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Highlights

- Depressive symptoms are associated with low vitamin D level in patients with RRMS.
- Vitamin D replacement is associated with improvement of depressive symptoms.
- Improvement of depressive symptoms are not related to neurological improvement.

Effect of Vitamin D Replacement on Depression in Multiple Sclerosis Patients

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Key words: Multiple sclerosis, Depression, Vitamin D

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Abstract

Background: Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system. Depression is common among MS patients. In patients without MS, lower vitamin D levels were associated with higher depression scores and severity. Supplementation of vitamin D was associated with significant improvement of depressive symptoms. **Objective:** to evaluate the relation between vitamin D levels and depression scores, and the effect of vitamin D replacement on the depressive symptoms in patients with MS. **Methods:** The study included 35 patients with relapsing remitting multiple sclerosis. Neurological, psychiatric, and radiological evaluations were done. Participants received 10,000 IU of cholecalciferol daily for 12 months. **Results:** Vitamin D level was low at baseline. Depressive symptoms were high at baseline and improved with vitamin D replacement although, Expanded Disability Status Scale (EDSS) score was not improving. Vitamin D levels correlated negatively with depressive symptoms at baseline and follow up periods. **Conclusion:** Lower vitamin D levels are associated with higher depressive scores, and vitamin D replacement could improve depressive symptoms in patients with relapsing remitting multiple sclerosis.

Keywords: Multiple sclerosis, Depression, Vitamin D

Introduction

Multiple sclerosis is a chronic, inflammatory demyelinating disease of the central nervous system. It appears to be linked to a complex interplay of genetic, immunologic, and environmental factors such as vitamin D level. Low vitamin D level is associated with increased risk of MS incidence and relapses (1-6).

Depression is common among MS patients; its life time risk has been estimated to be around 50% (7-9). Because of its high prevalence, it might affect MS course (10, 11). In depressed patients without MS, lower vitamin D level is associated with higher depression scores and severity (12-15). Supplementation of vitamin D, either alone or with antidepressant, is associated with significant improvement of depressive symptoms (16-19).

We hypothesized that, depression in MS might be related to vitamin D deficiency and the replacement of vitamin D might improve depressive symptoms in this group of patients. The study aim was to evaluate the relation between vitamin D levels and depressive scores, and the effect of vitamin D replacement on the depression symptoms in patients with Relapsing Remitting Multiple Sclerosis (RRMS).

Subjects and methods

The current study was a prospective cross-sectional observational study conducted at Prince Sattam Bin-Abdulaziz University Hospital, Alkharj, KSA over a period of 5 years (2013 – 2018). The study was approved by the Institutional Review Board. All patients with relapsing remitting multiple sclerosis according to McDonald criteria (20), older than or equal to 18 years, no exacerbations, no gadolinium enhancing lesions on MRI and did not receive any corticosteroid therapy within four weeks prior to recruitment, and on regular treatment with interferon beta were included in this study. Patients with current MS treatment other than interferon, received high-dose vitamin D (daily intake 1,000 IU) before inclusion to the study, or changed the immunomodulatory therapy within the past 3 months, had history of systemic glucocorticoid therapy or relapse within 30 days, had severe depression, pregnant patients, serum creatinine >1.5 mg/dL, hypersensitivity to vitamin D preparations, and history of hyperparathyroidism, tuberculosis, sarcoidosis, or nephrolithiasis were excluded from the study.

At baseline, all patients were evaluated clinically using the (EDSS) (21), and radiologically with MRI brain and cervical with contrast. Depression was assessed using Beck's depression inventory -II (BDI) (22).

To investigate the effect of vitamin D replacement on depressive symptoms, which is the aim of the study, antidepressant drugs were not given to our patients as we adopted the findings of Fournier et al., (2010) who concluded that, the magnitude of benefit of antidepressant medications compared with placebo increases with severity of depressive symptoms and may be minimal or nonexistent, on average, in patients with mild or moderate symptoms (23). Meanwhile, our patients were closely observed by the psychiatrist to provide the medical care when needed. During the period of study, no patient needed antidepressant medications. The following laboratory investigations were done before initiation of vitamin D replacement; parathyroid hormone, renal functions, serum calcium level, and Serum 25 (OH) D level.

Serum 25 (OH) D level was referred to the internationally accepted norms (24). The official international standard for serum 25-hydroxyvitamin D level has been established, with norms fall between 75 and 200 nmol/l, insufficiency existing below 75 nmol/l and deficiency below 25 nmol/l (25-31).

All patients were regularly followed up every 2 months for 25-OH-D serum levels. EDSS scores and BDI scores. MRI brain and cervical with contrast were done at the end of 12 months, as well as at the time of relapse if present. Furthermore,

patients were instructed to contact the hospital when they experienced symptoms of neurological impairment.

Written informed consent was taken from the patients. Participants received 10,000 IU of cholecalciferol daily for 12 months. Treatment was discontinued for adverse effects possibly related to the studied drug. Spot urine calcium: creatinine ratios were checked every 3 months, and if elevated (0.21 mg/mL), a 24-hour urine calcium measurement was performed. If the 24-hour urine calcium was also elevated (300 mg/24 h), the dosing frequency was decreased to every other day.

MRI was performed according to a standardized protocol comprising T2 weighted and T1weighted gadolinium-enhancing (Gd+) scans using a standard head coil with a 1.5 Tesla MRI unit. Radiologist evaluated scans to determine gadolinium enhancing (GE) lesions, and total volume of T2 lesions (baseline and follow up).

Statistical Analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) 13.0. Descriptive statistics were calculated. Analysis of variance (ANOVA) was used to compare baseline and follow up EDSS, vitamin D levels, and BDI scores. Pearson's correlation coefficient (r) was used to analyze the association between the different variables. Values of $p < 0.05$ were considered to be statistically significant.

Results

The present study included 56 patients with relapsing remitting multiple sclerosis. Twenty-one patients missed follow up, the remaining 35 patients continued to the end of the study. Of the participant patients sixteen (45.71%) were males. The mean (± SD) age in year was 27 (± 4). The mean (± SD) EDSS was significantly higher (P = 0.02) at end of the follow up period (2.6± 0.5) compared to the time of inclusion (2.2± 0.5). Baseline and follow up 25 (OH) D levels are showed in table 1. During the follow up period no patient needed discontinuation or reduction of cholecalciferol dose. The mean Beck's depression inventory score was significantly higher at baseline compared to the eighth, tenth, and twelfth month of follow up (table 1).

A significant negative correlation was observed between vitamin 25 (OH) D levels and Beck's depression inventory scores at baseline (P < 0.001), eighth, tenth, and twelfth month (P = 0.001) (table 2 & figures 1 - 4). It was approaching significant level (P = 0.056) at sixth month. The negative correlation existed even after controlling for EDSS. A significant positive correlation was observed between EDSS and Beck's depression inventory score at baseline, and during the follow up periods (table 2).

Table (1) Clinical and laboratory variables of patients at baseline and follow up periods

Variables	EDSS Mean ± SD	25 (OH) D level (nmol/L) Mean ± SD	Beck's depression inventory Mean ± SD
Baseline	2.2 ± 0.5	23.4 ± 9.8	21.3 ± 3.4
2 months	2.2 ± 0.5	39.5 ± 4.9	19.9 ± 2.8
4 months	2.3 ± 0.6	51.8 ± 6.2	19.7 ± 2.9
6 months	2.4 ± 0.6	65.4 ± 6.7	19.2 ± 3
8 months	2.4 ± 0.6	76.8 ± 6.4	18.5 ± 2.8#
10 months	2.5 ± 0.5	82.4 ±6.5	17.4 ± 2.7##
12 months	2.6 ± 0.5*	86.3 ± 7.3	16.8 ± 2.9###

EDSS Expanded Disability Status Scale

* Significant difference (P = 0.02) between baseline and 12 months

Significant difference (P = 0.003) between baseline and 8 months

Significant difference (P < 0.001) between baseline and 10 months

Significant difference (P < 0.001) between baseline and 12 months

Table (2) Correlation between Beck's depression inventory score and 25 (OH) D level and EDSS score

	25 (OH) D level		EDSS		25 (OH) D level (controlling for EDSS)	
	r	P	r	P	r	P
Beck's depression inventory						
Baseline	-.875	< 0.001	.681	< 0.001	-.793	< 0.001
2 months	-.077	0.659	.640	< 0.001	-.005	0.979
4 months	-.262	0.128	.683	< 0.001	-.301	0.083
6 months	-.326	0.056	.704	< 0.001	-.168	0.343
8 months	-.527	0.001	.666	< 0.001	-.369	0.032
10 months	-.520	0.001	.570	< 0.001	-.445	0.008
12 months	-.544	0.001	.605	< 0.001	-.432	0.011

EDSS Expanded Disability Status Scale

Figure (1) Correlation between 25 (OH) D level and Beck's depression inventory score at baseline

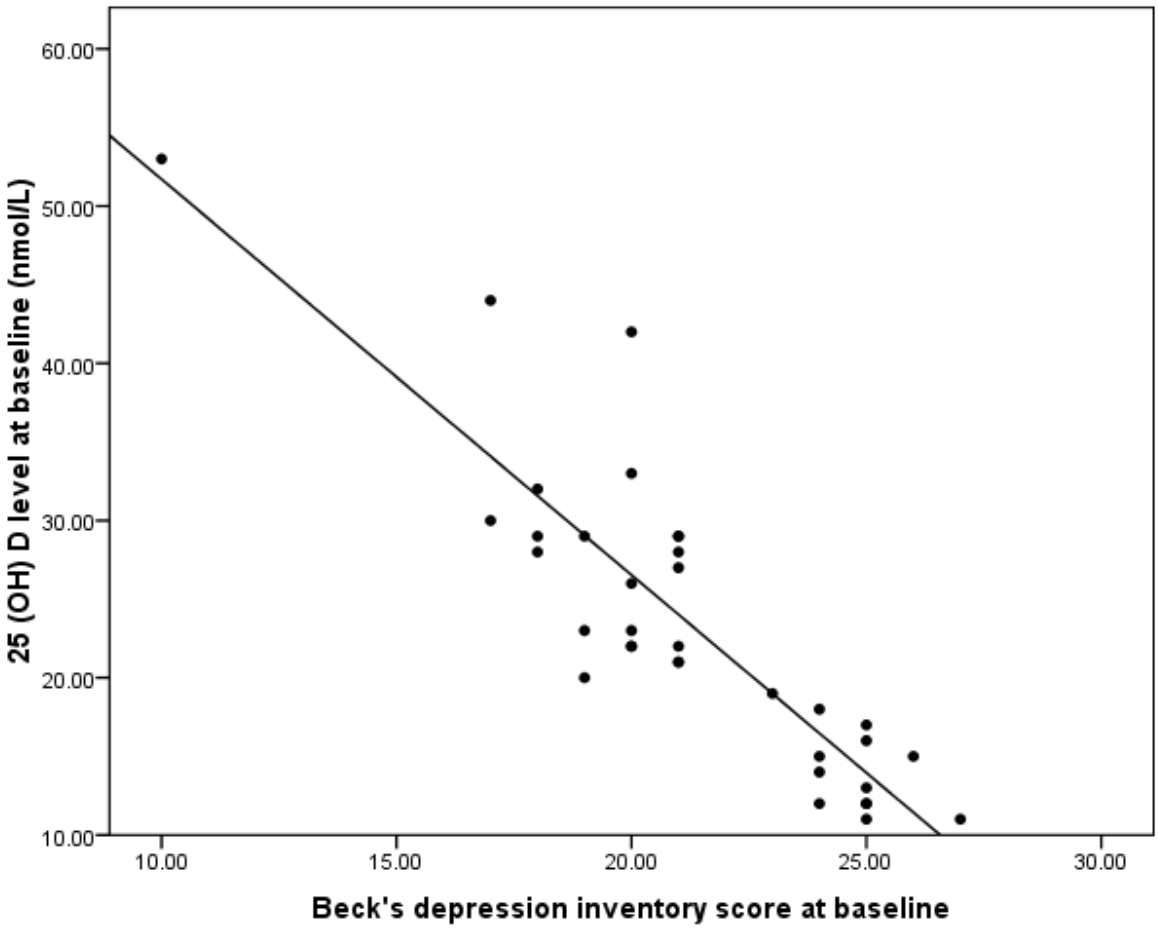


Figure (2) Correlation between 25 (OH) D level and Beck's depression inventory score at 8 months follow up

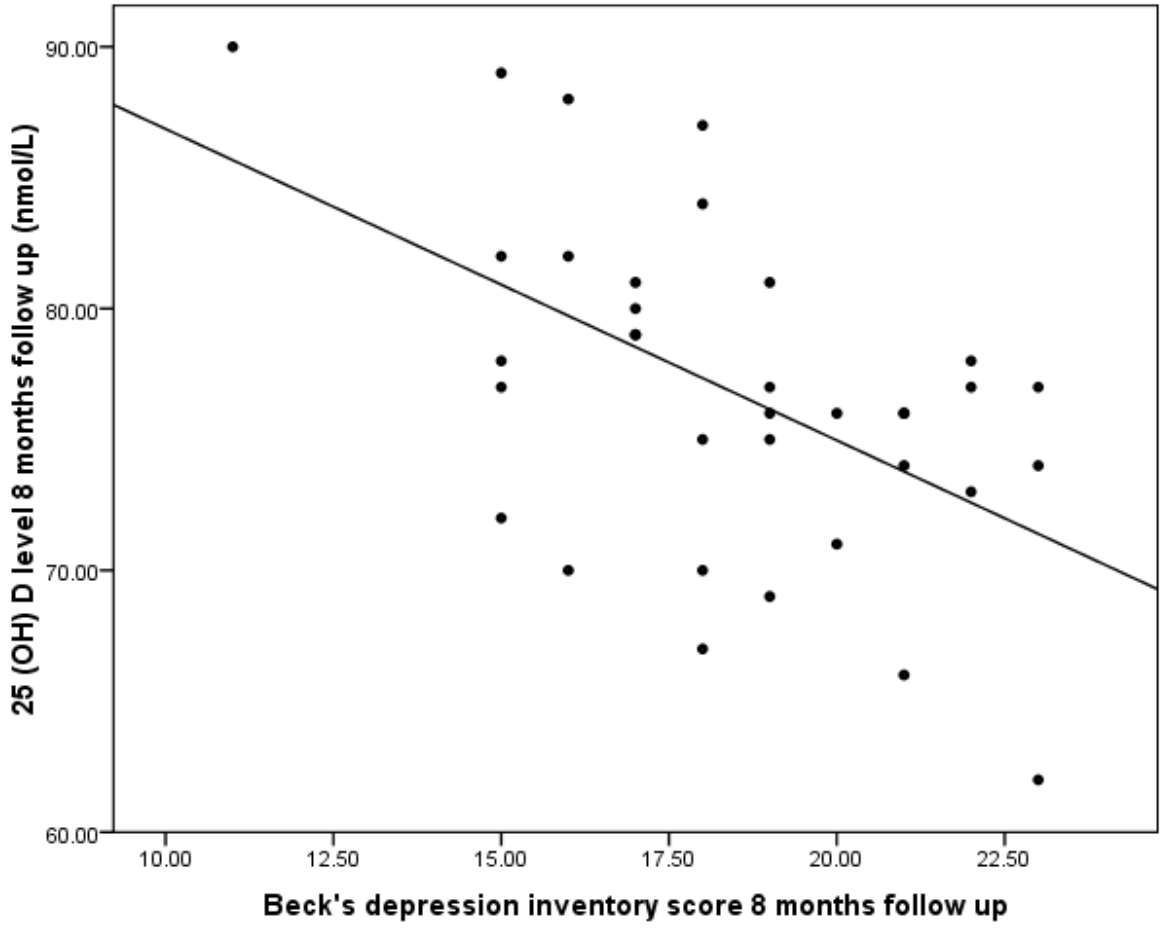


Figure (3) Correlation between 25 (OH) D level and Beck's depression inventory score at 10 months follow up

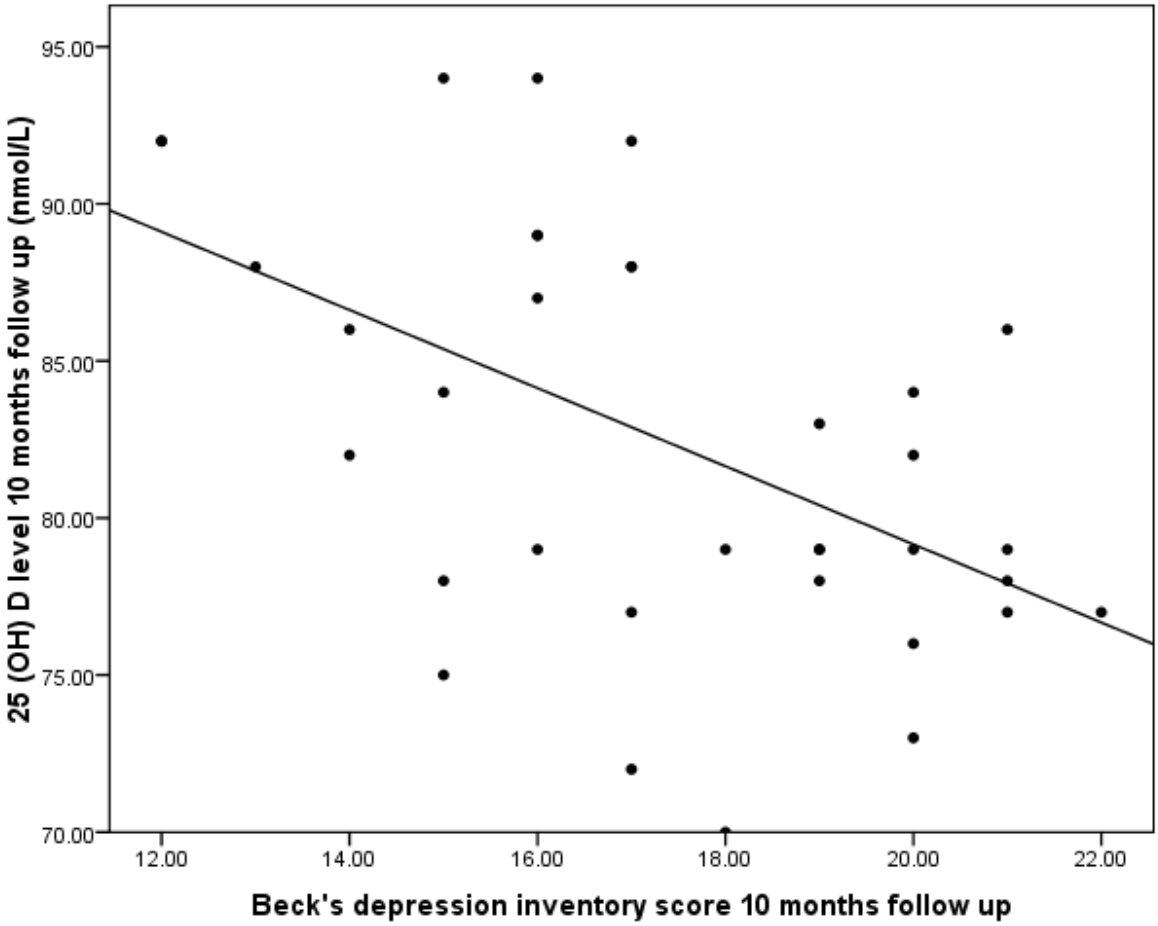
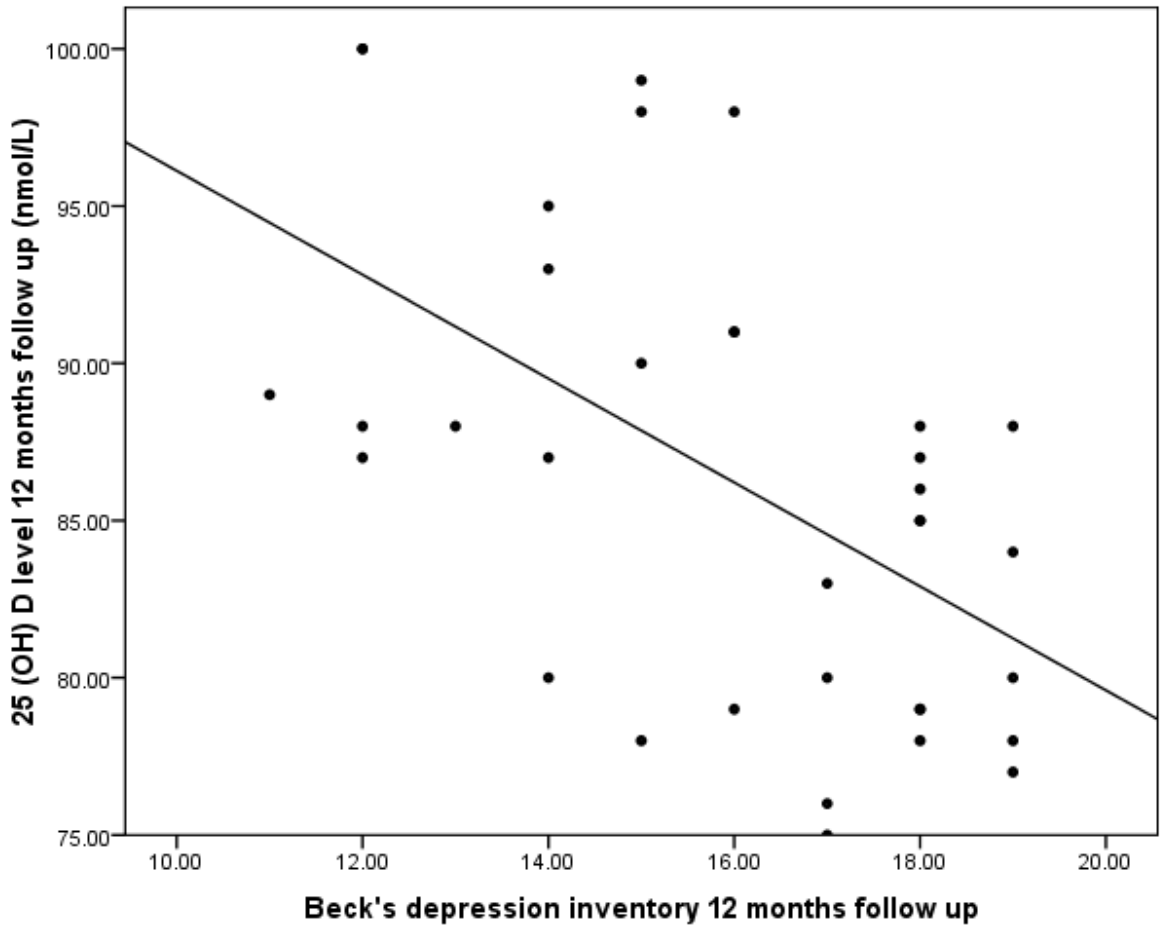


Figure (4) Correlation between 25 (OH) D level and Beck's depression inventory score at 12 months follow up



Discussion

In the present study, vitamin D levels ware low at the time of inclusion. Our result was in accordance with many previous studies which concluded that low vitamin D levels were associated with increased incidence of MS (1-3, 6).

At baseline, most of our patients had mild to moderate depression according to the Beck's depression inventory. Depression is common among patients with MS (7). The lifetime prevalence of depression in patients with multiple sclerosis had been reported to be around 50% (8, 9). The cause for the higher prevalence of depression among patients with MS is unknown but it might be related to the anatomical area of demyelination specially the temporal region (32-36), recent imaging studies showed that, MRI lesion load and brain atrophy in the fronto-temporal area including the hippocampus were related to the presence and severity of depression (37-39), or due to changes in some important immunological parameters resulted from the MS processes (40).

Also, we observed an inverse correlation between vitamin D level and Beck's depression inventory score at baseline, 8, 10, and 12 months of follow up. The negative correlation existed even after controlling for the effect of disability. A population-based cohort study reported that, lower levels of vitamin D were

associated with higher depression severity (12). Milaneschi et al. (2010 and 2013) reported that, patients with low 25 (OH) D levels had significantly higher depression scores compared to those with high levels (13, 14). Nearly the same result was reported by Almeida et al. (2015) (15). It has been reported that, Vitamin D has a role in neurotransmitter regulation including dopamine, noradrenaline, and acetylcholine, and it has a regulatory effect on neurotrophic factors (41). At the same time, prefrontal cortex and parts of the limbic system, which are implicated in the pathophysiology of depression, contain vitamin D receptors (42, 43). Another possible explanation for the association between vitamin D and depression is the effect of vitamin D on the inflammatory markers associated with depression (44).

The symptoms of depression, evaluated by Beck's depression inventory, improved significantly at 8 months of follow up (after vitamin D replacement) compared to baseline status, and the significant improvement continued until the end of the follow up period. In the general population; 80% of patients with major depressive episodes recover within one year (45, 46). In the study of Koch et al (2008), two-thirds of patients with MS who were depressed at baseline were depressed at 10 years follow up which means that, depressive symptoms in patients with MS appear to have longer duration (47). Depressive symptoms in patients with MS are less likely to be a reaction to MS diagnosis; particularly reactive depression is

usually of limited duration. In the study of Jord et al. (2008), vitamin D supplementation was associated with improvement of depressive scores at one year follow up (16). Depression symptoms improved significantly when vitamin D was added to the antidepressant treatment (17). Also depression symptoms improved when vitamin D was given alone (18). In the study of Sepehrmanesh et al. (2015), Beck depression inventory score was significantly decreased after 2 months of vitamin D supplementation (19).

Multiple sclerosis and depression are sharing a similar immune phenomenon, both have abnormally high level of interferon-gamma (IFNγ) produced by T cells (48, 49). It has been reported that, in patients with RRMS, increasing serum levels of 25-hydroxy vitamin D (after vitamin D replacement) are associated with decreased production of IFNγ by $CD4^+$ T cells (50). Bergman et al., (2012) suggested that, long term supplementation of vitamin D (more than 6 months) is necessary to affect the immune system (51). This could explain the improvement of depressive symptoms in our patients that became significant after 6 months of vitamin D replacement.

Limitations of the study

The main limitation of our study is the relatively small number of patients which is not sufficient enough to conclude such a major relation. This could be explained by

the fact that the prevalence of MS in KSA is relatively low. It was estimated to be around 25 per 100000 population (52); compared to the highest prevalence rate in Sweden and Canada that were reported to be 200 and 240 per 100000 respectively (53, 54).

Conclusion

Lower vitamin D levels are associated with higher depressive scores, and although vitamin D replacement was not associated with neurological improvement it could improve depressive symptoms in patients with relapsing remitting multiple sclerosis.

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