Effects of Soy Isoflavones on Glycemic Parameters and Blood Pressure in Peritoneal Dialysis Patients: A Randomized, Double Blind, Placebo-Controlled Trial

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Introduction. High serum concentrations of glucose, advanced glycation end products (AGEs), and hypertension are some of the major risk factors for cardiovascular disease and peritoneal membrane fibrosis in peritoneal dialysis (PD) patients. Some investigations in nonuremic individuals have indicated that isoflavones can reduce serum glucose, blood pressure, and increase insulin sensitivity. However, such study in this field in PD patients is still lacking. Therefore, we aimed to determine the effects of isoflavones on serum glucose, fructosamine, AGEs, and blood pressure in PD patients.

Methods. This study was a randomized, double blind, placebo-controlled trial. Thirty-eight PD patients were randomly assigned to either the isoflavone group or the placebo. The patients in the isoflavone group received 100 mg/d soy isoflavone for 8 weeks, while the control group received corresponding placebo. At baseline and the end of the 8th week, 7 mL of blood was collected from each patient and serum glucose, fructosamine, carboxymethyl lysine, pentosidine, accompanied by systolic and diastolic blood pressures were measured.

Results. Serum glucose and pentosidine reduced significantly in the isoflavone group at the end of 8th week compared with baseline ($P < .05$), whereas no statistically significant changes were observed in the placebo group. Serum carboxymethyl lysine, fructosamine, and systolic and diastolic blood pressures did not significantly change within each group during the study.

Conclusion. This study indicates that soy isoflavones could decrease serum glucose and pentosidine in PD patients.

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INTRODUCTION

Cardiovascular disease (CVD) is prevalent in patients with chronic kidney disease (CKD), including peritoneal dialysis (PD) patients, and accounts for more than 50% of mortality in this population.[1] In PD patients, high serum concentrations of glucose, fructosamine, and advanced glycation end products (AGEs) are some of the major causes for CVD,[2-4] peritoneal membrane fibrosis and ultrafiltration failure.[5] Also, hypertension as one of the most important risk factors for CVD is common in PD patients.[6]

Some investigations in nonuremic postmenopausal women have indicated that isoflavones or soy protein can reduce fasting serum glucose,[7-9] and increase insulin sensitivity in patients with type

2 diabetes.[10] Few in vitro studies showed that isoflavones including genistein could inhibit AGE formation.[11-13] Also, some investigations in nonuremic subjects showed that isoflavones or soy protein decreased systolic[8,9] and diastolic[8,14] blood pressures. According to the literature, such investigations have not been performed on uremic cases especially PD patients. Therefore, this study was designed to determine the effects of soy isoflavones on serum glucose, fructosamine, AGEs, and systolic / diastolic blood pressures in PD patients.

MATERIALS AND METHODS

Trial Design and Ethical Aspects

This study was a parallel, randomized, double blind, clinical trial performed from November 2019 to January 2020. The Ethics Committee of the National Nutrition and Food Technology Research Institute of Iran approved the study protocol. The study was conducted in accordance with the Declaration of Helsinki, and all enrolled patients signed informed consent. The clinical trial protocol has been registered at ClinicalTrials.gov with ID number NCT04185168.

Participants

The minimum sample size estimated for each group was 16 based on the formula $[(2\ S_p^2\ (Z_{1-\alpha} + Z_{1-\beta})^2) \div (\mu_1-\mu_2)^2]$ at a power $(1 -\beta)$ of 80% and $\alpha = 0.05$ for a two-arm parallel study with two-tailed testing to detect a difference of 13 mg/dL in fasting serum glucose with a pooled standard deviation of 13.1 mg/dL (0.73 mmol/L), obtained from Sathyapalan *et al.*'s study.[9] Forty-two patients (15 female and 27 male) undergoing continuous ambulatory peritoneal dialysis (CAPD) were selected by convenience sampling from the Peritoneal Dialysis Unit of Shafa Clinic in Tehran, Iran.

Inclusion criteria for the study were age ≥ 18 years and being on CAPD for at least 6 months. Patients with inflammatory diseases, thyroid dysfunction, infectious diseases especially peritonitis, history of cancer, and those receiving levothyroxine, glucocorticoids, nonsteroidal anti-inflammatory drugs, isoflavone supplement, and soy-based food were excluded.

Intervention, Randomization, and Blinding

The patients were stratified based on diabetes and then allocated to either a soy isoflavone or placebo group by block randomization with a block size of four and an allocation ratio of 1:1. A trained dietitian did the randomization. Patients in the soy isoflavone group received 100 mg of soy isoflavones as two tablets daily for 8 weeks; the placebo group received two doses of corresponding placebo containing starch. The tablets were taken as two doses in the morning and evening. The Gol Daru Pharmaceutical Company, Esfahan, Iran, produced soy isoflavone and placebo tablets. Each soy isoflavone 50 mg tablet contained 31.86 mg of genistin, 1.49 mg of genistein, 13.21 mg of daidzin, 1.75 mg of daidzein, 1.14 mg of glycitin, and 0.55 mg of glycitein. In our study, a trained dietitian performed blinding, and the patients and researchers were kept blinded to the allocation. Subjects were advised not to change their dietary habits, physical activities, and drug regimens. In addition, the study protocol did not change after the trial was commenced. At baseline and at the end of the 8th week, 7 ml of blood was collected from each patient after overnight fasting. After centrifugation of clotted blood at 2000 rpm for 10 min at room temperature, the separated serum was stored at -70°C until biochemical tests were run.

Measurements

In the present study, primary outcomes were serum glucose, carboxymethyl lysine, pentosidine, and fructosamine levels, and systolic / diastolic blood pressures. Serum concentration of carboxymethyl lysine and pentosidine as two AGEs and fructosamine as well were determined by enzyme-linked immunosorbent assay kits (ZellBio GmbH, Ulm, Germany). Intra-assay CVs for serum carboxymethyl lysine, pentosidine, and fructosamine were 6.6%, 6.9%, and 7.1%; respectively. Serum concentrations of glucose, creatinine, and urea were assessed using various colorimetry methods by commercial kits (Pars Azemoon, Tehran, Iran) with the aid of a Selectra 2 Autoanalyzer (Vital Scientific, Spankeren, The Netherlands). Intra-assay CVs for serum glucose, creatinine, and urea were 2.0%, 2.5%, and 2.5%; respectively.

Weight assessment was performed at baseline and the end of 8th week. For dietary assessment, a trained dietitian completed three 24 hours dietary recall questionnaires (2 weekdays and 1

weekend day) at baseline and after 4 and 8 weeks of intervention. In this dietary assessment method, the patients were asked to record the amount and type of their eaten foods, based on the instructions given to them, for 3 days. At the end of each day, patients were asked by phone carefully about their consumed foods. The analysis of patients' diets was performed by Nutritionist IV software (N Squared Computing, San Bruno, CA, USA) adjusted for some Iranian foods to assess daily intakes of energy, protein, carbohydrate, total fat, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, fiber, vitamins E, C and B6, potassium, magnesium, and calcium.

For blood pressure measurements at baseline and at the end of 8th week, patients were first asked to rest for 15 minutes, then a trained nurse measured the blood pressure twice in seated position, with a 10-minute interval, by using a standard mercury sphygmomanometer, and thereafter the mean of 2 measurements was considered as the participant's blood pressure.

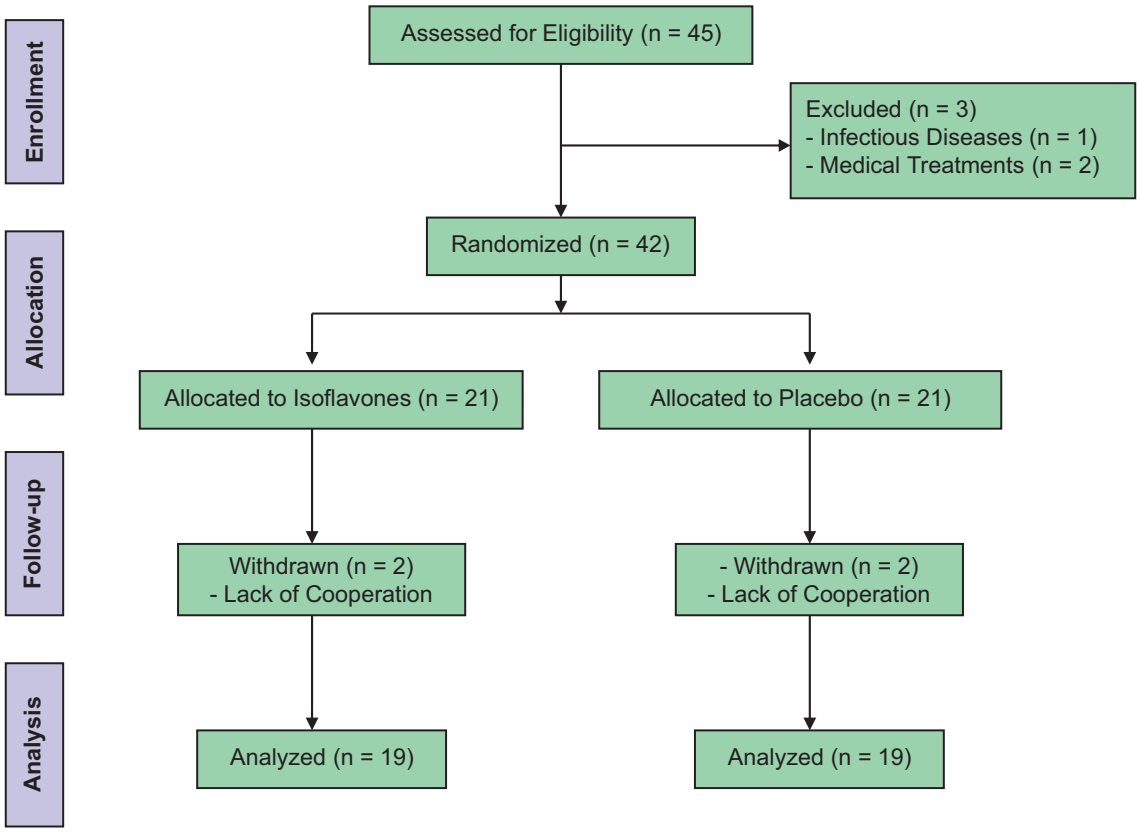
Dialysis adequacy was calculated as total Kt/V per week based on 24 hours urine volume, urine urea level, blood urea, dialysate urea, 24 hours dialysate drain volume, age, height, and weight using a Kt/V calculator.[15] The peritoneal equilibration test for glucose was done for each patient based on a 2-L 4.25% dextrose dwell with dialysate samples at 0 and 4 hours and the determination of the ratio of dialysate glucose level at time 4 to dialysate glucose concentration at time zero (D4/D0). The percent of glucose absorbed from the dialysate was calculated using the 1-D4/D0 formula.[16]

Compliance

To ascertain patients' compliance, we provided each patient with a fixed number of tablets and instructions to return the unused tablets at the end of the study. Based on the number of returned tablets by each patient, their degree of compliance was determined.

Statistical Analysis

All statistical analyses were done using the SPSS version 21. We used a chi-squared test to



Summary of the Patient Flow Diagram

compare categorical variables between the two groups. All quantitative parameters had normal distributions based on the Kolmogorov-Smirnov test; therefore, we used a t-test and paired t-test to compare parameters between and within groups, respectively. Also, because dietary parameters were measured 3 times during the study, analysis of variance for repeated measurements was used to compare data among these time points. We used an analysis of covariance test to compare serum glucose, carboxymethyl lysine, pentosidine, fructosamine, and systolic / diastolic blood pressures between the two groups and to adjust the effects of confounding factors (dietary factors and the percent of glucose absorbed from the dialysate). Continuous variables were expressed as mean ± standard error (SE), and a $P \leq .05$ was considered statistically significant.

RESULTS

Among 42 participants, 2 PD patients in each group were withdrawn due to a lack of cooperation (Figure). In this study, the degree of compliance was over 90% and no adverse event was reported.

Table 1 shows baseline characteristics of the PD patients. No significant differences were observed between the two groups regarding these characteristics.

Table 1. Baseline Characteristics of Patients in the Soy Isoflavone Group and the Placebo Group

Characteristics	Soy Isoflavone (n = 19)	Placebo (n = 19)
Sex		
Men	15.0 (79.0%)	11.0 (58.0%)
Women	4.0 (21.0%)	8.0 (42.0%)
Age, y*	54.5 ± 4.0	51.0 ± 3.0
Smokers	5.0 (26.0%)	2.0 (10.5%)
Diabetes	5.0 (26.0%)	4.0 (21.0%)
Type of PD Solutions		
1.5% Glucose	9.0 (47.5%)	7.0 (37.0%)
1.5% + 2.5% Glucose	2.0 (10.5%)	4.0 (21.0%)
1.5% Glucose + Icodextrin	3.0 (16.0%)	3.0 (16.0%)
2.5% Glucose + Icodextrin	0.0 (0.0%)	3.0 (16.0%)
1.5% + 2.5% + Icodextrin	5.0 (26.0%)	2.0 (10.0%)
Duration of Dialysis, y*	3.7 ± 0.7	3.4 ± 0.6
Intake of Supplements or Drugs		
Vitamin E or C	11.0 (58.0%)	9.0 (47.0%)
Vitamin B6	11.0 (58.0%)	10.0 (53.0%)
Calcitriol	10.0 (53.0%)	10.0 (53.0%)
Antihypertensive Drugs	16.0 (84.0%)	15.0 (79.0%)
Intravenous Erythropoietin	10.0 (53.0%)	14.0 (74.0%)
Serum Urea, mg/dL*	95.0 ± 7.0	93.0 ± 6.0
Serum Creatinine, mg/dL*	8.5 ± 0.5	7.0 ± 1.0
Weight, kg*		
Baseline	72.0 ± 3.0	65.0 ± 4.0
Week 8	72.5 ± 2.5	66.0 ± 4.0
BMI, kg/m^2*		
Baseline	26.0 ± 1.0	26.0 ± 1.0
Week 8	26.5 ± 1.0	26.0 ± 1.0
Dialysis Adequacy, Weekly Total Kt/V*		
Baseline	1.78 ± 0.08	1.73 ± 0.11
Week 8	1.83 ± 0.10	1.70 ± 0.09
Glucose Absorbed from PD Solutions, %*		
Baseline	68.0 ± 2.0	62.0 ± 3.0
Week 8	68.0 ± 2.0	64.0 ± 2.0

A chi-squared test was used to compare categorical variables between the two groups.
A t-test was used to compare quantitative variables between the two groups.
*Presented as mean ± standard error.
Abbreviations: PD, peritoneal dialysis; BMI, body mass index.

There were no significant differences in weight and body mass index between the two groups at the baseline and the end of 8th week (Table 1). The percent of absorbed glucose from PD solutions and total dialysis adequacy indicated no statistically significant difference between two groups at the baseline and at the end of the eighth week (Table 1). Also, no significant changes in these parameters

Table 2. Dietary Factors in the Soy Isoflavone Group and the Placebo Group*

Factors	Baseline	Week 4	Week 8
Energy, kcal/d			
Soy Isoflavone	1646.0 ± 132.0	1570.0 ± 62.0	1527.0 ± 59.0
Placebo	1443.0 ± 95.0	1426.0 ± 83.0	1333.0 ± 84.0
Protein, g/d			
Soy isoflavone	58.0 ± 4.0	61.0 ± 2.0	56.0 ± 3.0
Placebo	56.0 ± 5.0	52.0 ± 3.0	50.0 ± 3.0
Carbohydrate, g/d			
Soy Isoflavone	235.0 ± 20.0	217.0 ± 10.0	212.0 ± 7.0
Placebo	196.0 ± 12.0	199.0 ± 11.0	187.0 ± 12.0
Fat, g/d			
Soy Isoflavone	55.0 ± 5.0	53.0 ± 2.0	52.0 ± 2.0
Placebo	50.0 ± 4.0	48.0 ± 3.0	44.0 ± 3.0#
SAFA, g/d			
Soy Isoflavone	14.0 ± 1.0	14.0 ± 1.0	14.0 ± 1.0
Placebo	13.0 ± 1.0	12.0 ± 1.0	12.0 ± 1.0
MUFA, g/d			
Soy Isoflavone	17.0 ± 1.0	17.0 ± 1.0	16.0 ± 1.0
Placebo	15.0 ± 2.0	15.0 ± 2.0	13.5 ± 1.0
PUFA, g/d			
Soy Isoflavone	16.0 ± 1.0	15.0 ± 1.0	15.0 ± 1.0
Placebo	15.0 ± 1.0	16.0 ± 1.0	14.0 ± 1.0
Fiber, g/d			
Soy Isoflavone	12.0 ± 1.0	13.0 ± 0.5	13.0 ± 1.0
Placebo	11.0 ± 1.0	11.0 ± 1.0	11.0 ± 1.0
Vitamin E, mg/d			
Soy Isoflavone	7.0 ± 2.0	7.0 ± 2.0	6.0 ± 1.0
Placebo	7.0 ± 1.0	5.0 ± 1.0	4.0 ± 1.0
Vitamin C, mg/d			
Soy Isoflavone	67.0 ± 10.0	81.0 ± 11.0	83.0 ± 12.0
Placebo	58.0 ± 6.0	76.0 ± 12.0	62.0 ± 11.0
Vitamin B6, mg/d			
Soy Isoflavone	2.8 ± 0.2	2.8 ± 0.2	2.9 ± 0.3
Placebo	2.2 ± 0.2	2.7 ± 0.2	2.5 ± 0.2
Potassium, mg/d			
Soy Isoflavone	1909.0 ± 292.0	1802.0 ± 113.0	1716.0 ± 109.0
Placebo	1541.0 ± 154.0	1526.0 ± 133.0	1477.0 ± 91.0
Magnesium, mg/d			
Soy Isoflavone	150.0 ± 11.0	154.0 ± 10.0	146.0 ± 9.0
Placebo	129.0 ± 11.0	129.0 ± 11.0	128.0 ± 9.0
Calcium, mg/d			
Soy Isoflavone	519.0 ± 46.0	507.0 ± 47.0	576.0 ± 44.0
Placebo	477.0 ± 51.0	433.0 ± 45.0	455.0 ± 45.0

All values are presented as mean ± standard error.
A t-test was used to compare variables between the two groups.
An analysis of variance for repeated measurements was used to compare data among 3 time points within each group.
*n = 19 for all values.
#$P < .05$ vs. the Soy Isoflavone Group
Abbreviations: SAFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

were observed in the two groups (Table 1).

No significant changes were found in mean dietary intake of energy, carbohydrate, protein, monounsaturated fatty acids, saturated fatty acids, polyunsaturated fatty acids, fiber, vitamins C, E and B6, potassium, magnesium, and calcium between two groups at baseline and at the end of 4th and 8th weeks. Also, no significant changes in these factors were observed in the two groups (Table 2). Dietary intake of total fat was significantly lower in the placebo group at the end of eighth week ($P < .05$) in comparison with the soy isoflavone group. However, there was no significant change in the mean dietary intake of total fat within each group during the study (Table 2).

Serum glucose reduced significantly in the soy isoflavone group at the end of eighth week compared with baseline ($P < .05$), while no significant changes were found in the placebo group (Table 3).

Serum pentosidine levels reduced significantly in the soy isoflavone group at the end of eighth week compared with baseline ($P < .05$), whereas no significant change was found in the placebo group (Table 3). The reduction of serum pentosidine in the soy isoflavone group was significant compared with the placebo group ($P < .05$, Table 3).

Serum carboxymethyl lysine and fructosamine did not significantly change within each group during the study (Table 3).

Systolic and diastolic blood pressures showed no statistically significant changes within each group during the study (Table 3).

DISCUSSION

In CAPD, up to 80% of glucose is absorbed from PD solutions which can lead to high fasting serum glucose,[17] hyperinsulinemia, peritoneal membrane fibrosis, and high risk of CVD and mortality.[18] In our study, no significant difference was observed in the percent of glucose absorbed from the dialysate between the soy isoflavone group and the placebo group at baseline and at the end of eighth week; however, fasting serum glucose reduced up to 13% in the soy isoflavone group during 8 weeks, while

Table 3. Serum Concentrations of Fasting Glucose, Pentosidine, Carboxymethyl Lysine, Fructosamine, Systolic and Diastolic Blood Pressures in the Soy Isoflavone Group and the Placebo Group*

Parameters	Baseline	Week 8	Changes#
Fasting Serum Glucose, mg/dL&			
Soy Isoflavone	119.0 ± 7.0	103.0 ± 3.0[a]	-16.0 ± 7.0
Placebo	121.0 ± 8.0	112.5 ± 6.0	-8.5 ± 7.0
Pentosidine, ng/mL&			
Soy Isoflavone	5.5 ± 1.5	4.7 ± 1.1[a]	-0.8 ± 0.3[b]
Placebo	4.9 ± 1.5	4.9 ± 1.6	0.0 ± 0.5
Carboxymethyl Lysine, ng/mL&			
Soy Isoflavone	207.0 ± 76.0	190.0 ± 67.0	-17.0 ± 9.5
Placebo	148.0 ± 59.0	194.0 ± 82.0	46.0 ± 9.0
Fructosamine, mmol/L&			
Soy Isoflavone	3.0 ± 0.5	3.3 ± 0.6	0.3 ± 0.2
Placebo	2.3 ± 0.2	2.4 ± 0.3	0.1 ± 0.1
Systolic Blood Pressure, mmHg@			
Soy Isoflavone	148.0 ± 5.0	145.0 ± 4.0	-3.0 ± 5.0
Placebo	137.0 ± 5.5	145.0 ± 7.0	8.0 ± 5.0
Diastolic Blood Pressure, mmHg@			
Soy Isoflavone	91.0 ± 4.0	90.0 ± 2.0	-1.0 ± 4.0
Placebo	86.0 ± 4.0	89.0 ± 4.0	3.0 ± 3.0

All values are presented as mean ± standard error.
An analysis of covariance test was used to compare variables between the two groups and to adjust confounding variables.
A paired t-test was used to compare variables within each group.
*n = 19 for all values
#Changes reflect week 8 – baseline values.
&Adjustment for the percent of glucose absorbed from the dialysate and dietary factors including energy, protein, carbohydrate, total fat, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, fiber, vitamins E, C, and B6.
@Adjustment for dietary factors including energy, protein, carbohydrate, total fat, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, potassium, magnesium and calcium.
[a]$P < .05$ vs. baseline
[b]$P < .05$ vs. placebo

no statistically significant change was found in the placebo group. To the best of our knowledge still there is no other study investigating the effect of soy isoflavones on fasting serum glucose in dialysis patients, to compare with the results of our study. However, in agreement with this study, some research in nonuremic postmenopausal women have shown that isoflavones or soy protein can decrease fasting serum glucose,[7-9,19] and increase insulin sensitivity in patients with type 2 diabetes.[10] Also, few in vitro studies showed that soy isoflavones including daidzein could increase glucose uptake by myocytes[20] and adipocytes.[21] In contrast, some investigations showed that soy isoflavone consumption had no effect on serum glucose.[22-24] These contradictory findings may be due to the baseline serum glucose concentrations, the duration and the amount of isoflavone consumption.

The hypoglycemic effect of soy isoflavones can be explained by two mechanisms. First, soy isoflavone increases the gene expression of glucose transporter type 4 (GLUT4) via the activation of peroxisome proliferators-activated receptor gamma.[21] Second, soy isoflavones enhance GLUT4 translocation to the plasma membrane via the activation of adenosine monophosphate-activated protein kinase.[20]

In PD patients, AGEs including carboxymethyl lysine and pentosidine accumulate in serum and tissues[25,26] which can lead to CVD,[3] peritoneal membrane fibrosis and ultrafiltration failure.[5] The accumulation of AGEs in PD patients may result from low AGEs clearance due to kidney failure,[25] hyperglycemia due to glucose absorption from PD solutions,[25,26] reactive carbonyl compounds formed during heat sterilization of glucose-containing PD solutions,[26] and carbonyl stress.[27] In the present study, soy isoflavones significantly reduced serum pentosidine up to 14% during 8 weeks, whereas no significant change was found in the placebo group. In addition, serum carboxymethyl lysine decreased in the soy isoflavone group but this reduction did not reach statistically significance. To date, no studies have examined the effects of soy isoflavone consumption on serum AGE concentration in dialysis patients to compare with the results of our study. However, in agreement with our study, few in vitro studies indicated that isoflavones including genistein could inhibit AGE formation.[11-13] In contrast, Celec *et al.* showed that soybean consumption in healthy adults for one week had no effect on plasma AGEs.[28] The disagreement of Celec *et al.*'s findings with the results of our study may be due to the short duration of Celec *et al.*'s study.

In our study, soy isoflavone supplement had no effect on serum concentration of fructosamine as a marker of glycosylated plasma proteins. [29] No study was available in the literature about the effect of soy isoflavones on serum fructosamine in dialysis patients. However, Celec *et al.* indicated that soybean consumption in healthy adults had no effect on plasma fructosamine.[28] Similarly, some investigations in nonuremic subjects have indicated that isoflavones cause no change in the level of glycosylated hemoglobin.[23]

Hypertension as one of the most important risk factors for CVD is prevalent in PD patients.[6] In the present study, 82% of all participating PD patients received antihypertensive drugs and soy isoflavone supplement had no effect on systolic and diastolic blood pressures. No research was found on the effects of isoflavones on systolic and diastolic blood pressures in dialysis patients. However, in agreement with this study, some investigations in nonuremic subjects showed that soy isoflavone consumption had no effect on systolic[24,30,31] and diastolic [9,24,30,31] blood pressures. In contrast, some studies have shown that isoflavones or soy protein can reduce systolic[8,9] and diastolic[8,14] blood pressures. These contradictory findings may be due to the baseline systolic and diastolic blood pressures, duration, and the amount of isoflavone consumption.

We did not measure serum concentrations of isoflavones, and this was a limitation of our study.

CONCLUSION

This study indicates that soy isoflavones could decrease serum glucose and pentosidine in PD patients.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Glorieux G, Neirynck N, Pletinck A, Schepers E, Vanholder R. Uremic toxins: overview. In: Turner N, Lameire N, Goldsmith DJ, Winearls CG, Himmelfarb J, Remuzzi G, editors. Oxford Textbook of Clinical Nephrology. 4th ed. New York: Oxford University Press; 2016. p. 2161.
2. Wang Z, Yu D, Cai Y, et al. Dialysate Glucose Response Phenotypes During Peritoneal Equilibration Test and Their Association With Cardiovascular Death: A Cohort Study. Medicine (Baltimore). 2020; 99:e20447.
3. Machowska A, Sun J, Qureshi AR, et al. Plasma Pentosidine and Its Association with Mortality in Patients with Chronic Kidney Disease. PLoS One. 2016; 11:e0163826.
4. Shafi T, Sozio SM, Plantinga LC, et al. Serum fructosamine and glycated albumin and risk of mortality and clinical outcomes in hemodialysis patients. Diabetes Care. 2013; 36: 1522-33.
5. Zhou Q, Bajo MA, Del Peso G, Yu X, Selgas R. Preventing Peritoneal Membrane Fibrosis in Peritoneal Dialysis Patients. Kidney Int. 2016; 90: 515-24.
6. Sarafidis PA, Persu A, Agarwal R, et al. Hypertension in dialysis patients: a consensus document by the European Renal and Cardiovascular Medicine (EURECA-m) working group of the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) and the Hypertension and the Kidney working group of the European Society of Hypertension (ESH). Nephrol Dial Transplant. 2017; 32: 620-40.
7. Atteritano M, Marini H, Minutoli L, et al. Effects of the phytoestrogen genistein on some predictors of cardiovascular risk in osteopenic, postmenopausal women: a two-year randomized, double-blind, placebo-controlled study. J Clin Endocrinol Metab. 2007; 92: 3068-75.
8. Squadrito F, Marini H, Bitto A, et al. Genistein in the metabolic syndrome: results of a randomized clinical trial. J Clin Endocrinol Metab. 2013; 98: 3366-74.
9. Sathyapalan T, Aye M, Rigby AS, et al. Soy isoflavones improve cardiovascular disease risk markers in women during the early menopause. Nutr Metab Cardiovasc Dis. 2018; 28: 691-7.
10. Konya J, Sathyapalan T, Kilpatrick ES, Atkin SL. The effects of soy protein and cocoa with or without isoflavones on glycemic control in type 2 diabetes. a double-blind, randomized, placebo-controlled study. Front Endocrinol (Lausanne). 2019; 10: 296.
11. Kong Y, Li X, Zheng T, Lv L. Glycation of β-lactoglobulin and antiglycation by genistein in different reactive carbonyl model systems. Food Chem. 2015; 183: 36-42.
12. Lv L, Shao X, Chen H, Ho CT, Sang S. Genistein inhibits advanced glycation end product formation by trapping methylglyoxal. Chem Res Toxicol. 2011; 24: 579-86.
13. Silvan JM, Srey C, Ames JM, del Castillo MD. Glycation is regulated by isoflavones. Food Funct. 2014; 5: 2036-42.
14. Richter CK, Skulas-Ray AC, Fleming JA, et al. Effects of isoflavone-containing soya protein on ex vivo cholesterol efflux, vascular function and blood markers of CVD risk in adults with moderately elevated blood pressure: a dose-response randomised controlled trial. Br J Nutr. 2017; 117: 1403-13.
15. Burkart JM, Bargman JM. Adequacy of peritoneal dialysis, including fluid balance. In: Khanna R, Krediet RT, editors. Nolph and Gokal's Textbook of Peritoneal Dialysis. 3rd ed. New York: Springer; 2009. p. 469–503.
16. La Milia V, Cabiddu G, Virga G, et al. Ultrafiltration Failure Assessment (UFFA) Study of the Italian Society of Nephrology Peritoneal Dialysis Study Group. Peritoneal equilibration test reference values using a 3.86% glucose solution during the first year of peritoneal dialysis: results of a multicenter study of a large patient population. Perit Dial Int. 2017; 37: 633-8.
17. Ritz E, Adamczak M, Wiecek A. Carbohydrate metabolism in kidney disease and kidney failure. In: Kopple JD, Massry SG, Kalantar-Zadeh K, editors. Nutritional Management of Renal Disease. 3rd ed. Amsterdam: Academic Press; 2013. p. 21.
18. Wu HY, Hung KY, Huang TM, et al. Safety issues of long-term glucose load in patients on peritoneal dialysis--a 7-year cohort study. PLoS One. 2012; 7: e30337.
19. Maliehe A, Ghahremani S, Kharghani S, et al. Effect of isoflavones and genistein on glucose metabolism in peri- and post-menopausal women: an overview of meta-analysis. J Menopausal Med. 2019; 25: 69-73.
20. Cheong SH, Furuhashi K, Ito K, et al. Antihyperglycemic effect of equol, a daidzein derivative, in cultured L6 myocytes and ob/ob mice. Mol Nutr Food Res. 2014; 58: 267-77.
21. Cho KW, Lee OH, Banz WJ, Moustaid-Moussa N, Shay NF, Kim YC. Daidzein and the daidzein metabolite, equol, enhance adipocyte differentiation and PPARgamma transcriptional activity. J Nutr Biochem. 2010; 21: 841-7.
22. Liu ZM, Chen YM, Ho SC, Ho YP, Woo J. Effects of soy protein and isoflavones on glycemic control and insulin sensitivity: a 6-mo double-blind, randomized, placebo-controlled trial in postmenopausal Chinese women with prediabetes or untreated early diabetes. Am J Clin Nutr. 2010; 91: 1394-401.
23. Ye YB, Chen AL, Lu W, et al. Daidzein and genistein fail to improve glycemic control and insulin sensitivity in Chinese women with impaired glucose regulation: A double-blind, randomized, placebo-controlled trial. Mol Nutr Food Res. 2015; 59: 240-9.
24. Carmignani LO, Pedro AO, da Costa-Paiva LH, Pinto-Neto AM. The effect of soy dietary supplement and low dose of hormone therapy on main cardiovascular health biomarkers: a randomized controlled trial. Rev Bras Ginecol Obstet. 2014; 36: 251-8.
25. de Strihou CV, Miyata T. Advanced glycation and advanced oxidation protein products: the effect of peritoneal dialysis. Perit Dial Int. 2006; 26:185-7.
26. Miyata T, Horie K, Ueda Y, et al. Advanced glycation and

lipidoxidation of the peritoneal membrane: respective roles of serum and peritoneal fluid reactive carbonyl compounds. Kidney Int. 2000; 58: 425-35.

27. Miyata T, Kurokawa K, Van Ypersele De Strihou C. Advanced glycation and lipoxidation end products: role of reactive carbonyl compounds generated during carbohydrate and lipid metabolism. J Am Soc Nephrol. 2000; 11: 1744-52.
28. Celec P, Hodosy J, Pálffy R, Gardlík R, Halčák L, Ostatníková D. The short-term effects of soybean intake on oxidative and carbonyl stress in men and women. Molecules. 2013; 18: 5190-200.
29. Islam N, Akhter J, Kayani N, Khan MA. Fructosamine: an alternative assessment of past glycaemic control in developing countries. J Pak Med Assoc. 1993; 43: 238-40.
30. Lu LW, Chen NW, Nayeem F, Nagamani M, Anderson KE. Soy isoflavones interact with calcium and contribute to blood pressure homeostasis in women: a randomized, double-blind, placebo controlled trial. Eur J Nutr. 2019, In press.
31. Husain D, Khanna K, Puri S, Haghighizadeh M. Supplementation of soy isoflavones improved sex hormones, blood pressure, and postmenopausal symptoms. J Am Coll Nutr. 2015; 34: 42-8.

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