IJKD KIDNEY DISEASES

Kidney Function Improvement by Soy Milk Containing *Lactobacillus plantarum A7* in Type 2 Diabetic Patients With Nephropathy

A Double-Blinded Randomized Controlled Trial

Behnood Abbasi,[1] Reza Ghiasvand,[1] Maryam Mirlohi[2]

[1]Department of Community Nutrition, School of Nutrition and Food Sciences, Isfahan University of Medical Sciences, Isfahan, Iran
[2]Department of Food Technology, School of Nutrition and Food Sciences, Isfahan University of Medical Sciences, Isfahan, Iran

Original Paper

Keywords. diabetic nephropathy, probiotics, glomerular filtration rate, soy milk

Introduction. Even with the ultimate medical management, more than one-third of diabetic patients develop diabetic nephropathy. To our knowledge, there is no study that has examined the effect of probiotic soy milk on kidney function in type 2 diabetic patients with nephropathy. This clinical trial aimed to assess the effects of consumption of probiotic soy milk, compared with conventional soy milk, on kidney-related indexes in patients with diabetic nephropathy.

Materials and Methods. In a randomized double-blinded placebo-controlled trial, 44 patients were randomly assigned to receive 200 mL/d of either soy milk containing *Lactobacillus plantarum A7* or conventional soy milk for 8 weeks. Primary endpoints included urinary albumin excretion, estimated glomerular filtration rate, interlukin-18, serum sialic acid, and serum creatinine. Fasting blood samples and morning fasting spot urine samples were collected at the beginning and after 8 weeks for evaluation of biochemical parameters.

Results. Forty patients completed the study. Administration of probiotic soymilk resulted in a significant reduction in albuminuria ($P = .03$), serum creatinine ($P < .001$), serum interleukin-18 ($P = .002$), and serum sialic acid ($P = .001$) compared with conventional soy milk. Probiotic soymilk supplementation also led to a significant improvement in estimated glomerular filtration rate (15.9 ± 10.8 mL/min versus 3.2 ± 8.4 mL/min, $P < .001$) compared with the control group.

Conclusions. Probiotic soy milk was safe and well-tolerated by patients with diabetic nephropathy for 8 weeks. Probiotic soy milk also improved indexes of kidney function in type 2 diabetic patients with nephropathy.

IJKD 2017;11:36-43
www.ijkd.org

INTRODUCTION

Type 2 diabetes mellitus (DM) is a very common noncommunicable disease, comprising more than 90% of 415 million adults who are suffering from DM all over the world.[1] As a result of population aging, urbanization, and cultural and socio-economic changes in human life in the 21st century, the prevalence of DM is growing quickly globally to form an epidemic disease. By the year 2040, the total number of people living with DM is estimated to reach 642 million and 1 in 10 adults will have DM.[1] Diabetic nephropathy (DN), is defined as

relentless albuminuria or constant impairment of glomerular filtration rate (GFR).[2] Along with the global increase in the prevalence of DM, DN, a major complication of DM and the foremost cause of end-stage renal failure (ESRD), is becoming a bigger public health issue.[3] Between 25% to 40% of diabetic patients develop progressive DN,[4] which is responsible for about 40% of the newly diagnosed cases of ESRD.[5] In addition, DN not only increases the risk of developing ESRD, it is also associated with increment in the rate of morbidity and mortality.[4]

Tight control of blood pressure along with intensive glycemic control, lipid lowering agents, and lifestyle interventions are the most common and effective therapeutic strategies for renal protection and hindering the progression of nephropathy in diabetic patients.[6] Although the aforementioned therapeutic interventions postpone the progression of DN, the prevalence of DN and its comorbidities remains very high, and most of patients with DN continue to progress to ESRD.[7]

Although the consumption of probiotics for their health benefits has a long history and the biotherapeutic potential of probiotics has been reported in gastrointestinal disorders, DM and some infectious diseases,[8,9] only very limited number of studies have assessed the effect of probiotic consumption on nephropathy. Lu and colleagues' study showed that *Lactobacillus reuteri* may attenuate diabetic renal fibrosis due to regulation of glucose tolerance and oxidative stress in diabetic rats.[10] Based on our search, no human study has been conducted to evaluate the effect of probiotics in diabetic patients, yet. However, Ranganathan and coworkers have studied the effect of probiotic supplementation on kidney function in chronic kidney disease and reported some positive effects.[11] To our knowledge, our study was the first to evaluate the effect of probiotic soy milk in nephropathy to assess whether probiotic soy milk could have an additive or interacting effect on kidney function compared to soy milk.

MATERIALS AND METHODS

Participants and Study Design

The current study was a double-blinded randomized control trial, which was reported according to the Consolidated Standards of Reporting Trials guidelines.[12] Based on the sample size formula suggested for controlled trials, considering C-reactive protein (CRP) concentration as a key variable,[13] a power of 80%, and a type I error of 5% ($\alpha = 0.05$), the required sample size was calculated to be 20 individuals per group. Assuming a 10% drop-out rate, the final sample size was estimated to be 44 participants (22 participants per group). The inclusion criteria for the current study were an age of 25 years and older; proven type 2 DM for more than 1 year, with a fasting blood glucose (FBS) higher than 126 mg/dL and a 2-hour postprandial blood glucose higher than 200 mg/dL; and microalbuminuria and an estimated GFR higher than 60 mL/min. Patients with a prior history of inflammatory bowel disease, infection, liver disease, rheumatoid arthritis, smoking, alcoholism, recent antibiotic therapy, and consuming multivitamins, minerals, or omega-3 supplements, 1 month prior to beginning of the intervention were excluded from the study.

A total of 44 participants were randomly allocated to the soy milk group (control) or probiotic soy milk group who received 200 mL/d of soy milk or probiotic soy milk for 8 weeks. At each study visit, participants received sufficient bottles of soy milk for a 3-day period until the next visit, in a double-blinded design. Participants were asked to keep the bottles refrigerated at 2°C to 4°C and were required to return unused or empty bottles at the next study visit to assess study intervention adherence. Our protocol required a minimum intervention adherence of greater than 90% (more than 50 out of 56 bottles). Anthropometric measurements were done by trained staff according to the World Health Organization standards. The data were recorded in a general form. Anthropometric measurements were repeated again at the end of the 8th week of the study. Participants were refrained from consumption of any probiotic products 2 weeks before beginning of the study. All of the participants were instructed to consume a diet containing 0.8 g/kg of protein, 2000 mg of sodium, 2000 mg of potassium, and 1500 mg of phosphorus. The dietary intakes were assessed using 24-hour recall for 3 days (covered 2 weekdays and a weekend day). These dietary intakes were then analyzed using the modified version of Nutritionist-4 software program and were used for checking the diet compliance. If any correction was needed, after the run-in period or during the intervention, it was

made by a trained dietitian. Physical activity was assessed using the International Physical Activity Questionnaire (IPAQ). The study protocol was registered at the Iranian Registry of Clinical Trials (Register code: IRCT201601027479N2 available at: http://www.irct.ir).

Intervention

Conventional and probiotic soy milk were made available every 3 days and were dispensed among the participants. The probiotic soy milk contained 2×10^7 cfu/mL of *Lactobacillus plantarum A7*, was sampled on the day of delivery, and was microbiologically analyzed every 2 weeks. An MRS Broth (MRS agar, Merck, Darmstadt, Germany, and bile, Sigma-Aldrich, Reyde, USA) and the pour plate method were used to evaluate the total colony count of *Lactobacillus plantarum A7* in probiotic soy milk. The result of the colony counting test indicated that the survival rate and concentration of *Lactobacillus plantarum A7* in probiotic soy milk remained steady between the 1st day of production and the 3rd day at 2°C to 4°C. The nutrient composition of soy milk (per 100 mL) consumed by study participants, based on our analysis, is shown in Table 1. The current study had a 2-week run-in phase prior to the beginning of the intervention, in which participants should avoid from consumption of any fermented or probiotic foods. They were also asked to avoid consumption of any dietary supplement and report any change of their medications to the researchers. Conventional and probiotic soy milk were manufactured by Isfahan Soy Milk Company (Isfahan, Iran).

Biochemical Analysis

To analyze biochemical factors of participants, 10 mL of venous blood were collected at baseline and after the 8th week of intervention in the early morning after an overnight fast and within 1 to 2 hours, the blood samples were centrifuged at 3500 rpm for 10 minutes and the sera were put in a –80°C freezer until they were used for subsequent biochemical analysis. Appropriate biochemical analyses were used to assay concentration of creatinine (alkaline picrate), phosphorus (phosphomolybdate/UV) in sera (Biosystems Analyzer A-15, Spain). Morning fasting spot urine samples were used to measure urine albumin and creatinine (Hitachi 902 Autoanalyzer, Boehringer Mannheim, Germany); then, urinary albumin-creatinine ratio was calculated on the basis of its formula to estimate the daily albumin excretion. An enzyme-linked immunosorbent assay method was used to quantify the concentration of serum interleukin-18 (IL-18; Boster, USA) and serum Sialic acid (SSA; Eastbiopharm, China). All the tests were performed in a blinded fashion, in pairs (before and after the intervention) at the same time, in the same analytic run, and in random order to reduce systematic error and interassay variability. We also assayed the adherence to the intervention by measuring the serum concentration of genistein by a time-resolved fluorescence immunoassay method (Labmaster, Finland).Volunteers did not know that adherence was determined by serum concentration of genistein.

Table 1. Nutrient Composition of Soy Milk Used in Trial

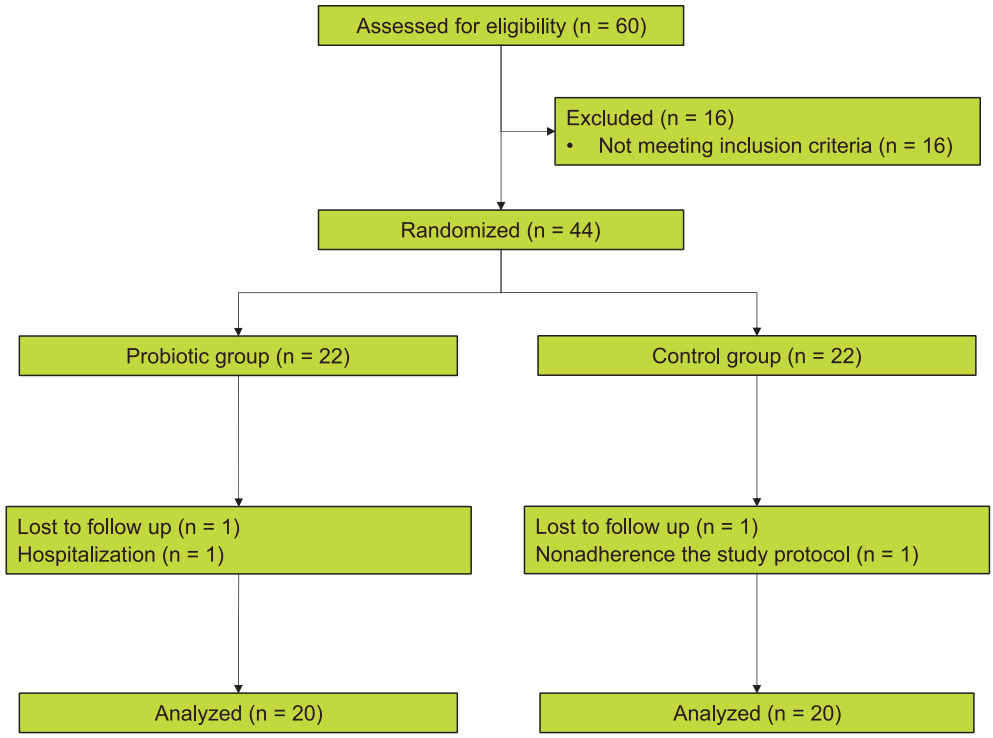
Nutrient	Amount per 100 mL
Energy, kcal	30
Protein, g	2.8
Carbohydrate, g	1.8
Fat, g	1
Saturated fatty acids, g	0.4
Phosphorus, mg	48
Iron, mg	1
Sodium, mg	3
Genistein, mg	7
Magnesium, mg	15

Statistical Analysis

Before conducting any statistical test, the normal distribution of variables was examined using the Kolmogrov-Smirnov test. Log transformation was conducted when the variables did not follow the normal distribution. For quantitative variables, mean and standard deviation were reported. The independent sample *t* test was used to determine whether significant difference existed between the control and the intervention groups. Furthermore, the paired *t* test was used to compare the means of each variable before and after the intervention in each group. To adjust the confounding factors and detect the effect of consumption of probiotic soy milk on kidney-related indexes between the two groups, the analysis of covariance was used. Statistical analyses were conducted using the SPSS software (Statistical Package for the Social Sciences, version 23.0, SPSS Inc, Chicago, IL, USA), and a *P* value less than .05 was reported significant.

RESULTS

Forty-four patients participated, and 40 completed the study (20 patients in each group; Figure). Two men in the probiotic group were excluded because of hospitalization (n = 1) and loss to follow-up (n = 1). One man and 1 woman in the control group were also excluded due to poor adherence and loss to follow-up. The mean body weight, body mass index, and age were 71.2 ± 10.9 kg, 26.63 ± 3.1 kg/m^2, and 55.2 ± 7.7 years, respectively. The baseline characteristic of the patients are presented in Table 2. There were no significant difference in the anthropometric characteristics at baseline between the probiotic soy milk and conventional soymilk groups. However, dietary carbohydrate intake was significantly



Flowchart of Random Allocation and Treatment of Participants

Table 2. General Characteristics and Nutrient Intake of Study Participants Who Received Either Conventional Soy Milk or Probiotic Soy Milk*

Characteristic	Probiotic Soy Milk Group (n = 20)	Soy Milk Group (n = 20)	*P*
Age, y	56.9 ± 8.1	53.6 ± 7.19	.18
Duration of disease, y	8.7 ± 2.1	6.9 ± 4.9	.46
Body weight, kg	70.8 ± 10.7	71.6 ± 11.4	.82
Height, cm	162.9 ± 6.6	163.6 ± 6.0	.74
Body mass index, kg/m^2	26.68 ± 3.19	26.58 ± 3.27	.92
Physical activity (%)			
Low	16 (80)	13 (65)	
Moderate	4 (20)	7 (35)	.29
Calorie intake, kcal/d	2105.8 ± 149.7	2173.4 ± 143.6	.15
Protein intake, g/d	61.6 ± 8.0	62.2 ± 5.3	.77
Fat intake, g/d	90.5 ± 8.6	92.9 ± 11.6	.47
Carbohydrate intake, g/d	275 ± 24.7	309.7 ± 29.2	< .001
Dietary cholesterol intake, mg/d	271.2 ± 19.8	279.2 ± 25.2	.62
Dietary fiber intake, g/d	17.6 ± 2.7	18.7 ± 3.7	.30

*All values are means ± standard deviation except for physical activity, which is frequency (percentage).

higher in the control group ($P < .001$) compared with the probiotic soy milk group. Hence, the probable effect of dietary carbohydrate intake was adjusted using the analysis of covariance test. No significant differences were detected in the other dietary intakes or physical activity between the two groups (Table 2). The baseline values of biochemical factors, including serum creatinine, serum genistein, urinary albumin-creatinine ratio, IL-18, and SSA are also presented in Table 3. These values were not markedly different between the two groups. There were no significant changes either in body weight, body mass index, or waist-hip ratio during the study (Table 4).

Administration of probiotic soymilk, containing *Lactobacillus plantarum A7* resulted in a significant reduction in albuminuria (-16.5 ± 12.2 mg/d versus -5.7 ± 15.04 mg/d, $P = .03$), serum creatinine (-0.17 ± 0.11 mg/dL versus -0.03 ± 0.08, $P < .001$), serum IL-18 (-49.18 ± 48.22 mg/dL versus -9.03 ± 18.65 mg/dL, $P = .002$), and serum sialic acid (-17.4 ± 11.43 mg/dL versus -4.37 ± 9.91 mg/dL, $P = .001$) compared with conventional soy milk. Probiotic soymilk supplementation also led to a significant improvement in estimated GFR (15.9 ± 10.8 mL/min versus 3.2 ± 8.4 mL/min, $P < .001$) and a marked increment in serum genistein (17.6 ± 15.3 mg/dL versus 4.5 ± 2.3 mg/dL, $P = .003$) compared with the control group.

Adherence to soy milk consumption was a problem for some of the participants, especially at the beginning of the study. However, adherence was good in 90% of of the participants who used at least 50 bottles out of 56 bottles of their probiotic or conventional soy milk. These results were also confirmed by measuring serum genistein concentration, which showed an increment of serum genistein in all of these participants. There were only negligible complaints about flatulence (4 people in the intervention group and 5 in the control group) and the specific taste of soy milk at the beginning of the intervention.

Table 3. Baseline Biochemical Factors of Study Participants Who Received Either Conventional Soy Milk or Probiotic Soy Milk*

Characteristic	Probiotic Soy Milk Group (n = 20)	Soy Milk Group (n = 20)	*P*
Interleukin-18, pg/mL	286.14 ± 207.80	335.14 ± 266.65	.52
Serum sialic acid, mg/dL	223.60 ± 44.72	232.33 ± 40.79	.52
Serum creatinine, mg/dL	1.01 ± 0.11	1.03 ± 0.16	.51
Serum genistein, nmol/L	24.31 ± 13.9	22.30 ± 13.46	.65
Glomerular filtration rate, mL/min/1.73m^2†	71.5 ± 9.5	72.1 ± 9.1	.84
Urinary albumin-creatinine ratio, mg/g	145.8 ± 29.1	147.0 ± 38.6	.91

*All values are means ± standard deviation.
†Calculated based on the CKD-EPI equation (2009) not adjusted for body surface

Table 4. Anthropometric Measures and Kidney Function Indices at Baseline and After Intervention in Study Participants Who Received Either Conventional Soy Milk or Probiotic Soy Milk*

Parameter	Probiotic Soy Milk Group (n = 20)			Soy Milk Group (n = 20)			*P*
	Before Intervention	After Intervention	Change	Before Intervention	After Intervention	Change	
Body weight, kg	70.84 ± 10.78	70.40 ± 10.42	-0.56 ± 1.07	71.61 ± 11.43	71.21 ± 11.45	-0.5 ± 0.51	.96
Body mass index, kg/m^2	26.68 ± 3.2	26.51 ± 3.07	-0.17 ± 0.29	26.58 ± 3.27	26.33 ± 3.34	-0.25 ± 0.21	.31
Waist-hip ratio	1.52 ± 0.41	1.49 ± 0.38	-0.03 ± 0.04	1.59 ± 0.51	1.54 ± 0.47	-0.05 ± 0.07	.35
Serum interleukin-18, pg/mL	286.14 ± 207.8	236.96 ± 181.87	-49.18 ± 48.22	335.14 ± 266.65	326.1 ± 260.34	-9.03 ± 18.65	.002
Serum sialic acid, mg/dL	223.6 ± 44.72	206.2 ± 43.24	-17.4 ± 11.43	232.33 ± 40.79	227.95 ± 40.5	-4.37 ± 9.91	.001
Serum creatinine, mg/dL	1.01 ± 0.11	0.83 ± 0.16	-0.17 ± 0.11	1.03 ± 0.16	1.00 ± 0.14	-0.03 ± 0.08	<.001
Serum genistein, nmol/L	24.31 ± 13.9	41.9 ± 16.0	17.6 ± 15.3	22.33 ± 13.4	26.8 ± 12.8	4.5 ± 10.6	.003
Glomerular filtration rate, mL/min/1.73m^2†	71.5 ± 9.5	87.5 ± 14.2	15.9 ± 10.8	72.1 ± 9.1	75.4 ± 11.13	3.2 ± 8.4	< .001
Urinary albumin-creatinine ratio, mg/g	145.8 ± 29.1	129.36 ± 31.9	-16.5 ± 12.2	147.0 ± 38.6	141.36 ± 37.9	-5.7 ± 15.04	.03

*All values are means ± standard deviation.
†Calculated based on the CKD-EPI equation (2009) not adjusted for body surface

DISCUSSION

This is the first time that the effect of administration of probiotic soy products is assessed and reported on kidney function of type 2 diabetic patients with nephropathy. Our findings demonstrated the beneficial effects of consumption of soy milk containing *Lactobacillus plantarum A7* on kidney-related indexes among diabetic patients with nephropathy for 8 weeks. Probiotic soy milk significantly amended GFR and led to a significant reduction in urinary albumin-creatinine ratio, serum creatinine, serum IL-18, and serum sialic acid concentrations. No significant differences were detected in weight, body mass index, waist-hip ratio, and physical activity among the intervention and the control groups, during the study. Hence, we concluded that the observed effects were not associated with change of anthropometric indexes.

Serum genistein concentration was assessed to detect the possible effect of *Lactobacillus plantarum A7* on bioavailability of bioactive compounds of soy milk. Our results showed that the adherence to the intervention was good and the increment of serum genistein was 4.5 ± 10.6 nmol/L (P = .07) and 17.6 ± 15.3 nmol/L (P < .001) for the control group and intervention group, respectively. After adjusting for baseline values the difference between the two groups was significant (P = .003). In agreement with our study, Kano and colleagues, Rekha and colleagues, and Tsangalis and colleagues showed that lactic bacteria glucosidase activity could increase the bioavailability of soy isoflavones.[14-16] This action is done by bioconversion of glycosidic form of isoflavones into aglyconic form, which is more bioavailable, more active and are absorbed more rapidly and efficiently than glycosides.[17]

In the current study, administration of probiotic soy milk containing *Lactobacillus plantarum A7* and conventional soy milk resulted in a significant decrease in serum concentration of IL-18 in the both groups. The between-group difference for IL-18 was also significant in probiotic soy milk group compared with the control group (P = .002). Concentration of IL-18 in serum is positively associated with the development of DN and can be used as a reliable prognosticator of vulnerability and progression of DN.[18] Additionally, it has been stated that IL-18 is independently associated with renal injury in type 2 diabetic patients with nephropathy,[19,20] and targeting IL-18 or its receptor can amend DN.[21] In line with our results, Azadbakht and associates, in a crossover clinical trial on 42 postmenopausal women with metabolic syndrome, showed that soy nut consumption can significantly reduce IL-18 compared with the control diet.[22] The underlying pathways is not understood well enough to give an exact mechanism. However, it has been suggested that soy isoflavones[23,24] or particular polyunsaturated fatty acids[25] are related to a lower concentration of pro-inflammatory cytokines. In addition, it has been suggested that ingestion of probiotic bacteria may have an independent effect on reduction of pro-inflammatory cytokines,[26] but the importance of anti-inflammatory role of probiotics on systematic inflammation is still unknown.

Findings from the present study showed that consumption of probiotic soy milk significantly decreased serum sialic acid concentration compared with conventional soy milk. Increased levels of SSA has been used as a biochemical marker for cell membrane injuries, particularly vascular damages. Linberg and colleagues showed that higher concentration of SSA was associated with increased risk of microvascular complications of DM such as DN and measuring of sialic acid could be used in discovering of degenerative complications of DM.[27] Moreover, Nayak and associates reported that increased SSA concentration in diabetic patients with nephropathy was related to renal tissue damage.[28] Crook and colleagues also suggested that SSA concentration was a risk factor for microvascular complication in diabetic patients with microalbuminuria and clinical proteinuria and it was possible to use it as a marker in these pathological conditions.[29] Our findings suggested that consumption of probiotic soy milk for 8 weeks was able to significantly reduce SSA concentration, maybe due to attenuation of kidney-related microvascular complications of DM, decrement of glomerular damage, or tubulointerstitial fibrosis, compared with conventional soy milk. These findings are in line with positive effects of soy product on kidney function in previous studies.[13 30-33] These effects could be explained by the influence of soy isoflavones on improvement of inflammation,[13] the effect of soy protein on renal function,[32] or independent effect of probiotics to reduce inflammation.[34]

The results indicated that soy milk containing *Lactobacillus plantarum A7* had a beneficiary

effect on albuminuria. In line with our findings, Azadbakht and colleagues showed that soy protein consumption significantly improved proteinuria in type 2 diabetic patients with nephropathy.[31,33] Ranganathan and colleagues, in a randomized controlled trial, showed that kidney function was improved as a result of probiotic administration while no serious adverse effect was observed in patients with chronic kidney disease.[11] It has been stated that beneficiary effects of probiotics on inflammation and the possible effect of lactic bacteria on reducing renotoxic metabolites of gut bacteria might be responsible in the reduction of urinary albumin excretion.[35,36] Moreover, probiotics and soy products might have an additive effect to attenuate albuminuria in type 2 diabetic patients.

Our findings indicated that taking probiotic soy milk among type 2 diabetic patients with nephropathy was associated with improvement of GFR compared with conventional soy milk. Probiotic soy milk also led to a significant decrement in serum creatinine compared with the control group. Regarding the findings of the previous studies which have evaluated the effect of probiotics or soy products on kidney function in patients with nephropathy, it can be suggested that probiotic soy milk might be able to improve kidney-related indexes due to the effect of either soy or lactic bacteria on reducing inflammation and the pro-inflammatory cytokines, attenuating glomerular injuries and tubulointerstitial lesions, and decrement of renotoxic bacterial products such as trimethylamine N-oxide, p-cresol, and indoxyl sulfate which may have toxic effects on renal tubules.[35] Moreover, it must be kept in mind that soy and probiotic might have synergistic biotherapeutic effects, too. Hence kidney function indexes might be promoted by the aforementioned mechanisms.[11,13,31,32,35] The effect of soy products on improving kidney functions in type 2 diabetic patients with nephropathy is well established. However, the novel achievement of the current study is that, it might possible to intensity the beneficiary effects of soy by using it as medium for probiotics.[37] Therefore, patients with DN can take more advantage of it, due to direct effect of lactic bacteria on inflammation and its indirect effect of probiotics to improve the bioavailability of soy bioactive compounds.

Some limitations of our clinical trial need to be taken into account. Although, we did not find any serious side effect, long-term consumption of soymilk contacting *Lactobacillus plantarum A7* must be investigated in future trials. Furthermore, it would be helpful to assess the composition of fecal residue and population of gut flora in the future studies. Additional studies are needed to confirm our results.

CONCLUSIONS

The key outcomes of this randomized controlled trial included a significant improvement in urinary albumin-creatinine ratio, GFR, and serum creatinine, and lack of any serious side effects in probiotic soy milk compared with conventional soy milk. Administration of probiotic soy milk also resulted in a significant decrease in IL-18 and SSA, which are markers of progression of DN.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. International diabetes foundation. Diabetes atlas. [Last accessed 2015, April, 20]. Available from: http://www.idf.org/diabetesatlas
2. de Boer IH, Rue TC, Hall YN, et al. Temporal trends in the prevalence of diabetic kidney disease in the United States. JAMA. 2011;305:2532-9.
3. Zhuo L, Zou G, Li W, et al. Prevalence of diabetic nephropathy complicating non-diabetic renal disease among Chinese patients with type 2 diabetes mellitus. Eur J Med Res. 2013;18:23432977.
4. MacIsaac RJ, Ekinci EI, Jerums G. Markers of and risk factors for the development and progression of diabetic kidney disease. Am J Kidney Dis. 2014;63:S39-62.
5. American Diabetes Association. Nephropathy in diabetes. Diabetes care. 2004;27:s79-83.
6. Shah IM, Mackay SP, McKay GA. Therapeutic strategies in the treatment of diabetic nephropathy - a translational medicine approach. Curr Med Chem. 2009;16:997-1016.
7. Elmarakby AA, Sullivan JC. Relationship between oxidative stress and inflammatory cytokines in diabetic nephropathy. Cardiovasc Ther. 2012;30:49-59.
8. Panwar H, Rashmi HM, Batish VK, et al. Probiotics as potential biotherapeutics in the management of type 2 diabetes - prospects and perspectives. Diabetes Metab Res Rev 2013;29:103-12.
9. Tanriover MD, Aksoy DY, Unal S. Use of probiotics in various diseases: evidence and promises. Polskie Archiwum Medycyny Wewnetrznej. 2012;122 Suppl 1:72-7.
10. Lu YC, Yin LT, Chang WT, et al. Effect of Lactobacillus reuteri GMNL-263 treatment on renal fibrosis in diabetic

rats. J Biosci Bioeng. 2010;110:709-15.

11. Ranganathan N, Ranganathan P, Friedman EA, et al. Pilot study of probiotic dietary supplementation for promoting healthy kidney function in patients with chronic kidney disease. Adv Ther. 2010;27:634-47.
12. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. Int J Surg (London). 2011;9:672-7.
13. Azadbakht L, Kimiagar M, Mehrabi Y, et al. Soy consumption, markers of inflammation, and endothelial function: a cross-over study in postmenopausal women with the metabolic syndrome. Diabetes Care. 2007;30:967-73.
14. Tsangalis D, Ashton J, McGill A, et al. Enzymic Transformation of Isoflavone Phytoestrogens in Soymilk by β-Glucosidase-Producing Bifidobacteria. J Food Sci. 2002;67:3104-13.
15. Kano M, Takayanagi T, Harada K, et al. Bioavailability of isoflavones after ingestion of soy beverages in healthy adults. J Nutr. 2006;136:2291-6.
16. Rekha CR, Vijayalakshmi G. Bioconversion of isoflavone glycosides to aglycones, mineral bioavailability and vitamin B complex in fermented soymilk by probiotic bacteria and yeast. J Appl Microbiol. 2010;109:1198-208.
17. Shimada K, Fujikawa K, Yahara K, et al. Antioxidative properties of xanthan on the autoxidation of soybean oil in cyclodextrin emulsion. J Agricul Food Chem. 1992;40:945-48.
18. Maeda S. Do inflammatory cytokine genes confer susceptibility to diabetic nephropathy? Kidney Int. 2008;74:413-15.
19. Moriwaki Y, Yamamoto T, Shibutani Y, et al. Elevated levels of interleukin-18 and tumor necrosis factor-α in serum of patients with type 2 diabetes mellitus: relationship with diabetic nephropathy. Metabolism. 2003;52:605-08.
20. Nakamura A, Shikata K, Hiramatsu M, et al. Serum interleukin-18 levels are associated with nephropathy and atherosclerosis in Japanese patients with type 2 diabetes. Diabetes Care 2005;28:2890-95.
21. Elsherbiny NM, Al-Gayyar MM. The role of IL-18 in type 1 diabetic nephropathy: The problem and future treatment. Cytokine. 2016;81:15-22.
22. Azadbakht L, Kimiagar M, Mehrabi Y, et al. Soy Consumption, Markers of Inflammation, and Endothelial Function A cross-over study in postmenopausal women with the metabolic syndrome. Diabetes Care. 2007;30:967-73.
23. Minchenko A, Caro J. Regulation of endothelin-1 gene expression in human microvascular endothelial cells by hypoxia and cobalt: role of hypoxia responsive element. Mol Cell Biochem. 2000;208:53-62.
24. Walker H, Dean T, Sanders T, et al. The phytoestrogen genistein produces acute nitric oxide–dependent dilation of human forearm vasculature with similar potency to 17β-estradiol. Circulation. 2001;103:258-62.
25. Grimble R, Tappia P. Modulation of pro-inflammatory cytokine biology by unsaturated fatty acids. Zeitschrift fur Ernahrungswissenschaft. 1997;37:57-65.
26. Isolauri E. Probiotics in human disease. The American journal of clinical nutrition 2001;73:1142S-46S.
27. Lindberg G, Eklund GA, Gullberg B, et al. Serum sialic acid concentration and cardiovascular mortality. BMJ. 1991;302:143-46.
28. Nayak BS, Roberts L. Relationship between inflammatory markers, metabolic and anthropometric variables in the Caribbean type 2 diabetic patients with and without microvascular complications. J Inflam. 2006;3:17.
29. Crook MA, Earle K, Morocutti A, et al. Serum sialic acid, a risk factor for cardiovascular disease, is increased in IDDM patients with microalbuminuria and clinical proteinuria. Diabetes Care. 1994;17:305-10.
30. Teixeira SR, Tappenden KA, Carson L, et al. Isolated soy protein consumption reduces urinary albumin excretion and improves the serum lipid profile in men with type 2 diabetes mellitus and nephropathy. J Nutr. 2004;134:1874-80.
31. Azadbakht L, Atabak S, Esmaillzadeh A. Soy protein intake, cardiorenal indices, and C-reactive protein in type 2 diabetes with nephropathy: a longitudinal randomized clinical trial. Diabetes Care. 2008;31:648-54.
32. Azadbakht L, Esmaillzadeh A. Soy-protein consumption and kidney-related biomarkers among type 2 diabetics: a crossover, randomized clinical trial. J Renal Nutr. 2009;19:479-86.
33. Azadbakht L, Shakerhosseini R, Atabak S, et al. Beneficiary effect of dietary soy protein on lowering plasma levels of lipid and improving kidney function in type II diabetes with nephropathy. Eur J Clin Nutr. 2003;57:1292-4.
34. Ejtahed HS, Mohtadi-Nia J, Homayouni-Rad A, et al. Probiotic yogurt improves antioxidant status in type 2 diabetic patients. Nutrition (Burbank). 2012;28:539-43.
35. Yacoub R, Kaji D, Patel SN, et al. Association between probiotic and yogurt consumption and kidney disease: insights from NHANES. Nutr J. 2016;15:1.
36. Vaziri ND, Wong J, Pahl M, et al. Chronic kidney disease alters intestinal microbial flora. Kidney Int. 2013;83:308-15.
37. Yeo SK, Liong MT. Effect of prebiotics on viability and growth characteristics of probiotics in soymilk. J Sci Food Agricult. 2010;90:267-75.

Correspondence to:
Reza Ghiasvand, Ph.D
Department of Community Nutrition, School of Nutrition and Food Sciences Isfahan University of Medical Sciences, Hezar Jarib St, Isfahan, Postal Code: 8174673461, Iran
Tel: +98 311 792 3153
Fax: +98 311 668 2509
E-mail: ghiasvand@hlth.mui.ac.ir

Received May 2016
Revised June 2016
Accepted July 2016