of calcium in the serum. Accordingly, 67 healthy men with a serum vitamin D level of about 70 nmol/L, received randomized daily doses of 0 to 10,000 IU of vitamin D. Dosages of 10000IU were administered daily for 20 weeks with no increase in serum calcium and the highest level of serum vitamin D was obtained between 160 nmol/L to 220 nmol/L (59).

The FNB also stated that the serum vitamin D level between 75-110 nmol/L is a normal range and 250 nmol/L (100 ng/ml) is considered as the maximum (66).

A group of researchers studied 24 MS patients as a control group and 24 MS patients as treatment group. In all MS patients, the mean vitamin D level was 78 nmol/L (31.25 ng/ml). The control group received 4000 IU vitamin D daily and the treatment group received an increasing dose of 4,000 to 40,000 IU per day and 1200 mg of calcium per day. Symptoms of calcium toxicity were studied in MS patients, including Serum calcium, kidney stones, and metabolic tests. In this study, vitamin D levels reached 413 nmol/L over a period of 18 weeks, which is above the stated limit (250 nmol/L). In this case, the reduction in the number of attacks in the patients in the treatment group was observed. In this study, hypercalcemia and even kidney stones or cardiac complications were not reported, and it was found that short-term administration of a daily dose of 40000 IU does not induce toxicity (67).

In a study of 187,000 women aged 25-55 years, it was concluded that women taking vitamin D regularly at a dose of 400 IU/day have higher serum levels of 25(OH)D and are at a lower risk of developing MS **(164)** (164). In a 28-week study, increasing the daily dose of cholecalciferol from 4,000 IU to 40000 IU resulted in a significant reduction in the total number of MRI ulcers(58).

In a study on EAE, the daily dose of 100, 400, 2000, 4000 and 4200 IU / Kg were chosen to select the maximum dose of vitamin D without increasing calcium levels. The smallest dose that reduces MS symptoms is a daily dosage of 2000 IU/kg but this dose boosts calcium levels (68). Smolders and Myhr, in separate studies, found that an increase in 25(OH)D levels to 100 nmol/L is associated with a reduction in the probability of developing MS in whites(37, 69). The researchers studied the effect of oral calcitriol on 15 patients with relapsing-remitting MS. Each patient received 100 IU calcitriol for 48 weeks. Patients were subjected to laboratory studies every 8 weeks and MRI was used to assess the severity of the disabilities, the rate of disease progression, and the number of plaques. Studies showed a slight decrease in severity of the disease (70).

Given the abundance of vitamin D deficiency-related diseases, for people who have little exposure to UVB, FNB recommends:

Daily intake of 200 IU for infants over 6 months of age

Daily intake of 400UI for infants between 6 and 12 months

Daily use of 600IU for people between 1-70 years

Daily use of 800 IU for people over 70 years of age

And for people over the age of 80 years, the maximum daily vitamin D level (up to a maximum of 4000 IU) (70).

According to Ramagopalan et al., there is a two-month lag between the effect of vitamin D treatment and the level of MS-detectable disorders (71). Therefore, in choosing the length of treatment with vitamin D, this should be considered. Some studies do not support the hypothesis about the positive effects of vitamin D on the course of MS disease. For example, in a study of 36 MS patients, 25(OH)D levels in CSF fluid were measured and a significant difference was not found between CSF 25(OH)D in relapsing-remitting MS patients with patients with other inflammatory diseases or with other non-inflammatory neurological diseases (72). Also, during a three-year follow-up, it was found that vitamin D levels were not associated with inhibition of developmental disability in progressive MS type (73).

Conclusion

Inflammation in the CNS causes neurons dysfunctions and a wide range of symptoms and diseases in the individual with Multiple sclerosis. MS disease has an important impact on the quality and quantity of patient's life. Many drugs were used to treat and improve the disease.

In the case of neurodegenerative diseases, most researchers believe that vitamin D deficiency, either due to nutrition or inadequate sunlight, can cause disease and these researchers have confirmed ameliorative effects of vitamin D. Also, most EAE studies showed the ameliorative effects of this vitamin on neurodegenerative diseases, including MS. But after extensive research, all scientists still have not arrived at a consensus on the effect of this vitamin as a positive allosteric.

A few scientists have concluded that the positive effect of vitamin D on MS is not significant and this vitamin cannot be considered as a beneficial factor. However because of affect on the immune system's responses and the genes, vitamin D is discussed to be a physiological factor affecting on clinical symptoms of MS.

Since the effect of vitamin D in the genetic level and on the immune system has been proven and according to research by most researchers, the effect of this vitamin cannot be ignored on MS.

However, some of the disagreements may be due to the following:

Vitamin D metabolism is different in women than men, it may be better to study the effect of this vitamin on a separate group of women or men and small numbers of articles have focused on this issue.

Also, because the sampling method can affect the amount of serum cytokines, this can be considered as a potential cause of the research error and may be considered as a reason for contradiction in the results.

According to some scientists, there is a two-month lag between the effect of vitamin D treatment and the level of its effect on MS, therefore in choosing the length of treatment period with vitamin D, this should be considered.

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