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Original Article

The effects of soybean-flour-enriched bread intake on inflammatory markers among type 2 diabetic women: a cross-over randomized controlled clinical trial

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Abstract

Introduction: Although soy-based foods have been reported to affect serum levels of inflammatory biomarkers, there was no study examining the effects of soybean flour-enriched bread in diabetic patients. The aim of this study was to determine the effects of consumption of soybean flour-enriched bread on inflammatory markers in type 2 diabetic women.

Methods: This randomized, cross-over, controlled clinical trial recruited 30 type 2 diabetic women. After a 2-week run-in period, participants were randomly assigned to either intervention (soy bread) or control groups (habitual diet). Participants in the intervention group were asked to consume 120 g of soybean flour-enriched bread instead of the same amount of usual bread intake or other cereals. Participants in the control group were asked to remain on the habitual diet. After a four-week washout period, the participants were crossed over for another six weeks.

Results: Mean (±SD) age, weight and BMI of the subjects was 45.7±3.8 years, 73.8±10.7 and 29.5±3.9 kg/m2, respectively. We found no significant effect of soybean flour-enriched bread on high sensitive C-reactive protein (change difference: -0.04, P=0.6), Tumor Necrosis Factor-alpha (change difference: -14.2, P=0.27), interleukin 6 (change difference: -0.06, P=0.15) and Soluble Vascular Cell Adhesion Molecule-1 among women in the intervention group compared with the control group. No significant effects were observed in serum levels of sVCAM1 after consumption of soybean flour-enriched bread.

Conclusion: Soybean flour-enriched bread consumption had no significant effects on inflammatory markers.

Introduction

Diabetes is one of the most common non-communicable diseases in the world (1) that has become a global challenge to the public health (2). The worldwide prevalence of diabetes among adults was 6.4% in 2010 and it is estimated to reach 7.7% in 2030 (3). Diabetic patients have higher levels of inflammatory markers such as high sensitive C-reactive protein, interleukin 6 and Tumor Necrosis Factor-alpha (4) which will develop their disease (5). Several dietary factors affect the levels of inflammatory markers. It is reported that adherence to the Mediterranean diet is associated with lower levels of inflammatory markers (6). In addition, recent observatory studies have reported an inverse relationship between fruit and vegetable intake and CRP serum levels (7). The effects of soy and soy components on many chronic diseases have recently been studied. Soybean is a unique source of fiber, unsaturated fatty acids and phytoestrogens (8, 9), which are associated with lower levels of inflammatory markers (10-12). Cross-sectional studies have reported that CRP and IL-6 levels are significantly associated with serum concentrations of glucose or glycosylated hemoglobin in diabetic patients (13, 14). Studies suggest the role of soy in improving inflammation. In a study on postmenopausal women, short-term consumption of soy lowered inflammatory markers levels (15). In contrast, consumption of soy milk did not have a significant effect on inflammation in patients with diabetic nephropathy (16). Soy consumption is possibly associated with a lower incidence of certain chronic diseases, but the results in this area are limited and contradictory. It appears that adding soy bread to the diet of diabetic patients can be beneficial as soy is associated with lower levels of inflammation. The enrichment of bread with soy flour can also increase the protein quality of food and enhance its health effects. To the best of our knowledge, there are no published studies on the effects of soy bread on diabetic patients. Due to the beneficial effects of soy on chronic diseases including type 2 diabetes, the present study was conducted to enrich bread with soybean flour and examine its effects on inflammatory markers in patients with type 2 diabetes.

Materials and Methods

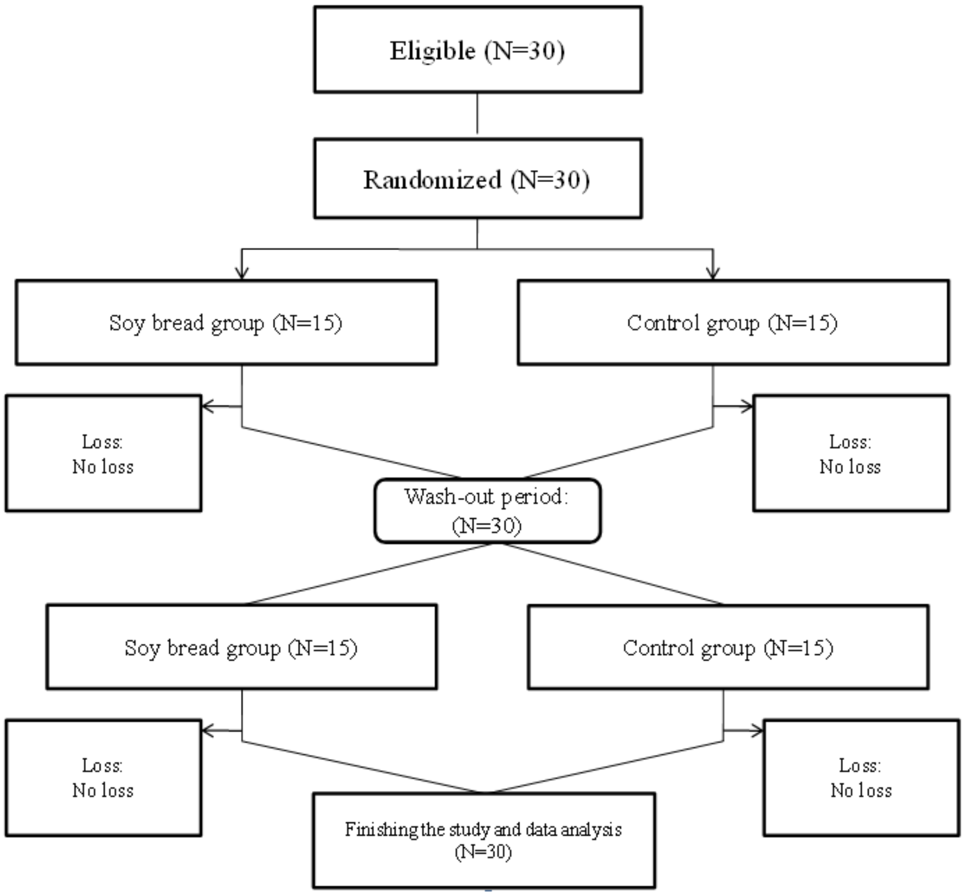
The study population

The study population consisted of premenopausal women 30-50 years old with type 2 diabetes, presenting to the Endocrinology and Metabolism Research Center at Isfahan University of Medical Sciences, Isfahan, Iran. Participants were randomly assigned to either intervention (soybean-flour-enriched bread) or control (normal diet) groups. The exclusion criteria were body mass index less than 25, daily insulin injections, use of hormone replacement therapy, hypo- or hyper-thyroidism, smoking, menopause due to surgery, and allergy or intolerance to soybeans. Pregnant or lactating women were excluded, too. The participants did not follow a special diet during the last three months. The sample size was calculated based on the formula proposed for cross-over clinical trials (17):

$$n= [(z_{1-\alpha/2} + z_{1-\beta})^2.s^2] / 2\Delta^2$$

Type I error and type II error were considered 5% and 20% (Power=80%), respectively, and CRP was considered as the key variable (16). According to the formula, the sample size for the study was 19 subjects. Since the loss in crossover studies will be high, 30 people were enrolled. All participants completed the study. Figure 1 shows a diagram of the follow-up of participants in the study. Written informed consent was obtained from all participants prior to entering the study. This study was approved by the Ethics Committee of the University. The clinical trial registration code was obtained from the Iran registry of clinical trials (www.irct.ir) (IRCT2013061613684N1).

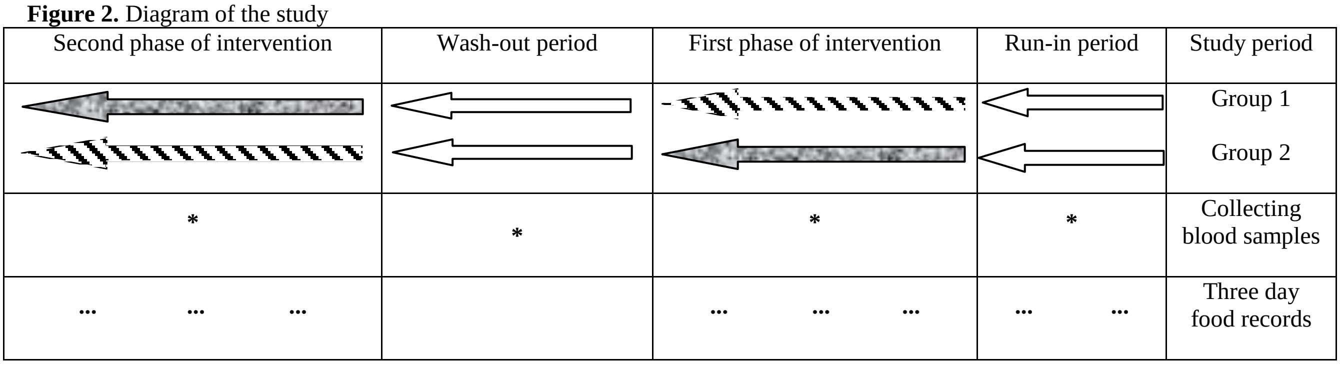
Figure 1. Diagram of the follow-up of participants in the study



Design

This cross-over clinical trial consisted of two 6-week intervention periods separated by a 4-week wash-out period. Initially, a 2-week run-in period was applied (before the start of the study). This period was designed to assess the diet and level of physical activity and acceptance of bread enriched with soybean flour by the subjects. The participants were asked to follow their routine diet and physical activity during the run-in period. The subjects were asked to have a serving of bread enriched with soybean flour per day to prepare for the intervention. During this period, two recording forms of 24-hour physical activity and two food recording forms (two non-consecutive days) were completed by each subject. At the end of the run-in period, all measurements, including anthropometric measurements and fasting blood sampling for biochemical measurements were performed, then subjects were randomly assigned to either intervention (soybean flour-enriched bread) or control (normal diet) groups. At the end of the first phase of the intervention, all measurements were performed again. After a 4-week period of wash-out, the second phase of the study began and the groups were crossed over for another six weeks. During the wash-out, period participants were asked to avoid the intake of foods containing soy and the bread enriched with soybean flour used during the intervention phase. All measurements were performed at the baseline, week 6, week 10 and week 16. Subjects' adherence was assessed through in-person visits and phone calls once a week. In addition, during the first and second phases of the study, all the participants completed the three-day food record forms (two normal days and a weekend) and physical activity recording forms every two weeks. Food records were analyzed by using the Nutritionist-IV software. A metabolic equivalent was calculated for recorded physical activities and the mean MET-h/d in each period was compared with the other period. Figure 2 shows a diagram of the study.

Figure 2. Diagram of the study



Intervention

Soybean-flour-enriched bread was prepared by replacing 30% of wheat flour with soybean flour. The intervention group subjects were asked to replace 120 grams of ordinary bread and, if necessary, carbohydrate-rich foods such as rice, pasta, and other grains with an equal amount of soybean-flour-enriched bread. On average, each 120 g bread contained 36 grams of soybean flour. Participants were given fresh bread every week. The bread was either consumed fresh or frozen before use by the participants. Participants were taught how to use soy bread. The control group subjects were asked to refrain from consumption of foods containing soy during this phase of the study and continue their normal diet consumption. Bread consumption by participants was monitored by a dietitian on a weekly basis and if the bread was consumed more or less than the advised amount, they were taught how to properly consume it. The nutrient content of soybean-flour-enriched bread is presented in Table 1. The bread was baked in Khajeh bakery in Isfahan, Iran.

Table 1. The nutrient content of soybean-flour-enriched bread and wheat bread (value in 100 g)

Nutrient	Wheat bread	Soy bread
Fat	1.4	7.2
Carbohydrates	75.2	44.31
Proteins	11.5	14.1
Energy	341	298

Evaluation of Biomarkers

After 12 hours of fasting, blood samples were taken between 7:30 am and 9:00 am in a laboratory in the Endocrinology and Metabolism Research Center, Isfahan University of Medical Sciences, Isfahan, Iran. Blood samples were centrifuged 30-45 minutes after sampling. The serum levels of hs-CRP were evaluated by immunoturbidimetry with high sensitivity using commercial kits (Bionik, Tehran, Iran). The sVCAM1 level was measured using the ELISA method with commercial kits (Glory Science, Del Rio, USA). The levels of IL-6 and TNF- α were measured using enzyme-mediated safety absorption test (Boster Biological Technology Co., Hubei, China).

Anthropometric measurements

Weights were measured using a digital scale with 100 g accuracy with the least clothing and without shoes. Heights were measured using a measuring tape in standing position next to the wall and without shoes with shoulders relaxed. BMI was calculated as a subject's weight in kilograms, divided by height in squared meter. Waist circumference (WC) was measured at the narrowest area close to the last rib at the umbilicus, at the end of normal exhalation. Hip circumference was measured at the maximum diameter over the clothes. Measurements were performed using a non-elastic measuring tape (Precision of 1.0 cm) without applying any pressure on the body.

Data Analysis

Data was analyzed using the SPSS 18 software. All participants entered the final analysis. The normal distribution of all variables was evaluated using QQ-plot test. The paired t-test was used to compare dietary intakes and physical activity. The paired t-test was also used to determine the main effects by comparing the difference between the means of variables in the two groups. The t-test was used to check the transition effect and the effect of the period. Data is expressed as means ± standard deviations. The statistical significance level was considered as $P<0.05$.

Results

The baseline characteristics of the participants are presented in Table 2. The mean of age, weight, BMI, and WC were, 45.7±3.8 years, 73.8±10.7 kg, 29.5±3.9 kg per square meter, and 87.4±6.7 cm, respectively. The food intake of the participants before the study are presented in Table 3. There was no significant difference between the two groups in terms of physical activity (36.7±3.2 MET-h/d in the intervention group and 37.2±3.4 MET-h/d in the control group, P=0.4). No negative effect of soy bread intake was reported by participants during the study. There was no significant difference in dietary intake of the participants throughout the study. Soybean-flour-enriched bread did not have a significant effect on anthropometric indices of the subjects at the end of the study. The effects of soybean-flour-enriched bread intake on inflammatory markers are presented in Table 4. The results of this study did not show a significant effect of the consumption of soybean-flour-enriched bread on inflammatory markers. There was a slight but not significant reduction in levels of hs-CRP (difference of changes: -0.04-, P=0.6), TNF- α (difference of changes:. 14.2, P=0.27), and IL-6 (difference of changes: -14.2‹ P=0.27) in the intervention group compared to the control group. The consumption of soybean-flour-enriched bread did not have a significant effect on serum levels of sVCAM1

Table 2. Demographic characteristics of the subjects at the baseline[1]

Age (Years)	45.7±3.8
Weight (kg)	73.8±10.7
Height (cm)	158±5.3
BMI (kg/m^2)	29.5±3.9
Waist circumference (cm)	87.4±6.7
Hip circumference (cm)	99.04±4.6

[1] Data is expressed as means ± standard deviations.

Table 3. Subjects' food intake before the study [1]

	Variable	Mean	Standard deviation
Macronutrients	Energy (kilocalories per day)	1499	766
	Carbohydrates (grams per day)	196	134
	Protein (grams per day)	63	49.3
	Fat (grams per day)	48	17.8
	Saturated fatty acids (grams per day)	11.7	5.01
	Polyunsaturated fatty acids (grams per day)	18.3	9.2
	Monounsaturated fatty acids (grams per day)	11.5	4.8
	Fiber (grams per day)	9	3
Micronutrient	Calcium (milligrams per day)	469	287
	Magnesium (milligrams per day)	195.8	271.7
	Folate (micrograms per day)	308.3	686.6
	Vitamin C (milligrams per day)	50.9	37.5
	Vitamin E (milligrams per day)	10.5	6.1
	Fiber (grams per day)	9	3

[1] Data is expressed as means ± standard deviations.

Table 4. The effects of soybean-flour-enriched bread intake on inflammatory markers among type 2 diabetic women [1]

Variables		Phase one		Phase two		Difference of changes [4]	P[5]
		Baseline	Week six	Week ten	Week Sixteen		
Reactive protein C (mg/L)	Intervention-control[2]	0.97±0.19	0.88±0.16	1.1±0.32	0.91±0.2	-0.04	0.6
	Control-intervention[3]	0.76±0.3	0.86±0.41	0.97±0.15	0.9±0.16		
Interleukin-6 (pg/mL)	Control-intervention	0.12±0.03	0.12±0.08	0.12±0.03	0.1±0.02	-0.06	0.15
	Control-intervention	0.13±0.04	0.21±0.27	0.16±0.07	0.1±0.03		
Tumour necrosis factor-alpha (pg/mL)	Control-intervention	27.9±659.4	27.4±61.5	61.5±100.4	60.9±108.3	-14.2	0.27
	Control-intervention	45.9±83.7	41.1±82.1	61.5±100.4	47.3±111.3		
Vascular cell adhesion molecule 1 (μg/L)	Control-intervention	1225±2660	930±2534	1039±3340	1314±2758	526	0.08
	Control-intervention	894±2890	1078±2076	2002±2468	1365±2253		

1. Data is expressed as means ± standard deviations.
2. Subjects received soybean-flour-enriched bread in the first phase and normal diet in the second phase.
3. Subjects received normal diet in the first phase and soybean-flour-enriched bread in the second phase.
4. Difference of changes is the difference between means of intervention and control groups.
5. Resulted from the paired t-test.

Discussion

The results of the study on women with type 2 diabetes showed that daily consumption of 120 grams of soybean-flour-enriched bread for six weeks had no significant effects on the levels of inflammatory biomarkers. According to our current knowledge, this study was the first study on the effects of soybean-flour-enriched bread on the levels of inflammatory biomarkers in diabetic patients. Increased levels of CRP and IL-6 predict the development of type 2 diabetes (4, 5, 18). Many dietary factors affect the levels of inflammatory markers. For example, it is reported that soy products have beneficial effects on levels of inflammatory biomarkers (19). In the present study, the consumption of soybean-flour-enriched bread for six weeks had no significant effect on inflammatory biomarkers. In line with these findings, Miraghajani et al. (16) demonstrated that consumption of soy milk for four weeks in patients with diabetic nephropathy had no significant effect on inflammation. A meta-analysis study showed that soy isoflavones had no significant effect on CRP levels in postmenopausal women (20). Another study also showed that replacing 25 grams of non-soya protein with a half cup of soy nuts for 8 weeks reduced sVCAM1 levels but had no effects on the levels of sICAM1 and IL-6 (21). Other studies found no positive results of the effects of soy on inflammatory biomarkers, either (22, 23). In contrast to this study, some studies have reported beneficial effects of soy on inflammation. A randomized cross-over study on postmenopausal women with metabolic syndrome showed that consumption of soy nuts reduces levels of inflammatory biomarkers (15). In another study on postmenopausal women, consumption of soy milk reduced circulating levels of TNF- α (24). Similar results were shown by other interventional studies(25, 26). In a crossover study on postmenopausal women, the daily consumption of 25 grams of soy protein for 8 weeks resulted in a significant reduction in serum levels of CRP and sICAM1(27). In another study, the soy protein resulted in significant reduction of Wish IL-6 levels (28). In this study, the treatment duration was six weeks and it appears that achieving the effects of soy on inflammatory biomarkers require more intervention duration. The low sample size of this study can also be another reason for not achieving significant results compared to other studies. The different products used in this study could also be involved in the lack of significant effects. The mechanisms of effect of soy on inflammation are largely unknown. However, several mechanisms have been proposed for the beneficial effects of soy including the fiber content of soy (11), polyunsaturated fatty acids in soy (12, 29, 30), and soy isoflavones (24). Previous studies have shown that fiber might have anti-inflammatory effects (6, 31). Butyrate, one of the major metabolites of dietary fiber, has strong anti-inflammatory effects (31). The beneficial effects of soy on inflammation might be mediated by isoflavone content of soy (32, 33). Soy is a rich source of polyunsaturated fatty acids (8). It has been shown that N-3 fatty acids have anti-inflammatory effects (29, 32). The N-3 fatty acids are precursors of eicosanoids (eicosapentaenoic acid and docosahexaenoic acid) that have potent anti-inflammatory effects (34). This study had several strengths as well as weaknesses. The main strength of this study was its cross-over design. Other strengths include a high percentage of participants who completed the study and enriching bread with soy for ease of bread consumption by participants. Despite the advantages, there were some limitations that should be considered when interpreting the results. Designing a double-blind study was not possible due to taste and texture of bread. The daily distribution of bread packages was not possible, either. Due to the financial limitations in the implementation of the project, the serum/urinary isoflavone levels of the participants were not measured to assess their adherence. It is suggested that the relationship between levels of serum/urinary isoflavones and inflammatory biomarkers be evaluated in future studies. The effects of soy on inflammatory biomarkers might be related to the consumed dose of soy. Due to adverse effects on the texture and flavor of bread, it was not possible to increase the dose of soybean flour more than 30%. This study cannot detect whether soy protein, soy isoflavones, and other substances were responsible for the decline in CRP, IL-6 and TNF- α levels.

Conclusion

In summary, the results of this study suggest that daily consumption of 120 grams of soybean-flour-enriched bread for six weeks had no significant effect on serum levels of inflammatory markers in diabetic women. Further studies with longer intervention period are necessary to determine the effects of soy on inflammatory and its mechanisms of action.

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