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Effect of Vitamin A Supplementation on Fatigue and Depression in Multiple Sclerosis Patients: A Double-blind Placebo-controlled Clinical Trial

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ABSTRACT

Decreasing the population and activation of inflammatory T helper cells in multiple sclerosis (MS) patients using vitamin A derivatives (retinoic acids) has been well documented. The present study determined the effect of vitamin A supplementation on psychiatric signs in MS patients.

The subjects were 101 relapsing-remitting MS patients enrolled in a placebo-controlled randomized clinical trial. The treatment group was administered 25000 IU/d retinyl palmitate (RP) for 6 months followed by 10000 IU/d RP for another 6 months. The results for baseline characteristics, modified fatigue impact scale and Beck Depression Inventory-II were recorded at the beginning and end of the one-year study.

The non-normal distribution data was compared between groups using a nonparametric test and normal distribution data was analyzed using a parametric test. (ClinicalTrials.gov Identifiers: NCT01417273).

The results showed significant improvement in the treatment group for fatigue (p=0.004) and depression (p=0.01). Vitamin A supplementation helped during interferon therapy in the treatment process and improved psychiatric outcomes for anti-inflammatory mechanisms.

Keywords: Depression; Fatigue; Multiple sclerosis; Vitamin A

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INTRODUCTION

Multiple sclerosis (MS) is an autoimmune disorder of the central nervous system (CNS) that is characterized by neurological disability. T helper cells Th1 and Th17 are known as major pathogenic cells that secret inflammatory cytokines in MS. Regulatory T cells and Th2 secret anti-inflammatory cytokines and are immune system modulators.[1,2]

Studies have indicated that retinoic acids (RAs) suppress the production and proliferation of pathogenic T cells and induce production of regulatory cells from naive T cells.[2-4] Qu et al.[4] reported that RAs can modulate disease progression in relapsing experimental allergic encephalomyelitis. They showed that Etretinate (synthetic RA) increases the effect of interferon beta on the function of suppressor T cells and thereby modulates MS activity.[5] Human studies have shown that supplementation with 25000 IU/d vitamin A elevated the RAs concentration in blood. Binding RAs to retinoic acid receptors (RARs) on peripheral blood mononuclear cells activates a cascade of intracellular pathways stimulating an anti-inflammatory effect by alteration in the expression of some related genes.[6-9]

RA can also induce neuroregeneration and reduce the psychiatric diseases such as long-term depression.[10,11] Psychiatric signs including fatigue and depression are common manifestations of an inflammatory process in MS patients.[12] The authors have previously demonstrated that RAs down-regulate the inflammatory cytokine genes.[13] The present study demonstrates that vitamin A as an immune modulator can improve psychiatric signs in MS.

MATERIALS AND METHODS

Inclusion Criteria for Participants

In accordance with the 2010 revised McDonald criteria, 101 relapsing-remitting MS (RRMS) patients, after providing informed consent, were enrolled in a double-blind placebo-controlled randomized clinical trial. The subjects were outpatients at Imam Khomeini Hospital Neurological Clinic. The current study was part of a larger study with a protocol designed to investigate the effect of vitamin A on several different outcomes in MS patients.[14]

The patients were in 20-45 years of age. The Expanded Disability Status Scale (EDSS) of patients ranged from 0 to 5. No patient had experienced a relapse for at least in 3 months prior to onset of the study. Patients were required to have a total score of modified fatigue impact scale (MFIS)>20 and of beck depression inventory-II (BDI-II)<15 patients (minimal depression). None of the patients was lactating. Patients received weekly interferon beta-1a injections for at least 3 months before intervention. The body mass index (BMI) of all patients was between 18.5 and 30. Patients with any type of addiction, alcohol intake, dysphagia, history of myocardial infarction, stroke, allergic reaction to vitamin A or who had experienced autoimmune diseases such as diabetes and inflammatory bowel disease and liver, pancreatic, or biliary disorders were excluded from the study.

Intervention

A co-worker in the clinic was designated by the author to obtain the vitamin A and placebo from the pharmaceutical company and pack them in boxes. The boxes containing vitamin A were labeled “A” and the boxes containing the placebo were labeled “B”. Researchers and patients were blind as to the contents of the A and B boxes. Patients were assigned to one of two blocks based on gender. Within the each block, the patients were randomly and blindly assigned to the treatment (A) or placebo (B) groups. The 13 men and 38 women in group A received 25000 IU RP daily (Zahravi Pharmaceutical, Iran) for the first 6 months and 10000 IU RP daily for another 6 mo. The 12 men and 38 women in group B received the placebo.

General and Clinical Measurements

The general and clinical characteristics of age, gender, duration of disease, BMI, and EDSS were recorded for each patient. The validated Farsi self-reported MFIS[15] and BDI-II,[16] the best questionnaires for evaluation of fatigue and depression, were used in the present study.[17] The MFIS was divided into three subscales for physical, cognitive, and psychosocial fatigue and was computed as a total fatigue score (0-84). Higher values denote greater fatigue in patients. The BDI-II contains 21 questions. Each answer was scored on a scale of 0 to 3. Higher total values denote more severe depressive symptoms. Three 24-hr food records were filled-out by each patient at the beginning and end of the study to determine dietary intake of vitamin A and were compared between groups.

Ethics

The research project has been approved by Ethics

Committee of Tehran University of Medical Sciences with code number of 8887, and ClinicalTrials.gov Identifiers: NCT01417273.

Statistical Analysis

SPSS 18 was used for data analysis (SPSS, USA). The normality of the data was assessed using the Kolmogorov-Smirnov test. Data with a non-normal distribution was analyzed using a nonparametric test (Mann-Whitney) and data with a normal distribution was analyzed using a parametric test (independent sample t-test). A value of $p<0.05$ was defined as being significant.

RESULTS

Out of the 101 RRMS enrolled patients, 4 patients in each group did not complete the study. One male and 3 female of patients in group A and 4 female of patients in group B were excluded from the study, because of changes in their use of interferon, supplementation with the other kinds of vitamins, or their primary diets.

The baseline characteristics were not significantly different between groups (Table 1). Total MFIS ($p=0.004$) and its subscales for physical ($p=0.02$), cognitive ($p=0.02$), and psychosocial ($p=0.02$) function, and BDI-II ($p=0.01$) improved significantly in Treatment group, over the Placebo group (Table 2).

Major psychosocial factors for evaluation of depression such as death of a close relative, marriage, and divorce, were measured. They were not different between groups before and after intervention (Table 3).

It was not found any significant difference in dietary intake of vitamin A ($p=0.07$) and carotenoids ($p=0.83$) between groups (Table 4 and Figure 1).

Table 1. Baseline characteristics of RRMS patients

Characteristics	Treatment group*	Placebo group*	*p* value
Age (year)	30.4±1.0	32.3±1.0	0.16‡
Disease duration (year)	4.3±0.6	5.4±0.6	0.24‡
BMI	23.9±0.5	24.5±0.5	0.41†
EDSS	1.30±0.14	1.40±0.16	0.58‡
MFIS	24.94±2.43	23.09±2.21	0.48†
Depression	12.43±1.28	11.43±0.97	0.54†
Gender	12/35	12/34	0.95‖

*Mean±SE / ‡Mann-Whitney test/ †Independent samples t-test/ ‖Chi square test

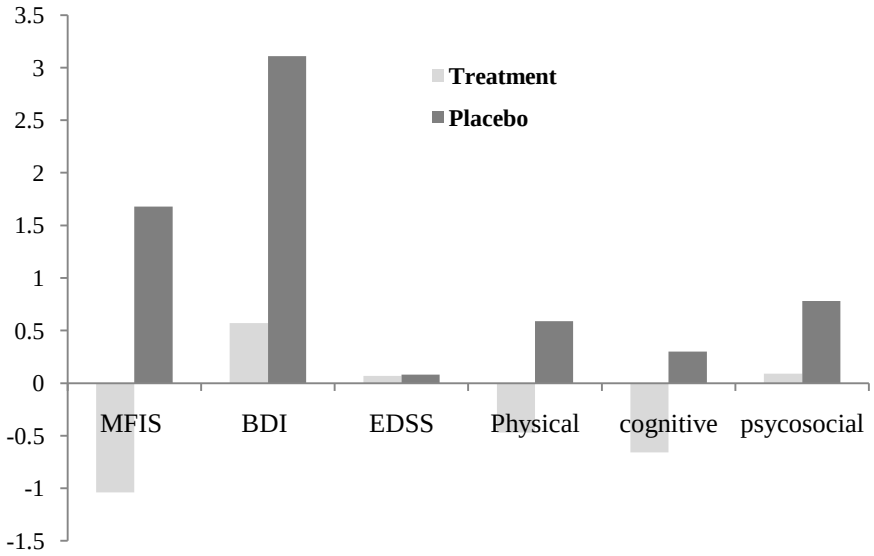

Figure 1. Changes in psychological and clinical endpoints

Table 2. Psychological and clinical endpoints

Clinic-cognitive endpoints		Treatment group*	Placebo group*	*p* value
Change in EDSS		0.07±0.03	0.08±0.03	0.73†
Change in MFIS score		-1.04±0.57	1.68±0.73	0.004**
Change in subgroups score	Change in physical	-0.47±0.28	0.59±0.42	0.02†
	Change in cognitive	-0.66±0.29	0.30±0.45	0.02†
	Change in psychosocial	0.09±0.16	0.78±0.22	0.02†
Change in BDI score		0.57±0.58	3.11±0.60	0.01†

*Mean±SE/ †Mann-Whitney test/ **Independent sample T test/

Table 3. Confounder factors for depression evaluation in MS patients

Important life events	Time	Treatment group*	Placebo group*	*p* value
Marriage	Before	1	1	0.98†
	After	1	0	0.32†
Divorce	Before	2	0	0.16†
	After	0	1	0.31†
Death of family member	Before	0	1	0.31†
	After	0	1	0.31†

*Number of events / †Chi-Square test

Table 4. Daily dietary intakes of vitamin A and carotenoids in MS patients

Dietary intake	Treatment group*	Placebo group*	*p* value
Change in carotenoids (µg/d)	77.9±104.2	-54.4±94.0	0.73†
Change in vitamin A (µg/d)	-11.2±9.9	17.8±13.4	0.08†

*Mean±SE/ †Mann-Whitney test/ µg/d: microgram per day

DISCUSSION

No study has demonstrated the effectiveness of vitamin A on the clinical problems of fatigue and depression in MS patients yet. This randomized trial study was designed with a large sample size (101 patients), long-term supplementation (1 yr), critical inclusion criteria, and high dose RP (25000 IU/d) to identify the potential effects of vitamin A on some clinical signs in MS patients. Confounding factors were considered by measurement of baseline characteristics, psychosocial stressors and dietary intake of vitamin A. There were no significant differences in confounding factors between groups (Tables 1, 3 and 4). In the present study, we used two validated questionnaires, the MFIS and BID-II, for detection of fatigue and depression in MS patients. It was found that scores for depression, total fatigue and the three subscales of fatigue (physical, cognitive and psychosocial) improved significantly with consumption of vitamin A (Table 2).

Fatigue is a major and disabling problem that affects the quality of life of MS patients. The mechanism of fatigue and its relationship with other clinical signs in MS is not well known.[18] The unknown pathogenesis of fatigue in MS makes it difficult to treat.[19] Comi et al.[20] showed that fatigue correlates with mood disorders in MS patients. They also noticed that the existence of inflammatory cytokines played a major role in the pathogenesis of fatigue. This finding was also reported by Flachenecker et al.[21] MS patients encounter with a higher risk of depression than healthy individuals.[22] Several mechanisms have been reported for the pathogenesis of depression in these patients. Immune dysfunction, level of disability and psychosocial stressors relate to depression in MS.[23,24] Inflammatory products in MS result in diffuse gamma-

aminobutyric acid-ergic (GABAergic) alteration in neurons. Depression has been shown to have a link to GABAergic neurotransmission.[25] Bakshi et al.[12] reported that fatigue in MS correlates significantly with depression, and those common mechanisms may play a role in the pathogenesis of these disorders.

Few studies have been focused on the evaluation of vitamin A derivatives or RAs on clinical signs in MS patients. To the best of our knowledge, one previous study administered etretinate (synthetic RA) to MS patients for 6 mo. Qu et al. detected many serious side effects that masked the probable positive effects of etretinate on clinical manifestations and detected no significant differences in fatigue and depression in treated patients.[5] The present study treated the patients with RP instead of RA to avoid the serious side effects of RA. The preferred mechanism for improvement of fatigue and depression in MS is the effect of vitamin A on the level of inflammatory cytokines.

Vitamin A converts to RA in response to liver regulatory functions and the level of circulating RAs will increase.[26,27] One study showed that, after 6 months of supplementation with 25000 IU/d RP, the level of circulating RAs increased to 3-4 ng/dl.[7] RAs in the blood stream will bind to their receptors on peripheral blood mononuclear cells including RAR-alpha and gamma effectively and functionally.[8] Previous cellular and molecular assessments by the authors have shown that 25000 IU/d RP inhibits the proliferation of inflammatory T helper cells[13,28] down-regulates gene expression of inflammatory cytokines and their transcription factors[9] and also altered the expression levels of RAR-alpha and gamma genes in MS patients.[8] Several studies have revealed that RAs alter the Th1/Th2 balance towards Th2, increase production of Foxp3+ T cells instead of Th17 from naive T cells, and regulate the immune response in MS patients.[2,29,30] This regulation may result to ameliorate the signs of fatigue and depression in MS patients.

None of the patients was excluded from the study, because of adverse effects of 25000 IU/d RP administration. Moreover, no pathological changes in lipid profile or liver laboratory tests were found following one year of intervention. Our previous reports also indicated no adverse effects of RP (25000 IU/d) supplementation in MS patients.[8,31] Lacking the toxicity of above mentioned dose of RP for 1 yr has been shown previously.[32] It is recommended to confirm our study using different types of questionnaires for measuring fatigue and quality of life.

Finally, we found that supplementing MS patients with RP alongside the interferon leads to promising results without complications. The results demonstrated that vitamin A improves fatigue and depression in MS patients through the modulation of inflammatory conditions.

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