

The relation between Vitamin D status with fatigue and depressive symptoms of multiple sclerosis

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Background: The relation between Vitamin D deficiency with depressive and fatigue symptoms in both Multiple sclerosis (MS) patients and healthy population have been reported. To represent our regional achievement in this field we investigated the relation between Vitamin D status with fatigue and depressive symptoms in MS patients. **Materials and Methods:** In two hundred MS patients, depressive symptoms and fatigue were measured using Beck PC (BDI-PC) and FFS scale, respectively. Venous blood sample was obtained from all participants and serum 25-hydroxy Vitamin D was measured by radioimmunoassay (RIA) method. Mean score of FFS, BDI-PC and EDSS were compared in patients with normal and low level of Vitamin D. The relation between FFS, BDI-PC score, EDSS and low Vitamin D status was determined. **Results:** There was a moderate significant correlation between MS disability evaluated by EDSS and fatigue ($r = 0.37, P < 0.001$) and depression ($r = 0.26, P < 0.001$). The prevalence of low Vitamin D status was 48.5%. Low Vitamin D status was inversely associated with depressive symptoms of patients with MS ($P = 0.02$ $r_s = -0.16$), but there was not significant correlation between Vitamin D and fatigue symptoms ($P = 0.2$). **Conclusion:** More interventional studies for determining the role of Vitamin D supplements in this regard is recommended.

Key words: Depressive symptom, fatigue, multiple sclerosis, Vitamin D

INTRODUCTION

Multiple sclerosis (MS) is an autoimmune disease of the human central nervous system (CNS). It is a disease of unknown origin which characterized by demyelination and inflammatory physiopathology resulting in axonal and neuronal damages.^[1,2] Though the exact etiology of MS is not determined yet, but many physiological, experimental, epidemiological, immunological and biological evidences have supported the role of hypovitaminosis D as one of the most important environmental factor in the etiology of it.^[3,4] The mechanisms responsible for the role of Vitamin D deficiency in the etiology of MS is still unknown, but it seems that Vitamin D has immune modulating potential and has an important role in T cell homeostasis.^[5,6] Some studies indicated that treatment of Vitamin D deficiency could improve the related disability of MS evaluated by EDSS score.^[7]

In addition to motor and sensory systems impairment, demyelination of nervous system may also induce other signs and symptoms such as fatigue and depression.^[8] These co- morbidities are common and could have deleterious effects on the process of the MS disease and its management including impair coping with MS treatment and decrease quality of life.^[9]

There is a significant relationship between fatigue and depression with disease progression.^[10] The prevalence of fatigue and depression have reported to be 92% and 50%, respectively, among patients with MS.^[11,12]

The underlying pathogenesis of these manifestations is not determined yet. Some studies indicated the relation between Vitamin D deficiency with both depressive and fatigue symptoms in both MS patients and healthy population.^[13-15] Moreover some of them showed improvement of these symptoms with Vitamin D supplementations.^[16,17]

Isfahan is a medium- to high-risk area for MS but recent study reported a sharp increase in the incidence and prevalence of MS in this region,^[18] in a way that Isfahan considered as one of the regions with the highest prevalence of MS in Asia and Oceania.^[18] Accordingly, Vitamin D deficiency considered as the most important risk factor for this dramatic increase in Isfahan.^[19] Recently hypovitaminosis D is interested as a risk factor in MS and different symptoms that decrease the quality of life. There are many controversies in this field and no study could confirm exact relation between Vit D and disease yet. Therefore in the world many studies in different geographic areas are doing to find some the possible role of Vit D as a risk factor.

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So considering the increasing rate of MS in our region and the importance of proper management of MS and its related manifestations for improving the quality of life of affected patients, in this study we investigated the relation between Vitamin D status with fatigue and depressive symptoms.

MATERIALS AND METHODS

This cross-sectional study conducted from March 2011 to September 2011, in Isfahan.

Patients aged 18-50 years, known to have definite MS according to McDonald's criteria,^[20] were enrolled. The studied patients were selected from 723 registered patients in Kashani MS clinic affiliated to Isfahan University of Medical Sciences. The study was performed in spring/summer, in the base of results of one study that showed no significant difference in the level of Vitamin D in spring/summer in Isfahan.^[21]

Patients with MS who were relapse free for more than 8 weeks prior to the study selected, because during the relapse, the patients have new symptom and disabilities that many of them will relief a few weeks after treatment, so evaluation of disability by EDSS during this time make bias. They selected by convenient sampling method.

The majority of MS patients in current study have a relapsing remitting form of the disease (94%) which all of them have been treated by interferon beta at least for one year.

The Medical Ethics Committee of the Isfahan University of Medical Sciences approved the study protocol (Research project Number; 390090), and all subjects gave their written consent.

Characteristics of studied patients and information regarding their disease including type of MS and expanded disability status scale (EDSS)^[22] were assessed by an experienced neurologist.

Depression and fatigue were measured using the Beck Depression Inventory for Primary Care (BDI-PC)^[23] and Fatigue Severity Scale (FFS) scale,^[24] respectively. The check list was completed by the patients. Patients diagnosed with depression were referred to psychiatrists for consultation and treatment.

The BDI-PC is a 7-item instrument measuring the presence and severity of depressive symptoms. Each of the 7 items is rated on a four-point scale ranging from 0 to 3, for a maximum total score of 21. Items are symptoms of sadness,

pessimism, past failure, loss of pleasure, self dislike, self criticalness, and suicidal thoughts and wishes.^[23]

The FSS is a nine-item standardized measure with items scored on a scale ranging from 1 to 7. An average score across the nine items was calculated by dividing the total FSS score by the number of items. This mean composite was used to split the sample into two groups: Patients with scores of 4 or higher, indicating severe fatigue, and those with scores below 4.^[24]

Fasting venous blood sample was obtained from all participants and serum 25-hydroxy Vitamin D was measured by radioimmunoassay (RIA) method using Biosource kit (Europe SA, Belgium).

The participants were classified into two categories on the base of their 25-hydroxy Vitamin D serum level as follows: Low Vitamin D level (serum level below 75 nmol/L) and normal Vitamin D level (serum level higher than 75 nmol/L).^[13,21] Vitamin D deficiency (serum level below 25 nmol/L) and Vitamin D insufficiency cases (serum level between 25 nmol/L and 75 nmol/L) considered as low Vitamin D level in this study.

Mean score of FSS, BDI-PC and EDSS were compared in patients with normal and low level of Vitamin D. The relation between FSS, BDI-PC score, EDSS with low Vitamin D status were determined.

Statistical analysis

Obtained data was analyzed using SPSS version 18 (SPSS Inc., Chicago, IL, USA) and Chi-square, independent sample *t*-test and Pearson or spearman's correlation test. *P* value <0.05 were considered as significant.

RESULTS

In this study 200 patients [154 female (77%) and 46 (23%) male] with MS were studied. Regarding the type of MS, 94%, 5% and 1% had RR (relapsing-remitting), SP (secondary-progressive) and PP (primary progressive) respectively. The characteristics of studied population and those with low and normal Vitamin D level are presented in Table 1.

The prevalence of low Vitamin D status was 48.5 % (97/200).

There was no significant difference in Vitamin D level in depressed (79 [37-107]) and non-depressed (65.5 [32.5-99]) patients (*P* = 0.3).

Non parametric correlations between all studied variables evaluated by spearman's test are presented in Table 2.

DISCUSSION

In this study the relation between Vitamin D status with fatigue and depressive symptoms was evaluated. Our results indicated that low Vitamin D status was associated with depressive symptoms of patients with MS, but there was not significant correlation between Vitamin D and fatigue symptoms.

As mentioned many studies have confirmed the role of Vitamin D in the pathogenesis of MS and its neuropsychiatric manifestations mainly due to its immunomodulatory effect.^[25-28]

In this study 48.5% of patients with MS had low Vitamin D status. In the study of Knippenberg *et al.*, the prevalence of low Vitamin D status (<75 nmol/L), as defined in our study, was 73%, which was higher than our study.^[13] The difference probably is due to different geographical location or genetic and environmental variation.

Several studies indicated the role of Vitamin D deficiency in the pathogenesis of many diseases. Vitamin D imbalance results in a variety of disorders, including brain pathogenesis such as depression and immune-mediated disorders such as MS.^[25,26] According to recent studies, the receptors of Vitamin D have been identified in immune cells and different

part of the brain, which explain its role in the pathogenesis of MS and depression.^[29,30] Moreover, others indicated that treatment of Vitamin D deficiency or preventing it with its supplements in children and adults, could reduce the risk of many neurological disorders.^[31] However many studies have suggested that Vitamin D supplementation could have anti-inflammatory and neuroprotective effect in different types of MS, and the EVIDIMS Trial (Efficacy of Vitamin D Supplementation in Multiple Sclerosis) is an ongoing phase II study that evaluate the efficacy of high-dose Vitamin D supplementation as a safe orally available and cheap treatment options in MS patients.^[32,33] Our findings in this regard were similar to the study of Knippenberg *et al.*, in the Netherlands. They indicated that Vitamin D status was correlates negatively with depression.^[13] Several studies indicated the role of Vitamin D in the depressive symptoms of different disease.^[34,35]

The accurate diagnosis of depression seems to be difficult in MS patients due to the potential for overlapping of symptoms in depression and MS. But some studies indicated that using is a valid measure and a useful clinical tool in this regard.^[36]

In current study there was not any correlation between Vitamin D status and fatigue which was similar to the results of Knippenberg *et al.*^[13] Whereas other studies among other group of patients have shown significant relationship between Vitamin D status and fatigue.^[37]

It seems that more studies with larger sample size would be helpful in this regard. However, it seems that this is a challenging issue. It is difficult to qualify fatigue because its diagnosis is subjective and the questionnaire which commonly used cannot properly define its qualitative effects.^[38,39] The limitation of our study was that because the duration of the study, seasonal variation of 25 (OH)D was not considered in this study, so, more studies with consideration of mentioned limitations should be designed.

Regarding the disease and its related psychiatric disorders, it is not clear that these manifestations are the illness indicator or the co-morbid condition or both. It seems that improving the methodologies used in study design, including stricter definitions of fatigue and depression and time of onset would help us to obtain more accurate results in this field.

In this study there was significant correlation between MS disability evaluated by EDSS and fatigue and depression, which was in line with other studies. Evidences indicated a complex interplay of MS disability with depression and fatigue.

Table 1: The characteristics of MS patients with low and normal Vitamin D level

| Variables | All studied patients (n=200) | Normal Vitamin D (n=103) | Low Vitamin D (n=97) | P value 1 |
|--------------------------------|------------------------------|--------------------------|----------------------|----------------------|
| Age (year) | 33.5±8.4 | 34.6±8.7 | 32.3±8.1 | 0.6* |
| Sex (female/male) | 154/46 | 74/29 | 80/17 | 0.074 [†] |
| Duration of the disease (year) | 4 (2-8) | 5 (2-8) | 4 (1-7) | 0.2 [‡] |
| EDSS | 2 (1-3) | 2 (1.5-3) | 2 (1.5-2.5) | 0.6 [‡] |
| FSS | 4.8 (3.4-5.7) | 4.8 (3.1-5.9) | 4.7 (3.7-5.5) | 0.7 [‡] |
| BDI-PC | 4 (3-7) | 3 (1-7) | 5 (3.5-7) | 0.001 [‡] |
| Vitamin D (nmol/L) | 76 (35.5-00.7) | 98 (82-138) | 35 (18-54) | <0.0001 [‡] |

1 between normal and low Vitamin D groups. P values calculated by *Independent sample t-test, [†]Chi-square and [‡]Mann-Whitney. EDSS=Expanded disability status scale; FSS=Fatigue severity scale; BDI-PC=Beck depression inventory for primary care

Table 2: Correlations between all studied variables evaluated by spearman's test

| | EDSS | FSS | BDI-PC | Vitamin D | Age |
|-----------|--------|---------|--------|-----------|---------|
| EDSS | 1.00 | 0.37** | 0.25** | 0.17* | 0.30** |
| FSS | 0.37** | 1.00 | 0.43** | 0.08 | 0.261** |
| BDI-PC | 0.25** | 0.43** | 1.00 | -0.16* | 0.10 |
| Vitamin D | 0.17* | 0.08 | -0.16* | 1.00 | 0.11 |
| Age | 0.30** | 0.261** | 0.10 | 0.11 | 1.00 |

*Correlation is significant at the 0.05 level; ** Correlation is significant at the 0.01 level

Others indicated that, though physical disability of MS patients is the main cause for impaired Quality of Life (QOL) of these patients, but MS related fatigue and depression are independently associated with impaired QOL and diagnosis and treatment of these co morbidities would improve QOL of MS patients.^[40]

In sum, considering the relation between Vitamin D and depression in our studied population, it seems that further studies should be designed including depression as outcome measure and considering the mentioned limitations. More interventional studies for determining the role of Vitamin D supplements in this regard is recommended also.

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