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High dose Vitamin D intake and quality of life in relapsing-remitting multiple sclerosis: a randomized, double-blind, placebo-controlled clinical trial

Fereshteh Ashtari[1], Nafiseh Toghianifar[2], Sayyed Hamid Zarkesh-Esfahani[3], Marjan Mansourian[4]

[1]Department of Neurology, Isfahan University of Medical sciences, Isfahan, Iran, [2]Isfahan Neuroscience Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [3]Department of Biology, University Of Isfahan, Isfahan, Iran, [4]Department of Biostatistics and Epidemiology, Health School, Isfahan University of Medical Sciences, Isfahan, Iran

Background: Low level of vitamin D is associated with a more severe course and low quality of life in relapsing-remitting multiple sclerosis (RRMS). Low dose vitamin D intake has improved quality of life in RRMS patients.
Objective: This study explored the effect of high dose vitamin D intake on quality of life in RRMS patients in a double blind randomized clinical trial.
Methods: 94 RRMS patients were randomized to two groups. One group received 50,000 IU vitamin D3 every five days for 3 months. The other group received placebo. Interferon-β (IFN-β) continued as the main treatment in both groups. Quality of life was assessed using MSQOL-54 Persian version at the beginning and at the end of the study.
Results: After 3 months, the vitamin D group had a significant difference in mental health composite with placebo group, 62.41 ± 13.99 vs. 60.99 ± 17.99 (p-value = 0.041). Change in health was 75.74 ± 25.73 and 70.59 ± 26.45 in vitamin D and placebo group, respectively (p-value = 0.036).
Conclusions: Mental QOL improved significantly after taking high dose vitamin D for 3 months in vitamin D group relative to placebo.

Keywords: Multiple sclerosis, Vitamin D, Quality of life, Mental health, Physical health

Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating autoimmune disease of the nervous system.[1] It involves various parts of the nervous system with sensory, motor, visual, sphincter, and psychological problems.[2] As a chronic, relapsing disease affecting mainly young people, MS deteriorates quality of life of patients in different ways.[3] The progressive physical and neurologic disability, and psychiatric symptoms decrease quality of life.[4] Many studies have shown lower quality of life in MS patients, even lower than other inflammatory conditions such as inflammatory bowel disease.[3,5–8] Quality of life scores are lower even in the early stages of MS when physical symptoms and disability are still minimal.[9]

Many studies have shown that MS patients have lower levels of vitamin D relative to healthy subjects.[1,3,10,11] Low vitamin D levels have been related to higher number of relapses and a more disabling course.[11] Vitamin D has immunomodulatory effects on immune cells that may affect disease development and progression.[12] It may improve several disease parameters such as anti-inflammatory mediators, MRI findings, and disease course.[10–13]

Findings from many studies on diseased populations other than MS indicate that vitamin D supplementation may be helpful in improving quality of life.[2,4,6,8,14] This helpful effect has been observed both for low and high dose vitamin D supplementation.[15] However, less attention has been paid to the effect of vitamin D supplementation on quality of life in MS patients. We compared quality of life in relapsing-remitting multiple sclerosis (RRMS) patients receiving high dose vitamin D vs. placebo in a double-blind, placebo-controlled clinical trial. We hypothesized that high dose vitamin D intake improves quality of life in MS patients.

Materials and methods

Design

The details of the study has been described previously and is presented here briefly.[16] The study started on 22

Correspondence to: Nafiseh Toghianifar, MD, Neurology Assistant, Isfahan University of Medical Sciences, Alzahra Hospital, Soffeh St, Isfahan, Iran, Tel: 09132048818, Email: n.toghiani@gmail.com

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December 2013 with a double-blind randomized clinical trial design. Ninety-four eligible patients were randomized to receive high dose vitamin D or placebo. The intervention group received oral vitamin D3 50,000 IU every five days for three months. All patients were receiving interferon-β. The study was approved by the Isfahan University of Medical Sciences Ethical Committee.

Study participants

Inclusion criteria were: a definite diagnosis of RRMS according to Mc Donald criteria,[17] age 18–55 years, EDSS score of less than 4, no relapse 30 days before inclusion, negative β-HCG test for women in child-bearing age. Exclusion criteria were: pregnancy, lactation, any other disease than MS, 25(OH)D3 serum level >85 ng/ml, past history of renal or hepatic disease, relapse during the study, received corticosteroids in the previous 30 days, calcium (Ca) >11 mg/dl, aspartate transaminase (AST) or alanine transaminase (ALT) >3 times normal values, alkaline phosphatase (ALP) >2.5 times normal values. All patients continued conventional treatment regimen with β-interferon. All patients had given informed consent before entering the study.

Randomization and intervention

Eligible patients were randomized to intervention or placebo groups. A neurologist visited patients at the beginning of the study and gave medication or placebo to them according to randomization and allocation. The intervention group received 50,000 IU vitamin D every five days (Vitamin D3 Pearl, 50,000 IU, Zahravi pharmaceutical Co., Tabriz, Iran). This is the only high dose oral formula of vitamin D in Iran. Patients received medication/placebo for three months. They could refer to the physician whenever they had new neurologic complaints or problems with medication. Patients were free to discontinue medication (see Fig. 1).

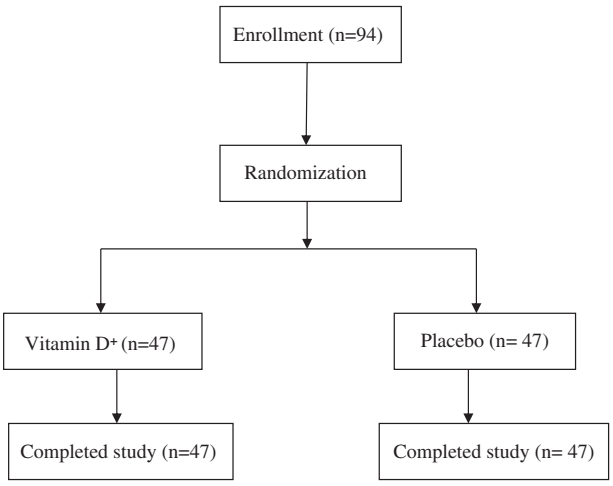

Fig. 1 Trial design for comparison of quality of life after receiving oral high dose vitamin D (50,000 IU every 5 days) with placebo in RRMS.

Study variables

Demographic and disease characteristics were recorded by a trained nurse. Demographic characteristics included age, sex (female/male), marital status (single/ married), education level (undergraduate/high school/ college degree), and living area (city or nearby towns). Disease characteristics included EDSS scores, disease duration, number of attacks last year and medication. Blood samples were obtained at the baseline and end of the study to check BUN, Cr, Ca, AST, ALT, ALP, and 25OHD. 25(OH)D3 serum level was measured by electrochemiluminsecence method by Elecsys system (made in Germany, Roch Co.).

Quality of life was measured using MSQOL-54 Persian version.[18] This questionnaire is widely used in assessing quality of life in MS patients.[19,20] It includes 54 items that are grouped in 12 subscales plus two single items. Mental and physical health composites are derived from these subscales. Physical health composite includes physical function, health perceptions, energy/fatigue, role limitation-physical, pain, sexual function, social function, and health distress. Mental health composite includes health distress, overall quality of life, emotional well-being, role limitation-emotional and cognitive function. Persian version has been translated and validated in Iranian MS patients.[18]

Statistical analysis

Data distributions are reported as mean ± SD for continuous variables and as proportions for categorical variables. Unadjusted analyses compared data across the two different groups using the chi-squared test, Student's *t*-test, and the Wilcoxon rank sum test.

The change in quality of life subgroups after three months in intervention and control groups was analyzed using the following incremental simple and multiple linear regression models: unadjusted model, Model 1 (adjusted EDSS); Model 2 (adjusted for sex, age, disease duration, and EDSS). All statistical analyses were performed using statistical package for the Social Sciences version 18.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was established at a *P* value of, 0.05.

Results

Sociodemographic and disease characteristics are shown in Table 1. As is shown, demographic characteristics including age, sex, marital status, education, and living area did not have significant difference between two groups.

Disease characteristics including disease duration and number of attacks in the previous year did not have significant difference between intervention and placebo groups (*p*-values 0.649 and 0.749, respectively). However, EDSS scores showed a significant difference between intervention and placebo groups ($p = 0.033$).

Physical composite of quality of life was 66.32 ± 17.87 and 70.01 ± 16.5 in the intervention and placebo groups,

Table 1 Sociodemographic characteristics of the intervention and placebo group at the beginning of the study

	Vitamin D+	Vitamin D–	*p*
Age (mean ± SD)	31.4 ± 7.6	34.6 ± 10.1	0.998
Sex (%Female)	80	88.9	0.290
Marital status (%)			0.381
Single	28.9	31.1	
Married	68.9	62.2	
Education (%)			0.341
College	52.3	38.6	
High school	36.4	40.9	
Living area (% urban)	91.1	86.7	0.278
Disease duration (yr)	4.1 ± 3.73	4.4 ± 3.9	0.649
Number of attacks last year	0.7 ± 0.9	0.8 ± 0.9	0.749
EDSS (mean ± SD)	1.7 ± 0.6	2.0 ± 0.9	0.033*
Quality of life (mean ± SD)			
Physical	66.3 ± 17.87	70.01 ± 16.50	0.464
Mental	61.28 ± 15.07	58.31 ± 15.68	0.403
Sexual satisfaction	68.10 ± 34.01	62.52 ± 38.81	0.541
Health change	69.05 ± 29.11	65.34 ± 31.07	0.456

*Significant at level of 0.05.

Table 2 Quality of life scores as Mean ± SD at the end of the study after 3 months according to sociodemographic characteristics in intervention and placebo groups

			P-value		
QOL component	Vitamin D+	Vitamin D–	Unadjusted Model	Model 1	Model 2
Physical	71.74 ± 13.46	69.55 ± 17.18	0.69	<0.001*	0.127
Mental	62.41 ± 13.99	60.99 ± 17.99	0.72	<0.001*	0.041*
Sexual satisfaction	70.83 ± 33.51	76.14 ± 28.32	0.56	<0.001*	0.418
Health change	75.74 ± 25.73	70.59 ± 26.45	0.42	<0.001*	0.036*

*Significant at level of 0.05.
Model 1: Adjusted by EDSS variable as significant variable at baseline measurements between two groups.
Model 2: Adjusted by sex, age, disease duration and EDSS scores.

respectively ($p = 0.464$). Mental composite of quality of life was 61.28 ± 15.07 and 58.31 ± 15.68 in the intervention and placebo groups, respectively ($p = 0.403$). The two groups have not significant difference regarding QOL scores at the beginning of the study (Table 1).

Table 2 shows QOL scores after 3 months in intervention and placebo groups. After adjustment for EDSS (that had a significant difference between intervention and placebo groups at baseline), QOL measures showed significant difference between intervention and placebo groups. After adjustment for age, sex, disease duration, and EDSS, the intervention group had a significant difference in mental health composite with placebo group, 62.41 ± 13.99 vs. 60.99 ± 17.99 (p value = 0.041). Change in health was 75.74 ± 25.73 and 70.59 ± 26.45 in vitamin D and placebo group, respectively (p value = 0.036).

Vitamin D levels (median ± IQR) were 70.56 ± 72.45 nmol/L and 98.84 ± 52.34 nmol/L in vitamin D and placebo groups at baseline, respectively (p value = 0.412). After three months, vitamin D levels were 211.33 ± 107.00 nmol/L and 71.53 ± 63.24 nmol/L in vitamin D and placebo groups, respectively (p value <0.001). There was a significant difference in vitamin D levels between baseline and endpoint in intervention (p value = 0.034) but not in placebo group (p value = 0.765). (Not shown in tables)

Discussion

In this study, we compared quality of life in RRMS patients receiving high dose vitamin D for 3 months with placebo group. Mental QOL showed significant improvement in vitamin D group after 3 months after adjusting for sociodemographic and EDSS scores. A positive change in health status was reported by patients receiving high dose vitamin D relative to placebo group. As presented previously, high dose vitamin D was safe in our patients and patients showed good compliance.[16]

While many studies have assessed efficacy of vitamin D in MS patients, only a few have specifically assessed quality of life measures in these patients. A recent study used alfacalcidol in MS patients with significant fatigue. In this clinical trial patients with severe fatigue according to self-report Fatigue severity scale (FSS) was randomized to one of two groups. One group received alfacalcidol 1mcg/d for 6 months and the other group received placebo. The alfacalcidol group showed improved fatigue scale, improved QOL, and lower number of relapses relative to placebo group. Quality of life improved in psychological and social subscales of RAYS scale.[21] There are major differences between two studies regarding sample characteristics, QOL scale, and study period. However, the findings of this study are similar to our findings. Our patients were randomly selected

RRMS patients who were younger and with shorter disease duration ranging from 1 to 8 years. They received vitamin D3 for 3 months. However, after a three-month intervention with vitamin D3, they showed significantly higher mental QOL subscale and change in health item relative to placebo group.

Other factors might affect QOL, such as sleep quality,[22] depression,[23] physical activity level[24,25], and diet.[26] We did not measure these parameters. However, patients in intervention and placebo group did not have significant difference regarding age, sex, marital status, education level, living area, disease duration, and number of attacks in the previous year. They had low EDSS scores and minimal disability. Patients were similar regarding baseline vitamin D serum level. Patients were not deficient in vitamin D. Further studies with more prolonged follow-up periods may be more helpful in assessing QOL specially the physical component.

Conclusion

Mental QOL improved significantly after taking high dose vitamin D for 3 months in vitamin D group relative to placebo. Also a positive change in health status was reported by patients receiving high dose vitamin D relative to placebo group. Subjective feelings of improvement in mental and health status subgroups of QOL can be helpful in deciding whether to give high dose vitamin D to RRMS patients. Further studies are needed to clarify the mechanism of vitamin D effect on quality of life.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed were in accordance with the ethical standards of the Isfahan University of Medical Sciences Ethical committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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