**RESEARCH**

# Vitamin D deficiency and its association with fatigue and quality of life in multiple sclerosis patients

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## Abstract

**Background** Vitamin D deficiency is associated with the incidence and prevalence of a variety of neurologic disorders, including multiple sclerosis. However, available studies to date have not provided convincing evidence that vitamin D treatment improves fatigue and life quality in patients with multiple sclerosis.

**Aim** To assess the relationship of vitamin D deficiency with health-related quality-of-life issues and fatigue in multiple sclerosis patients.

**Methods** Vitamin D3 levels were measured in 149 multiple sclerosis patients. In patients with lower than 30 ng/mL levels, vitamin D was administered. Fatigue and health-related quality of life scores were measured at baseline and months 1, 3, 6, and 12 after the beginning of vitamin D3 administration.

**Results** Among 149 patients, 90% were vitamin D deficient. After vitamin D supplementation, health-related quality of life and fatigue scores improved significantly. There was a direct association between health-related quality of life with absence of fatigue and vitamin D status at the end of study.

**Conclusion** The 90% frequency of multiple sclerosis patients with vitamin D deficiency, together with the significant association of vitamin D status with the absence of fatigue and improved physical and functional well-being, points to vitamin D supplementation as a potential therapy to enhance the patient's quality of life.

**Relevance of the article for predictive, preventive, and personalized medicine** This article emphasizes that vitamin D supplementation can improve clinical outcome in multiple sclerosis patients providing immune modulation and neuroprotection. Identification and correction of vitamin D deficiency has the potential to treat the related quality of life in patients with multiple sclerosis.

**Keywords** predictive · preventive personalized medicine · multiple sclerosis · vitamin D · health-related quality of life · fatigue

## Introduction

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system, characterized by focal inflammation, demyelination, and axonal injury. The findings suggest that axonal integrity loss and neurodegeneration can also be detected in very early MS disease stages, even in the absence of white matter lesions and before brain volume loss takes place [1]. Brain atrophy is a sensitive, global measure of neurodegeneration in MS. Disability and cognitive decline have been observed to be significantly associated with brain atrophy. Cognitive dysfunction in MS leads to functional impairments in daily activities of the patients [2]. Moreover, it has been suggested that cervical spinal cord atrophy may herald the onset of progressive MS in individuals with radiological isolated syndrome [3].

Fatigue is one of the most common and debilitating symptoms affecting patients with MS, reported by at least 75% of patients with MS at some point in the disease course.

A large MS cohort addressed that MS greatly affects the quality of life, even during its early stages because fatigue, depressive symptoms, and cognitive dysfunction were common in patients with clinically isolated syndrome (CIS).

Since there are no biomarkers for fatigue, the effect of structural brain damage on fatigue in MS was investigated by only few neuroimaging studies. Penner and Paul have

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described alterations in a cortico-subcortical pathway including the prefrontal cortex, thalamus, and basal ganglia in PET and functional MRI studies associated with MS-related fatigue [4].
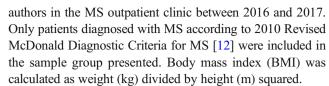
It is also one of the most difficult symptoms to treat, due to its subjective nature and complex pathophysiology [5]. The etiology of MS is still uncertain, but the most updated working model for disease pathogenesis proposes the interplay between genetic and environmental factors as necessary for MS manifestation. Cumulating results suggest that vitamin D plays a significant role in both pathogenesis and treatment of MS because of its immunoregulatory function [6]. Also, vitamin D supplementation is both a low-cost and low-risk intervention. It is safe and well-tolerated, with no concerning adverse events triggered by high doses of vitamin D. Adding vitamin D may potentiate the efficacy of disease-modifying therapies in MS, and the synergy between vitamin D and MS therapies may play a crucial role in developing personalized approaches to MS treatment [7].

Observational studies have shown that patients with MS have lower mean 25-hydroxy vitamin D (25(OH)D) levels than healthy controls [8, 9], but whether this is a causal or noncausal association has not been clear [10]. Several studies have reported an inverse association of both past vitamin D intake or serum vitamin D 25(OH)D levels and future risk of MS. Lower levels of 25(OH)D seem to be associated with higher clinical and radiographic disease activity in MS. Furthermore, Behrens et al. suggested that low 25(OH)D levels in CIS patients are a risk factor for the development of MS [11].

Due to the significant fatigue, physical, and functional impairment in MS patients, the very limited therapeutic measures currently available to reduce them, and the benefits of a normal vitamin D status on the functional integrity of multiple physiologic systems in the body, we hypothesized that a significant proportion of MS patients has vitamin D deficiency, that is, 25(OH)D < 30 ng/mL, and that there is an association between serum vitamin D levels and the patient's quality of life, as well as with the patient's capacity to perform daily living activities. Therefore, the aim of this study was to establish a relationship between serum vitamin D levels and patient-perceived quality of life, as well as fatigue, then evaluate the change in quality of life and fatigue in 25 (OH)D-deficient patients after supplementation with oral vitamin D3. This may be relevant for predictive and/or personalized medicine and may inform individualized treatment strategies for patients with MS.

## Material and methods

**Study design and patients** The study population consisted of 149 consecutive MS patients followed and treated by the

authors in the MS outpatient clinic between 2016 and 2017. Only patients diagnosed with MS according to 2010 Revised McDonald Diagnostic Criteria for MS [12] were included in the sample group presented. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared.

Exclusion criteria comprised MS patients with disorders related to vitamin D deficiency such as parathyroid pathologies or other acute or chronic disease at time of blood withdrawal determined by routine tests or receiving vitamins (vitamin D or multivitamin compounds) as supplements in the 6 months preceding data collection, and patients having experienced a relapse in the last 30 days. The rest of the exclusion criteria included pregnant or breast-feeding females; patients with other neurological or immune-mediated disease; and those with skin diseases or medication use with a medical recommendation to avoid exposure to the sun. Concomitant medication with hydrochlorothiazide, barbiturates, phenytoin, or digitalis is not allowed. No dietary restrictions were imposed on the subjects of this study, except for fasting for at least 8 h at the time of blood sampling allowed. To ensure homogeneity in terms of sunlight intensity and duration as a possible confounder, patients were recruited from a single geographic region.

### Measurement of vitamin D

Quantification of serum levels of 25(OH)D was measured in nanograms per deciliter using high-performance liquid chromatography in the biochemistry department of the same center. Serum 25(OH)D was measured at baseline and months 1, 3, 6, and 12. The patients were categorized as deficient when 25(OH)D < 30 ng/mL. In patients with serum 25(OH)D levels under 30 ng/mL, a weekly dose of 50,000 IU vitamin D3 (oral pearl of cholecalciferol) was administered for 8 weeks to reach a minimum serum 25(OH)D level of 30 ng/mL [13]. In the maintenance phase, 1500 to 2000 IU vitamin D3 was administered daily. Patients with serum 25(OH)D levels between 20 and 30 ng/mL received 1500–2000 IU vitamin D3 (oral pearl of cholecalciferol) daily.

### Questionnaires

All patients were clinically evaluated for disability using the Expanded Disability Status Scale (EDSS) [14]. Fatigue Severity Scale (FSS) and MS-related quality of life inventory (MSQOLI) were used to measure, respectively, fatigue and quality of life.

Fatigue was assessed by the Turkish version of the Fatigue Severity Scale (FSS) [15]. This 9-item scale measures the severity of fatigue and the impact of fatigue in daily functioning. All items are evaluated on a 7-point Likert scale (1 = I totally disagree, to 7 = I totally agree). A total score of 36 or

higher indicates severe fatigue. The FSS is a valid and reliable scale for the assessment of fatigue in MS patients.

Health-related quality of life was assessed using the Turkish version of MSQOLI [16]. The MSQOLI is a battery consisting of 10 individual scales providing a quality of life measure that is both generic and MS-specific. MSQOLI includes the medical outcome study short form-36 (SF-36) and 9 symptom-specific scales. MSQOLI comprised 31 items describing nine dimensions. Each dimension was named according to its constitutive items: activity of daily living (8 items), psychological well-being (4 items), symptoms (3 items), friends relationships (4 items), family relationships (3 items), satisfaction with health care (3 items), sentimental and sexual life (2 items), coping (2 items), and rejection (2 items). For the first 7 scales, higher scores indicate more severe problems in each of these areas. For the last 2 scales, which assess mental health status and perceived social support, higher scores are indicative of better mental health status and a stronger social support system, respectively.

EDSS, FSS, and MSQOLI were measured at baseline and months 1, 3, 6, and 12 after the beginning of vitamin D3 administration.

The patients were not informed that vitamin D supplementation might improve fatigue and quality of life in order not to affect the results.

This study was approved by the hospital Medical Ethical Committee, and written informed consent was obtained from all participants.

## Statistical analyses

All calculations were performed using SPSS 22.0 for Windows. The normal distribution suitability of numerical variables was tested with the Shapiro-Wilk test. Comparisons of patient characteristics were performed using Student's $t$ test for continuous variables or the chi-squared test for categorical variables. The GPower 3.1 program was used to calculate the rationale for the sample size (power 95%, margin of error 5%, effect size 0.32). Per the results, a minimum of 113 patients were necessary. We included 149 patients because of the risk of loss or drop of patients throughout the study. For analysis of the quality of life and fatigue scores, paired $t$ test and Pearson correlation analysis were used. Multiple comparisons were not performed as it is an exploratory study. A statistically significant difference was accepted at $p < 0.05$.

## Results

One hundred forty-nine MS patients were included in this study. One hundred seven (72%) were women and 42 (28%) were men. Of 149 patients, 142 (95%) had the relapsing remitting MS. The progressive forms of MS were verified in 7

patients; 4 patients had the secondary progressive MS, whereas only 3 patients presented the primary progressive MS. The mean age of MS patients was 37.52 years (SD ± 9.82), the youngest being 16 years and the oldest 66 years. Regarding treatment with immunomodulation therapy, 53 patients were using interferon α or β, 48 glatiramer acetate, and 41 natalizumab, and 7 patients were not using immunomodulators.

Table 1 shows the baseline demographic and clinical characteristics of MS patients. The clear majority of patients, 134 (90%), showed vitamin D deficiency, and only 15 (10%) patients had normal D vitamin level. The mean 25 (OH)D serum level was 13.12 ± 7.07 ng/mL (min 4, max 29) in the deficient group and 38.73 ± 13.16 ng/mL in 25 (OH)D normal group ($p < 0.001$). Based on the values of vitamin D in the deficient group, the sample was partitioned into patients with values lower than 10 ($n = 56$), from 10 to values lower than 20 ($n = 49$), and patients with concentrations of 21 to 29 ($n = 29$).

The variables including gender, age, BMI, treatment for MS, disease duration, and EDSS did not differ between those with and without vitamin D-deficient status. MSQOLI was 74.89 ± 20.41 and 78.00 ± 20.97 in the patients with vitamin D deficiency and patients without vitamin D deficiency, respectively ($p = 0.555$). FSS was 36.02 ± 18.19 and 34.80 ± 20.68 in the patients with vitamin D deficiency and patients without vitamin D deficiency, respectively ($p = 0.740$). The two groups have no significant difference regarding MSQOLI and FSS at the beginning of the study.

Serum 25(OH)D values and outcome variables at baseline and changes over the study period (at months 1, 3, 6, and 12) including MSQOLI and FSS scores are shown in Table 2.

### Visit at month 1

After supplementation with high-dose vitamin D3, 37 patients were lost to follow-up; 97 had their serum 25 (OH)D level tested and underwent the quality of life tests. At the first month, the 25 (OH)D level increased to 45.50 ± 21.39 ng/mL. A significant difference was obtained in vitamin D levels ($p < 0.001$); however, MSQOLI and FSS scores showed no significant difference after 1 month when compared to baseline scores (Table 2).

### Visit at month 3

Table 2 shows vitamin D levels and MSQOLI and FSS scores at month 3. The mean change in serum 25(OH)D levels from baseline to month 3 was 46.41 ± 20.24. There was a significant difference in vitamin D levels between baseline and month 3 ($p < 0.001$). The mean MSQOLI was found to be 82.83 ± 22.10, and the mean FSS score was 30.53 ± 17.14. There was a significant difference regarding MSQOLI and FSS at the 3 months when compared to baseline scores ($p < 0.001$).

**Table 1** Baseline demographic and clinical characteristics of MS patients

| | Patients with vitamin D deficiency | Patients with normal vitamin D | Total | $p$ |
|---|---|---|---|---|
| Age (mean ± SD) | 37.91 ± 9.94 | 34.00 ± 8.12 | 37.52 ± 9.82 | *0.151* |
| Gender (*n*, %) | | | | |
|   Women | 97 (72.4) | 10 (66.7) | 107 (71.8) | *0.642* |
|   Men | 37 (27.6) | 5 (33.3) | 42 (28.2) | |
| BMI (mean ± SD) | 24.76 ± 4.66 | 24.33 ± 3.81 | 24.72 ± 4.57 | *0.692* |
| Disease duration (year) (median, IQR) | 5.0 (7.0) | 3.0 (7.0) | 5.0 (7.0) | *0.730* |
| EDSS (median, IQR) | 1.50 (8.5) | 1.25 (6)] | 1.50 (8.5) | *0.830* |
| Vitamin D level (ng/mL) (mean ± SD) | 13.12 ± 7.52 | 38.73 ± 13.16 | 15.70 ± 11.27 | ***< 0.001*** |
| $MSQOLI_0$ (mean ± SD) | 74.89 ± 20.41 | 78.00 ± 20.97 | 75.20 ± 20.42 | *0.555* |
| $FSS_0$ (mean ± SD) | 36.02 ± 18.19 | 34.80 ± 20.68 | 35.90 ± 18.38 | *0.740* |

Bold-italicized numbers in the table ($P < 0.05$) was chosen as the minimum level of statistical significance

## Visit at month 6

Serum 25(OH)D levels were gradually increased from base-line to month 6 (mean 38.70 ± 13.78), and this change was statistically significant ($p < 0.001$) (Table 2). Also, while comparing the results obtained at beginning of this study, the mean MSQOLI (84.26 ± 20.57) and FSS (27.74 ± 15.69) scores were significantly better at month 6 ($p < 0.001$) (Table 2).

## Visit at month 12

From the original list of 134 patients, 84 patients were lost to follow-up at 12 months. Thus, our final analysis was based on 50 patients at study completion. The mean 25 (OH)D level

**Table 2** Serum vitamin D levels, MSQOLI, and FSS scores at baseline and months 1, 3, 6, and 12

| | Number | Min | Max | Mean | SD |
|---|---|---|---|---|---|
| $D_0$ | 134 | 0.5 | 29.9 | 13.12 | 7.07 |
| $D_1$ | 97 | 10 | 144 | 45.50 | 21.39 |
| $D_3$ | 77 | 18.4 | 150 | 46.41 | 20.24 |
| $D_6$ | 70 | 10 | 103.8 | 38.70 | 13.78 |
| $D_{12}$ | 50 | 10.1 | 66.4 | 37.96 | 11.29 |
| $FSS_0$ | 134 | 8 | 83 | 36.02 | 18.19 |
| $FSS_1$ | 97 | 8 | 78 | 34.71 | 17.24 |
| $FSS_3$ | 77 | 9 | 63 | 30.53 | 17.14 |
| $FSS_6$ | 70 | 8 | 69 | 27.74 | 15.69 |
| $FSS_{12}$ | 50 | 7 | 72.0 | 22.70 | 15.82 |
| $MSQOLI_0$ | 134 | 29 | 115 | 74.89 | 20.41 |
| $MSQOLI_1$ | 97 | 34 | 120 | 78.67 | 21.78 |
| $MSQOLI_3$ | 77 | 20 | 120 | 82.83 | 22.10 |
| $MSQOLI_6$ | 70 | 40 | 120 | 84.26 | 20.57 |
| $MSQOLI_{12}$ | 50 | 41 | 125 | 90.96 | 21.92 |

increased from 13 to 37 ng/mL at the end of the study ($p < 0.001$) (Table 2). Concordantly, the mean MSQOLI (90.96 ± 21.92) and FSS (22.70 ± 15.82) scores improved with duration since the beginning of the study ($p < 0.001$) (Table 2). At the end of the 1-year study, there was a significant association between life quality including fatigue and vitamin D levels ($p < 0.001$).

Table 3 shows the differences of vitamin D levels, MSQOL, and FSS at the follow-up period. EDSS was unchanged throughout the study. During the study, none of the patients experienced at least one intravenous methylprednisolone-treated relapse. Seven patients reported untreated relapses characterized with mild sensory deficits at clinic visits.

## Discussion

The application of predictive, preventive and personalized treatment (PPPM) is highly relevant to neurological disorders. Also, in neurological diseases there is a great unmet medical need, calling for early diagnosis, prognostic evaluation, personalization of therapeutic regimes, and a better prediction of treatment outcomes. The PPPM approach could represent the "golden answer" to the challenges in the management of neurological disorders [17, 18].

In MS, several studies reported a relationship between the severity of fatigue on the one hand and other clinical findings, such as depression, cognitive deficits, disability, disease course, sleep disorders, as well as radiologic features (high lesion load and brain atrophy, abnormal cervical cord function), and medication (disease-modifying therapies and symptomatic treatment, on the other [19].

Fatigue is one of the most frequent symptoms experienced in MS, affecting up to 90% of patients [20]. Although MS fatigue contributes to poor health-related quality of life, efficacious treatment options are scarce. Numerous studies have

**Table 3** Paired differences of vitamin D levels, MSQOL and FSS in months

| Vitamin D MSQL FSS | Mean | SD | Std. error of the mean | 95% confidence interval of the difference | | $t$ | df | $p$ |
|---|---|---|---|---|---|---|---|---|
| | | | | Lower | Upper | | | |
| D0–D1 | − 32.98 | 23.74 | 2.42 | − 37.79 | − 28.17 | − 13.61 | 95 | **<0.001** |
| D0–D3 | − 34.13 | 21.27 | 2.42 | − 38.96 | − 29.30 | − 14.08 | 76 | **<0.001** |
| D0–D6 | − 26.70 | 15.06 | 1.80 | − 30.29 | − 23.11 | − 14.83 | 69 | **<0.001** |
| D0–D12 | − 25.48 | 13.35 | 1.88 | − 29.28 | − 21.69 | − 13.49 | 49 | **<0.001** |
| D6–D12 | 3.30 | 17.18 | 2.43 | − 1.58 | 8.18 | 1.35 | 49 | *0.181* |
| MSQOLI0–MSQOLI1 | − 1.96 | 13.14 | 1.33 | − 4.61 | 0.68 | − 1.47 | 96 | *0.143* |
| MSQOLI0–MSQOLI3 | − 5.48 | 13.88 | 1.58 | − 8.63 | − 2.32 | − 3.46 | 76 | **<0.001** |
| MSQOLI0–MSQOLI6 | − 7.11 | 13.07 | 1.56 | 10.23 | − 3.99 | − 4.55 | 69 | **<0.001** |
| MSQOLI0–MSQOLI12 | − 12.84 | 14.7 | 1.99 | − 16.84 | − 8.84 | − 6.45 | 49 | **<0.001** |
| MSQOLI6–MSQOLI12 | − 6.66 | 10.50 | 1.48 | − 9.64 | − 3.67 | − 4.48 | 49 | **<0.001** |
| FSS0–FSS1 | 2.30 | 12.54 | 1.27 | − 0.21 | 4.83 | 1.81 | 96 | *0.073* |
| FSS0–FSS3 | 6.71 | 13.07 | 1.49 | 3.74 | 9.68 | 4.50 | 76 | **<0.001** |
| FSS0–FSS6 | 9.82 | 13.07 | 1.56 | 6.71 | 12.94 | 6.29 | 69 | **<0.001** |
| FSS0–FSS12 | 16.74 | 15.17 | 2.14 | 12.42 | 21.05 | 7.80 | 49 | **<0.001** |
| FSS6–FSS12 | 6.18 | 9.71 | 1.37 | 3.42 | 8.94 | 4.50 | 49 | **<0.001** |

Bold-italicized numbers in the table ($P < 0.05$) was chosen as the minimum level of statistical significance

been conducted to improve life quality in MS patients by reducing fatigue. A randomized, sham-controlled phase I/IIa study evaluated the safety, tolerability, and preliminary efficacy of deep brain H-coil repetitive transcranial magnetic stimulation (rTMS) as treatment of fatigue and depression in MS. Their exploratory analysis showed that rTMS significantly reduced fatigue in 27 of 28 patients in the cohort of 27 [21]. Usefulness of rTMS has been reported in the symptomatic treatment of MS, but has not been confirmed by clinical trials.

There might be an association between dietary habits and levels of sustained disability in MS. Brenton et al. assessed the safety and tolerability of a ketogenic diet in a single-arm, open-label study including 20 patients with relapsing remitting MS as ketogenic diet promotes weight loss and reduces serologic pro-inflammatory adipokines. Their results provided evidence supporting the clinical benefits of ketogenic diet on fatigue and depression in MS. This early-phase study was not designed to study the efficacy of a ketogenic diet on MS, and thus, future next steps include a prospective randomized, case-control study to define the effect of ketogenic diet on disease control [22]. Another study related to diet evaluated the feasibility and estimated the potential effect of flavonoid-rich cocoa on fatigue in relapsing remitting MS. Flavonoids have been found to increase cerebral blood flow by inducing widespread stimulation of brain perfusion, and this could also influence mood, cognitive performance, fatigue perception, and ability to perform a specific movement task. The investigators proposed that a flavonoid approach for managing MS-related fatigue may be moderately effective, inexpensive, and safe, and that it may be exerting its effects by reducing inflammation and oxidative stress [23].

Optimizing treatment in relapsing-remitting MS is an unmet need. Immunomodulators or immunosuppressants are efficient to lower relapse rate, but they are not deprived of adverse effects, and poor response to treatment is still a concern. Camu et al. assessed the safety and efficacy of cholecalciferol in clinically active relapsing-remitting MS patients with vitamin D insufficiency, already treated with interferon beta-1a 44 µg subcutaneously 3 times per week. Patients received high-dose oral cholecalciferol 100,000 IU or placebo every other week for 96 weeks. The primary outcome measure was the change in the annualized relapse rate at 96 weeks. Secondary objectives included safety and tolerability of cholecalciferol and efficacy assessments. Although the primary end point was not met, their data suggested a potential treatment effect of cholecalciferol in patients with relapsing-remitting MS already treated with interferon beta-1a and low serum 25(OH)D concentration. Together with the good safety profile, their data supported the exploration of cholecalciferol treatment in such patients with relapsing remitting MS [24].

Vitamin D deficiency presumably plays a causative role in the pathogenesis and course of various neuroinflammatory and neurodegenerative diseases. Serum vitamin D levels of 75 nmol/L (30 ng/mL) appear safe and may potentially exert therapeutic effects in MS patients such as reduced disability worsening, improved bone health, and improved cognition [25]. Whether higher serum levels and/or a personalized high-dose vitamin D supplementation are superior in the prevention or modification of individual disease courses remains to be clarified [26].

This study examined the relationship between vitamin D serum levels and daily performance in patients with MS. We

demonstrated that there was a highly significant association between an increase in the life quality of MS patients and vitamin D support. Vitamin D3 supplementation increased serum vitamin D to a mean level of 37.96 ng/mL, and appeared to affect the daily life functions positively as assessed by measures of MSQOLI and FSS. Also, vitamin D status was associated with fatigue symptoms of patients with MS, and there was a significant association between vitamin D and fatigue symptoms. Our findings suggest that patients with MS retrieve daily activities more easily if they have higher vitamin D levels.

Past epidemiologic researches have demonstrated a link between vitamin D deficiency and MS onset, course, and severity, and the human and nonhuman animal experimental literature provides additional evidence that vitamin D helps prevent relapses [27]. Several studies have suggested that low vitamin D levels increase the incidence of MS. In a retrospective study of 100 hospitalized patients with CIS, low serum vitamin D levels were associated with an increased risk of developing MS during a mean follow-up of 7 years [28]. Among Caucasian US military personnel, MS incidence decreases by 41% for every 20 ng/mL (50 nmol/L) greater serum 25(OH)D [27]. Additionally, vitamin D levels are inversely associated with subsequent relapse rate in children and adults [29–31] and with disability progression [29–31] in MS, even if not all studies were able to confirm these results [32]. Observational studies have shown that patients with MS have lower mean 25 (OH)D levels than healthy controls [8, 9], but whether this is a causal or noncausal association has not been clear [10].

Effects of vitamin D on health-related quality of life and fatigue are unclear. Three studies reported quality of life outcomes using three different validated health-related quality of life scales (38- 40). Achiron et al. (158 participants) used the RAYS Scale and reported that vitamin D led to improvement in the psychological and social components of RAYS but had no effects on the physical components [33]. Ashtari et al. (94 participants) measured physical, mental, and sexual satisfaction and health change components of the MSQOL and found no difference in any component between comparison groups [34]. Golan et al. (45 participants) used the FAMS questionnaire, a functional assessment of MS, and found no differences between groups [35]. Two studies reported fatigue using different scales [33, 36]. One study used the Fatigue Impact Scale (FIS) (158 participants) and reported that vitamin D reduced fatigue compared with placebo at 26 weeks' follow-up [33]. In the other study, Kampman used the FSS (71 participants) and found no effect on fatigue at 96 weeks' follow-up [36].

In the present study, a poor vitamin D status was found often in most of our patient population and this was associated with the presence of fatigue symptoms. Fatigue in patients with MS is often multifactorial. In addition to associated immunologic abnormalities, several other conditions that may be disproportionately prevalent in MS can contribute to fatigue. In general, causes of MS-related fatigue can be divided into 2 categories: primary and secondary. Primary causes involve immunologic or hormonal mechanisms implicated in the disease process or central nervous system changes associated with MS. Secondary causes include accumulation of disease burden, medication effect, or other conditions frequently associated with MS. Although fatigue does not correlate with life expectancy or the disease course of MS, its presence increases the risk of several psychosocial and socioeconomic complications. Persistent fatigue adversely affects activities of daily living and social interactions, such as housework, shopping, and engagement in social activities [5]. Fatigue also has a profound impact on occupational performance. In a study of MS patients who had reduced their work hours to part-time status, 90% reported fatigue as a primary reason for work status change [37]. As social and occupational functions contribute to quality of life, these aspects should be taken into consideration when assessing the impact of fatigue.

This study has several limitations. First, it includes relatively a small sample size at study completion because 84 patients were lost during follow-up. However, it would have been ideal to access regular 25(OH)D measurements of all patients throughout follow-up. Second, it should also be noted that we did not assess sleep disorders in our patients, which often co-occur or overlap with fatigue in MS. Sleep disorders are frequent in MS and have been significantly associated with higher MFIS values [19, 38]. Two polysomnographic studies investigating sleep disorders and fatigue in consecutive MS patients have demonstrated a significant relationship between fatigue and sleep disorders [38–40]. Besides depression and disability, sleep disturbances decrease health-related quality of life [19, 38]. Also, diet, sun exposure, or smoking habits were not assessed although they might influence 25(OH)D levels which were not assessed and therefore could not be adjusted for. Another limitation is that genetic variants of vitamin D-binding protein which determine the binding affinity of 25(OH)D and thus the fraction of bioavailable vitamin D were also not considered. Finally, while we accounted for the possible independent effect of gender, age, BMI, treatment for MS, disease duration, and EDSS, we did not account for other parameters such as brain and spinal lesion volume.

In conclusion, we have shown that most MS patients referred to our MS-outpatient clinic have insufficient levels of vitamin D. Low levels of vitamin D have been associated with increased fatigue symptoms and decreased performance on daily life in MS patients. In the present study, higher vitamin D levels were associated with better performance in patients with MS. There was a strong association between quality of life scores and vitamin D levels, and there was a clear relationship between low vitamin D levels and fatigue. Finally, there was a significant effect of the intervention on the

MSQOLI and FSS. Therefore, correction of vitamin D insufficiency could be important for reducing fatigue symptoms and improving general state of MS patients.

## Expert recommendations

Personalized medicine is a promising new therapeutic strategy to treat MS-related fatigue. Fatigue is one of the most disabling and medically refractory symptoms of MS, and it can have a major impact on quality of life in MS patients. This study supports strong clinically and statistically significant associations between health-related quality of life in patients with MS and vitamin D supplementation. Vitamin D should be considered when devising a comprehensive preventive medical approach to managing MS-related fatigue.

**Author contribution** The authors (Yesim Beckmann and Sabiha Ture) contributed equally to the manuscript.

## Compliance with ethical standards

**Competing interests** The authors declare that they have no competing interests.

**Ethical approval** The research did not involve any risk for the participants. All ethical guidelines were followed as required for conducting human research. The procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research, the study being approved to be run by the manager of the Izmir Katip Celebi University, where the study was conducted and by the Committee for Ethical Research of Izmir Katip Celebi University (Ethical approval number 307/2016). The research complies with the provisions of the Declaration of Helsinki. All the participants gave their informed consent for the research, and their anonymity was preserved.

**Consent for publication** Not applicable

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