Research Paper

The Effects of Vitamin D on Sexual Function and Hormones in Women with Multiple Sclerosis

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ABSTRACT

Background: Sexual dysfunction (SD) is the most common and challenging complication among women with multiple sclerosis (MS). Despite investigations into the impact of taking vitamin D on sexual function (SF), findings have not definitively recommended its use. This study aimed to evaluate the effects of vitamin D supplementation on SF and sex hormones among women with MS.

Methods: This triple-blind, randomized, placebo-controlled clinical trial was conducted on 62 married women with MS and vitamin D deficiency. They were recruited from a specialized clinic for neurology in Tehran City, Iran, between August 2017 and February 2018. The subjects were randomly allocated to experimental or control groups (n=31/each group). Subjects in the experimental and control groups, respectively, received two 2000-IU vitamin D and two placebo tablets daily for 12 consecutive weeks. Serum levels of sex hormones and their SF were evaluated before and after the intervention. The SF assessment was performed using the female SF index. The obtained data were analyzed using an independent samples t-test, paired t-test, Fisher exact test, Mann-Whitney U test, and the chi-square test in SPSS software, version 22. The significance level was determined at <0.05.

Results: The findings revealed no significant difference between the two groups regarding sex hormones, Vitamin D, and SF levels before the intervention. The study results indicated that taking vitamin D supplementation for 12 weeks significantly impacts the improvement of SF and sex hormones (P<0.05).

Conclusion: Twelve weeks' consumption of vitamin D supplementation may improve SF and sex hormones among women with MS.

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Highlights

• One of the most common complications of multiple sclerosis (MS) in women is sexual dysfunction.

• This study aimed to evaluate the effects of vitamin D supplementation on sexual function (SF) and sex hormones among women with MS.

• The results revealed that vitamin D supplementation for 12 weeks significantly improves SF and sex hormones.

Plain Language Summary

MS, especially in women, can have significant physical and psychological effects, including sexual dysfunction (SD) and hormonal disturbances. The effects of vitamin D supplementation as an adjunct medical therapy on SF and hormonal management in women with MS are controversial. Our study investigated the effects of vitamin D supplementation on SF and sex hormones among women with MS. The results showed that taking vitamin D supplementation for 12 weeks can improve SF and sex hormone status in women with MS.

Introduction

Multiple sclerosis (MS) is a chronic and the most common disorder of the central nervous system. It is thought to be an autoimmune disorder. It is estimated that over 1.8 million people suffer from MS worldwide (WHO, 2023). MS is more common among women, particularly those aged 20–50 years (Thompson et al., 2018b).

Sexual dysfunction (SD) is regarded as one of the most common and challenging problems in women with MS (Bartnik et al., 2017). According to the World Health Organization (WHO), SD refers to a wide range of disorders, such as decreased libido, loss of sexual pleasure, lack of sexual arousal, orgasmic disorders, vaginal dryness, dyspareunia, and sexual dissatisfaction (Wh, 2016). MS is associated with a higher SD prevalence than other neurologic disorders (Zhao et al., 2018a). The prevalence of SD among women with MS is reported to be 40%–80% globally and 62% among Iranian women (Ghasemi et al., 2019).

The etiology of SD among women with MS is still unknown. However, SD in people with MS is believed to be primarily caused by lesions in neural pathways (Alehashemi et al., 2019). Medication side effects, fatigue, muscular weakness, pain, spasm, and sleep disorders can contribute to SD. The other factors predisposing SD include mental and sociocultural issues, low self-confidence, negative body image, feelings of non-attractiveness, depression, anxiety over the inability to establish a sexual relationship, and hormonal imbalances, including 17beta-estradiol, testosterone, progesterone, and prolactin (Zhao et al., 2018b; Alehashemi et al., 2019).

Vitamin D supplementation is one of the adjacent medical therapies for SD management in women with MS (Yuan et al., 2021). In addition to its positive effects on calcium metabolism and ossification, vitamin D has significant roles in the reproductive system (Krysiak et al., 2018a). Vitamin D is believed to improve sexual function (SF) among women by regulating the blood flow, the neurohormonal function of the genital system, and aromatase expression (Krysiak et al., 2018a; Robles et al., 2022).

Despite research findings regarding the impact of vitamin D on SF among men and women, there are no conclusive findings (Vitale et al., 2018). However, the results of a study in Turkey indicate a direct relationship between vitamin D levels and SF in menopausal women. Therefore, the researchers suggested the need for more detailed studies in this field (Vitale et al., 2018). Similarly, a systematic review study reveals a direct relationship between lower levels of vitamin D and erectile dysfunction in men (Crafa et al., 2020). However, study limitations in a comprehensive review have identified the need for larger controlled clinical trials of vitamin D supplementation as the standard of care for MS patients (Sintzel et al., 2018). Therefore, there is a need to conduct further studies with a larger sample size and higher quality (Crafa et al., 2020). Hence, the present study was conducted to narrow this gap by evaluating the effects of vitamin D supplementation on SF and sex hormones among women with MS.

Materials and Methods

Design, setting, and sample

This triple-blind, randomized, placebo-controlled clinical trial was conducted on all married women with MS and vitamin D deficiency referred to Dr Nabavi's referral clinic for specialized neurology in Tehran City, Iran, from August 2017 to February 2018. Those willing to participate in this experiment were selected based on the following inclusion criteria: married women aged 20-40 years; confirmation of diagnosis of MS by a neurologist within the past year, along with the use of therapeutic regimen in both groups; no acute or chronic disease other than MS; no record of disorders associated with vitamin D malabsorption (constipation, diarrhea, celiac sprue, short bowel syndrome, and cystic fibrosis); absence of chronic diseases or mental illnesses; with at least one sexual intercourse per month; the vitamin D serum level of lower than 50 ng/mL; no record of vitamin D supplementations, and special diet; the expanded disability status scale score of lower than 4; no history of a severe mental crisis; not using hormonal contraception at least in the last 3 months; and no pregnancy and breastfeeding and intention to get pregnant in the last 3 months. In addition, the subjects were excluded from the study if they were reluctant to continue participation, exacerbation the disease and pregnancy during the study, faced a critical situation (such as the death of a family member or hospitalization in the last three months); not taking vitamin D regularly or taking more than one dose per day during the study period; and the presence of severe side effects that require neurological intervention.

The sample size was calculated based on a previous study that reported the average SF scores among young women with and without vitamin D deficiency at 34.02 and 30.26, respectively (Krysiak et al. 2016). Accordingly, with a mean difference of 3 (i.e. one-tenth of the mean in that study), a standard deviation of 4, a confidence level of 95%, and a power of 80%, the appropriate sample size should include 31 participants in each group according to the Equation 1. The final sample size was 34 for each group, given the possibility of 10% sample attrition.

$$1.\ n = \frac{\left(Z_{1-\alpha/2} + Z_{1-\beta}\right)^2 \times 2 \times SD^2}{d^2} = \frac{(1.96 + 0.84)^2 \times 2 \times 4^2}{2.9^2}$$

Eligible subjects were consecutively recruited and randomly assigned to study groups A and B through a lottery.

Instruments and data collection

We used the personal information questionnaire (including socio-demographic information, disease and drug information, and laboratory information), the expanded disability status scale, and the female SF index (FSFI) to collect the study data.

Personal information questionnaire

The personal information questionnaire included socio-demographics (age, educational level, employment status, financial situation, and length of marriage), disease and drug information (MS duration, age of disease onset, and any supplementary drugs), and laboratory information (vitamin D, estrogen, and testosterone levels). The questionnaire was completed through interviews with the subjects, and hormonal information was recorded following measurements.

Expanded disability status scale

The expanded disability status scale is the most common standard scale to evaluate disability in people with MS. The scale measures seven distinct aspects of the functional system: pyramidal, cerebellar, brainstem, sensory, bowel and bladder, cerebral or mental, and visual functions. The scores range from 0 to 10. The first levels, 1.0 to 4.5, refer to people with a high degree of ambulatory ability, while the subsequent levels, 5.0 to 9.5, refer to the loss of ambulatory ability. Accordingly, the higher scores indicate the greater disability and the higher the risk of death (Kurtzke, 1983). Notably, a neurologist specialist assessed and completed the questionnaire at the onset.

Female SF index

The FSFI is used to assess female SF (Rosen et al., 2000). It includes 19 questions in six independent domains: desire (2 items), arousal (4 items), lubrication (4 items), orgasm (3 items), satisfaction (3 items), and pain (3 items). Desire and satisfaction items are rated on a 5-point Likert scale, ranging from 1 to 5, and the other items are rated on a 6-point Likert scale, ranging from 0 to 5. The full-scale score ranges between 2 and 36. Higher scores represent better SF, while 0 shows the absence of sexual activity during the last month. Various studies have confirmed this questionnaire's reliability and validity (Rosen et al., 2000; Daescu et al., 2023). The Persian version of FSFI also shows acceptable psychometric properties. The result of the test re-test indicates acceptable reliability (r= 0.79 – 0.86). The Cronbach α values of FSFI and dimensions among menopausal women are

greater than 0.80 for almost all dimensions, revealing excellent internal consistency reliability (Ghassamia et al., 2013; Babakhanian & Ghazanfarpour, 2018). The cutoff score of the FSFI has been calculated at 28 to distinguish women with sexual disorders from those with normal SF (Heydari & Faghihzadeh, 2008).

Vitamin D and sex hormone

The levels of sex hormones and vitamin D were measured using a 10-mL antecubital venous blood sample, obtained from the subjects in the morning (before and after the intervention). Moreover, a high-performance liquid chromatography vitamin D kit (Novin Tajhiz Gostar Laal Pharmaceutical Company, Tehran, Iran) was used to measure vitamin D levels. The subjects with less than 50 ng/mL serum vitamin D levels were included. Electrochemiluminescence was used to measure sex hormones (estrogen and testosterone). Since the subjects included women of fertility age, the normal range for estrogen and testosterone was assumed to be 44-196 pg/mL and 0.1-0.9 ng/mL, respectively. All laboratory tests were performed in a designated laboratory.

Study procedure and intervention

The socio-demographic information questionnaire was distributed among the subjects, and the researchers decided to interview those subjects who were not literate enough to complete it. Next, a 10-mL venous blood sample was obtained from each subject for pretest measurement of serum vitamin D and estrogen and testosterone levels. Additionally, they were asked to complete FSFI.

The experimental and control group subjects were provided with vitamin D (2000 IU, Zahravi Pharmaceutical Co, Tabriz, Iran) and placebo tablets (containing oral paraffin, Zahravi Pharmaceutical Co, Tabriz, Iran), respectively. They were asked to take two tablets per day for 12 consecutive weeks. We contacted each subject at the end of each week during the study. We reminded her of taking the tablets, trained her again on how to take them, and asked her about the potential side effects, such as nausea and vomiting, poor appetite, and constipation. All subjects were asked to deliver the empty boxes of the tablets. At the end of the intervention, a 10-mL venous blood sample was obtained from each subject for posttest measurement of serum vitamin D, as well as estrogen and testosterone levels. Moreover, they were asked to complete the FSFI again.

Outcome measures

The primary outcomes were the level of sex hormones, including (estrogen and testosterone) and serum levels of 25 hydroxy vitamin D3. They were measured in the laboratory after the intervention. The secondary outcome was the sexual performance of the women, which was measured by FSFI on a self-report basis after the intervention. In case of a lack of proper literacy, the researcher completed these questionnaires through interviews.

Blinding

In this study, neither the research team members, the statistician, nor the subjects were aware of the group allocation. To ensure blinding, vitamin D and placebo tablets had the same shape and size, were packaged in identical boxes, and labeled group A or B by someone outside the research team.

Data analysis

The obtained data were analyzed using the SPSS software version 22. The independent samples t-test, Fisher exact test, and chi-square test were used for between-group comparisons respecting the subjects' demographic and clinical characteristics, the mean scores of SF and its domains, and the mean of serum vitamin D, estrogen and testosterone level. Within-group comparisons of quantitative variables were performed using paired t-test. The level of significance was determined to be $P<0.05$.

Results

At the beginning of the study, 96 subjects were recruited according to the eligibility criteria, and 68 subjects were randomly assigned to the control and experimental groups. Three subjects from the experimental group were excluded due to voluntary withdrawal (n=1) and recurrence of MS (n=2). Moreover, three subjects from the control group were excluded due to the over-the-counter injection of vitamin D ampoule (n=1), irregular consumption of tablets (n=1), and voluntary withdrawal (n=1). Eventually, the analysis was performed on the data obtained from 31 subjects in each group (Figure 1).

The mean ages of the subjects in the experimental and the control groups were 32.4±6.0 and 34.3±4.5 years, respectively. The mean durations of MS disease in these groups were 5.3±4.2 and 4.7±3.1 years, respectively. Most subjects in both groups (66.13%) had a university degree. There were no statistically significant differences regarding socio-demographic characteristics and clinical status (Table 1).

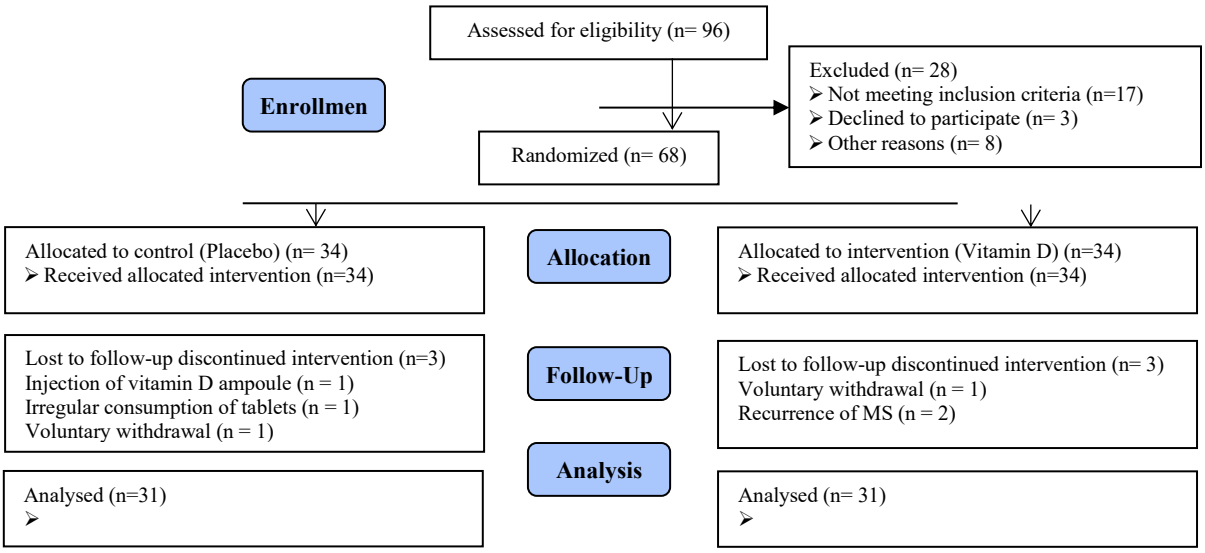

Figure 1. The CONSORT study diagram

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Table 1. Demographic and clinical characteristics of the intervention and control groups

Variables		Mean±SD/No. (%)		P
		Intervention	Control	
Age (y)		32.4±6	34.3±4.5	0.14[a]
MS duration (y)		5.3±4.2	4.7±3.1	0.93[a]
Age of disease onset (y)		27±6.5	29.5±4.6	0.18[a]
Length of marriage (y)		10.5±6.2	11.8±7.8	0.49[b]
Disability status		2.5±1.9	1.9±1.3	0.84[b]
Sexual relationships (per month)		4.5±1.9	4.1±1.3	0.44[a]
Education level	Elementary	3(9.7)	2(6.4)	0.78[c]
	Diploma	9(29)	7(22.5)	
	University	19(61.4)	22(70.9)	
Employment status	Employee	14(45.2)	9(29)	0.18[c]
	Housewife	17(54.8)	22(70.9)	
Financial situation	Poor	2(6.4)	5(16.1)	0.45[c]
	Relatively good	20(64.6)	19(61.4)	
	Good	9(29)	7(22.5)	
Supplementary drug	Iron	4(12.9)	8(25.8)	0.19[d]
	Multivitamin	3(9.6)	3(9.6)	
	Zink	3(9.6)	5(16.1)	

[a]Independent samples t-test, [b]The Mann-Whitney U test, [c]The chi-square test, [d]Fisher exact test.

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The within-group comparisons show no difference between SF and its dimensions and the studied hormones and vitamin D levels before and after the intervention in the control group. However, SF scores and their domains, except pain, hormones, and vitamin D levels, increased significantly after the intervention in the experimental group (Table 2).

Between-group comparisons indicate no significant differences between the two groups regarding SF and its dimensions, hormone levels, and vitamin D before the intervention, and the groups were homogenous. Nonetheless, taking vitamin D supplementation for 12 weeks significantly changed SF regarding orgasm, pain, satisfaction, and total score. Besides, the effect size for these dimensions was reported between 0.51 and 0.84, indicating medium to high effect sizes. However, no statistically significant difference was observed in other dimensions, such as desire, arousal, and lubrication (Table 2). The independent t-test results revealed that taking vitamin D for 12 weeks significantly increased the level of estrogen and testosterone hormones in the experimental group. Moreover, the effect size of such changes was reported to be medium (P<0.001).

Table 2. The mean scores of sexual function and sex hormone and vitamin D levels in the intervention and control groups

	Outcomes		Mean±SD		P[a]	Effect Size[b]
			Intervention	Control		
Sexual function	Desire	Before	2.98±0.17	3.17±0.16	0.42	0.21
		After	3.56±0.16	3.32±0.16	0.32	
		P[c]	0.03	0.3		
	Arousal	Before	2.8±0.11	3±0.12	0.21	0.46
		After	3.56±0.12	3.26±0.11	0.07	
		P[c]	<0.001	0.06		
	Lubrication	Before	2.91±0.1	3±0.11	0.49	0.33
		After	3.56±0.11	3.36±0.09	0.20	
		P[c]	<0.001	0.2		
	Orgasm	Before	2.67±0.12	3.09±0.12	0.31	0.84
		After	3.85±0.1	3.26±0.14	0.001	
		P[c]	<0.001	0.3		
	Satisfaction	Before	2.87±0.1	3.08±0.12	0.12	0.51
		After	3.65±0.12	3.3±0.12	0.04	
		P[c]	<0.001	0.7		
	Pain	Before	3.27±0.16	3.25±0.18	0.72	0.71
		After	2.9±0.13	3.4±0.11	0.001	
		P[c]	0.9	0.7		
	Total	Before	17.58±0.39	18.76±0.33	0.24	0.46
		After	21.09±0.5	19.93±0.38	0.001	
		P[c]	<0.001	0.1		

Outcomes			Mean±SD		P[a]	Effect Size[b]
			Intervention	Control		
Hormone	Estrogen	Before	143.09±11.46	115.23±7.4	0.13	0.51
		After	180.17±14.03	116.48±8.25	0.001	
		P[c]	0.003	0.8		
	Testosterone	Before	0.83±0.04	0.85±0.04	0.66	0.41
		After	0.94±0.17	0.91±0.16	0.03	
		P[c]	0.03	0.2		
	Vitamin D	Before	27.48±8.96	27.56±9.58	0.97	0.56
		After	39.3±8.5	29.2±7.2	0.02	
		P[c]	<0.001	0.6		

ES: Effect size.

[a]Independent samples t-test, [b]Cohen's d, [c]Paired t-test.

Discussion

This study evaluated the effects of a 12-week vitamin D supplementation on SF, vitamin D, and sex hormones, including estrogen and testosterone, among women with MS. The findings reveal that taking vitamin D supplementation by women with MS significantly improves the total score of SF and the dimensions of pain, orgasm, and satisfaction.

The mean scores of SF and its domains in the present study are lower than those reported in the study of Krysiak et al. (2016) among healthy women. This difference could be attributed to the different study populations; our participants were women with MS, which is known to have adverse effects on SF (Kolzet et al., 2015; Merghati Khoei et al., 2012); Krysiak et al. (2016) studied SF in healthy women.

We found that vitamin D supplementation significantly improved SF among women with MS. Consistent with our findings, several studies report that women with low serum vitamin D levels are significantly poorer in terms of SF (Canat et al., 2016; Jalali-Chimeh et al., 2019), and serum vitamin D levels have a significant correlation with SF (Jalali-Chimeh et al., 2019). A clinical trial on 38 women also concludes that vitamin D supplementation has improved SF among women with vitamin D deficiency and SD (Jalali-Chimeh et al., 2019). We also found that vitamin D supplementation had significantly positive effects on the pain, orgasm, and satisfaction domains of SF. Similarly, a former study reports that serum vitamin D level is significantly correlated with the mean scores of pain, orgasm, and satisfaction domains of SF in premenopausal women (Canat et al., 2016). In contrast, another study shows no significant correlation between serum vitamin D levels and the mean score of dyspareunia among healthy women (Krysiak et al., 2016).

Another study finds that women with vitamin D deficiency show significantly lower scores for the desire, orgasm, and satisfaction domains of SF compared with healthy women (Krysiak et al., 2016). The present study findings indicate that taking vitamin D supplementation is associated with an enhancement in SF and an increase in the level of sex hormones. An explanation for the significant positive effects of vitamin D on SF is its effectiveness in correcting hormonal and metabolic alterations caused by vitamin D deficiency (Krysiak et al., 2018b). Low serum vitamin D level significantly affects the production of hormones that regulate SF, especially testosterone (Thompson et al., 2018a). Low testosterone level among women is associated with libido reduction and alterations in different aspects of SF (Davis & Wahlin-Jacobsen, 2015). Studies have reported that alterations in sex hormones are related to sexual desire, arousal, orgasm, and satisfaction (Davis & Wahlin-Jacobsen, 2015; Basson, 2021), reduced vaginal elasticity and secretions, vaginal dryness, painful coitus, and reduced libido (Basson, 2021). Moreover, estradiol, a steroid estrogen, and the major female sex hormone, plays a significant role in promoting vaginal blood flow and lubrication (Cunningham et al., 2015). Accordingly, regulating these hormones by vitamin D can improve SF and reproduction (Tirabassi et al., 2018; Talebi et al., 2022).

Conclusion

It can be concluded that taking vitamin D supplementation (2000 IU tablets twice a day) for 12 weeks resulted in positive impacts on SF, particularly orgasm, pain, and satisfaction. It could also improve sex hormones (testosterone and estrogen) among women with MS who reported low levels of vitamin D at the beginning of the study. Consequently, it is recommended that the vitamin D level in women with MS be regularly monitored to prescribe appropriate vitamin D supplementation along with routine treatment and medicine. Nonetheless, similar studies should be conducted with different vitamin D dosages and time spans in the future. Future studies should also consider the effects of factors such as depression and MS drug treatment regimens when evaluating the impact of vitamin D supplementation on SF. Future studies are recommended to use block randomization for group allocation. The replication of the present study on participants with other neurologic disorders, such as spinal cord injuries, is also recommended.

The researchers' inability to evaluate and control the effects of participants' dietary regimen and sunlight exposure were among the limitations of this study. Meanwhile, one of the strengths of the present study is its triple-blind, randomized, controlled design. To our knowledge, we did the first study into vitamin D supplementation's effects on SF among MS women.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Iran University of Medical Sciences (Code: IR.IUMS.REC 1395.9311373017) and registered to the Iranian Registry of Clinical Trials (IRCT) (Code: IRCT2016061528449N4). All subjects signed written informed consent forms. They were provided with information about the aim and methods of the study, confidential management of the study data, their right to voluntarily withdraw from the study without any change in their treatment program, and their access to free medical visits in case of any problem during blood sampling for serum vitamin D measurement or any side effect of vitamin D supplementation. At the end of the intervention, subjects in the control group who were willing were given twelve weeks of vitamin D supplements with the same dose as the intervention group.

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Authors' contributions

Conceptualization, research, and supervision: Leila Amini; Data gathering: Simin Zaraabadipour; Data analysis: Simin Zaraabadipour and Hamid Haghani; Consultation: Seyed Masoud Nabavi; Initial draft preparation: Leila Amini, Simin Zaraabadipour, and Mohammad Eghbali; Final approval: All authors.

Conflict of interest

The authors declared no conflict interests.

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