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Wael Zeid

Department of family medicine, Faculty of medicine, Suez Canal University, Ismailia, Egypt,
waelzeid@med.suez.edu.eg

Eman Ezzeldeen

Department of family medicine, Faculty of Medicine, Suez Canal University, Ismailia, Egypt,
emanezzfmd@med.suez.edu.eg

Maged Khattab

Department of family medicine, Faculty of Medicine, Suez Canal University, Ismailia, Egypt,
mskhatab@yahoo.com

Safwat Ahmed

Department of Pharmacology, Faculty of Pharmacy, Suez Canal University, Ismailia, Egypt,
safwat_aa@yahoo.com

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Muhammed Abdo

Department of internal medicine, Faculty of Medicine, Suez Canal University, Ismailia, Egypt,
d_m.abdo2014@yahoo.com

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Effect of Vitamin D₃(Cholecalciferol)Supplementation on Gastrointestinal Symptoms in Patients with Irritable Bowel SyndromeAttending El-Mahsama Family Practice Center, Ismailia, Egypt: A Randomized Clinical Trial.

Wael Zeid^{*1} PhD, Eman Ezz eldeen¹ MSc, Maged Khattab¹ PhD,Safwat Ahmed ² PhD, and Muhammed Abdo³ PhD

***Corresponding Author:**

Wael Zeid

waelzeid@med.suez.edu.eg

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¹Family Medicine Department, Faculty of Medicine, Suez Canal University.

²Pharmacognosy Department, Faculty of Pharmacy, Suez Canal University.

³Internal Medicine Department, Faculty of Medicine, Suez Canal University.

ABSTRACT

Background: Irritable bowel syndrome (IBS) is a functionalgastrointestinal condition, in which patients suffer from abdominal pain, bloating, and change in bowel habits. Some researchers examined the potential therapeutic role of vitamin D3 (Cholecalciferol) to alleviate symptoms of IBS, however, the outcomes of their studies werecontroversial.

Objective: to assess the effect of vitamin D3 supplement on gastrointestinal symptoms in patients suffering from irritable bowel syndrome.

Methods: a double-blinded, randomized, placebo-controlled trial. Eighty patients with IBS attending the family practice center in El-Mahsama, Ismailia, Egypt were recruited, after applying inclusion and exclusion criteria. The study participants were allocated randomly into two groups, (1) the intervention and (2) the control group. The intervention group received 4000 IU of vitamin D3 orally and the control group received a placebo of edible paraffin orally. Both groups received their assigned treatment daily for 12 weeks. Irritable bowel syndrome symptom severity score (IBSSSS) was assessed at baseline and after 12 weeks.

Results: IBSSSS was significantly reduced in the intervention group (114.36 ± 67.36) after 12 weeks compared to the control group (292.13 ± 74.77) ($p < 0.001$). Regarding IBSSSS difference, patients receiving vitamin D were found to have significantly higher score difference (-164.72 ± 67.77) than participants who took the placebo (-12.13 ± 50.78) ($p < 0.001$).

Conclusion: Patients suffering from IBS felt better and their gastrointestinal symptomsimproved after taking vitamin D3 supplementation.

Keywords:irritable; bowel; syndrome; vitamin D; cholecalciferol

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INTRODUCTION

Irritable bowel syndrome (IBS) is a recurrent chronic functional gastrointestinal disorder. Patients with IBS suffer from abdominal pain, distention, and change in bowel habits with either predominate constipation, diarrhea or both.^{1,2} IBS is diagnosed clinically using the Rome IV criteria after excluding any warning signs, without the need for any biochemical markers.³

Worldwide, IBS affects around 10%–25% of the population, which can burden any health care system and impair patients' quality of life.^{2,4} IBS symptoms are among the most common causes of primary health care consultations.⁴

The exact etiology of IBS is still undefined. However, many multifactorial theories were proposed including psychosocial disturbance, visceral hypersensitivity, dietary factors, bacterial overgrowth, genetic factors, and brain-gut interaction.⁵ To date, treatment strategies for IBS are only directed to alleviate symptoms, with no specific cure.⁵

Vitamin D₃(Cholecalciferol) has immunological, anti-inflammatory, and antimicrobial properties which encouraged researchers to investigate its therapeutic effects on different chronic diseases such as, multiple sclerosis and cardiovascular diseases.^{6,7} To the best of our knowledge, only one study was conducted in Egypt to evaluate the effect of vitamin D₃ on IBS symptoms in pediatric and adolescent

patients,⁸ but no similar studies were performed for adult patients. Therefore, this study aimed to evaluate the effect of vitamin D supplementation on IBS symptoms in adult patients attending a rural primary health care setting using a randomized controlled trial.

PATIENT AND METHODS

Participants and study setting

The study participants (100) were enrolled from patients attending a family practice center in El-Mahsama village, Ismailia, Egypt from October 2018 to March 2019. The study setting is a rural primary health care center, which provides medical health services at a reduced cost. Out of the enrolled sample, 20 were excluded (15 not fulfilling Rome IV criteria, 2 pregnant and 3 already taking vitamin D supplementations). The included sample was male and female adults aged 18 years or more, who met the diagnostic criteria of irritable bowel syndrome (Rome IV) which include frequent abdominal pain associated with two or more of the following: (1) defecation, (2) altered stool frequency; (3) or altered stool consistency. These symptoms should occur for at least 1 day per week in the last 3 months.³

Baseline sociodemographic characteristics

The sociodemographic status of participants was assessed at the baseline, using a valid and reliable questionnaire in Arabic. The overall score of sociodemographic scale was 84, from which it is sub-grouped into very low (score = 21 or less), medium (score 22-42), high (score= 43-63) and very high levels(64-84).⁹

Study design and follow-up

A randomized control double-blinded trial was designed. Participants were allocated by simple random technique, where every participant had an equal chance to be included in any of the study groups. The intervention group (40 participants) received oral 4000 IU vitamin D₃ pearls once daily for 12 weeks, while the control group (40 participants) received oral placebo pearls containing edible paraffin once daily for the same period. Both vitamin D and placebo pearls had the same shape, size, weight, texture, and packing. Allocation of the participant to either vitamin D or placebo had been done by an independent colleague. Double-blinding, to both the participants and the researcher, was applied. In the follow-up period, two participants discontinued the study (one in the intervention group, who became pregnant after 2 months and one in the placebo group, who was lost after one month of follow up). The study steps are illustrated in figure 1.

IBS symptoms and severity scoring system

At baseline and post-intervention, the total irritable bowel syndrome symptom severity scale (IBSSSS) was assessed in both groups, by a valid and reliable tool. Participants were asked to assess five items related to abdominal pain severity and frequency, distension, bowel habits satisfaction, and impact of IBS in general. The maximum score for each item is 100, while the minimum score is 0, with a total score ranged from 0 to 500. Accordingly, the IBSSSS was

classified as: mild (75-175), moderate (176-300), and severe (above 300). A post-intervention score became below 75 or reduced by 50 or more was considered a clinically significant improvement.^{10,11} The questionnaire was translated into Arabic, then the Arabic version was back-translated into English by two independent translators.

Statistical analysis

The statistical analysis of the results was performed using the 22nd version of the "Statistical Package of Social Science" program. Qualitative results were presented as frequencies and percentages, and comparison between them was done using Chi-square or Fisher's test. The quantitative variables were presented as means \pm standard deviations, and independent sample t-test or Mann-Whitney U test were used to compare these variables. The pre- and post-intervention data were compared using the dependent t-test or Mann-Whitney U test. Results with P values <0.05 were statistically significant.

RESULTS

The socioeconomic and household characteristics were studied in both groups. The mean age was 37.64 ± 11.13 years in the intervention group and 38.03 ± 6.37 years in the placebo group. Seventy percent of the participants were females. About half of the study participants had secondary education and worked in semi-professional occupations. The percentages of participants depending on free governmental health services were 51.3% and 43.6% for the intervention and control groups, respectively. In both study groups, more than half of the participants reported that they have more than one person per room with percentages of 51.3% for the intervention group, and 64.1% for the control group. About half of the participants can just meet their routine expenses in both groups. The baseline characteristics were not statistically significantly different between the two study groups, which implies that these two groups are more or less the same, which can be a matching equivalent.

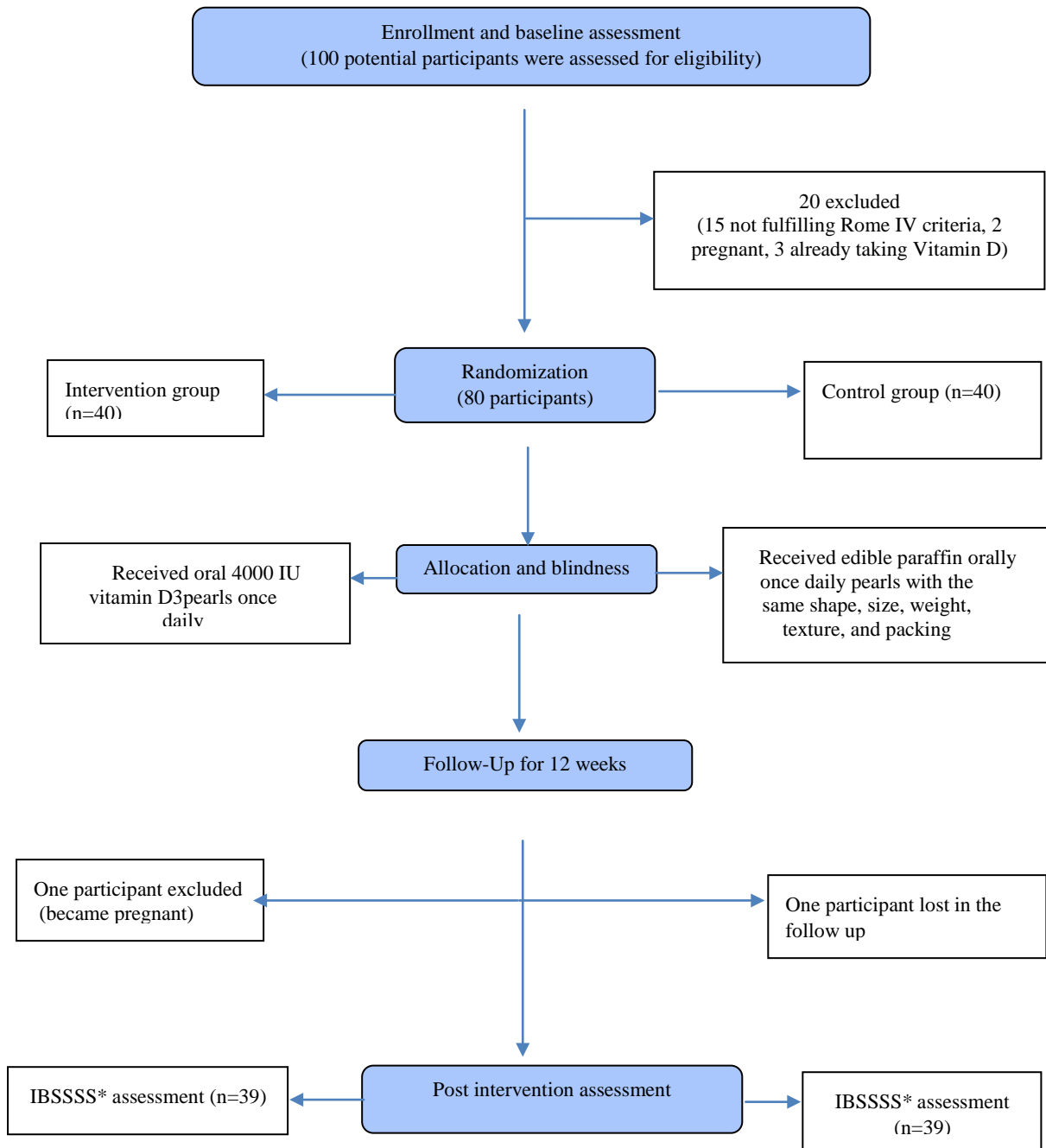
According to the categories of the socioeconomic scale, figure 2 showed that the majority of the participants in the studied sample belonged to the middle socioeconomic level (80%).

Table 1 compares the symptoms of irritable bowel syndrome among the intervention group and the placebo group after intervention. Results showed that the five items of IBS, related to abdominal pain severity and frequency, distension, bowel habits satisfaction, and impact of IBS in general, were statistically significantly improved ($p < 0.001$) for patients who received vitamin D compared to those who received placebo (Table 1).

Table 2 presents IBSSSS for the two study groups in the pre and post-intervention. Results showed that the baseline difference between the intervention and the control groups regarding IBSSSS was statistically insignificant ($p = 0.078$). However, after the intervention, patients receiving vitamin D₃ had statistically significantly lower ($p < 0.001$) IBSSSS

(114.36 ± 67.36) compared to participants who received a placebo (292.13 ± 74.77). The IBSSSS difference was statistically significantly higher

(p<0.001) for patients receiving vitamin D (-164.72 ± 67.77) compared to participants who took a placebo (-12.13 ± 50.78) (Table 2).



*IBSSSS: Irritable bowel syndrome severity score

Figure 1. Steps of the study

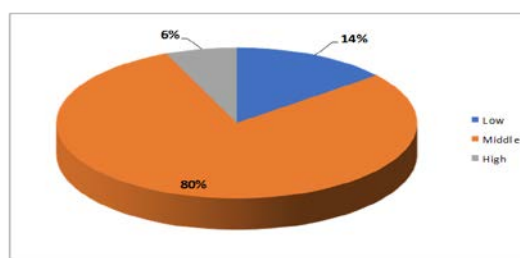


Figure 2. Socioeconomic levels of the total study sample

Variable	Vitamin D (n=39)	Placebo (n=39)	Test value	p-value
Abdominal pain				
Absent	16 (41)	3 (7.7)	11.76	0.001^a
Present	23 (59)	36 (92.3)		
Severity of pain	20.31 ± 17.94	55.15 ± 27.90	257	<0.001^b
Number of days with pain	1.64 ± 1.58	3.13 ± 1.64	375	<0.001^b
Abdominal distention				
Absent	15 (38.5)	0	19.77	<0.001^a
Present	24 (61.5)	37 (94.9)		
Severity of distention	22.00 ± 19.05	66.10 ± 15.37	83	<0.001^b
Dissatisfaction with bowel habits	33.05 ± 22.87	63.56 ± 17.78	231.5	<0.001^b
Interference of IBS with life in general	26.23 ± 20.29	72.18 ± 18.73	98.5	<0.001^b

^a P values are based on the Chi-square test. Statistical significance at P < 0.05

^b P-values are based on the Mann-Whiney U test. Statistical significance at p < 0.05

Table 1. Comparison of irritable bowel syndrome symptoms between vitamin D group and placebo group after intervention.

Variable	Vitamin D (n=39) mean ± SD	Placebo (n=39) mean ± SD	test value	p-value
Pre-intervention	279.08 ± 57.36	304.26 ± 66.89	-1.78	0.078 ^a
Post-intervention	114.36 ± 67.36	292.13 ± 74.77	-11.03	<0.001^a
Score difference*	-164.72 ± 67.77	-12.13 ± 50.78	63	<0.001^b

^ap values are based on independent t-test. Statistical significance at P < 0.05

^bp values are based on Mann-Whitney U test. Statistical significance at P < 0.05

Table 2. Irritable bowel syndrome symptom severity score (IBSSSS) in both vitamin D group and placebo group at different time points

DISCUSSION

Irritable bowel syndrome is a worldwide health problem, however, its pathophysiologic process is still unknown. IBS affects people at any age causing economic burdens and deterioration in patients' quality of life. Eventhough some studies reported that vitamin D supplementation can alleviate symptoms of IBS,^{7,8} the mechanism behind this is still a controversy.¹² The present study was conducted to assess the effect of oral vitamin D₃ supplementation (Cholecalciferol) on gastrointestinal symptoms in patients with IBS.

In this study, the mean age for patients in both groups was less than 50 years old, which was 37.64 ± 11.13 in the intervention group and 38.03 ± 6.37 in

the control group. This finding resembled an Iranian study that was conducted on 90 participants and found that the mean age of their study population was 37.45 ± 9.85.¹ The same results were reported in an English pilot study which revealed that the mean age was 34 ± 12 in the intervention groups and 36 ± 15 in the placebo group.¹³ Similarly, another Iranian study, which included 100 participants revealed that the mean age group in that target population was 39.76 ± 13.46 years.¹⁴ Furthermore, in a meta-analysis study involving 50 epidemiological studies,

the prevalence of IBS decreased after the age of 50 years old, while half of the patients below the age of 35 years experienced symptoms of IBS.¹⁵

In this study, 70% of the participants were females. This was also reported in other studies, which indicated that IBS is more prevalent among females.^{15, 16}

According to the overall socioeconomic scale, the majority of participants in this study lies in the middle socioeconomic level. This could be explained by the fact that the current study setting was a governmental institution that offers medical health services at a reduced cost. In a Colombian study conducted on 1022 patients, the majority of participants with IBS were in the middle socioeconomic level.¹⁷ This indicated that IBS is more prevalent among patients with low socioeconomic status. In accordance with this finding, a European review article concluded that patients with lower socioeconomic status are more likely to have IBS and that income is directly related to health care outcomes, and quality of life and inversely related to life stressors.¹⁸

At the end of this intervention study, patients with IBS who received vitamin D₃ had statistically significantly improved symptoms of IBS (abdominal pain severity and frequency, distension, bowel habits satisfaction, and its general impact in life) compared to patients who received placebo (p<0.001). This was in accordance with the results reported in another Egyptian study conducted on 112 adolescents which reported a significant improvement in the clinical status of patients with IBS who received vitamin D compared to the placebo group.⁸

In an Iranian study, there was a statistically significant improvement (p < 0.05) in most IBS symptoms among patients receiving 50,000 IU vitamin D₃ every two weeks for 6 months¹. Contrary to these results, IBS symptoms were not significantly improved in an English pilot trial conducted on 51 patients with IBS after 12 weeks of daily 3000 IU vitamin D₃ supplementation.¹³

At the baseline of our study, the IBSSSS was matching in both groups, and the score difference between them was statistically insignificant (p=0.078). However, after the intervention, patients who received vitamin D were found to have significantly lower IBSSSS (114.36 ± 67.36) than participants who received a placebo (292.13 ± 74.77) (p<0.001). Similarly, in relation to IBSSSS difference, patients receiving vitamin D were found to have a statistically significant reduction (-164.72 ± 67.77) than participants who received a placebo (-12.13 ± 50.78) (p<0.001). Similarly, an Egyptian study reported that patients with IBS who received vitamin D showed significant improvement in IBSSSS (167.6 ± 46.9) compared to the placebo group (233 ± 68.2) (P < 0.001).⁸ A similar finding was found in an Iranian randomized control trial. In this study, women with IBS were randomly allocated into 4 groups that received either vitamin D, soy

isoflavones, placebo, or combined vitamin D and soy isoflavones for 6 weeks. Participants who received vitamin D had a statistically significant reduction of IBSSSS (p = 0.047), and the adjusted mean was lower compared to patients who received soy isoflavones or placebo (13.59 versus 16.64).¹⁴ The results of this study revealed that receiving 4000 IU of vitamin D₃ for 12 weeks can alleviate gastrointestinal symptoms in patients with IBS.

Limitations of the study

The non-availability of measuring vitamin D₃ in primary health care settings with minimal resources and the reluctance of patients to be referred to more advanced laboratories, limit our ability to assess serum vitamin D₃ level. Second, the study was conducted in one center in a rural area, so we can't generalize the results of our study and the findings are limited to our population.

CONCLUSION

The present study had concluded that patients with IBS in primary health care settings, may get benefit from adding a daily dose of 4000 IU of oral vitamin D₃ supplementation to their management plan to improve gastrointestinal symptoms.

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