Clinical Nutrition ESPEN 29 (2019) 41–48

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Randomized Controlled Trial

Effect of flaxseed or psyllium vs. placebo on management of constipation, weight, glycemia, and lipids: A randomized trial in constipated patients with type 2 diabetes

Noureddin Soltanian, Mohsen Janghorbani*

Isfahan Endocrine and Metabolism Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

ARTICLE INFO

Article history:
Received 20 October 2018
Accepted 2 November 2018

Keywords:
Flaxseed
Psyllium
Efficacy
Constipation
Diabetes
Lipid
Glucose

SUMMARY

Background: Both flaxseed and psyllium have previously been shown to reduce constipation symptoms, weight, glycemic and lipid levels, and we postulate that treatment with flaxseed and psyllium may have similar benefits.

Objective: To compare constipation symptoms, weight, glycemia, and lipids in constipated patients with type 2 diabetes (T2D) who received baked flaxseed or psyllium versus those who received a placebo.

Methods: In a single-blinded, randomized controlled trial, 77 constipated patients with T2D were randomized into three groups. Patients received either 10 g flaxseed or psyllium pre-mixed in cookies or placebo cookies twice per day for a total of 12 weeks. The constipation symptoms, body mass index (BMI), fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c), and lipid profile were determined at the beginning and end of 4, 8, and 12-week period. Constipation was assessed with the ROME III criteria score.

Results: The flaxseed appear to be superior to psyllium for improving constipation symptoms, weight, glycemic, and lipid control. The change from baseline of constipation symptoms ($P = 0.002$), stool consistency ($P < 0.001$), weight ($P < 0.001$), BMI ($P < 0.001$), FPG ($P = 0.004$), cholesterol ($P = 0.010$), LDLC ($P = 0.031$), and cholesterol/HDLC ratio ($P = 0.019$), was significantly improved in both flaxseed and psyllium groups than in the placebo group. The compliance was good and no adverse effects were observed.

Conclusion: Although both flaxseed and psyllium may decrease constipation symptoms, weight, glycemic and lipid levels, treatment with flaxseed appear to be superior to psyllium.

Trial registration: Registered under Iranian Clinical Trials Identifier no. IRCT20110416006202N2.

1. Introduction

Compelling evidence supports the role of diet in the management of type 2 diabetes (T2D) and constipation. Both flaxseed (a rich source of polyunsaturated fatty acid, mainly alpha linolenic acid, an (n-3) fatty acid, as well as soluble fiber, lignan precursors, and other substances [1,2]) and psyllium (a mixture of polysaccharides contained pentoses, hexoses, anduronic acids, a soluble, viscous, gel forming non-fermented fiber supplement [3]) have previously been shown to reduce constipation symptoms, weight, glycemic and lipid levels [4–17]. No clinical trial has compared the effect of flaxseed with psyllium on reducing constipation symptoms, weight, glycemic and lipid levels in constipated patients with T2D. Therefore, we postulate that treatment with flaxseed and psyllium may have similar benefits. It is reasonable to require evidence of clinically meaningful health benefit before selecting or recommending a flaxseed or psyllium supplement to patients being treated for T2D and chronic constipation.

The aim of this single-blinded, randomized, placebo-controlled trial, therefore, was to compare the beneficial effects of flaxseed or psyllium versus a placebo among constipated patients with T2D. We designed this trial to test the hypothesis that the 10 g flaxseed is similar to 10 g psyllium to reduce constipation symptoms, body

* Corresponding author. Fax: +98 31 36682509.
E-mail address: janghorbani@hlth.mui.ac.ir (M. Janghorbani).

https://doi.org/10.1016/j.clnesp.2018.11.002
2405-4577/

weight and improve the glycemic and lipid levels in constipated patients with T2D.

2. Patients and methods

The study was approved by the Isfahan University of Medical Sciences ethics committee (approval no. IR.MUI.REC.1396.3.464), and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients. The study protocol was registered at irct.ir as IRCT20110416006202N2.

2.1. Patients and trial design

This is a single-blinded, parallel-design, randomized, placebo-controlled trial of 77 consecutive patients with T2D and symptoms of chronic constipation (Rome III) [18] attending outpatient clinics in Isfahan Endocrine and Metabolism Research Center affiliated to Isfahan University of Medical Sciences, Iran from Jan. to Oct. 2017. A one-week baseline placebo phase, where patients were not allowed any laxative treatment, preceded a 12-week treatment phase, and followed by 4-week no treatment phase. Eligible patients were ≥30 years, had a bowel movement frequency of <3/week during the past three months [18], and diabetes duration >3 year. Patients were excluded from the study if they had type 1 diabetes, weight loss, use of lipid-lowering drugs, fiber supplementation, anorectal problems, abdominal pain, and history of opioid use in the last 48 h, any other factors which would interfere with constipation assessment and management, or pre-existing chronic diseases (such as severe heart, pituitary, thyroid, hematological, liver, renal, neurological or mental diseases). Pregnant or nursing women were excluded. Women of childbearing potential were required to use effective birth control during the study. Noncompliant patients during baseline or treatment phases as evaluated by taking <75% of either of the cookie during a one-week period throughout the course of the study and unable in giving informed consent were excluded from the evaluable patient data analysis. Participants were counseled at the initial visit to maintain their usual lifestyle, diet, physical activity, and diabetic treatment throughout the study. Participants were instructed to take 2 cookies (flaxseed, psyllium, or placebo) with a glass of water or tea twice a day at 10 am and 4 pm as a snack. The formulation of the flaxseed and psyllium cookies was such that each cookie contained about 2.5 g of flaxseed or psyllium. Thus, the 4 cookies per day consumed by each participant containing about 10 g of flaxseed or psyllium. The stool diary was used to provide a stool accounting system and to obtain a subjective measure of efficacy. The participants were contacted at the end of week 1 to evaluate compliance to intervention. The clinician examined patients at baseline and each month after the start of therapy to evaluate the possible appearance of side effects of the interventions, and efficacy parameters.

The ROME III [18] definition was used for the chronic constipation by the presence of two or more of the following six complains with at least 25% of bowel movements: straining, feeling of incomplete evacuation, hard or lumpy stool, feeling of anorectal obstruction/blockage, use of manual maneuvers, and less than 3 bowel movements/week.

2.2. Randomization scheme

A total of 90 consecutive patients was recruited. Six patients refused to participate, and 3 patients did not meet our study criteria. The 81 participants (15 (18.5%) men, 66 (81.5%) women) were assigned randomly and equally to one of three treatment groups. Of those randomized, one patient in the flaxseed group and 4 patients in the psyllium group were not evaluated (Fig. 1). Patients were randomized according to a preexisting list produced by a computer program that differed from a random number generator only in that it assigned equal numbers of patients to each treatment group, and the group assignments were concealed in an opaque sealed envelope.

2.3. Intervention

Participants in the control group received sugar-free orange-flavored maltodextrin cookies as placebo. The flaxseed group receives 10 g flaxseed pre-mixed in a sugar-free orange-flavored maltodextrin cookies. The psyllium group receives 10 g psyllium pre-mixed in a sugar-free orange-flavored maltodextrin cookies. Participants were instructed to consume two cookies two times per

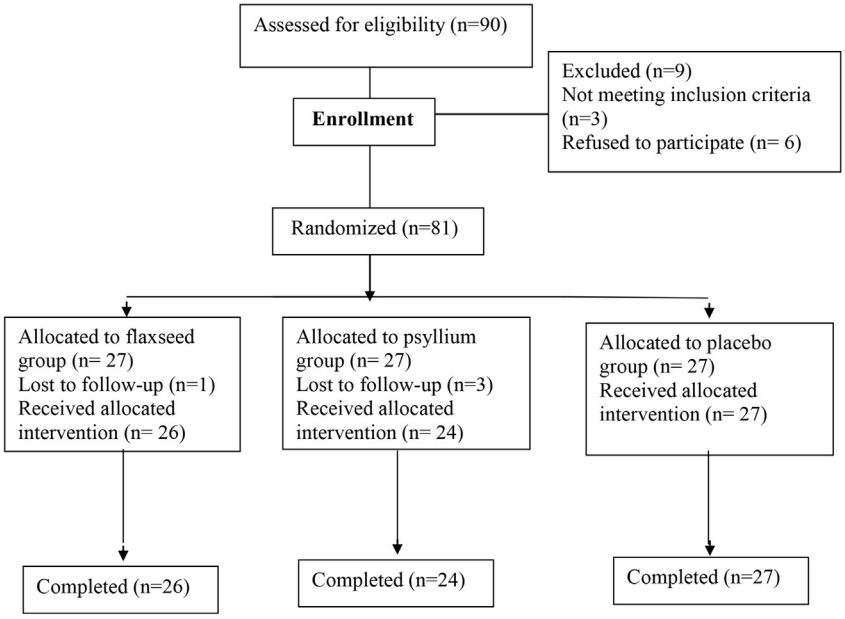

Fig. 1. Design of the study.

day as a snack for a period of 12 weeks. A regimen of 4 cookies/day was packed in individually labeled packs and provided to the individuals on a weekly basis. Cookie packs were labeled as cookie A, B, and C. The study cookies described above was prepared by the Kamvar Co., Isfahan, Iran not involved in patient care.

In order to assess the durability of flaxseed and psyllium, constipation symptoms, glycemic, and lipid profile were assessed for another four weeks after stopping intervention, and the data from baseline, after 12 weeks of intervention, and the post-intervention periods were compared.

2.4. Evaluation

The trial was single-blinded in that patients were blind to the treatment. Masking of the two treatments was preserved by creating cookies that looked, tasted, and textured identical. The differences in taste were minimal because the prominent flavor was that of the orange-flavor in which cookies was mixed. The data were extracted and analyzed by one investigator (MJ) who was not involved with the study conduct. Only one author (NS) was not blinded to subject allocation and did not participate in data analysis.

2.5. Measurements

All participants were 12-h overnight fast and data on age, gender, body size, fasting plasma glucose (FPG) (measured using the glucose oxidase method), glycosylated hemoglobin (HbA1c) (measured by ion-exchange chromatography), total cholesterol, high-density lipoprotein cholesterol (HDLC), triglyceride (measured using standardized procedures), and low-density lipoprotein cholesterol (LDLC) (using the Friedewald equation [19]), was collected at baseline and at follow-ups. Height (assessed at baseline only) and weight (assessed at baseline and after the 12-week intervention) were measured in light indoor clothing without shoes to the nearest 0.5 cm and 0.1 kg, respectively. Body mass index (BMI) (kg/m^2) was calculated as weight (kg) divided by the squared of height (m^2). The physician defined T2D (as defined by the American Diabetes Association [20]) and all participants were under anti-diabetes medication for more than 3 years.

Participants in all three groups maintained a constipation symptom diary for 12 weeks of intervention and for 1 week run-in phase and a 4-week without treatment. Constipation was assessed with a 5-point Likert Scale (not at all to all of the time) included bowel movement frequency, feelings of complete evacuation, use of digital maneuvers, stool consistency (Bristol Stool Form Scale), straining during bowel movement, pain during bowel movement, and overall feeling of constipation by a previously validated stool and symptom diary [21]. In addition, at the end of 4, 8, 12 and 16 week, patients were asked to fill out a global constipation symptom score. This validated Rome III outcome measure rated current constipation-related symptoms on a seven-point Likert scale (-3 = markedly worse, -2 = somewhat worse, -1 = a little bit worse, 0 = no change, $+1$ = a little better, $+2$ = somewhat better, $+3$ = markedly better) when compared to baseline symptoms. Participants were asked about any gastrointestinal disturbances or physiological changes. At the end of 12-week treatment period, patients was also asked to rate the looks, taste, and texture of the flaxseed and psyllium cookies that they had consumed on a visual analog scale (0 = worst, 10 = best).

2.6. Statistical analysis

Primary outcome measures included analysis of numerical values of constipation intensity according to global constipation symptom score at the beginning, 4, 8, 12 and 16 weeks after entry in flaxseed, psyllium, and placebo groups. Secondary outcome measures included analysis of the body weight, glycemic, and lipid control in the beginning, 4, 8, 12 and 16 weeks after entry in three groups. The sample size was calculated when the study was designed and was based on the comparison of two means. Assuming an SD for the treatment differences in global constipation symptom score of 2.5, as observed in other studies [22], we calculated that 27 patients per treatment group would be required to provide the study with 80 percent power to detect (with a two-sided alpha of 0.05) a mean difference in global constipation symptom scores of at least 1.5 between patients who received flaxseed vs. those who received the psyllium. Statistical analysis was based on an intention-to-treat evaluation. The results for the groups that received flaxseed, psyllium, or placebo was compared with one-way analysis of variance (ANOVA) and Bonferroni correction for multiple comparisons for continuous variables and the chi-square or Fisher's exact test to compare proportions. Comparisons between basal and post-treatment periods were done by analysis of variance with repeated measures over time. The sphericity assumption, which is required for the validity of repeated measure ANOVA was tested using Mauchly's criteria, and when the sphericity assumption was not met, the Huynh-Feldt-Lecoutre Epsilon correction was used for P-values. Paired-Student's *t*-test was conducted to analyze the difference between the baseline and week 12 for each of the three treatment groups, flaxseed, psyllium, or placebo. The results are expressed as the mean (SD), and $P < 0.05$ was considered statistically significant. All statistical tests were two-sided, and all analyses were performed using SPSS software for Windows (Ver. 19, SPSS Inc., Chicago, IL).

3. Results

3.1. Characteristics

All 77 (flaxseed = 26; psyllium = 24, and placebo = 27) patients who completed treatment were available for follow-up at 4, 8, 12, and 16 weeks. Except for the higher LDLC and some constipation symptoms in the flaxseed group than in the psyllium and placebo groups and lower cholesterol in the psyllium group than in the flaxseed and the placebo groups at baseline, the three treatment groups were generally matched with regard to age, gender, diabetes duration, constipation symptom scores, and Bristol Stool Form scale, weight, height, BMI, FPG, HbA1c, triglyceride, and HDLC (Table 1). Patients had mean (SD) duration of diabetes 8.8 (4.6) (flaxseed 8.7 (3.9), psyllium 9.5 (4.7), Placebo 8.3 (5.3)) years and mean age of 56.5 (9.3) (31.0–74.0) years at initial registration. Women accounted for 64 (83.1%), while men accounted for 13 (16.9%) of the 77 patients. Flaxseed and psyllium cookies were well tolerated, with no serious adverse events.

3.2. Constipation

Although within-group analysis showed a decrease in the mean of global constipation symptom score in all three groups ($P < 0.001$ for flaxseed, $P = 0.030$ for psyllium, and $P = 0.003$ for the placebo), change from baseline were different between the groups ($P = 0.002$). This change from baseline were only different between the flaxseed and placebo groups (2.46 vs. -0.41; $P = 0.001$ after Bonferroni adjustment) (Table 2).

On the global constipation symptom survey, 2 (7.4%) patients who received placebo and 11 (42.3%) patients who received flaxseed and 5 (20.8%) patients who received psyllium cookies reported improvement of symptoms and rated their improvement as at least somewhat better' ($+2$) when compared to baseline symptoms. The

Table 1
Characteristics of constipated patients with type 2 diabetes by treatment group at baseline.

Characteristics	Treatment group Mean (SD)		
	Flaxseed	Psyllium	Placebo
Number of patients	26	24	27
Age (years)	55.7 (11.6)	58.0 (7.2)	55.9 (8.7)
Years since diabetes diagnosis	8.7 (3.9)	9.5 (4.7)	8.3 (5.3)
Weight (kg)	75.4 (10.6)	78.9 (13.8)	73.1 (12.0)
Height (cm)	161.2 (7.9)	164.5 (8.3)	160.3 (7.2)
BMI (kg/m^2)	29.1 (3.8)	29.3 (5.2)	28.7 (5.9)
FPG (mg/dl)	164.8 (45.2)	167.0 (38.2)	165.6 (43.5)
Triglyceride (mg/dl)	161.1 (39.1)	154.1 (26.9)	172.2 (81.2)
Cholesterol (mg/dl)	178.1 (31.2)	151.5 (23.2)	177.3 (33.7)
LDLC (mg/dl)	115.1 (22.4)	84.1 (25.1)	94.5 (23.1)
HDLC (mg/dl)	43.1 (8.8)	44.1 (7.1)	43.5 (7.2)
Cholesterol/HDLC ratio	4.3 (1.2)	3.5 (0.9)	4.2 (1.0)
HbA1c (%)	8.4 (2.0)	8.5 (2.1)	8.0 (2.2)
Global constipation symptom scores	−1.38 (0.8)	−1.45 (0.9)	−1.00 (1.4)
Bristol Stool Form Scale	1.35 (0.5)	1.54 (0.7)	1.26 (0.5)
	No (%)		
Constipation symptoms			
Straining	17 (65.4)	13 (54.2)	9 (33.3)
Hard stool	22 (84.6)	18 (75.0)	14 (51.9)
Pain with bowel movement	13 (50.0)	8 (33.3)	2 (7.4)
Feeling of incomplete evacuation	15 (57.7)	7 (29.2)	7 (25.9)
Digital maneuver	4 (15.4)	1 (4.2)	1 (3.7)
Fleeing of blockage	10 (38.5)	7 (29.2)	6 (22.2)
<3 bowel movements/week	18 (69.2)	11 (45.8)	10 (37.0)
Therapeutic regimen			
Insulin	11 (42.3)	10 (41.7)	11 (40.7)
Metformin	21 (80.8)	16 (66.7)	20 (74.1)
Glibenclamide	3 (11.5)	6 (25.0)	8 (29.6)
Losartan	12 (46.2)	14 (58.3)	8 (29.6)
Metoral	2 (7.7)	5 (20.8)	1 (3.9)
Aspirin	11 (42.3)	8 (33.3)	8 (29.6)
Statin	12 (46.2)	14 (58.3)	15 (55.6)
BMI (kg/m^2)			
Normal (BMI <25)	4 (15.4)	4 (16.7)	8 (29.6)
Overweight (BMI 25–29.9)	12 (46.2)	13 (54.2)	12 (44.4)
Obese (BMI ≥ 30)	10 (38.5)	7 (29.2)	7 (25.9)
Gender			
Male	4 (15.4)	4 (16.7)	5 (18.5)
Female	22 (84.6)	20 (83.3)	22 (81.5)
Education			
Less than high school	15 (57.7)	11 (45.8)	11 (40.7)
High school	7 (26.9)	9 (37.5)	14 (51.9)
College graduate	4 (15.4)	4 (16.7)	2 (7.4)

Comparison across all three groups. BMI, body mass index; FPG, fasting plasma glucose; LDLC, low-density lipoprotein cholesterol; HDLC, high-density lipoprotein cholesterol.

mean (SD) global constipation symptom scores after 12 week treatment were 1.08 (1.4), −0.04 (1.9), and −0.59 (1.4) for flaxseed, psyllium, and placebo respectively (P = 0.001).

When comparing placebo vs. flaxseed and psyllium the stool consistency were different at 4 (P = 0.007), 8, and 12 weeks (P < 0.001). Comparing week 12 vs. baseline for placebo, psyllium, and flaxseed, stool consistency in flaxseed groups improved (1.96; P < 0.001), but not in psyllium and placebo groups (0.29; P = 0.125 and 0.59; P = 0.307, respectively). Stool consistency change from baseline were only different between the flaxseed and psyllium or placebo groups (P < 0.001 after Bonferroni adjustment). There were no differences between psyllium and placebo groups (0.29 vs. 0.59; P = 1.00 after Bonferroni adjustment).

3.3. Body weight

Participants who were in both flaxseed and psyllium groups were more likely to achieve higher weight loss; that is, a decrease in body weight and BMI observed in both treatment groups (P < 0.001) whereas no change was observed in the placebo group (P = 0.947 and P = 0.930). Mean weight loss and BMI changes from baseline was different between the both treatment groups versus the placebo group (P < 0.001 after Bonferroni adjustment). Participants who were in the flaxseed group were more likely to achieve higher weight loss (−3.8 kg vs. −2.0 kg; P = 0.039 after Bonferroni adjustment) and decrease BMI (−1.5 kg/m^2 vs. −0.8 kg/m^2; P = 0.019 after Bonferroni adjustment) than participants who were on psyllium (Table 2).

3.4. Glycemic control

FPG and HbA1c were reduced in both flaxseed and psyllium group while no changes observed in the placebo group. The HbA1c reduced about 0.7% in flaxseed and 0.8% in psyllium, in which these reductions were not significant (P = 0.137 and P = 0.520). Mean FPG changes from baseline were different between flaxseed and the placebo group (−27.8 vs. −1.9 mg/dl; P = 0.014 after Bonferroni adjustment) and psyllium and placebo groups (−19.7 vs. −1.9 mg/dl; P = 0.028 after Bonferroni adjustment) whereas no difference was observed between psyllium and flaxseed groups (−27.8 vs. −19.7; P = 1.00 after Bonferroni adjustment). There was no difference in mean HbA1c changes from baseline between neither the flaxseed, psyllium or placebo groups.

3.5. Lipid control

Cholesterol levels decreased throughout the study period in both the flaxseed and psyllium groups (P < 0.001), but not in the placebo group (P = 0.311). Mean cholesterol changes from baseline were different between flaxseed and the placebo groups (−36.9 vs. −10.4 mg/dl; P = 0.008 after Bonferroni adjustment) but not between psyllium and placebo groups (−21.5 vs. −10.4 mg/dl; P = 0.636 after Bonferroni adjustment). No significant difference in mean cholesterol changes from baseline observed between flaxseed and psyllium groups (−36.9 vs. −21.5 mg/dl; P = 0.226 after Bonferroni adjustment).

Although within-group analysis showed a decrease in the mean of triglyceride in all three groups (P = 0.045 for flaxseed, P = 0.021 for psyllium, and P = 0.045 for the placebo groups), change from baseline were not different between the groups (P = 0.852).

While LDLC was decreased in the flaxseed group (changes from baseline, −21.0 mg/dl; P < 0.001), no changes observed in the psyllium (−3.7 mg/dl; P = 0.488) or a placebo group (−3.9 mg/dl; P = 0.482). Changes from baseline in LDLC differed only between the flaxseed and placebo groups (−21.0 vs. −3.9 mg/dl; P = 0.029 after Bonferroni adjustment).

While HDLC was increased in both flaxseed and psyllium groups (non-significant), no changes observed in the placebo group. Changes from baseline in HDLC nearly differed between the groups (P = 0.069). This difference was only between flaxseed and placebo groups (6.0 vs. −1.6 mg/dl; P = 0.084 after Bonferroni adjustment).

Although within-group analysis showed a decrease in the mean of cholesterol/HDLC ratio in flaxseed (P = 0.021) and psyllium (P = 0.050), but not in the placebo group (P = 0.332), change from baseline had only been different between the flaxseed and placebo groups (−1.3 vs. −0.0 mg/dl; P = 0.016 after Bonferroni adjustment).

After 4-week no treatment phase, the beneficial effects of flaxseed and psyllium for glycemic and lipid levels, but not for constipation symptoms, appear to persist (Table 2).

Patients rated flaxseed and psyllium cookies as palatable, looks, and texture with mean taste, looks and texture scores of 7.4, 7.7, and

Table 2
Comparison of body weight, fasting plasma glucose (FPG), HbA1c, cholesterol, triglyceride, low-density lipoprotein cholesterol (LDLC), high-density lipoprotein cholesterol (HDLC), and Total cholesterol/HDLC (mg/dl) in 77 constipated patients with type 2 diabetes before and after treatment with flaxseed, psyllium, and placebo.

Variable	Treatment group Mean (SD)			P value[b]
	Flaxseed	Psyllium	Placebo	
Global constipation symptom scores				
Baseline	−1.38 (0.8)	−1.46 (0.9)	−1.00 (1.4)	0.252
After 4 week therapy	−1.77 (1.5)	−1.38 (1.3)	−1.74 (0.8)	0.443
After 8 week therapy	−0.50 (1.7)	−0.54 (1.7)	−1.76 (0.8)	0.004
After 12 week therapy	1.08 (1.4)	−0.04 (1.9)	−0.59 (1.4)	0.001
P value[a]	<0.001	0.030	0.003	–
Change from baseline	2.46 (1.7)	1.42 (2.3)	−0.41 (1.8)	0.002
After 4 week without therapy	−0.42 (1.6)	−0.58 (1.5)	−0.80 (1.5)	0.651
Bristol Stool Form Scale				
Baseline	1.35 (0.5)	1.54 (0.7)	1.26 (0.5)	0.219
After 4 week therapy	2.38 (0.6)	1.71 (0.8)	1.59 (1.2)	0.007
After 8 week therapy	2.96 (0.6)	2.04 (0.8)	1.33 (0.6)	<0.001
After 12 week therapy	3.31 (0.7)	1.83 (1.0)	1.85 (1.6)	<0.001
P value[a]	<0.001	0.125	0.307	–
Change from baseline	1.96 (0.8)	0.29 (1.1)	0.59 (1.6)	<0.001
After 4 week without therapy	1.92 (0.8)	1.63 (0.7)	1.44 (0.8)	0.082
Weight (kg)				
Baseline	75.4 (10.6)	78.9 (13.8)	73.1 (12.0)	0.237
After 12 week therapy	71.6 (8.8)	76.9 (12.9)	73.1 (11.3)	0.228
P value[a]	<0.001	<0.001	0.947	–
Change from baseline	−3.8 (3.4)	−2.0 (2.1)	0.0 (1.4)	<0.001
Body mass index (kg/m^2)				
Baseline	29.1 (3.8)	29.3 (5.2)	28.7 (5.9)	0.908
After 12 week therapy	27.6 (3.1)	28.5 (4.9)	28.6 (5.6)	0.680
P value[a]	<0.001	<0.001	0.930	–
Change from baseline	−1.5 (1.2)	−0.8 (0.7)	−0.01 (0.6)	<0.001
FPG (mg/dl)				
Baseline	164.8 (45.2)	167.0 (38.2)	165.6 (43.5)	0.982
After 4 week therapy	163.8 (45.1)	156.7 (41.6)	166.0 (42.5)	0.737
After 8 week therapy	143.4 (34.2)	151.7 (40.7)	168.0 (38.5)	0.061
After 12 week therapy	137.0 (26.4)	147.3 (43.0)	163.7 (39.5)	0.049
P value[a]	0.018	0.056	0.483	–
Change from baseline	−27.8 (31.0)	−19.7 (29.4)	−1.9 (27.9)	0.004
After 4 week without therapy	140.0 (26.5)	152.4 (38.0)	170.1 (50.3)	0.031
HbA1c (%)				
Baseline	8.4 (2.0)	8.5 (2.1)	8.0 (2.2)	0.683
After 4 week therapy	8.2 (1.8)	7.7 (1.8)	8.9 (2.4)	0.122
After 8 week therapy	7.7 (2.1)	7.5 (3.2)	8.6 (2.2)	0.343
After 12 week therapy	7.7 (2.0)	7.7 (2.1)	9.0 (2.2)	0.160
P value[a]	0.137	0.520	0.978	–
Change from baseline	−0.7 (1.6)	−0.8 (2.1)	1.0 (2.3)	0.277
After 4 week without therapy	7.0 (1.5)	7.3 (2.2)	8.5 (1.2)	0.006
Cholesterol (mg/dl)				
Baseline	178.1 (31.2)	151.5 (23.2)	177.3 (33.7)	0.003
After 4 week therapy	160.8 (31.1)	142.2 (25.3)	171.2 (30.1)	0.003
After 8 week therapy	148.1 (31.9)	134.6 (23.2)	171.4 (37.8)	<0.001
After 12 week therapy	141.2 (29.1)	130.0 (18.4)	166.9 (39.8)	<0.001
P value[a]	<0.001	<0.001	0.311	–
Change from baseline	−36.9 (22.1)	−21.5 (16.7)	−10.4 (42.0)	0.010
After 4 week without therapy	147.6 (29.7)	135.4 (23.2)	170.0 (34.3)	<0.001
Triglyceride (mg/dl)				
Baseline	161.1 (39.1)	154.1 (26.9)	172.2 (81.2)	0.501
After 4 week therapy	154.0 (45.3)	142.3 (29.6)	168.0 (58.0)	0.167
After 8 week therapy	154.0 (48.8)	132.0 (40.1)	165.0 (56.6)	0.064
After 12 week therapy	148.8 (45.7)	138.9 (35.0)	164.3 (56.3)	0.190
P value[a]	0.045	0.021	0.045	–
Change from baseline	−12.3 (17.0)	−15.2 (29.1)	−7.9 (38.0)	0.852
After 4 week without therapy	149.8 (40.1)	140.0 (27.0)	167.6 (58.3)	0.120
LDLC (mg/dl)				
Baseline	115.1 (22.4)	84.1 (25.1)	94.5 (23.1)	<0.001
After 4 week therapy	106.8 (22.5)	82.7 (15.2)	92.7 (26.6)	0.001
After 8 week therapy	99.7 (21.1)	79.7 (16.0)	96.1 (27.6)	0.007
After 12 week therapy	94.1 (19.9)	80.4 (13.6)	90.6 (17.9)	0.062
P value[a]	<0.001	0.488	0.482	–
Change from baseline	−21.0 (11.0)	−3.7 (26.4)	−3.9 (20.2)	0.031
After 4 week without therapy	105.0 (24.6)	85.8 (11.5)	100.3 (31.4)	0.049
HDLC (mg/dl)				
Baseline	43.1 (8.8)	44.1 (7.1)	43.5 (7.2)	0.901
After 4 week therapy	44.2 (9.3)	46.0 (7.1)	41.1 (7.9)	0.221
After 8 week therapy	45.6 (9.2)	50.5 (14.6)	42.0 (6.1)	0.152

(*continued on next page*)

Table 2 (*continued*)

Variable	Treatment group Mean (SD)			P value[b]
	Flaxseed	Psyllium	Placebo	
After 12 week therapy	49.1 (7.9)	46.2 (8.3)	41.9 (10.0)	0.041
P value[a]	0.316	0.429	0.607	–
Change from baseline	6.0 (6.6)	2.1 (5.4)	−1.6 (7.1)	0.069
After 4 week without therapy	42.5 (8.1)	45.8 (7.7)	40.7 (6.5)	0.486
Cholesterol/HDLC ratio (mg/dl)				
Baseline	4.3 (1.2)	3.5 (0.9)	4.2 (1.0)	0.025
After 4 week therapy	3.9 (1.3)	3.2 (0.8)	4.4 (1.3)	0.003
After 8 week therapy	3.4 (1.2)	2.9 (0.9)	4.2 (1.2)	0.001
After 12 week therapy	3.0 (0.8)	2.9 (0.6)	4.2 (1.2)	0.003
P value[a]	0.021	0.050	0.332	–
Change from baseline	−1.3 (1.0)	−0.6 (0.6)	0.0 (1.6)	0.019
After 4 week without therapy	3.6 (0.9)	3.2 (0.9)	4.5 (1.4)	0.004

[a] Within group comparison.
[b] Comparison across all three groups. Means were calculated using one-way analysis of variance (ANOVA) with Bonferroni correction for multiple comparisons.

7.4 for flaxseed, respectively and 5.5, 6.6, and 5.2 for psyllium, respectively.

4. Discussion

The aim of the present study was to compare the beneficial effects of flaxseed or psyllium versus a placebo in constipated patients with T2D. This study shows that although consumption of both 10 g of flaxseed or psyllium baked in cookies daily for 12 weeks may decrease constipation symptoms, weight, glycemic and lipid levels, treatment with flaxseed is superior to psyllium. In the present study, although both flaxseed and psyllium groups increased the subjective measures of constipation, the flaxseed treatment group was superior to the psyllium group. The increased subjective measures of constipation by the flaxseed and psyllium observed in this study is consistent with previous studies in healthy and constipated individuals [7,23–25] and suggesting that flaxseed is a more comprehensive treatment for the constipation symptoms. No study compared the beneficial effects of flaxseed with psyllium. There were significant differences in subjective measures of constipation between treatment groups after 8-week of treatment. Stool consistency, straining with bowel movement, pain with bowel movement and evacuation completeness showed directional improvement of constipation symptoms for both flaxseed and psyllium groups.

This study revealed significant, clinically meaningful reduction of 1.5 and 0.7 kg/m^2 BMI and 3.8 and 2.0 kg body weight when the flaxseed and psyllium groups at baseline was compared with the flaxseed and psyllium groups after 12 weeks therapy. This study shows that the flaxseed treatment group is superior at weight loss to the psyllium treatment group. In addition, the superior weight loss effect of flaxseed increased over the12-week treatment period, suggest that the effect may increase with continued consumption. These results are consistent with those of other studies in which the body weight and other anthropometric measurements were significantly improved in flaxseed and psyllium groups [5,9–11,26]. This change in body weight might be achieved by stimulation of satiety hormone production that's enhancing satiety [27]. Even slight reductions in weight can produce metabolic improvements. The improved glycemic and lipid control in both flaxseed and psyllium groups could be attributed to changes in body weight, since statistically significant weight loss was seen 12 weeks after therapy. 2–5% weight loss was linked to improvements in FPG, HbA1c, total cholesterol, triglyceride, HDLC but not LDLC [28]. However, it appears that increase intake of soluble fiber in both flaxseed and psyllium groups has certainly contributed to the observed results. The effect of flaxseed and psyllium consumption on glycemic and lipid control has been reported in some studies [6–8,12–17,29].

Effect of flaxseed on glycemic control which showed an improvement in both FPG and HbA1c, is clinically meaningful which is comparable to the effect of many medications that are used to treat T2D, such as long term metformin therapy in the Diabetes Prevention program [30].

Furthermore, we conducted a 4-week follow-up assessment and found that the beneficial effects of flaxseed and psyllium for glycemic and lipid levels, but not for constipation symptoms, appear to persist even after four weeks, suggest a durable effect on glycemic and lipid levels, at least in the short term. The constipation symptoms returned to the pre-study baseline levels, suggesting that the improvements observed during the study were due to the treatments and not a placebo effect or observational bias. It looks like that this benefit of flaxseed and psyllium did not persist in the long term.

Thus, consistent with these results, this study provides evidence for the first time, to our knowledge, that both flaxseed and psyllium may have a favorable impact on constipation symptoms, body weight, glycemic and lipid control in constipated patients with T2D while treatment with flaxseed is superior to psyllium.

One limitation of flaxseed and psyllium supplementation that may cause people to discontinue treatment include taste, texture of the drink and dissolvability in a solution. We used cookies and the participants scored the taste and texture of cookies as acceptable.

The mechanism of action of flaxseed and psyllium in reducing body weight, glucose and lipid levels and constipation symptoms in constipated patients with T2D remains unclear. Limited evidence suggests that the abundance of polyunsaturated fatty acid in the diet might serve as an important modulator for body fat deposition. In a small clinical trial, Summers et al. [26] reported that changing from a diet rich in saturated fatty acid to one abundant in polyunsaturated fatty acid resulted in changes abdominal fat distribution and improves insulin sensitivity. A cross-sectional study also reported that a high dietary polyunsaturated fatty acid: saturated fatty acid ratio was inversely associated with waist circumference and waist: hip ratio [29]. The most plausible mechanism of action of flaxseed in reducing lipid profiles is through an interference with bile acid metabolism, where an increased intraluminal viscosity can hinder micelle formation and thus diminishes lipid uptake and inhibit re-uptake of bile acids causing the increased hepatic synthesis of bile acids which diverts cholesterol away from lipoprotein synthesis in the liver, thereby reducing serum cholesterol [7,31]. It is believed that gel-forming fibers improved glucose homostasis and lipid and lipoprotein profiles [32], by increase the viscosity of chyme in the upper intestine which may reduce the contact with digestive enzymes and delays absorption. The fiber fermentation in

the intestine produces short-chain fatty acids that have been shown to be effective in enhancing peripheral insulin sensitivity [33]. The fermentation of fiber may influence gut microbiota and the alterations of microbiota may be responsible for improved levels of systemic inflammatory cytokines [34].

The limitations of this trial are single-blind design, the short follow-up and small sample size. Albeit the value of the double blind, controlled trial is widely recognized, this design is not always appropriate or indicated. The treating physicians dealing with clinical and laboratory adverse events can easily become unblinded. The duration of this trial, although fairly typical for dietary interventions, may be relatively short for evaluating the impact of flaxseed and psyllium. Whether the beneficial effects of this short-term flaxseed and psyllium supplementation will persist in the longer term is not clear. It is possible that a 4-week post treatment follow-up may be short to appreciate the real impact of the therapy. Assessing the efficacy in the long-term period is therefore warranted. While the number of patients studied was small, the effect was robust. Although we recruited constipated patients with T2D from the tertiary care center who fulfilled the Rome III criteria, generalizability to other populations is unknown.

Based on the partial therapeutic benefit obtained with flaxseed and psyllium cookies, their ease of administration, and lack of major side-effects, these results suggest that flaxseed and psyllium in the form of cookies are useful in the treatment of constipation symptoms and the control of weight, glycemia, and lipids in people with T2D.

In conclusion, in constipated patients with T2D, flaxseed consumption is superior to psyllium consumption for the relief constipation and management of weight, glycemic and lipid levels. Our findings highlight the need for a larger sample size and longer follow-up period, probably blinded, to confirm these findings.

Conflict of interest

The authors declare that there is no conflict of interest associated with this manuscript.

Funding

Kamvar Co., Isfahan, Iran provided flaxseed, psyllium, and placebo cookies and the study was supported by the Isfahan Endocrine and Metabolism Research Center under award number IR.MUI.REC.1396.3.464, Isfahan, Iran.

Availability of data and materials

We would like to inform you that all the datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

Authors' Contributions

Soltanian N recruited samples, provided treatment to the patients, and collected samples and contributed to discussion and revision of the manuscript, Janghorbani M conceived and designed, supervised, and lead the study and analyzed the data and wrote the manuscript. All authors approved the final version of the manuscript.

Acknowledgments

We express our gratitude to all of the participants who consented to participate and Kamvar Co., Isfahan, Iran for the products used in this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2018.11.002.

References

[1] Naran R, Chen G, Carpita NC. Novel rhamnogalacturonan I and arabinoxylan polysaccharides of flax seed mucilage. Plant Physiol 2008;148:132–41.
[2] Hall Iii C, Tulbek MC, Xu Y, Steve LT. Flaxseed. Advances in food and nutrition research. Fargo: Academic Press; 2006. p. 1–97.
[3] Rotblatt M. Herbal medicine: expanded commission E monographs. Ann Intern Med 2000;133:487.
[4] Pan A, Yu D, Demark-Wahnefried W, Franco OH, Lin X. Meta-analysis of the effects of flaxseed interventions on blood lipids. Am J Clin Nutr 2009;90:288–97.
[5] Wu H, Pan A, Yu Z, Qi Q, Lu L, Zhang G. Lifestyle counseling and supplementation with flaxseed or walnuts influence the management of metabolic syndrome. J Nutr 2010;140:1937–42.
[6] Pan A, Sun J, Chen Y, Ye X, Li H, Yu Z, et al. Effects of a flaxseed-derived lignan supplement in type 2 diabetic patients: a randomized, double-blind, cross-over trial. PLoS One 2007;2:e1148.
[7] Kristensen M, Jensen MG, Aarestrup J, Petersen KEN, Søndergaard L, Mikkelsen MS, et al. Flaxseed dietary fibers lower cholesterol and increase fecal fat excretion, but magnitude of effect depend on food type. Nutr Metab 2012;9:8.
[8] Thakur G, Mitra A, Pal K, Rousseau D. Effect of flaxseed gum on reduction of blood glucose and cholesterol in type 2 diabetic patients. Int J Food Sci Nutr 2009;60:126–36.
[9] Lu C, Lee W, Wang J. Clinical assessment of the effects of psyllium on weight control and the lipid profile of obese adults. Nutr Sci J 2012;37:136–46.
[10] Pal S, Khossousi A, Binns C, Dhaliwal S, Ellis V. The effect of a fibre supplement compared to a healthy diet on body composition, lipids, glucose, insulin and other metabolic syndrome risk factors in overweight and obese individuals. Br J Nutr 2011;105:90–100.
[11] Abutair AS, Naser IA, Hamed AT. Soluble fibers from psyllium improve glycemic response and body weight among diabetes type 2 patients (randomized control trial). Nutr J 2016;15:86.
[12] Ziai SA, Larijani B, Akhoondzadeh S, Fakhrzadeh H, Dastpak A, Bandarian F, et al. Psyllium decreased serum glucose and glycosylated hemoglobin significantly in diabetic outpatients. J Ethnopharmacol 2005;102:202–7.
[13] Rodriguez-Moran M, Guerrero-Romero F, Lazcano-Burciage G. Lipid- and glucose lowering efficacy of plantago psyllium in type II diabetes. J Diabet Complicat 1998;12:273–8.
[14] Cicero AFG, Derosa G, Bove M, Imola F, Borghi C, Gaddi AV. Psyllium improves dyslipidemia, hyperglycemia and hypertension, while guar gum reduces body weight more rapidly in patients affected by metabolic syndrome following an AHA Step 2 diet. Mediteranean J Nutr Metab 2010;3:47–54.
[15] Feinglos M, Gibb R, Ramsey D, Surwit R, McRorie J. Psyllium improves glycemic control in patients with type-2 diabetes mellitus. Bioact Carbohydr Diet Fibre 2013;1:156–61.
[16] Aller R, de Luis DA, Izaola O, La Calle F, del Olmo L, Fernandez L, et al. Effect of soluble fiber intake in lipid and glucose levels in healthy subjects: a randomized clinical trial. Diabetes Res Clin Pract 2004;65:7–11.
[17] Kamalpour M, Ghalandari H, Nasrollahzadeh J. Short-term supplementation of a moderate carbohydrate diet with psyllium reduces fasting plasma insulin and tumor necrosis factor-α in patients with type 2 diabetes mellitus. J Diet Suppl 2017;28:1–9.
[18] Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroentrology 2006;130:1480–91.
[19] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1971;18:499–502.
[20] Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 2003;(Suppl. 1):S5–20.
[21] Meduri KBCK, Attaluri A, Valestin J, Rao SSC. Validation of prospective stool diary for assessment of constipation. Neurogastroentrol Motil 2011;23:21.
[22] Numata T, Takayama S, Tobita M, Ishida S, Katayose D, Shinkawa M, et al. Traditional Japanese medicine daikeenchuto improves functional constipation in poststroke patients. Evid Based Complement Alternat Med 2014;2014:231258.
[23] Hanif Palla A, Gilani AH. Dual effectiveness of Flaxseed in constipation and diarrhea: possible mechanism. J Ethnopharmacol 2015;169:60–8.
[24] Ghosh A. Comparison of anthropometric, metabolic and dietary fatty acids profiles in lean and obese dyslipidaemic Asian Indian male subjects. Eur J Clin Nutr 2006;61:412–9.
[25] Ramos CI, Andrade de Lima AF, Grilli DG, Cuppari L. The short-term effects of olive oil and flaxseed oil for the treatment of constipation in hemodialysis patients. J Ren Nutr 2015;25:50–6.
[26] Summers LK, Fielding BA, Bradshaw HA, Ilic V, Beysen C, Clark ML, et al. Substituting dietary saturated fat with polyunsaturated fat changes abdominal fat distribution and improves insulin sensitivity. Diabetologia 2002;45:369–77.

[27] Ye Z, Arumugam V, Haugabrooks E, Williamson P, Hendrich S. Soluble dietary fiber (Fibersol-2) decreased hunger and increased satiety hormones in humans when ingested with a meal. Nutr Res 2015;35:393–400.
[28] Wing RR, Lang W, Wadden TA, safford M, Knowler WC, Bertoni AG, et al. Look AHEAD Research Group. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. Diabetes Care 2011;34:1481–6.
[29] Prasad K. Secoisolariciresinol diglucoside from flaxseed delays the development of type 2 diabetes in Zucker rat. J Lab Clin Med 2001;138:32–9.
[30] Knowler WC, Barrett-Connor E, Fowler S, Hamman R, Lachin J, Walker E, et al. Diabetes Prevention Program Research Group Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403.
[31] Theuwissen E, Mensink RP. Water-soluble dietary fibers and cardiovascular disease. Physiol Behav 2008;94:285–92.
[32] Rigaud D, Ryttig KR, Leeds AR, Bard D, Apfelbaum M. Effects of a moderate dietary fibre supplement on hunger rating, energy input and faecal energy output in young, healthy volunteers. A randomized, double blind, cross-over trial. Int J Obes 1987;11(Suppl 1):73–8.
[33] Robetson MD, Wright JW, Loizon E, Debard C, Vidal H, Shojaee-Moradie F, et al. Insulin-sensitizing effects on muscle and adipose tissue after dietary fibre intake in men and women with metabolic syndrome. J Clin Endocrinol 2012;97:3326–32.
[34] Martinez I, Lattimer JM, Hubach KL, Case JA, Yang J, Weber CG, et al. Gut microbiome composition is linked to whole grain-induced immunological improvements. ISME J 2013;7:269–80.