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Clinical Aspects of Vitamin D Deficiency in Multiple Sclerosis

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Abstract

Introduction
Multiple Sclerosis (MS) is a multifactorial, immune-mediated disorder that occurs in genetically predisposed people. Vitamin D might be an important environmental factor in the development and prevention of MS disease. We aimed to investigate the role of vitamin D in MS disease activity.

Material and Methods
The study was designed as a prospective study. Thirty-two patients and 15 healthy subjects were included. Variables were MS disease duration, number of relapses, Expanded Disability Status Scale (EDSS) scores, serum vitamin D levels, assessments through neuropsychological tests relevant to depression, cognition, anxiety and fatigue.

Results
The mean age of the subjects was 32.6±6.9 years. A significant positive correlation was found between the vitamin D level during relapse and remission. A statistically significant difference was found between the patients in relapse and controls in serum vitamin D levels (p=0.002). A statistically significant difference was found between the patients in relapse and patients in remission, in serum vitamin D concentrations (p<0.001). Statistically significant differences were found between the patients in relapse and controls in Mini-Mental State Test, Beck Depression Inventory, Benedict's Cognition Test, Fatigue Severity Scale, Paced Auditory Serial Addition Test, State-Trait Anxiety Inventory scores (p=0.01, p<0.001, p=0.01, p<0.001, p=0.007, p<0.001 and p<0.001, respectively).

Conclusions
Vitamin D in association with other therapies may prevent the progression of MS-related disabilities and the relapses in Relapsing-Remitting Multiple Sclerosis. Vitamin D levels may have effects on the symptoms (depression, anxiety, cognitive deterioration and fatigue) which are frequently seen in the course of MS.

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Introduction

Multiple Sclerosis (MS) is a multifactorial, immune-mediated disorder that occurs in genetically predisposed people. Although the reasons underlying the wide variations in its prevalence and incidence around the world have not been fully understood yet, certain genetic or environmental assumptions have been made. Data from recent observational studies have indicated that vitamin D3 [25(OH)D], synthesized upon the exposure to sunlight or ingested from diet, might be an important environmental factor in developing MS and preventing MS.[1-3] A reduced exposure to sunlight directly correlates with low serum 25(OH)D levels. Low serum 25(OH)D levels have been demonstrated to be a risk factor for developing MS and serum 25(OH)D levels have been demonstrated to be further decreased during relapses, in comparison to the levels measured during remissions.[1,2] These data suggest that vitamin D may have a possible role in autoimmune mechanisms.[4] Previous studies revealed an association between low serum 25(OH)D levels and high Expanded Disability Status Scale (EDSS) scores.[1,3,5] In patients with Relapsing Remitting Multiple Sclerosis (RRMS), the 25(OH) D levels have been found to be even lower during relapses than those in the remission periods.[1,2] Recent studies have revealed the associations between sunlight exposure, disability and 25(OH) D levels and shown that supplemental 25(OH) D given in adequate amounts have led to the proliferation of anti-inflammatory cytokines in the blood of MS patients.[1,2]

Data from recent observational studies have indicated that 25(OH)D, synthesized upon the exposure to sunlight or ingested from diet, might be an important environmental factor in developing MS and preventing MS.[1-3] Recent studies have focused on traditional parameters such as relapse activity, disability progression, and Magnetic Resonance Imaging (MRI) parameters, but should also be cautious in other MS symptoms that may be associated with low vitamin D levels, such as depressive symptoms and cognitive impairment.[6]

The aim of this study is to evaluate the serum vitamin D levels in relapse and remission periods of MS patients, and investigate the correlations with disease severity, number of relapses, disease duration, fatigue, and neuropsychological tests.

Material and Methods

The study was designed as a prospective study and 32 patients diagnosed with RRMS according to the McDonald diagnostic criteria[7], who were on the follow-up in the outpatient clinic of MS, the Department of Neurology, aged between 20 and 50 years, have not concurrent neurological disorder, graduated from primary school at least, absence of a metabolic disorder that might affect cognitive performance were included to the study. None of the patients had received vitamin D therapy 3 months before the study held, due to any reason. The control group consisted of 15 healthy individuals. Written informed consent was taken from all participants.

Patients were prospectively re-assessed 2 months after relapse, during remission periods. None of the patients leave the study during the follow up period. All of the patients were treated with steroids during the relapse period. All of the subjects in the patient and control groups received an adequate diet and exposed to the sunlight for at least 1 or 2 hours daily. None of the subjects had received vitamin D therapy by then.

Main demographic characteristics for both patient and control groups included age, gender and educational attainment. Disease associated variables were MS disease duration, number of relapses, EDSS scores, serum Vitamin D levels, assessments through neuropsychological tests relevant to depression, cognition, anxiety and fatigue.

Considering their potential impact on cognition, subjects' vitamin B12 and folic acid levels were determined. Subjects included in the study, in the event that their vitamin B12 and folic levels were within normal limits.

The tests relevant to depression, cognition, anxiety, and fatigue were administered twice to the subjects in the patient group and once to the subjects in the control group, by an expert psychologist during one-hour sessions. Patients were administered Fatigue Severity Scale (FSS), Paced Auditory Serial Addition Test (PASAT), Beck Depression Inventory (BDI), State-Trait Anxiety Inventory (STAI Form TX-1-2), Mini Mental State Examination (MMSE), Benedict's Cognitive Dysfunction test in MS.[8-15]

Regarding the metabolism of vitamin D, tests

including 25(OH)D, parathyroid hormone (PTH), thyroid stimulating hormone (TSH), calcium (Ca^{+2}), phosphorus (P), magnesium (Mg^{+2}), chlorine (Cl^{-1}), alkaline phosphatase (ALP) and creatinine were performed twice in the patient group, in the serum samples of each patient obtained during remission and relapse periods, while controls underwent testing once. Based on the kit, calibration of the measuring device, and laboratory standards used in our study, the refence range for serum 25(OH)D was determined as 11 to 43 ng/dL and values less than 11 ng/dL indicated vitamin D deficiency.

Statistical Analysis

According to the distribution of the data, the independent samples t-test or Mann-Whitney U test were used in the comparisons between two independent groups. The Wilcoxon test was used to compare two dependent groups. The Pearson's chi-square test was used to compare categorical variables. Correlations between the variables were analyzed using the Spearman's correlation analysis. Descriptive statistics included mean±standard deviation or median (minimum-maximum). A p value less than 0.05 was considered as statistically significant. An SPSS 13 statistical software package was used for statistical analyses.

Results

The mean age of the subjects was 32.634±6.89 years. Age and gender distribution of MS patients and control group were similar (31.84±7.10 vs. 34.33±6.32 years, female to male ratio: 26/6 vs. 13/2, respectively, p=0.253). Education level ratios of MS patients and control groups were not significantly different (elementary 46.9% vs. 40%, high school 28.1% vs. 13.3% and university education 25% vs. 46.6%, respectively, p=0.278).

The EDSS scores of the patients in the relapse period were higher than those in the remission period (3.5 [1.5-5] vs. 2 [0-3.5], p<0.001). Serum vitamin D levels of MS patients were significantly lower in relapse period compared with remission periods. A significant positive correlation was found between the number of relapses and the EDSS scores during relapse and remission. A negative correlation was found between the number of relapses and serum vitamin D levels in patients during the relapse and remission periods, although this correlation did not reach a statistically significant level (*Table 1*).

There was no statistically significant relationship between MS disease duration with EDSS scores and vitamin D levels in relapse and remission periods. A significant difference was observed in serum vitamin D concentrations between the patients in relapse and controls (p=0.002). No statistically significant difference was found in serum PTH concentrations (p=0.405). No statistically significant difference was found in serum vitamin D concentrations between the patients in remission and controls. However, the p value was close to the significance level (p=0.058). No statistically significant difference was found in serum PTH (p=0.690). A statistically significant difference was found in serum vitamin D

Table 1. The association between the vitamin D levels of patients during relapse and remission periods, EDSS scores and number of relapses

	VIT-D (relapse)	VIT-D (remission)	EDSS (relapse)	EDSS (remission)
VIT-D (relapse)	-	p<0.001 r=0.764	p=0.875	-
VIT-D (remission)	p<0.001 r=0.764	-	-	P=0.866
Number of relapses	p=0.491	p=0.287	**p=0.028** **r=0.389**	**p=0.016** **r=0.422**

VIT-D: vitamin D, VIT-D (relapse): serum 25(OH)D levels in patients during relapse, VIT-D (remission): serum 25(OH)D levels in patients during remission, EDSS (relapse): EDSS scores during relapse, EDSS (remission): EDSS scores during remission.

Table 2. Parathyroid hormone and vitamin D levels according to groups

	All subjects (n=47)	MS Patients in Relapse (n=32)	MS Patients in Remission (n=32)	Controls (n=15)
PTH	27(9.6-63.5)	25.3(9.6-63.5)	28.5(15.5-65.4)	33.4(11.1-53.4)
VIT-D	9.9(4-40)	8.9(4-29)	10.8(5-30)	16.2(6-40)

PTH: parathyroid hormone, VIT-D: vitamin D.

concentrations between the patients in relapse and patients in remission (p<0.001). No statistically significant difference was found in serum PTH concentrations (p=0.161) (*Table 2*).

Statistically significant differences were found between the patients in relapse and controls in MMSE, BDI, Benedict's Cognition Test, FSS, PASAT, State-Trait Anxiety Inventory scores (p=0.01, p<0.001, p=0.01, p<0.001, p=0.007, p<0.001 and p<0.001, respectively). There was no significant difference in MMSE scores between the patients in remission and controls, but the p value was close to the significance level (p=0.055). Significant differences were found in BDI, Benedict's Cognition Test, FSS, PASAT, State-Trait Anxiety Inventory scores between the patients in remission and controls (p=0.022, p=0.002, p=0.01, p=0.018, p=0.001 and p=0.001, respectively). A statistically significant difference was found in MMSE scores between the patients in relapse and patients in remission (p=0.016). Although differences were found in other neuropsychological tests between the patients in relapse and patients in remission, these differences did not reach a statistically significant level (p=0.377, p=0.482, p=0.428, p=0.082, p=0.238 and p=0.708, respectively) (*Table 3*).

The number of relapses correlated positively with PASAT scores. There were no statistically significant relationships between serum vitamin D levels and neuropsychological test scores of the patients in relapse or remission periods (*Table 4*). However, when serum vitamin D concentrations increased, BDI, Benedict, FSS and state-trait anxiety scale scores decreased while MMSE and PASAT scores increased.

Discussion

In our study we found that serum vitamin D levels of MS patients were significantly lower in relapse period compared with remission periods. A statistically significant difference was observed in serum vitamin D concentrations of the patients in relapse and controls and also between the patients in relapse and patients in remission.

One of the most frequently investigated and discussed functions of vitamin D is its effects on autoimmune diseases and particularly on the pathogenesis of MS. Unlike other vitamins, vitamin D can be synthesized in the body, and actually, it has been accepted as a hormone. The discovery of the vitamin D receptors (VDR) in numerous tissues demonstrated that vitamin D had many functions other than calcium homeostasis and bone metabolism.[16,17]

Table 3. Neuropsychological test results according to groups

	All subjects (n=47)	MS patients in relapse (n=32)	MS patients in remission (n=32)	Controls (n=15)
MMSE	28(19-30)	26.5(19-30)	27(19-30)	29(24-30)
BDI	11(0-33)	12.5(2-33)	11.5(0-41)	3(0-16)
Benedict	11(0-49)	15(0-52)	13(0-49)	0(0-24)
FSS	29(9-63)	40(13-63)	35(9-63)	17(9-63)
PASAT	44(13-60)	39.5(13-57)	43(5-59)	53(18-60)
State anxiety	41(20-70)	44(25-70)	42(20-62)	31(20-48)
Trait anxiety	44(22-67)	49(28-67)	46(24-72)	31(22-58)

MMSE: Mini Mental State Examination, BDI: Beck Depression Inventory, Benedict: Benedict's Cognitive Dysfunction test, FSS: Fatigue Severity Scale, PASAT: Paced Auditory Serial Addition Test.

Table 4. The comparisons of serum vitamin D levels, EDSS scores and neuropsychological test results of the patients in relapse and remission periods

	VIT-D (relapse)	VIT-D (remission)	Number of relapses	EDSS (relapse)	EDSS (remission)
MMSE	p=0.883	p=0.797	p=0.188	p=0.193	p=0.548
BDI	p=0.974	p=0.896	p=0.533	p=0.193	p=0.123
Benedict	p=0.257	p=0.351	p=0.191	**p=0.014**	p=0.590
FSS	p=0.508	p=0.716	p=0.318	p=0.639	p=0.066
PASAT	p=0.323	p=0.480	**p=0.015**	p=0.084	p=0.236
State Anxiety	p=0.576	p=0.560	p=0.363	p=0.440	**p=0.011**
Trait Anxiety	p=0.509	p=0.562	p=0.772	p=0.702	p=0.100

VIT-D: vitamin D, MMSE: Mini Mental State Examination, BDI: Beck Depression Inventory, Benedict: Benedict's Cognitive Dysfunction test, FSS: Fatigue Severity Scale, PASAT: Paced Auditory Serial Addition Test.

Normal serum 25(OH)D concentrations vary in a range 8 to 80 ng/mL (20-200 nmol/L). In a number of studies on serum 25(OH)D concentrations, values ranged between 0 and 20 nmol/L have been considered as severe hypovitaminosis, values ranged between 20 and 37 nmol/L have been considered as mild hypovitaminosis, while a value of 37 nmol/L has been accepted as adequate.[2,4,18] Based on the kit, calibration of the measuring device, and laboratory standards used in our study, the refence range for serum 25(OHD was determined as 11 to 43 ng/dL and values less than 11 ng/dL indicated vitamin D deficiency. In this study all of the subjects in the patient and control groups received an adequate diet. All subjects adequately exposed to the sunlight (at least 1 or 2 hours daily). None of the subjects had received vitamin D therapy.

In a study conducted in a large MS population consisting of 267 patients, an inverse correlation was found between the serum 25(OH)D concentrations and EDSS scores, while a similar correlation was not found between serum 1,25-dihydroxyvitamin D3 [1,25$(OH)_2$D] concentrations and EDSS scores. Furthermore, no difference was observed between the relapse and remission periods in serum 1,25$(OH)_2$D concentrations. This study was the first study evaluating both 1,25$(OH)_2$D and 25(OH)D concentrations in a large MS population. Results from subsequent studies have also supported these data.[1,19] Thus, in studies on this issue, serum 25(OH)D concentrations have always been the criterion to assess the effects of vitamin D. On the basis these data, we evaluated serum 25(OH)D levels and we exclude serum 1,25$(OH)_2$D levels.

Recent studies have emphasized the presence of a direct association between vitamin D and MS-related disability. These studies revealed a statistically significant negative correlation between EDSS scores and serum 25(OH)D levels in patients with MS.[11,20] Certain related studies demonstrated that the inverse correlation between serum vitamin D levels and EDSS scores was stronger in Primary Progressive Multiple Sclerosis (PPMS) and Secondary Progressive Multiple Sclerosis (SPMS) patients in comparison to Progressive Relapsing Multiple Sclerosis (PRMS) patients.[1] In line with the literature, a graphically displayable inverse correlation was observed between the serum 25(OH)D levels and EDSS scores, although it did not reach a statistically significant level.

A positive correlation was found between the number of relapses and EDSS. However, unlike previous data in the literature, in our study no statistically significant correlation was found between the number of relapses and serum 25(OH) D levels during the relapse and remission periods.

Recent studies have demonstrated an association between the relapse activity and serum 25(OH) D concentrations. In RRMS populations, serum 25(OH)D concentrations were found to be lower in relapse periods in comparison to the remission periods and higher relapse rates were associated with lower serum 25(OH)D levels.[2,4] In a study in patients who had been diagnosed with RRMS more than 5 years ago, serum 25(OH)D levels were found to be considerably lower in patients who had experienced 1 or more relapse during the last

2 years in comparison to the patients who had not experienced any relapse.[1] A large, longitudinal and prospective study in RRMS patients demonstrated that every reduction of 10 nmol/L in serum concentration levels was associated with 9 to 12% reduction in the risk of relapse.[21] In our study, the serum 25(OH)D levels in RRMS patients during remissions were found to be lower than those of control group and the difference was found to be close to the significance level. This difference was more prominent during the relapse periods. The comparisons between serum 25(OH)D levels during the relapse periods and those of controls, revealed a statistically significant difference. Similarly, a statistically significant difference was found between the serum 25(OH)D levels during the relapse and remission periods.

There are studies indicating that an adequate dose of supplemental vitamin D administered concurrently with other therapies, may reduce the disabling progression of MS and may prevent relapses.[22-26]

In line with the literature, no statistically significant differences were found in serum PTH, TSH, ALP, creatinine, Cl^{-1}, Ca^{+2}, Mg^{+2} and phosphorus levels between the patients in relapse and patients in remission, between the patients in relapse and controls and between the patients in remission and controls.[2, 27]

Vitamin D deficiency has been linked to an increased incidence of autoimmune diseases, including thyroiditis, asthma, psoriasis, type 2 diabetes, rheumatoid arthritis and type 1 diabetes and MS in particular.[28-30] Preventive effect of vitamin D on the activation of MS is an immune-mediated effect. 25(OH)D is a potent immune modulator, inhibits pro-inflammatory cells and cytokines and supports anti-inflammatory cells and cytokines. 25(OH)D receptors are found to be widely distributed in immune cells. 25(OH)D is known to play a role in the anti-inflammatory immune response and in the regulation of T-cell functions.[3,31,32] Although any quantitative analysis on the immune-modulator role of vitamin D was not carried out in our study, the presence of a concurrent autoimmune disease (including thyroiditis, asthma and diabetes) in 21.8% of our MS patients suggests the above autoimmune mechanisms.

In numerous studies common depressive symptoms and cognitive deterioration in MS patients have been linked to 25(OH)D deficiency and it has been emphasized that the inclusion of this parameter in the future studies might ensure the integrity of the knowledge.[4] A study held in our country demonstrated that neurodegeneration associated with vitamin D receptor (VDR) gene polymorphism and low serum 25(OH)D levels, might led to the Alzheimer disease and cognitive deterioration.[33] In another study, low serum 25(OH)D levels were suggested to cause cognitive dysfunction and it was emphasized that vitamin D might be a neuroprotective agent and its deficiency might be diagnostic mediator in dementia.[34] During the last decade, studies on the effects of vitamin D on brain functions revealed that vitamin D was a neuroactive steroid affecting brain development and modulation of brain functions and its deficiency might be associated with a number of neuropsychiatric disorders including schizophrenia, Parkinson, Alzheimer, depression, muscle weakness and cognitive deterioration. It was emphasized that vitamin D deficiency was associated with poor performance in neurocognitive testing.[35,36]

Strong associations were demonstrated between low serum vitamin D levels and depression or anxiety or depressive symptoms such as sleep disorders and vitamin D supplements added to antidepressant therapy were found to increase treatment success.[37-44]

Certain studies pointed out that vitamin D deficiency might cause chronic fatigue that that showed a significant improvement after vitamin D supplementation.[45-47] Another study investigated the associations between serum vitamin D levels in MS patients and fatigue and depressive symptoms and a statistically significant positive correlation between the low serum 25(OH)D levels and depressive symptoms, while no statistically significant correlation was found between the serum 25(OH)D levels and fatigue.[48]

In our study, certain neuropsychological tests were administered to the patients during attacks and remission periods and the controls, to investigate the effects of vitamin D on cognition, depression, fatigue and anxiety. There was statistically a significant differences in neuropsychological test scores between the control group and MS patients both in relapse and remission, while no statistically significant differences were found between the patients in relapse and patients in remission. No

statistically significant correlations were found between the neuropsychological test scores and serum 25(OH)D concentrations in relapse and remission. However, as the serum 25(OH)D concentration increased, Beck, Benedict, and fatigue and anxiety scales scores reduced and the increases in the MMSE and PASAT scores were shown graphically. In conclusion, low serum 25(OH)D levels in MS patients were found to have negative impacts on cognition depression, fatigue and anxiety scale scores and these impacts were more prominent during relapses, when significant reductions occurred in the serum 25(OH)D levels. The failure to attain a statistically significant level was considered to be related to the small sample size and the study population consisting of the patients with RRMS, a less disabling form compared to the progressive forms of MS.

According to the promising data from these studies, vitamin D in association with other therapies may prevent the progression of MS-related disabilities and the relapses in RRMS. Vitamin D levels may have effects on the symptoms (depression, anxiety, cognitive deterioration and fatigue) which are frequently seen in the course of MS.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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