

Effects of Vitamin D Supplementation in Patients with Irritable Bowel Syndrome: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

Abstract

Objective: There are some evidence that Vitamin D supplementation may be beneficial for patients with irritable bowel syndrome (IBS). The aim of this study was to evaluate the effects of Vitamin D supplementation on symptoms and quality of life (QOL) in patients with IBS. **Methods:** In a randomized, double-blind, placebo-controlled clinical trial, 116 patients with IBS were supplemented weekly with either a pearl of 50,000 IU Vitamin D or an identical pearl of placebo containing medium chain triglyceride for 6 weeks. **Results:** Mean age of patients was 42.24 ± 12.26 , and 40.06 ± 13.37 in Vitamin D and placebo groups, respectively. Dietary intakes were similar between and within groups. Serum concentration of 25-hydroxy Vitamin D increased significantly from 21.10 ± 5.23 to 36.43 ± 12.34 in the Vitamin D group ($P < 0.001$), while it was not significantly different before and after the trial in placebo group. The IBS symptoms severity scores (SSSS), disease-specific QOL, and total score were evaluated at weeks 0 and 6. IBS-SSS, IBS-QOL, and the total score were improved significantly more in Vitamin D group in comparison to the placebo group ($P < 0.05$).

Conclusions: This study indicates that Vitamin D therapy can improve the severity of symptoms and QOL in patients with IBS; however, the long-term effects remained to be elucidated.

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Keywords: Clinical trial, irritable bowel syndrome, quality of life, supplementation, Vitamin D

Introduction

Irritable bowel syndrome (IBS) is one of the most common gastrointestinal conditions, characterized by chronic abdominal pain, discomfort, bloating, and alteration of bowel habits without any organic cause.^[1] There has not yet been found any effective cure for IBS; however, some remedies have shown promising effects in the management of it.^[2,3] Recently, an analysis of social media (blogs/forums) reported that from 37 patients with IBS, 70% described improvements in their symptoms with Vitamin D supplementation and the majority of these individuals reported being Vitamin D deficient before supplementation.^[4] This study suggested a role for Vitamin D in the management of IBS, which was supported by another recent study showing the high prevalence of Vitamin D deficiency in patients with IBS.^[5] On the other hand, two recent clinical trials have shown promising effects of Vitamin D supplementation on IBS symptoms.^[6,7] Furthermore, a recent review article has shown immune

system activation is more frequent in IBS patients in comparison to healthy controls.^[8] Given the immunomodulatory role of Vitamin D,^[9,10] we hypothesized that patients with IBS who have low serum level of Vitamin D, might benefit from Vitamin D supplementation. Thus, we designed this randomized, double-blind, placebo-controlled clinical trial to evaluate the effects of Vitamin D supplementation on symptoms and quality of life (QOL) in patients with IBS.

Methods

Recruitment and eligibility screening

IBS patients were recruited from two gastroenterology clinics from October 2013 to January 2016. IBS was diagnosed according to the ROME III criteria.^[11] Inclusion and exclusion criteria were the same as our previous study.^[6] All participants were examined for serum Vitamin D, and those with serum Vitamin D level of >30 ng/ml were also excluded from the study.

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Study design

The study protocol was explained for all the participants, and those who agreed to participate and signed the written informed consent were enrolled in the study. The study protocol was approved at our local ethics committee. The participants were randomly assigned to receive either 50,000 IU Vitamin D or identical placebo weekly for 6 weeks according to the available guidelines.^[12] Randomization lists were computer-generated by a statistician, and given to the interviewer. The investigators and patients were not aware of the supplements content.

Intervention

The Vitamin D pearls (Zahravi co., Iran) consisted of 50,000 IU cholecalciferol that was taken one pearl weekly. The placebos were in the same shape and color of Vitamin D pearls and contained 10 mg medium-chain triglyceride oil.

Clinical, paraclinical, and dietary intake assessments

Data on the anthropometric characteristics and 3 days dietary recalls were measured at the baseline and the end of the study. The nutrients compositions of dietary intakes were calculated using the available composition tables.^[13]

Validated IBS Symptoms Severity Score (IBS-SSS) questionnaire,^[14] IBS-QOL questionnaire,^[15] and total score of IBS (visual analog scale)^[16] were filled out at the beginning and the end of the study period.

Patients were followed by phone call to ask the probable side effects and participants' compliance. Furthermore, adherence to the study protocol was assessed using tablet count at the end of the study.

Statistical analysis

Data were analyzed using SPSS software (version 16; SPSS, Chicago, IL, USA). Continuous and categorical data were presented as means \pm standard deviation and frequency, respectively. Demographic variables were analyzed using a Chi-square or *t*-test, as appropriate. Paired *t*-test and Student's *t*-test were used to compare variables between and within groups, respectively. If the distribution of variables were not normal, Wilcoxon and Mann-Whitney U-tests were used to compare quantitative variables between groups, respectively. The data were analyzed according to the intention-to-treat principle. To eliminate the effects of confounding factors, the analysis of covariance test was used.

Results

The consort flow chart of participants through the trial is presented in Figure 1. Two participants from each group were withdrawn from the study; however, they were included in the intention to treat analysis. General characteristics of the participants are shown in Table 1. There was no significant difference between

two groups at the baseline characteristics. Table 2 shows the dietary intakes of two groups at the baseline of the study, which was not different between the two groups. The dietary intakes were not different between and within the groups at the end of the study too. Serum concentration of 25-hydroxy Vitamin D increased significantly from 21.10 ± 5.23 to 36.43 ± 12.34 in the Vitamin D group ($P < 0.001$), while it was not different before (21.33 ± 5.54) and after (21.25 ± 4.98) the trial in placebo group. IBS-SSS, IBS-QOL, and the total score were improved in both groups significantly ($P < 0.001$). As it is shown in Table 3, IBS-QOL and total score at week 6 were improved significantly more in Vitamin D group in comparison to placebo group; however, this significance was not observed in IBS-QOL before adjusting for the

Table 1: Demographic characteristics of the study participants

Baseline characteristic	Vitamin D group	Placebo group	P
Age (mean \pm SD)	42.24 \pm 12.26	40.06 \pm 13.37	0.571
Weight (mean \pm SD)	66.15 \pm 9.37	66.28 \pm 12.39	0.968
BMI (mean \pm SD)	25.85 \pm 3.78	25.27 \pm 4.07	0.619
Smoking (%)	0	2 (8.7)	0.489
Vitamin D consumption (%)	0	0	1.00
SSS (mean \pm SD)	250.87 \pm 96.92	245.78 \pm 112.82	0.737
IBS-QOL (mean \pm SD)	57.35 \pm 27.96	46.70 \pm 31.37	0.231
Total score (mean \pm SD)	81.30 \pm 15.17	80.00 \pm 13.40	0.759

Significances are based on independent *t*-test for quantitative variables and Pearson's Chi-squared test/Fisher exact test for qualitative factors. SSS=Symptoms severity score, QOL=Quality of life, SD=Standard deviation, IBS=Irritable bowel syndrome, BMI=Body mass index

Table 2: Dietary intake of selected nutrients in the study participants at baseline

Dietary intakes	Mean \pm SD		P
	Vitamin D group	Placebo group	
Calorie	1585.89 \pm 403.60	1538.25 \pm 504.98	0.725
Protein	71.72 \pm 23.40	62.17 \pm 32.72	0.261
Carbohydrate	198.50 \pm 66.36	202.16 \pm 70.63	0.857
Total fat	58.99 \pm 20.36	57.34 \pm 29.22	0.824
Cholesterol	261.08 \pm 170.83	227.81 \pm 266.28	0.617
Vitamin C	83.73 \pm 82.87	132.57 \pm 155.80	0.191
Calcium	658.30 \pm 339.98	634.78 \pm 281.25	0.803
Vitamin D	1.09 \pm 1.41	1.27 \pm 2.64	0.772
Zinc	5.92 \pm 3.88	7.45 \pm 4.32	0.212
Magnesium	177.98 \pm 125.30	220.03 \pm 100.30	0.216
Phosphor	889.59 \pm 409.13	965.47 \pm 495.98	0.580
Fiber	15.80 \pm 15.11	23.38 \pm 18.58	0.136
Ferrous	9.99 \pm 3.32	9.90 \pm 4.29	0.939
Vitamin B2	1.20 \pm 0.43	1.22 \pm 0.59	0.882

Significances are based on independent *t*-test. SD=Standard deviation

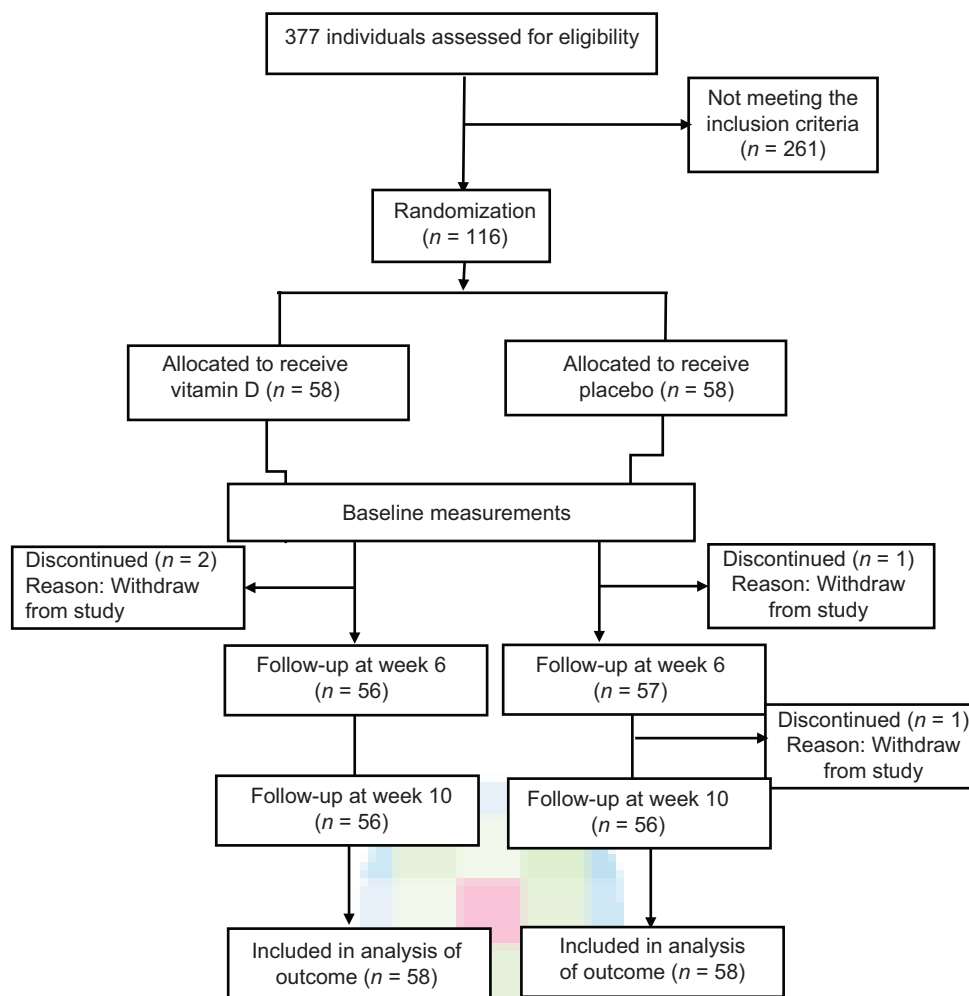


Figure 1: Study flow chart

Table 3: The mean difference of the effect of Vitamin D versus placebo on symptoms severity score, irritable bowel syndrome-quality of life, and total score between the groups

Characteristic	Vitamin D group		Placebo group		Crude (P)	Adjusted (P)
	Crude	Adjusted	Crude	Adjusted		
SSS (mean±SE) ^a	60.23±12.67	61.46±14.54	34.45±13.76	35.55±13.54	<0.05	<0.05
IBS-QOL (mean±SE) ^a	44.17±6.98	48.13±4.24	39.13±4.87	35.18±4.24	0.556	0.039*
Total score (mean±SE) ^a	66.52±5.35	66.69±4.08	26.30±3.30	26.14±4.08	<0.001*	<0.001*

Crude significances are based on independent *t*-test and adjusted significances are based on ANCOVA adjusting the effects of age, IBS-QOL baseline score, and baseline value of each factor as covariates, *Statistically significant, ^aOn week 6, ^bOn week 10. SSS=Symptoms severity score, QOL=Quality of life, SE=Standard error, IBS=Irritable bowel syndrome, ANCOVA=Analysis of covariance

baseline values. IBS-SSS changes were not significantly different between two groups; however, this difference was near significant after adjustment for the baseline values ($P = 0.05$) [Table 3].

Discussion

Our results have shown that 6 weeks supplementation with Vitamin D improves the symptoms and QOL in patients with IBS. It seems that Vitamin D supplementation improves the IBS characteristics through improving the factors involved in the development of IBS.

Although the exact pathophysiology of IBS has not yet been elucidated, it has been shown that alterations in the gut microbiome, intestinal permeability, gut immune function, visceral sensation, brain-gut interactions, and psychosocial status are involved in the development of this syndrome.^[2,17] Furthermore, it has been shown previously that Vitamin D can modulate all of these probable mechanisms involved in IBS pathogenesis. Bashir *et al.*^[18] have shown that 8-week Vitamin D supplementation changes the human gastrointestinal microflora with a reduction in opportunistic pathogens and an increase in bacterial richness. The

effects of Vitamin D on the improvement of intestinal barrier function have been demonstrated in *in vitro*,^[19,20] experimental,^[21] and human studies.^[22] Moreover, it has been shown that Vitamin D regulates immune cell trafficking and differentiation, gut barrier function, and antimicrobial peptide synthesis, all of which, has been shown that play a role in the development of IBS. Vitamin D regulates the innate immune response to the microbiota. Vitamin D is a critical regulator of T-cell function, and the expression of several pattern recognition receptors involved in intestinal inflammation is regulated by Vitamin D.^[23] In the absence of Vitamin D, there are many effector T-cells that produce inflammatory cytokines in the intestine. Vitamin D promotes regulatory T-cell development and function to turn off the Th1 and Th17 cells and to control inflammation in the intestine. The ability of Vitamin D to inhibit Th1, Th17 cells, induce regulatory T-cells, and reduce inflammation resulted in a shift in the microbiome and maintenance of tolerance in the gut.^[24-26] Furthermore, it has been shown that low Vitamin D levels are associated with increased central sensitivity, particularly augmented pain processing on mechanical stimulation in chronic pain,^[27,28] depression,^[29,30] and anxiety,^[31] which all are related with the risk of IBS development. Thus, Vitamin D can improve the IBS symptoms through reduction in all known risk factors that are involved in the pathogenesis of this syndrome.

This study has several advantages; it was designed as a randomized, double-blind, placebo-controlled, clinical trial on the IBS patients who did not receive any medication for their problems, which shows the net effects of Vitamin D supplementation in the study participants. The study was continued 4 weeks after the end of supplementation; remaining effects 4 weeks after supplementation indicates that these beneficial effects are related to the treatment of Vitamin D deficiency, and it confirms the hypothesis that Vitamin D deficiency might be involved in the pathogenesis of IBS. Finally, the dietary intakes were similar in both the groups that reduced the effects of dietary confounders, which shows that our results are independent to the effects of dietary intakes of the study participants.

This study has some limitation; although the sample size was calculated with an accepted power for the study, the results need to be confirmed in larger studies. Moreover, since we recruited only women for this study, the results may not be implemented in men. Another limitation of this study is that we did not measure the sun exposure in participants; however, we measured the serum Vitamin D concentration, which is the most accurate assessment of the Vitamin D status.

Conclusions

This study indicates that Vitamin D therapy has some beneficial effects in the management of IBS in women; however, the long-term effects remained to be elucidated.

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Conflicts of interest

There are no conflicts of interest.

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