Soy Isoflavones Supplementation for Patients with Irritable Bowel Syndrome: A Randomized Double Blind Clinical Trial

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ABSTRACT

BACKGROUND

Irritable bowel syndrome (IBS) is one of the common gastrointestinal disorders with unknown etiology. In experimental models, it is proposed that soy isoflavones may suppress the clinical and psychological symptoms of IBS by alteration of gut barrier tight junctions.

METHODS

We conducted this study to evaluate the effects of soy isoflavones on IBS symptoms and patients' quality of life. In a randomized double blind placebo-controlled clinical trial, 67 patients with IBS were allocated to consume either soy isoflavones capsules or a placebo for 6 weeks. The primary outcome was a significant reduction in symptoms severity score and the secondary outcome was a significant improvement in quality of life.

RESULTS

45 participants completed the study. There was no significant changes in mean differences of symptoms severity score between the two groups; however soy isoflavone supplementation could significantly improve the quality of life scores (p=0.009).

CONCLUSION

Soy isoflavones supplementation could improve the quality of life in patients with IBS; however it did not suppress the symptoms severity in 6 weeks. Further research with a longer duration is needed to determine the sustained clinical efficacy. This study was registered at clinicaltrials.gov as NCT02026518

KEYWORDS
Irritable Bowel Syndrome; randomized clinical trial; quality of life; Soy Isoflavone

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INTRODUCTION

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disease.[1] The etiology of this frequent disorder has not yet been well elucidated. The proposed mechanisms involved in the pathophysiology of IBS are microbial overgrowth, high intestinal permeability, microinflammation, psychological factors, dietary habits, and visceral hypersensitivity. Current treatments are insufficient and unconvincing.[2,3]

Owing to more susceptibility to develop emotional psychological

disorders, women are more susceptible to IBS and their symptoms are more severe compared with men.[4,5] In female patients with IBS, ovarian steroids protect against aggravation of IBS symptoms ahead of menstrual cycles.[6]

Soy isoflavones are defined as phytoestrogens that are structural analogs of 17- β estradiol. Their affinity for ERβ (Esterogen Receptor β) in intestinal mucosa is high.[7] There is evidence supporting the role of estradiol and estradiol like molecules in a healthy epithelial line through their receptors in colonic mucosa.[8] The safety of soy isoflavones supplementation has been shown previously.[9] Thus, we hypothesized that soy isoflavones might alter IBS symptoms and quality of life in affected patients. We designed this randomized clinical trial to determine the effects of soy isoflavones supplementation on IBS symptoms severity score (SSS) and the quality of life (QOL) in women with IBS.

MATERIALS AND METHODS

Women with IBS were recruited at Shariati Hospital in Tehran, Iran from September 2013 to June 2014. The diagnosis of IBS was determined on the basis of the Rome III criteria.[10] The inclusion criteria were: age 18-75 years, no organic intestinal diseases, no intestinal infection, no history of chronic colorectal diseases, no major surgery, no pregnancy and lactation, not being athletes or on bed rest, no history of breast cancer in herself or her family, and no severe psychosis. Patients with history of regular use of antibiotics, anti-constipation and anti-diarrhea drugs, immune suppressors, metoclopramide, cisapride, diphenoxylate, opium, and non-steroidal anti-inflammatory drugs were not included in the study either.

The exclusion criteria were: use of soy isoflavones one year before the study, use of soy nuts or milk during study, dieting during the study, no desire to complete the study, presenting adverse effects of the supplement, and pregnancy during the study.

Study Design

The study protocol was approved by the Ethics Committee of the National Nutrition and Food Technology Research Institute of Shahid Beheshti University of Medical Science (NNFTRI-92-459). All the patients signed an informed consent to be aware of all the qualifications for the study, advantages and disadvantages of this intervention. At the start point, all the patients were randomly assigned to take either soy isoflavones or the placebo (containing corn starch) twice per day for 6 weeks. The placebos were produced manually were identical to the real supplements in appearance, taste and size.

The baseline data of the patients were collected using valid questionnaires. Patients' adherence was assessed by calling them up every week and counting the remained capsules at the end of the intervention. In accordance with a random sampling approach, of the 1022 subjects registered in IBS database at gastroenterology clinics of Shariati Hospital and Masoud Clinic, Tehran, Iran, 427 were selected for this clinical trial based on the eligibility criteria (Figure 1). The subjects who agreed to participate were randomly assigned to take either soy isoflavones or placebo. The computer generated codes were adopted by a statistician to randomize all the participants and they were handed out to the interviewer.

All the participants and research team were unaware of the assignment until the endpoint of intervention. In the first session, baseline data were collected and half of the capsules were handed out to the participants. At week 3, the remaining capsules were delivered to all of them. Each capsule of soy isoflavones (21st century Co., USA) consisted 20 mg of isoflavones (10 mg of diadzein, 8.5 mg genistein, 1.5 mg glycetin). Both groups were advised to maintain a normal diet and not change their daily dietary intakes.

Clinical, psychological, and dietary intake assessments

The weight, height, and waist circumference of all participants were measured. The body mass index (BMI) was calculated by dividing weight (kg) by height (m^2).

After random assignment, all the participants were asked to answer the questions of a validated

IBS quality of life (IBS- QOL) questionnaire. It was shown that the IBS- QOL questionnaire is the most widely validated QOL instruments in patients with IBS. It has enough psychometric qualifications to assess QOL in patients with Persian language.[11] The IBS-QOL consists of 34 items that has 5-choice response scale (0 to 4) and it encompasses all aspects of Health Related Quality of Life (HRQOL) measures including dysphoria (8 items), interference with activity (7 items), body image (4 items), food avoidance (3 items), health related worry (3 items), sexual worry (2 items), social reactions (4 items), and relationships (3 items).[11]

Moreover, IBS-SSS questionnaire was used to assess the clinical outcomes. This instrument consists of 5 items that determine the severity of abdominal pain, frequency of pain, severity of flatulence, satisfaction regarding to bowel movements, and the impact of IBS on quality of life by Visual Analogue Scale (VAS). The total score of IBS-SSS is from 0 to 500 and the higher scores imply more severity of disease symptoms. The differences of scores in this instrument are positively associated with scores of QOL and anxiety and depression.[10] A 100-mm VAS was used to assess the pain, bloating, flatulence, and stool emergency and calculate the total score of the disease.[12,13]

The patients received prospective serial assessment of nutritional intake with three days of written food records. All enrolled subjects received instructions to record their daily dietary intake for three days including a weekend day at the first and the end of the study. Dietary intakes were analyzed by Nutritionist 4 (First DataBank, San Bruno, CA), incorporating use of food scales, and models to enhance portion size accuracy. National composition food tables were used as a reference.[14]

Follow up

Each participant was assessed every week by phone call. Any adverse effects was recorded. Also, capsule counts at the end of intervention was used to determine adherence to intervention and the VAS questionnaire on severity score 0 to 100 was filled in for the long term effect of supplementation even after cessation of the intervention. The last follow-up was two weeks after the end of intervention in June 2014.

Primary and secondary outcomes

The primary outcome measure was a statistically significant dedecrease in IBS-SSS. The secondary outcome measure was a statistically significant improvement in IBS-QOL scores.

Statistical Analyses

Quantitative variables are reported as mean (SD) and qualitative variables are presented through frequencies (percentages). The independent t test was used to compare the mean of quantitative outcomes between the two groups. We used analysis of covariance (ANOCVA) to compare the mean of post-operative continuous outcomes between the two groups by adjustment on preoperative results.

We compared the distribution of qualitative variables between the two groups using chi-square test or Fisher exact test. Statistical analysis was performed using STATA software (version 11, StataCorp, College Station, TX, USA). P values less than 0.05 were considered as statistically significant. We analyzed the data according to intention to treat principle.

RESULTS

Characteristics of the patients

All data on participants' enrollment and detainment are shown in figure 1. The baseline characteristics of the two groups were similar according to demographic data such as age, smoking, menopause status, and clinical data. Nonetheless, the mean of weight, and BMI were significantly different between the two groups (Table1). Moreover, the mean of dietary food items were not significantly different between the two groups before and after the intervention (Table 2).

Primary outcome

Eighty-two percent of the participants accomplished the 6 weeks intervention and the clinical outcomes were obtained from the participants at

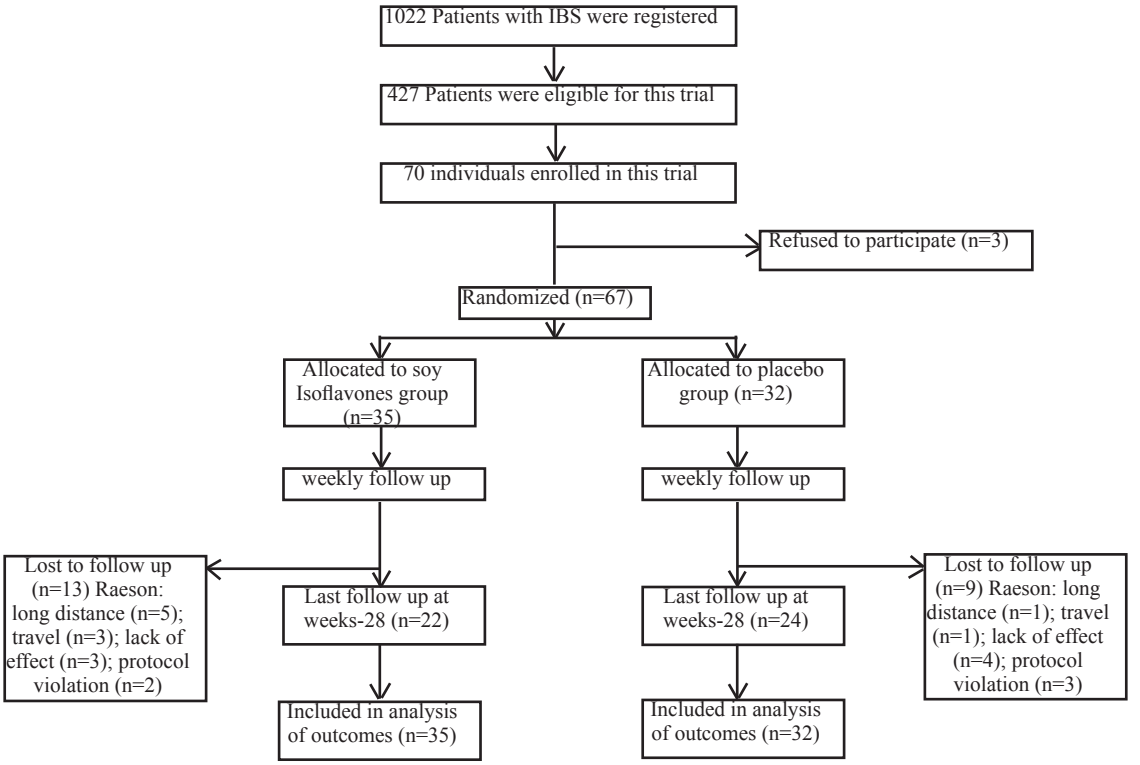

Fig.1: The flow chart of study participants

Table 1: Demographic characteristics of the study participants

Baseline Characteristic	Soy (n=22)	Placebo (n=23)	P value
Age, Mean (SD) (y)	45.54 (9.89)	40.04 (13.39)	0.126
Weight, Mean (SD) (kg)	73.95 (9.73)	66.28 (12.39)	0.026*
BMI ,Mean (SD) (kg/m2)	28.83 (4.64)	25.27 (4.07)	0.009*
Smoking, (%)	2 (9.1%)	2 (8.7%)	1.00
Menopause, (%)	10 (45.54%)	7 (30.4%)	0.299
Soy consumption (%)	0 (0.0%)	0 (0.0%)	1.00
SSS baseline, Mean (SD)	23.64 (8.17)	24.78 (11.82)	0.708
QOl baseline, Mean (SD)	64.41 (27.78)	46.70 (31.37)	0.052
Total score, Mean (SD)	21.14 (14.63)	20.00 (13.40)	0.787

Note: Significances are based on independent t test for quantitative variables and Pearson's chi-square test / Fisher exact test for qualitative factors. *: Statistically significant. BMI: Body mass index, SSS: Severity scoring system, QOL: Quality of life.

weeks 0 and 6 of the study. Moreover, the total score was measured at week 10 as follow-up measure. The loss to follow-up was the same at week 6 and week 10. The data of participants were entered in analysis of primary outcome measure as reduction of IBS-SSS, which was not significantly different between the two groups after adjustment for the confounding baseline covariates (Table 3).

Secondary outcomes

The mean IBS- QOL scores were significantly increased even after adjusting for age, BMI and baseline IBS-QOL score (p=0.009). Furthermore, the total score of IBS as a VAS measure was signifi-

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

Intake	Soy (n=22) Mean (SD)	Placebo (n=23) Mean (SD)	p value
Calorie	1528.97 (433.04)	1538.25 (504.98)	0.948
Protein	69.04 (25.29)	62.17 (32.72)	0.437
Carbohydrate	209.85 (64.40)	202.16 (70.63)	0.713
Total fat	49.21 (19.90)	57.34 (29.22)	0.284
Cholesterol	192.15 (120.80)	227.81 (266.28)	0.559
Vitamin C	103.57 (113.65)	132.57 (155.80)	0.484
Calcium	553.89 (247.79)	634.78 (281.25)	0.313
Vitamin D	1.00 (1.15)	1.27 (2.64)	0.663
Zinc	6.89 (3.88)	7.45 (4.32)	0.649
Magnesium	200.74 (133.44)	220.03 (100.30)	0.585
Phosphor	889.59 (409.13)	965.47 (495.98)	0.580
Fiber	19.08 (17.86)	23.38 (18.58)	0.433
Ferrous	10.67 (3.29)	9.90 (4.29)	0.506
Vitamin B2	5.10 (18.86)	1.22 (0.59)	0.309
Fluoride	1118.69 (961.16)	1251.68 (784.77)	0.613

Note: Significances are based on independent t test.

cantly reduced considering confounders (age, BMI, IQB (IBS- QOL baseline) at the end of the study (p<0.001). In patients who supplemented with soy isoflavones, the improvement of each item of IBS-QOL questionnaire was significantly more than the placebo group (p<0.05, Table 4).

DISCUSSION

To our knowledge, this study was the first randomized, double blind, placebo controlled, clinical trial evaluating the effects of soy isoflavones supplementation on patients with IBS. The findings of our study indicate that administration of soy isoflavones supplementation may improve the QOL in patients with IBS, although it could not affect the IBS-SSS significantly. Our results confirm the results of the only recent study evaluating the effects of soy isoflavones on IBS in an experimental model of IBS. Moussa and colleagues[15] have found that soy isoflavones mimic estradiol function and can abolish IBS- like symptoms through binding to estrogen receptors in enterocytes.

These effects could be explained by the effects of soy isoflavones on gut barrier function and intestinal microflora. It has been shown that soy isoflavones, diadzein and genistein, can improve gut barrier function through binding to the ER β in enterocytes.[16] It seems that soy isoflavones can improve epithelial tight junctions and protect against the onset of symptoms of IBS by imitating ovarian estradiol secreted during follicular period of menstrual cycle.[17]

Moreover, soy isoflavones can play a role as protective agents for gut environment due to their antioxidant properties, which have been shown previously.[18,19] A recent study has shown that soy proteins and isoflavones can reduce IL-6 as an inflammatory cytokine[20], which might be involved in pathogenesis of IBS.[21] Furthermore, the pathogen bacteria overgrowth may be reduced in response to soy isoflavones supplementation.[22]

This study has some limitations; firstly the study population was not sufficient to analyze the subtypes of IBS. Moreover, the period of the supplementation was short to judge for the long term role of soy isoflavones on clinical and psychological parameters. Additionally, the lack of stool samples hinders the explanation for these results in aspect of microflora.

This study has several strengths; using valid questionnaires for assessment of IBS-SSS, and QOL is the most important advantage of this study. The randomized, placebo controlled, double blind design is another advantage of this study.

In conclusion, our results support the concept that soy isoflavones can improve the quality of life in patients with IBS. Further research with longer duration are needed to determine the effects of soy isoflavones on IBS symptoms and addressing its mechanism of action.

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Table 3: **The mean difference of the effect of soy isoflavones versus placebo on SSS, IBS-QOL and total score between the two groups**

Characteristic	Soy (n=22)		Placebo (n=23)		Crude p-value	Adjusted p-value	R^2
	Crude	Adjusted	Crude	Adjusted			
SSS, Mean (SE)	12.77(1.74)	13.36(2.09)	19.74(2.52)	19.18(2.04)	0.029	0.068	0.371
IBS-QOL, Mean(SE)	41.68 (6.07)	33.34(4.63)	44.17(6.98)	52.15(4.52)	0.789	0.009	0.607
Total score, Mean(SE)	69.76 (5.39)	68.97(3.88)	26.30(3.30)	27.03(3.68)	<0.001	<0.001	0.734

Notes: Crude Significances are based on independent t test and adjusted significances are based on ANCOVA with factors age, BMI, IQB (IBS- QOL baseline) and before baseline value of each factor as covariates. SSS: Severity scoring system. IBS- QOL: Inflammatory bowel syndrome-Quality of life

Table 4: **The comparison of items of IBS- quality of life between means (SD) of the two groups in univariate analysis of variance***

Items of quality of life	Soy isoflavones group (n=22)	Control group (n=23)	Adjusted R^2	Sig.
Dysphoria	7.24(1.20)	11.24 (1.17)	0.56	<0.001
Interference	8.01 (1.00)	10.64 (0.98)	0.52	<0.001
Body image	3.95 (0.54)	6.09 (0.53)	0.69	<0.001
Health worry	3.56 (0.68)	5.42 (0.67)	0.15	0.030
Food avoidance	3.85 (0.58)	4.67 (0.56)	0.41	<0.001
Social reaction	3.46 (0.56)	5.3 (0.54)	0.66	<0.001
Sexual items	1.59 (0.30)	2.70 (0.30)	0.66	<0.001
Relationship	3.27 (0.50)	5.09 (0.49)	0.33	<0.001

*The covariates in the model are age, baseline BMI, and item of IBS-QOL before intervention.

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Author Contributions: Dr. Hekmatdoost had full access to all of the data in the study and takes the responsibility for the integrity of the data and the accuracy of the data analysis.

- Study concept and design: Jalili, Hekmatdoost, Vahedi, Malekzadeh.
- Data acquisition: Vahedi, Malekzadeh, Poustchi.
- Analysis and interpretation of data: Janani, Jalili.
- Drafting of the manuscript: Jalili, Hekmatdoost.
- Critical revision of the manuscript for important intellectual content: Hekmatdoost, Vahedi, Malekzadeh, Poustchi, Jalili.
- Statistical analysis: Janani, Jalili.
- Obtained funding: Hekmatdoost, Vahedi, Malekzadeh, Poustchi.
- Administrative, technical, or material support: Hekmatdoost, Vahedi, Poustchi, Malekzadeh, Jalili.
- Study supervision: Hekmatdoost, Vahedi, Malekzadeh, Poustchi.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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