Soy protein intake, cardio-renal indices and C-reactive protein in type 2 diabetes with nephropathy: a longitudinal randomized clinical trial

Leila Azadbakht$^{1,2}$ (PhD), Shahnaz Atabak$^3$ (MD), Ahmad Esmaillzadeh$^{1,2}$ (PhD)

$^1$Department of Nutrition, School of Public Health, Isfahan University of Medical Sciences, Isfahan, Iran
$^2$Food Security and Nutrition Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
$^3$Modarres Hospital, School of Medicine, Shaheed Beheshti University of Medical Sciences, Tehran, Iran.

Running Title: Soy protein and diabetes

Corresponding Author:
Leila Azadbakht, PhD
Department of Nutrition
School of Public Health
Isfahan University of Medical Sciences
Isfahan, PO Box 81745
Iran
azadbakht@hlth.mui.ac.ir

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ABSTRACT

Background: Several short-term trials on the effect of soy consumption on cardiovascular risks are available, but little evidence exists regarding the impact of long-term soy protein consumption among type 2 diabetic patients with nephropathy.

Objectives: To determine the effects of long-term soy consumption on cardiovascular risks, C-reactive protein and kidney-function indices among type 2 diabetic patients with nephropathy.

Design: This longitudinal randomized clinical trial was conducted among 41 type 2 diabetic patients with nephropathy (18 men and 23 women). Twenty patients in soy protein group consumed a diet containing 0.8 g protein/kg body weight (35% animal proteins, 35% textured soy protein, and 30% vegetable proteins) and 21 patients in control group consumed a similar diet containing 70% animal proteins and 30% vegetable proteins for 4-years.

Results: Soy protein consumption significantly affected cardiovascular risks like fasting plasma glucose (mean change in soy vs. control groups: -18±3 vs. 11±2 mg/dl; P=0.03), total cholesterol (-23±5 vs. 10±3 mg/dl; P=0.01), LDL-C (-20±5 vs. 6±2 mg/dl; P=0.01), and serum triglyceride concentrations (-24±6 vs. -5±2 mg/dl; P=0.01). Serum CRP levels was significantly decreased by soy protein intake as compared to control group (1.31±0.6 vs. 0.33±0.1 mg/L; P=0.02). Significant improvements were also seen in proteinuria (-0.15±0.03 vs. 0.02±0.01 g/d; P=0.001) and urinary creatinine (-1.5±0.9 vs. 0.6±0.3 mg/dl, P=0.01) by consuming soy protein.

Conclusions: Longitudinal soy protein consumption significantly affected cardiovascular risk factors and kidney-related biomarkers among type 2 diabetic patients with nephropathy.
Dietary intervention has long been considered challenging in the treatment of renal disease. A usual prescribed diet for nephropathy contains 0.8 g protein/kg body weight with 70% of total dietary protein as animal protein (1, 2). Such a diet might adversely affect blood cholesterol and atherosclerosis (3). It seems that not only the quantity but also the type of protein has important implications in renal disease (4).

The precise mechanisms leading to the progression of renal injury are not yet completely understood. Activated immunity and inflammation are relevant factors in the pathogenesis of diabetes and its microvascular complications, including nephropathy. In addition to inflammation, some investigators have accused dyslipidemia as being an influencing factor for renal impairment in diabetic patients (5). This new pathogenic perspective leads to some therapeutic considerations that can be administered into clinical treatments for diabetic nephropathy (6). Several studies have shown that substitution of soy protein for animal protein might have beneficial effects on lipid profiles (4, 7, 8), circulating levels of inflammatory biomarkers (9, 10) and renal-function indices (4, 11). However, most data available in this regard comes from short-term clinical trials and no study has assessed the consumption of soy protein as a stable component of the diet for a long time. Furthermore, it is not completely understood that after awhile how the body responds to soy consumption. Therefore, the current longitudinal clinical trial was carried out to determine the long-term effects of soy consumption on lipid profiles, renal-function indices and CRP levels among type 2 diabetic patients with nephropathy.

MATERIALS AND METHODS

Patients. A total of 50 diabetic patients with nephropathy (22 men and 28 women) were recruited in this study. Type 2 diabetes was defined as fasting plasma glucose ≥ 126 mg/dl (two times repeated) or taking the oral glucose lowering agents or insulin (12). All subjects had proteinuria with total urinary protein excretion between 300 and 1000 mg/day, serum creatinine between 1 and 2.5 mg/dl and blood urea nitrogen between 20 and 40 mg/dl. Their systolic and diastolic blood pressures were more than 140 and 90 mmHg, respectively. Nephropathy was established by the mentioned characteristics. Mean age of the patients at baseline (n=50) was 62.1±12.1 y. The diagnosis of retinopathy was based on indirect ophthalmoscopic examination (after pupil dilatation with topical 0.5% tropicamide) and fundus photographs. Totally, 60% of the patients (n=30) had family history of diabetes (having at least one first-degree relative with a diagnosis of diabetes after 30 years of age). Mean duration of diabetes and hypertension among these patients were 10±3 and 8±2 years, respectively, and mean HbA1c levels was 6.2±0.5 percent, showing a good glycemic control. No other diabetes complications were reported by the patients. Eighty one percent of them were using oral glucose lowering agents and twenty three percent were using insulin. All were on antihypertensive medications. 40% (n=20) were using ACE inhibitors, 44% (n=22) ARB and 76% (n=38) diuretics. 20% (n=10) were using both diuretics and ARB while 18% (n=9) were using both diuretics and ACE and 8% (n=4) were using all three medications. 12% (n=6) were using both ARB and ACE. After matching for age, BMI and diabetes duration, we randomly divided the patients into two groups: soy protein group (n=25) and control group (n=25). All patients have provided informed written consent.

Experimental protocol. In this longitudinal randomized clinical trial study the soy protein group followed a diet containing 0.8 g
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protein/kg body weight (35% animal proteins, 35% soy protein, and 30% vegetable proteins) and the control group consumed a similar diet with 0.8 g protein/kg body weight containing 70% animal and 30% vegetable proteins for 4 years. Both diets had 2000 mg sodium and 2000 mg potassium. Patients in the soy protein group used the textured soy protein (Sobhan textured soy protein, Sobhan Inc, Behshahr, Iran). They also received education regarding the preparation of their meals with soy protein. A dietitian explained them to wash soy protein and soak them for 30 minutes and then cook them in boiling water with turmeric, lemon juice and tomato paste for 10 minutes. Based on our analysis, the nutrient composition (per 30 gram) of soy protein consumed by the study participants was as follows: protein (15 g), fat (0.3 g), fiber (10 g), total phytoestrogen (84 mg), sodium (9 mg), magnesium (91 mg), calcium (83 mg), copper (0.5 mg), potassium (1 mg), iron (2.3 mg), phosphorus (223 mg). The soy protein we used in the current study was a commercially available product. The protein and fat contents of the soy were measured according to Kjeldahl and Soxhlet methods, respectively (13). Fiber content was determined gravimetrically as the difference in weights of a test sample before and after extraction in a solution. Calcium, magnesium, iron, copper, and phosphorus of soy were analyzed by atomic absorption based on titrimetric method. Sodium and potassium contents of soy protein were measured by flame photometry and its isoflavones by HPLC (13).

Calorie requirements of each participant were calculated individually based on equations suggested by Institute of Medicine, Food and Nutrition Board (14). Each patient was visited every three months, for 45-60 minutes. Subjects called the dietitian whenever they had questions regarding their diets. Dietitians called them to remind about soy intake, recording 3-day dietary records, and encourage them to follow their diets. Patients were recorded their physical activities for three days every three months. Diet compliance was assessed by dietary records and plasma phytoestrogen levels. They also recorded 3-day dietary records every three months. Diet compliance was assessed by dietary records and plasma phytoestrogen levels. Medications and their dosage were also reported for each patient during the study.

Measurements. All measurements were done at baseline and every six months up to four year. Body weight was measured while the subjects were minimally clothed without shoes using digital scales and recorded to the nearest 0.1 kg. Height was measured in a standing position, without shoes, using a tape meter while the shoulders were in a normal state. Blood pressure was measured twice after the participants sat for 15 min.

Twelve-hour fasting blood samples were collected into tubes containing 0.1% EDTA and were centrifuged at 4°C and 500×g for 10 min to separate the plasma. Blood glucose was measured on the day of blood collection by an enzymatic colorimetric method using glucose oxidase. Renal function indices including urinary and serum creatinine, blood and urinary urea nitrogen, proteinuria were all measured. All subjects provided a 24-hour urine sample at baseline and every six months. The correct method for collecting 24-hour urine sample was educated to each patient. Both urinary and serum concentrations of creatinine were determined by the Jaffe method (15), which was performed in a Hitachi 705 automatic analyzer (Boehriner, Mannheim, Mannheim, F.R.G.), that was set to record the mean absorbance in the interval of 60-140 seconds after the start of the reaction. The absorbance was measured bichromatically with primary and secondary wavelengths (505/570 nm). Blood and urinary urea nitrogen were analyzed by enzymatic methods; the enzyme
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Urease converts urea to ammonia and carbonic acid. Proteinuria was assessed by using trichloroacetic acid and sulfosalicylic acid (15). GFR was calculated based on the following formula: GFR = \[140 - \text{age (y)}\] \[\times\] \[\text{weight (Kg)}\]/72 \[\times\] (serum creatinine) (16). Serum total cholesterol and triacylglycerol concentration were measured by commercially available enzymatic reagents (Pars Azmoon, Iran) adapted to Selectra autoanalyzer. HDL-cholesterol was measured after precipitation of the apolipoprotein B containing lipoproteins with phosphotungstic acid. LDL-cholesterol was calculated according to the Friedewald method (17). It was not calculated when serum triacylglycerol concentration was greater than 400 mg/dl. All samples were analyzed when internal quality control met the acceptable criteria. Plasma phytoestrogen levels were measured by high performance liquid chromatography according to Franke et al (18) to check soy compliance. Inter- and intra-assay coefficients of variation were both < 5% for all measurements.

Statistical methods. Statistical analysis was performed using SPSS for Windows version 13.0 (SPSS, Chicago IL) and SAS version 8.2 (SAS Institute Inc, 1999). Kolmogrov-Smirnov test was used to assess if the variables were normally distributed. Skewed variable (CRP) was treated as log-transformed value in all analyses and reported as geometric mean. To avoid long tables, we used the mean of two measurements in each year to obtain one value for each year. Two-way analysis of variance was applied to assess the effect of time (baseline, 1st year, 2nd year, 3rd year, and 4th year), group and the interaction term between time and group. For comparing mean changes of the variables in soy protein and control groups, Student’s t test was used. For executing this procedure the difference between the 4th year and the first year were calculated as a new variable for each group and then the mean of these two new variables were compared by using the Student’s t test. To adjust for potential confounders, we used analysis of covariance (ANCOVA) with changes in lipid profiles, plasma glucose, body weight, and phytoestrogen intake as covariates. Further adjustments were also made for changes in plasma phytoestrogen levels.

RESULTS

Totally, 9 patients (out of 50) were excluded from the study due to different reasons: four subjects for not following the diet (n=3 in soy protein group vs. n=1 in control group) and five for starting dialysis (n=3 in soy protein group vs. n=2 in control group). Finally, 41 patients (20 in the case and 21 in the control group) with type 2 diabetes completed the entire 4-year trial. There were 18 men (43%) and 23 women (57%) in the study. Mean age of patients completed the whole trial (n=41) was 62.0 ±12.0 y [soy protein group (n=20): 61.9±11.8 y and control group (n=21): 62.1 ±12.1 y] and 67% of them (n=27 out of 41) had positive family history of diabetes [70 % (n=14) in soy protein group vs. 61% (n =13) in the control group]. The proportion of patients using ACE inhibitors, ARB and diuretics in soy protein group was 32% (n=8), 40% (n=10) and 80% (n=20). These proportions in control group were 48% (n=12), 48% (n=12) and 72% (n=18), respectively. 73 percent of the patients had retinopathy (34% in soy protein group and 39% in the control group). Nutrient intakes of participants based on the mean of the 3-day dietary records at baseline and during each year are shown in Table 1. Soy protein was well tolerated. Patients’ activity level remained unchanged across all study periods.

Means for cardiovascular risk factors are separately provided by groups in Table 2. Fasting plasma glucose (values for 4th year in soy protein vs. control groups: 121±42 vs. 147±57mg/dl; P time =0.03, P group = 0.01, P
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time*group = 0.02), total cholesterol (201±35 vs. 218±38 mg/dl; P_{time} = 0.01, P_{group} = 0.01, P_{time*group} = 0.01), LDL-C (128±14 vs. 158±31 mg/dl; P_{time} = 0.01, P_{group} = 0.01, P_{time*group} = 0.09), and serum triglyceride levels (224±43 vs. 232±49 mg/dl; P_{time} = 0.01, P_{group} = 0.01, P_{time*group} = 0.14) declined significantly in soy protein group as compared to control group. C-reactive protein, a marker of the inflammation, also decreased significantly by soy protein consumption (2.4±0.1 vs. 3.9±0.2 mg/L; P_{time} = 0.01, P_{group} = 0.01, P_{time*group} = 0.01). Proteinuria (513±39 vs. 725±81 mg/d; P_{time} = 0.01, P_{group} = 0.01, P_{time*group} = 0.01), urinary urea nitrogen (12.8±3.6 vs. 19.5±5.6 mg/dl; P_{time} = 0.04, P_{group} = 0.02, P_{time*group} = 0.08) and urinary creatinine (3.1±0.3 vs. 5.2±0.4 mg/dl; P_{time} = 0.01, P_{group} = 0.01, P_{time*group} = 0.01) were improved significantly in soy protein group.

Mean change of cardio-renal risk factors and CRP are indicated in Figure 1. Soy protein consumption significantly affected fasting plasma glucose (mean change in soy vs. control groups: -18±3 vs. 11±2 mg/dl; P = 0.03), total cholesterol (-23±5 vs. 10±3 mg/dl; P = 0.01), LDL-C (-20±5 vs. 6±2 mg/dl; P = 0.01), and serum triglyceride concentrations (-24±6 vs. -5±2 mg/dl; P = 0.01). C-reactive protein decreased significantly by soy protein intake (1.31±0.6 vs. 0.33±0.1 mg/L; P = 0.02). Changes in proteinuria (-0.15±0.03 vs. 0.02±0.01 g/d; P = 0.001) and urinary creatinine were also significant (-1.5±0.9 vs. 0.6±0.3 mg/dl) comparing soy protein and control groups. The significant findings on proteinuria were disappeared after controlling for changes in blood lipid profiles; however, adjusting for other covariates like changes in plasma glucose, phytoestrogen intake and body weight had minimal effects on this finding. Significant changes in urinary creatinine and urinary urea nitrogen did not affected by controlling for changes in covariates. Further adjustments for changes in plasma phytoestrogen levels made soy impacts on fasting plasma glucose marginally significant (P = 0.06), with other dependent variables minimally affected.

**DISCUSSION**

The results of the present study, performed among a group of type 2 diabetic patients with nephropathy, showed that 4-year soy substitution in the diet was resulted in significantly lower level of fasting blood glucose, total cholesterol, LDL-C, and triglyceride levels. The circulating level of CRP, the most popular inflammatory marker, decreased after 4-year soy consumption. Besides cardiovascular risks, renal indices also improved significantly.

Although several short-term studies are available regarding the effect of soy on kidney-related biomarkers and cardiovascular risk factors (4, 7, 8), to our knowledge this is the first study that have assessed such effects for a long time (4-year). So, the results would be useful in interpreting the stability of soy effects. As shown in the current study, the beneficial effects of soy consumption on cardiovascular risks and kidney-related biomarkers were stable in long time soy consumption. As the diabetic nephropathy is a progressive disease, we expected that the conditions of these patients got worse after 4-year but because of medical and dietary control their situation got better in some points.

It seems that soy protein consumption might have a favorable effect on diabetic nephropathy through its impact on serum lipid levels (19, 4). The association between hypercholesterolemia and diabetic nephropathy has been demonstrated earlier (20). The results of the present study are also in line with previous ones in indicating that the effects of soy protein consumption on proteinuria could be mediated through its impact on lipid profiles. Plasma glucose
levels have also been reported to modulate kidney function (21). Our results do not support this because soy consumption affected proteinuria independent of changes in plasma glucose. The interaction between prevailing blood glucose levels and protein intake in the regulation of the renal response to a protein load has not been identified exactly (22).

The beneficial effects of soy protein on cardiovascular risks might be mediated through its impacts on abdominal fat. Sites et al (23) suggested that soy protein containing isoflavones may prevent the accumulation of fat in the abdominal depot. Their study showed a significant effect of soy intake on total and subcutaneous abdominal fat. Even after adjusting for total body fat, they found a strong trend toward an effect of soy to prevent visceral fat accumulation. This finding could have important implications in the prevention of insulin resistance and cardiovascular disease.

We used naturally occurring isoflavones in the form of isolated soy protein in our intervention trial instead of purified isoflavones. The isoflavones and fiber content of the soy protein and probably its inositol-derived substances such as lipintol and pinitol might have beneficial effects on the blood lipid level and glycemic control (24, 25). The improvement in blood lipid and glucose levels might explain, to some extent, improvements we observed in kidney function.

Diabetic patients have been reported to have high circulating levels of inflammatory markers (1), however, few studies have assessed the effect of soy consumption on inflammatory biomarkers particularly among diabetic patients. Our findings suggest that 4-year soy substitution in the diet decrease C-reactive protein significantly in soy protein group as compared to control group. The decline in cardiovascular risks and also renal failure in soy protein group might be explained by improvements in inflammation status. We have just studied C-reactive protein from among a large number of inflammatory markers because of the cost limitation. For accurate judgment, assessing the impact of soy consumption on other inflammatory markers seems warranted.

The amount of soy protein intake in the present study was approximately 16 grams per day. Higher amounts might have better results on cardiovascular risks and kidney-related indices. However, large doses might be associated with some other health risks (26). In some situations, excessive soy protein intake could do more harm than good; existing evidence suggests that genistein can stimulate estrogen-receptor positive breast cancers to grow (26).

We recommended textured soy protein in the current study. Previous studies have shown that other soy products such as soy nut might have more beneficial effects on cardiovascular risks (7), inflammatory markers (8) and oxidative stress (27) than that textured soy protein. Further studies are required to assess the effects of soy nut among type 2 diabetic patients with nephropathy.

We did not evaluate the effects of soy protein according to estrogen receptor genotype in our participants; in some studies responses to isoflavones consumption have varied according to the estrogen receptor genotype (28). Also, further studies might be warranted to assess the effect of soy consumption on different complications of diabetic patients with nephropathy while taking the “equol producer” or “equol non-producer” status into account (28).

Several points need to be clarified in the current study. Poor adherence to the diet has been reported in the management of type 2 diabetes (29). In the current study, the adherence to both diets was good based on the results of 3-day dietary records (12 records every year) and plasma phytoestrogen levels. Adherence to diet was supported by the close
relationship between dietitian and patients via monthly phone calls encouraging them to follow their diets. Patients were also taking recommendations on dietary adherence by their physician every three months they were attending.

Patients' mean HbA1c was 6.2% suggesting a good glycemic control. This could be attributed to oral glucose lowering agents and insulin injections they were taking. Because of the good glycemic control in these patients, one might assume that diabetes was not established in these patients. While the patients were typical cases of type 2 diabetes (mean duration of diabetes was 10 y) and normal values of the HbA1c might be just resulted from medication use or insulin injections. As we all know even a few days of normal plasma glucose within a month would result in a near normal HbA1c values. The population studied is not grossly different from patients usually studied in Europe or North America. Also, the method of measurement of HbA1c did not differ significantly from usually employed techniques. However, the accuracy of measurements might be different. HbA1c levels reported from Iranian studies are in the range of 5-9%, most are for diabetics not using medications or insulin. Anyway, the finding of mean HbA1c of 6.2% might warrant further investigations.

Hypertension was present in all patients (mean duration of hypertension was 8 y). Even the diets we prescribed could not affect hypertension more substantially. One possible explanation for persistent hypertension among these patients is involvement of vessel's injuries in its etiology. As mentioned above, most of these diabetic patients had retinopathy; a consequence of diabetes resulting from vessels' deterioration (30). The other point that must be taken into account is that blood pressure's response to hypertensive medications mostly takes longer time, particularly when several factors involved in its etiology (30). Mean values of serum creatinine in our study might bring this question that some patients had hypertensive nephropathy instead of diabetic nephropathy. It should be kept in mind that the creatinine clearance is more important than serum creatinine for interpretation of the situation in these patients. It's so hard to differentiate if their nephropathy was the result of hypertension or diabetes. What is clear is that all had diabetes at first and after awhile their nephropathy has been occurred [they were attending to their physician (SA) for long times]. All patients were in the stage 1 or 2 of nephropathy. Therefore, it takes time to progress to the point of needing dialysis. Both groups had minimal progression (compared to what is expected) in nephropathy during the four years which could be attributed to the medications' use and the stage of nephropathy. None of the patients were in the third stage of nephropathy. The control group received all medications and treatments that the case group was receiving except for the soy protein.

One of the limitations of the current study is that urinary urea nitrogen and urinary creatinine were measured as concentrations rather than as 24-h excretion. Concentrations of these variables are less relevant to kidney function than 24-h excretion.

In conclusion, longitudinal soy protein consumption has beneficial effects on cardiovascular risk factors, C-reactive protein and kidney-related indices among type 2 diabetic patients with nephropathy.

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REFERENCES

TABLE 1. Nutrient intakes of the study participants

<table>
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<th>Nutrient intake</th>
<th>Soy protein group</th>
<th>Control group</th>
<th>P values</th>
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<td>baseline</td>
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<td>2\textsuperscript{nd} y</td>
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<td>Energy (kcal/day)</td>
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T: time; G: group
\textsuperscript{1}Mean±SD
### TABLE 2. Cardiovascular risk factors, C-reactive protein and markers of the renal function among type 2 diabetic patients with nephropathy

<table>
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1Mean ± SD
SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FPG: Fasting plasma glucose; TC: Total cholesterol; TG: serum triglyceride; UUN: Urinary urea nitrogen; S-Creatinine: Serum creatinine; U-Creatinine: Urine creatinine; Bun: Blood urea nitrogen; GFR: Glomerular filtration rate; CRP: C-reactive protein; T: time; G: group
FIGURE LEGEND

Figure 1. Mean (±SD) changes from baseline in cardio-renal indices and CRP levels. Mean changes in weight, and FPG are shown in panel A. Panel B shows mean changes in cardiovascular risks (lipid profiles, blood pressure, and C-reactive protein). Panel C shows mean changes in renal function indices. A statistically significant difference was found comparing soy protein and control groups with regard to changes in fasting plasma glucose, total cholesterol, triglyceride, LDL and CRP levels and also proteinuria and urinary creatinine (P<0.05 for all).

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FPG: Fasting plasma glucose; TC: Total cholesterol; TG: serum triglyceride; UUN: Urinary urea nitrogen; S-Creatinine: Serum creatinine; U-Creatinine: Urine creatinine; Bun: Blood urea nitrogen; GFR: Glomerular filtration rate; CRP: C-reactive protein.
FIGURE 1

Panel A

Panel B

Panel C

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