Review Article

Soy Protein and Chronic Kidney Disease: An Updated Review

Abstract

Chronic kidney disease (CKD) is a serious universal problem that is the main risk for several diseases including cardiovascular disease. Dietary factors are important to prevent and control the kidney disease. Some evidence has shown that modifying the amount and the types of dietary protein exert a major effect on renal failure so limiting dietary protein and substituting animal protein with soy protein has suggested. However, there is a lot of controversy about it, especially in human. Thus, this paper will review the clinical trial studies conducted on the effects of soy protein intake on CKD in both animal and human and its effect mechanism.

Keywords: *Chronic kidney disease, soy protein, soybeans*

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Introduction

Chronic kidney disease (CKD) is a serious, universal, and popular health problem that its incidence is increasing rapidly[1-4] and more than one million people with CKD are dying every year.[5-7] It is an important risk for cardiovascular disease, inflammation, dermatitis and bone disease.[7-10] African–American race, elevated blood pressure (BP), male sex, obesity, hypertension, type 2 diabetes, smoking, family history of CKD, and aging are main risk factors of CKD.[11-15] A number of studies indicated that prevalence of the chronic renal disease is higher in native population in various countries due to several factors such as lifestyle so having a healthy lifestyle plays a key role in decreasing the risk of kidney disease.[7] One of the important lifestyle factors is diet.[16,17] Dietary factors are valuable to prevent and manage the kidney disease.[18-20] The needs and consumption of nutrients change the significantly during the progression of CKD, and in these patients, the occurrence of protein-calorie malnutrition is the main predictor of weak outcomes.[21-24] Some studies are clearly indicating that intake of protein diminished in malnutrition. The daily protein intake is a marker to evaluate the nutritional status of CKD.[20]

Some evidence has revealed that altering the quantity and the types of dietary protein exert the main effect on renal failure.[25-27] It is well-known that limiting dietary protein alleviate renal injury while high protein intake accelerates the development of CKD.[28-30] In recent times, protein quality by changing animal protein with plant protein, especially soy protein has been considered.[31]

Soybeans supply high-quality plant protein and exclusive isoflavones (genistein and daidzein).[32] Soy protein contains a unique amino acid profile that is different from animal and soy peptides including 4 to 20 amino acids which may have been very worthy effects on high BP and hyperlipidemia; therefore, soy peptides may affect renal function. In the animal, it seems to be well established the ability of soy protein to reduce proteinuria and consequently, to lower the progression of renal disease. Some investigators have shown in rats that were received a soy protein diet, a considerable recovery of creatinine clearance and a significant decrease in proteinuria compared with rats that were fed with casein, although the effect of soy protein is well studied in rats, this statement is not true for humans. In humans, this issue was not yet carefully investigated, and there is a lot of controversy about it. Thus, this paper will review the research conducted on the effects of soy protein intake on CKD.[33-35]

Animal Study

To better understand the mechanisms of the effect of soy on kidney disease progression, Aukema *et al*. investigated the distinctive

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influence of plant protein sources in experimental polycystic kidney disease. In this study, hemp, pea, and soy protein-based diets were compared with a standard diet with casein in Weanling Han:Sprague-Dawley rats. The kidney of Rats that had soy or hemp protein-based diets compared Rats with casein-based diet were less puffed-up, had minor cyst volumes, lower fluid amount, less chemokine receptor 2 (CCR2) levels and fibrosis, also serum creatinine (SCr) levels were normalized. Kidneys from rats fed with pea protein were more enlarged and had more cyst volumes and higher fluid amount, in spite of growing better and having lesser renal CCR2 quantities, SCr and equal degrees of renal fibrosis. Hence, it is concluded that all plant proteins did not similarly protect against kidney disease.[36]

Ogborn (2010) to study the effect mechanism of soy in improving renal function, divided male Han: SPRD-cy to four group that, respectively, were fed casein (C), high isoflavone soy protein (HIS), alcohol-extracted low isoflavone soy protein (LIS) or mixed soy protein diet (MIS). LIS and MIS were related with a little reduction in animal weight compared with HIS or C. Soy diets maintained natural renal function and decreased grades for cystic variation, renal weight, fibrosis, tissue oxidized low-density lipoprotein (LDL) amount, epithelial cell proliferation, and inflammation. In *post hoc* testing, in LIS group epithelial proliferation, relative renal weight, reduced but cystic variation increased. In HIS group oxidized-LDL was reduced significantly more than LIS group. Soy diets related with the raised hepatic amount of ^{18}C polyunsaturated fatty acid. LIS and HIS diets caused a little rise in body fat content, and LIS maintained its main protective influences. This study highlights various mechanisms of effect with diet interventions.[37]

To investigate the contribution of nitric oxide (NO) and caveolin-1 in protective impression of replacement of animal protein with soy, Trujillo *et al*. evaluated proteinuria, renal structural lesions, nitrites, nitrates urinary excretion (UNO_2^-/NO_3V), creatinine clearance, and protein and mRNA levels of caveolin-1, endothelial NO synthase (eNOS) and neuronal NO synthase (nNOS) in lean and fatty Zucker rats. They fed with 20% soy protein or casein for 160 days. In fatty Zucker rats nourished by casein, renal insufficiency progressed, proteinuria and renal structural injuries increased, and these changes possibly related to a significant reduction of UNO_2^-/NO_3V, variations in nNOS and eNOS mRNA quantities, with the enhanced quantity of eNOS and caveolin-1 in the kidney's plasma membrane proteins. In fatty Zucker rats fed with soy, was detected that soy diet improved kidney function, proteinuria, and UNO_2^-/NO_3V, and decreased interstitial fibrosis, glomerulosclerosis, extracapsular proliferation, and tubular dilation. Therefore, they concluded that renal protecting influence of soy protein seems to be due to an increase of NO production and caveolin-1 over expression.[33]

Philbrick *et al*. studied the effect of soyasaponins on retarding polycystic kidney disease progress. Pcy mice in two separate, 90-day trials were investigated. In the first study, mice were nourished with a casein-based (control) diet that was supplemented with saponin-enriched alcohol extract (SEAE) and a diet in which soy protein separate (soy protein isolate [SPI])-based diet substituted the casein. In the next study, mice were nourished with the control diet without supplemented with either soyasaponins and isoflavone was compared with mice were fed soy product (Novasoy 400 supplement, or a 99.5% pure soyasaponins powder). In the first study, in the SEAE nourished animals compared to the control group's tissues, plasma creatinine, and urea levels, water content, and kidney weight significantly decreased also; plasma creatinine decreased in mice fed the SPI-based diet, but plasma urea reduced slightly. In the second study, in mice nourished with the Novasoy-400 supplement and the soyasaponins powder compared to the control group, plasma creatinine, urea amounts, kidney weight, and water content significantly decreased. Hence, it is concluded that Soyasaponin can inhibit kidney and cyst enlargement in the pcy mouse.[38]

Fair *et al*. to determine whether soy protein can change primary kidney disease progression in Han: SPRD-cy rats assessed cyst growth, fibrosis, prostaglandin E(2) (PGE(2)) production, and fatty acid composition in kidney between two groups that were consumed casein-based diets or soy protein for 1 or 3 weeks. Renal fibrosis reduced significantly by 22% and 38% after 1 and 3 weeks, respectively, and cyst growth was 34% lesser after 3 weeks in soy protein feeding group. In normal and diseased rats, kidney 18:2(n-6) levels decreased after 1 week of ingesting the soy protein diet. Inhibition of PGE(2) production, which is seen in diseased kidneys, ameliorated in soy protein consuming group also *ex vivo* PGE(2) release was 31%–32% higher in this group compared with casein-fed rats. These data expressed that disease development in the primary stage of CKD retarded in dietary soy protein compared with casein.[34]

Aukema *et al*. (2001) surveyed the effects of soy protein on insulin-like growth factor-1 (IGF-1) and disease in Han: SPRD-cy rats. Normal and diseased weanling rats were fed soy protein or casein-based diets for 6 weeks. Kidney weight, cyst size, water content, serum urea, kidney IGF-1, and creatinine were lower and creatinine clearance was higher in soy protein-fed diseased male and female animals. As a result, soy protein diet compared with casein retarded the progress of the disease in Han:SPRD-cy rats and IGF-1 that take part in the control of renal growth and may have a role in the pathogenesis of kidney disease[39] [Table 1].

Human Study

The effect of an oral protein load on renal function has been studied in several surveys. Some studies have suggested

Table 1: Characteristics of animal study

Study	Subject	Number of subject	Intervention	Duration (weeks)
Aukema (1999)[25]	Han:SPRD-cy rats	20	Soy hemp pea casein	5
Ogborn (2010)[29]	Han:SPRD-cy rats	57	Casein HIS Alcohol-extracted LIS MIS	8
Trujillo (2005)[33]	Zucker rats	65	Soy casein	23
Philbrick (2003)[38]	Pcy mice	48	SPI casein SEAE soy product	13
Fair (2004)[34]	Han:SPRD-cy rats	87	Soy casein	3
Aukema (2001)[35]	Han:SPRD-cy rats	60	Soy casein	6

SPI=Soy protein isolate, HIS=High isoflavone soy protein, LIS=Low isoflavone soy protein, MIS=Mixed soy protein diet, SEAE=Saponin-enriched alcohol extract, SPRD= Sprague-Dawley

that vegetable protein, especially soy protein, may have less effect on renal function compared to animal protein. Studies performed in normoalbuminuric individuals with diabetes have suggested that changing the composition of the diet by altering the source of protein from animal to plant, might produce beneficial renal effects, however, results have not been constant.

In a study which set out to determine "acute effect of a soy protein-rich meal-replacement application on renal parameters in patients with the metabolic syndrome," Deibert *et al.* found that glomerular filtration rate (GFR) and renal plasma flow in healthy controls significantly raised after ingestion 1 g protein (containing 83% soy protein) per kilogram body weight of a commercial soy-yoghurt-honey formulation. This rise was more in patients with the metabolic syndrome. However, a protein of the soy-based produce of 0.3 g protein per kg body weight had no significant impact on kidney function. This effect is attributable to the amino acids ingested, as the applied amount of sodium is too low to have a significant impact on renal function.[39]

To determine the effects of soy protein on renal function, Ahmed *et al*. (2010) evaluated "the effect of soy protein on proteinuria and dyslipidemia, in patients with proteinuric glomerulopathy." In this study, a diet with a protein of animal origin was compared with a diet with soy protein with the same amount of protein (0.8 g/kg/day) in 8 weeks. No beneficial effect was observed when using soy protein instead of animal protein.[26] It seems possible that these results are due to the baseline low levels of proteinuria, short-term use of soy protein and a low number of cases.

Kao *et al*. used a randomized clinical trial survey to assess the influence of soy protein on serum albumin in patients with CKD for 6 months that no significant difference was observed between control and intervention group.[40]

Zhang (2014) in a double-blind, randomized, placebo-controlled trial identified utilization whole soy in 6 months have a moderate improvement effect on renal function in prehypertensive postmenopausal women with lowered renal function. In this study, 270 eligible Chinese women were prescribed randomly to any one of the three diets: 40 g soy flour, 40 g low-fat milk powder +63 mg daidzein (one major isoflavone) or 40 g low-fat milk powder daily. The most of the renal parameters did not change significantly. Subgroup analysis among women with reduced renal function indicated whole soy utilization made better indications of renal function comparative to control.[8]

In a meta-analysis of nine randomized controlled trials, Zhang *et al*. revealed soy protein ingestion compared with animal protein feeding significantly improve SCr and serum phosphorus concentrations in predialysis patients. The reduction of serum phosphorus is probably due to the decreased phosphate intake and intestinal absorption so this could cause the control of hyperphosphatemia simpler and more effective.[41]

In another meta-analysis of 12 studies (280 participants), Jing and Wei-Jie (2016) indicated that soy was related to a significant reduction of proteinuria, SCr, C-reactive protein (CRP) and serum phosphorus in the predialysis subgroup, however, serum phosphorus and CRP did not change in the dialysis subgroup. In the soy-treated group, blood urea nitrogen (BUN) was significantly reduced compared with control when two subgroups were analyzed as a whole. Creatinine clearance and GFR did not change significantly.[42]

Azadbakht and Esmaillzadeh carried out a number of investigations into the effect of soy protein on renal function. In a crossover, randomized clinical trial on 14, they prescribed two diets contained 0.8 g/kg protein in each phase of the trial for 7 weeks: one diet contained 70% animal and 30% vegetable proteins, and another diet contained 35% animal protein, 35% soy protein, and 30% other vegetable proteins. In this study, they determined soy-protein ingestion versus animal protein decreased urinary urea nitrogen, proteinuria, blood sodium, and SCr, but serum calcium, potassium, and BUN levels were not significantly changed.[43] In another longitudinal randomized clinical trial that carried out among 41 type 2

Table 2: Characteristics of human study

Study	Subject	Number of subject	Intervention	Duration	Design
Deibert (2011)[39]	Metabolic syndrome	20	Soy	1 weeks	RCT
Ahmed (2010)[26]	Proteinuric glomerulopathy	27	Soy animal	4 weeks	RCT
Kao (2012)[40]	CKD	26	Soy meat	24 weeks	RCT
Zhang (2014)[41]	Prehypertensive postmenopausal women	207	Soy flour Low-fat milk powder + 63 mg daidzein Low-fat milk powder	24 weeks	DBRCT
Azadbakht (2009)[43]	Type II diabetic patients	14	70% animal and 30% vegetable proteins 35% animal protein, 35% soy protein, and 30% other vegetable proteins	7 weeks	CRCT
Azadbakht (2008)[44]	Type II diabetic patients with nephropathy	41	70% animal and 30% vegetable proteins 35% animal proteins, 35% textured soy protein, and 30% vegetable proteins	4 years	LRCT

CKD=Chronic kidney disease, RCT=Randomized controlled trial, LRCT=Longitudinal randomized clinical trial, CRCT=Cluster randomized, controlled trials, DBRCT=Double-blind randomized controlled trial

diabetic patients with nephropathy by Azadbakht *et al*. two diet such as above study prescribed for 4 years, soy protein intake significantly improved proteinuria and urinary creatinine[44] [Table 2].

Discussion

Most animal and human studies revealed that soy protein compared with animal protein can improve functional renal. Soy is considered as a unique food that contains several nutrients, complex carbohydrates, vegetal protein, soluble and insoluble fibers, oligosaccharides, photochemistry, especially isoflavones, and minerals that it is not clear which compound is responsible for its effects.[26,45] Several mechanisms have suggested explaining soy effect. A component of soy that mentioned has a renoprotective effect is the isoflavones, which mechanisms are not clear. One of the possibilities mechanisms is hydrolyzing isoflavones by bacterial β-glucosidases and changing to the bioactive compound: genistein and daidzein in the intestine.[46,47] Another mechanism is their antioxidant properties, which can prevent the formation of free radicals and may enhance NO accessibility.[48,49] Amino acid dissimilarities between the protein sources are another possible mechanism. Arginine and glycine are more in soy than in animal protein that both of them could be directly involved in vasodilatory processes. The lower level of phosphorous and sodium in soy protein compared animal protein has been proposed as a mediator of the protecting effects of soy protein.[26,45] One possible mechanism that was suggested is the effect of soy protein on IGF-1. IGF-1 is the main regulator of renal remodeling and in animal studies revealed soy protein caused a reduction in circulating and renal IGF-1.[37] The effect of soy protein on blood lipid and glucose levels is another suggested mechanism for reducing kidney malfunction. Some evidence shows that iatrogenic reasons or uremia may cause the intestinal dysbiosis in patients with renal disease. Dysbiotic gut microbiome may be a factor to progress CKD and CKD-associated complications.[50-54] As regard to the composition of soy, it may be influenced on gut microbiome and consequently on renal disease.[55]

Lack of significant effect of some renal markers could probably be due to the participants with a relatively normal renal function or low amount of soy protein intake also use of creatinine as the main marker of renal function which is dependent on sex, age, muscle mass, and diet,[56-58] thus future studies among patients with more lowered renal function and more amount of soy protein are required to verify the role of soy protein ingestion on renal function, also using of cystatin C, which is a better marker of initial kidney dysfunction and estimates direct determines of GFR with more accuracy and sensitivity than creatinine, is suggested.[59-64]

Conclusions

Soy protein is possible a valuable substitution for animal protein that we can suggest to prevent and control the CKD.

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Conflicts of interest

There are no conflicts of interest.

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