Review Article

Beneficial effects of soy protein consumption for renal function

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Alterations in dietary protein intake have an important role in prevention and management of several forms of kidney disease. Using soy protein instead of animal protein reduces development of kidney disease in animals. Reducing protein intake preserves kidney function in persons with early diabetic kidney disease. Our clinical observations led us to the soy-protein hypothesis that "substitution of soy protein for animal protein results in less hyperfiltration and glomerular hypertension with resulting protection from diabetic nephropathy." These components of soy protein may lead to the benefits: specific peptides, amino acids, and isoflavones. Substituting soy protein for animal protein usually decreases hyperfiltration in diabetic subjects and may reduce urine albumin excretion. Limited data are available on effects of soy peptides, isoflavones, and other soy components on renal function on renal function in diabetes. Further studies are required to discern the specific benefits of soy protein and its components on renal function in diabetic subjects.

Key Words: soy protein, kidney function, diabetes, nephropathy, prevention

INTRODUCTION

Soy protein foods have many beneficial effects on renal function. Soy protein intake slows or prevents development of kidney disease in several different animal models.[1-4] In healthy humans, substituting soy protein for animal protein decreases renal blood flow and glomerular filtration rate.[5,6] In humans with diabetic kidney disease (nephropathy), replacing animal protein with soy protein improves renal function and decreases protein loss (proteinuria).[7-9] We have proposed the "soy-protein hypothesis" suggesting that substitution of soy protein for animal protein in diabetic individuals results in less hyperfiltration and glomerular hypertension resulting in protection from diabetic nephropathy.[10]

Most soy protein products provide these components: soy protein with its unique amino acid profile, soy peptides, and isoflavones. Each of these components appears to have specific and unique effects on renal function. The amino acid profile of soy protein, differing from that of most animal proteins, may specifically affect renal blood flow and glomerular filtration rates.[6] Soy peptides—with sizes ranging from four to 20 amino acids—have very important effects on vascular reactivity, blood pressure[11] and blood lipid values.[12] Thus, soy peptides may affect renal function in many different ways and may be the most active component of the soy protein package. However, soy isoflavones also have a wide range of activities that probably act synergistically with the soy peptides to mediate favorable effects on renal function.[7]

Chronic kidney disease is a increasing in frequency at rapid rate. Approximately 40% of new cases of end-stage renal disease is related to diabetes.[7] The purpose of this review is to focus on the beneficial effects of soy protein consumption on risk for diabetic nephropathy and on reversal of this condition. This review will include these areas: effects of soy protein components on renal function; soy protein and animal models of renal disease; pathophysiology of diabetic renal disease; soy consumption and diabetic renal disease; and proposed mechanisms of action.

SOY PROTEIN COMPONENTS

Before the discovery of isoflavones early investigators attributed the physiologic effects of soy protein compared to animal protein to differences in amino acid composition.[13] As interest in soy isoflavones increased, most of the hypocholesterolemic effects, for example, were attributed to isoflavones.[14] However, as further research emerged, soy peptides became the focus of attention and, at this time, current understanding indicates that various peptides may have the predominant role in many of the physiologic effects of the soy protein package.[12,15] Since it is difficult to separate the effects of intact protein (or its amino acids) from the effects of isoflavones or peptides, the independent roles that these two latter components will be briefly reviewed.

Genistein and other isoflavones have many in vitro effects that could affect renal function; some include these: potent inhibition of protein tyrosine kinase;[16] endothelium-dependent relaxation of arteries;[17] action to regulate the expression of peroxisome proliferator-activator receptor-γ (PPAR-γ);[18] and a variety of effects on insulin sensitivity.[19] Recently we[7] suggested that soy isoflavones might affect renal function in these threeways: inhibition of mesangial cell proliferation; alterations in nitric oxide production by

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endothelial cells and direct inhibition of the Na-K-Cl co-transporter of the thick ascending limb of the loop of Henle. Some these renal-specific activities may have contributed to the reduction in the glomerular hyperfiltration observed in our clinical trial of Type 1 diabetic volunteers with early diabetic nephropathy.[7]

Interest in soy bioactive peptides has accelerated in the past decade .[15] Perhaps of greatest interest related to vascular biology are the peptides that inhibit angiotensin I converting enzyme activity (ACE).[20,21] Pharmacotherapy with ACE inhibitors is highly recommended for persons with diabetes because of the proven protective effects of these agents related to diabetic nephropathy.[22,23] The ACE-inhibitor effects and other activities of soy peptides would exert antihypertensive actions.[15] Soy peptides, as well as isoflavones, also have antioxidant activities that may have renoprotective effects.[21,24-26]

SOY PROTEIN AND ANIMAL MODELS OF RENAL DISEASE

Soy protein intake has remarkable effects in protection from development of renal disease in a number of animal models. Compared to animal protein such as casein, including soy protein in the diet has protective effects for these animal models of kidney disease: remnant kidney of rat after unilateral nephrectomy and partial infarction of remaining kidney;[1] aging Fischer rat model;[27] rat model of polycystic kidney disease;[28] mouse model of polycystic kidney disease;[29] obese Zucker rat fed high-fat diet;[2] chemically-induced chronic nephrotic syndrome;[30] and mouse model of diabetic nephropathy.[3]

The potential actions of soy protein that contribute to these renoprotective effects are under intensive study. Proposed mechanisms include the following. 1. *Improved lipid metabolism*: One of the most consistent observations that relate to renal disease in animals are the reductions in serum lipids with soy protein diets.[1,2,4,30-32] Of interest, pharmacologic agents, such as lovastatin, that inhibit cholesterol synthesis and decrease serum cholesterol values appear to slow progression of certain forms of renal disease in animals.[33] 2. *ACE inhibitory activity*: Because pharmacologic agents that serve as ACE inhibitors have renoprotective effects,[22;23;33] it is likely that some of the soy peptides with ACE-inhibitory properties may contribute to this protection.[20,21] 3. *Blood pressure reduction:* Hypertension has an important role in development and progression of nephropathy and lowering of blood pressure has protective effects; the antihypertensive effects of soy components may contribute to renoprotective effects.[2,4] 4. *Reduced reanl blood flow and glomerular filtration rate*. According to the Brenner hypothesis,[34] excessive protein intake results in hyperfiltration and glomerular hypertension leading to progressive deterioration of kidney function. Soy protein intake reduces renal blood flow and glomerular filtration rate.[7,35] 5. *Inhibition of inflammation*: Anti-inflammatory agents, such as methylprednisone, also slow progression of experimental renal disease suggesting that the anti-inflammatory properties of soy protein or its associated isoflavones may have these protective effects. 6. *Antioxidant effects*: The antioxidant properties of soy isoflavones also may contribute to renoprotective effects.[2,30;33] 7. *Tyrosine kinase inhibition*: The important tyrosine kinase inhibitory properties of genistein may also contribute to the protective effect.[33] 8. *PUFA effects:* Recent research has focused on the role of fatty acid content of the diet and changes in concentrations of polyunsaturated fatty acids (PUFAs) in liver and kidney; these PUFAs may mediated important changes in inflammatory and cell-proliferative pathways.[36-38] 9. *Decreased IGF-1*: Soy feeding is associated with a putative risk factor for renal disease insulin-like growth factor-1 (IGF-1).[39] 10. *Improved PGE-2 production*. Soy protein feeding appears to reverse abnormal reductions in production of prostaglandin E-2 PGE-2.[40] 11. *Decreased 6-keto PGF-1α production*: Soy protein also appears to suppress the excessive production of 6-keto prostaglandin-F 1α.[41]

The components of soy protein diets that deliver the renoprotective effects have not been delineated. Soy protein is a rich source of the amino acid L-arginine and the higher intake of this amino acid has been suggested as an important protective component;[42] however, addition of arginine to a low protein diet did not have an observed effect on renal disease in another study.[33] Only limited data are available on effects of soy peptides on renal disease although these peptides have profound hypocholesterolemic effects.[12] Chen and colleagues[4] recently documented that low-molecular-weight soy protein hydrolysates have greater blood pressure-lowering effects and increases in glomerular filtration rates than either isolated soy protein isolate or high-molecular-weight fractions. Much further work is required to assess effects of specific soy protein hydrolysates and peptides. The role of soy isoflavones also is unclear. In one study, because genistein supplementation of a casein-based diet did not slow progression of polycystic kidney disease the authors concluded that the beneficial effects were related to the soy protein and not genistein.[29]

PATHOPHYSIOLOGY OF DIABETIC RENAL DISEASE

Diabetic nephropathy follows a well-defined progression from glomerular hyperfiltration to microalbuminuria to frank albuminuria with decreased creatinine clearance. Clinically, the earliest indicator of renal dysfunction is glomerular hyperfiltration manifested by lower than expected serum creatinine values. This is followed by increased urine albumin excretion and then by significant albuminuria. Hyperglycemia accelerates the development and progression of nephropathy. Associated hypertension, further aggravates the progression. Obesity, present in >75% of persons with type 2 diabetes, is associated with increased renal blood flow, larger glomeruli and increased glomerular filtration rates, factors that accelerate the derangements seen in diabetic individuals.[2] In addition, the elevated serum cholesterol and triglyceride values may initiate and perpetuate glomerular injury.[2] Schrijvers and colleagues[43] provide an excellent review of the pathophysiology of diabetic nephropathy.

Hyperglycemia is central to renal damage and development of nephropathy.[44] Glycosylation of proteins, lipids or nucleic acids leading to advanced glycation end-products (AGE) appear to contribute to nephropathy but soy protein intake probably does not affect this process.

Soy protein intake, however, may affect production and action of various vasoactive factors that include vasoconstrictors such as angiotensin II and endothelin as well as vasodilators such as nitric oxide; all of these pathways may be affected by soy protein consumption. In diabetic individuals the diacylglycerol protein kinase C pathway is activated and affects intracellular pathways and concentrations of several growth factors and cytokines; soy protein feeding may affect these processes. Growth factors that may be affected by soy protein intake include insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF).[43]

SOY PROTEIN CONSUMPTION AND DIABETIC RENAL DISEASE

Observational studies in humans suggest that substituting soy protein for animal protein in the diet of individuals with diabetic nephropathy decreases proteinuria. However, only five randomized controlled trials are available in this area and the results are mixed. Historically, Jabani and colleagues[45] compared the effects of control and vegetarian diets in diabetic subjects with proteinuria. The vegetarian diet was associated with no changes in glomerular filtration rates but significantly decreased albuminuria compared to the control diet. D'Amico and Gentile[32] reported that soy protein diets decreased serum lipids and albuminuria in patients with chronic renal disease. Barsotti and colleagues[46] reported that a very-low protein, vegetarian diet slowed progression of diabetic nephropathy in an observational study. Despite their limitations, these three studies support observations in the animal models suggesting that replacing animal protein for soy protein has the potential to reverse the nephropathy of diabetic individuals.

The five RCTs provide additional guidance for drawing tentative conclusions.[7,8,10,47,48] Subjects in our study of type 1 diabetes had abnormally high GFRs and low levels of urinary albumin. Soy protein intake improved their renal function by significantly decreasing the abnormally high GFRs.[7] The subjects with microalbuminuria (values of >30 mg/g creatinine) showed reduced albuminuria but those with normal values had variable responses (Anderson, JW. Unpublished observations). Similar observations were made by Teixeira.[48] The four studies of patients with type 2 diabetes included subjects with established kidney disease, decreased creatinine clearance and albuminuria with urine albumin values of 83 to approximately 400 mg/g creatinine. In two studies significant reductions in urinary albumin excretion were observed with soy protein intake compared to animal protein intake.[8,48] However, in two other studies the soy diets did not reduce urinary albumin excretion.[10,47]

In type 1 diabetes the nephropathy is usually related to the diabetic state without confounding elements of hypertension and dyslipidemia. Hyperfiltration occurs early followed by albuminuria. In this stage it seems likely that substitution of soy protein for animal protein will decrease hyperfiltration and, perhaps, decrease albuminuria.[7] In type 2 diabetes, hypertension usually precedes the diabetes and many persons with nephropathy have hypertension as a major contributor. Hyperlipidemia also is common and may contribute to renal dysfunction.[10] Ideally, nephropathy in type 2 diabetic individuals should be studied in those individuals without a major hypertensive factor and without dyslipidemia. The variable response of individuals with decreased GFRs and albuminuria may reflect the variable causative factors contributing to the nephropathy in the limited number of subjects studied. Further controlled clinical trials of well-defined nephropathy in diabetic individuals are required to determine the clinical benefits of soy protein intake for these individuals.

AUTHOR DISCLOSURES

James W Anderson, no conflicts of interest.

REFERENCES

1. Walls J, Williams AJ. Influence of soya protein on the natural history of a remnant kidney model in the rat. Contr Nephrol. 1988;60:179-87.
2. Maddox DA, Alavi FK, Silbernick EM, Zawada ET. Protective effects of a soy diet in preventing obesity-linked renal disease. Kidney Int. 2002;61:96-104.
3. Teixeira SR, Tappenden KA, Erdman JW Jr. Altering dietary protein type and quantity reduces urinary albumin excretion without affecting plasma glucose concentrations in BKS.cg-m +Lepr db/+Lepr db (db/db) mice. J Nutr. 2003; 133:673-8.
4. Chen ST, Yang HY, Huang HY, Peng SJ, Chen JR. Effects of various soya protein hydrolysates on lipid profile, blood pressure and renal function in five-sixths nephrectomized rats. Br J Nutr. 2006;96:435-41.
5. Bosch JP, Saccaggi A, Lauer A, Ronco C, Belledonne M, Glabman S. Renal functional reserve in humans. Effect of protein intake on glomerular filtration rate. Am J Med. 1983;75:943-50.
6. Viberti G, Bognetti E, Wiseman MJ, Dodds R, Gross JL, Keen H. Effect of protein-restricted diet on renal response to a meat meal in humans. Am J Physiol. 1987;87:F393.
7. Stephenson TJ, Setchell KD, Kendall CW, Jenkins DJ, Anderson JW, Fanti P. Effect of soy protein-rich diet on renal function in young adults with insulin-dependent diabetes mellitus. Clin Nephrol. 2005;64:1-11.
8. Azadbakht L, Shakerhosseini R, Atabak S, Jamshidian M, Mehrabi Y, Esmaill-Zadeh A. 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.
9. 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.
10. Anderson JW, Blake JE, Turner J, Smith BM. Effects of soy protein on renal function and proteinuria in patients with type 2 diabetes. Am J Clin Nutr. 1998;68:1347S-53S.
11. Imura T, Kanazawa T, Watanabe T, Fukushi Y, Kudou S, Uchida T, Osanai T, Onodera K. Hypotensive effect of soy protein and its hydrolysate. Ann N Y Acad Sci. 1993; 676:327-30.
12. Hori G, Wang MF, Chan YC, Komatsu T, Wong Y, Chen TH, Yamamoto K, Nagaoka S, Yamamoto S. Soy protein hydrolyzate with bound phospholipids reduces serum cholesterol levels in hypercholesterolemic adult male volunteers. Biosci Biotechnol Biochem. 2001;65:72-8.

13. Vahouny GV, Adamson I, Chalcarz W, Satchithanandam S, Muesing R, Klurfeld DM, Tepper SA, Sanghvi A. Kritchevsky D Effects of casein and soy protein on hepatic and serum lipids and lipoprotein lipid distributions in the rat. Atherosclerosis. 1985; 56:127-37.
14. Anderson JW, Johnstone BM, Cook-Newell ME. Meta-analysis of effects of soy protein intake on serum lipids in humans. New Engl J Med. 1995;333:276-82.
15. Wang W, de Mejia EG. A new frontier in soy bioactive peptides that may prevent age-related chronic diseases. Comprehensive Reviews in Food Science and Food Safety. 2005;4:63-78.
16. Akiyama T, Ishida J, Nakagawa S, Ogawara H, Watanabe S, Itoh N, Shibuya M, Fukami Y. Genistein, a specific inhibitor of tyrosine-specific protein kinases. J Biol Chem. 1987;262:5592-5.
17. Mishra SK, Abbot SE, Choudhury Z, Cheng M, Khatab N, Maycock NJ, Zavery A, Aaronson PI. Endothelium-dependent relaxation of rat aorta and main pulmonary artery by the phytoestrogens genistein and daidzein. Cardiovasc Res. 2000;46:539-46.
18. Dang Z-C, Audinot V, Papapoulos SE, Boutin JA, Löwik CWGM. Peroxisome proliferator-activated receptor γ(PPAR γ) as a molecular target for the soy phytoestrogen genistein. J Biol Chem. 2003;278:962-7.
19. Abler A, Smith JA, Randazzo PA, Rothenberg PL, Jarett L. Genistein differentially inhibits postreceptor effects of insulin in rat adipocytes without inhibiting the insulin receptor kinase. J Biol Chem. 1992;267:3946-51.
20. Lo WMY, Li-Chan ECY. Angiotensin I converting enzyme inhibitory peptides from in vitro pepsin-pancreatin digestion of soy protein. J Agr Food Chem. 2005;53:3369-76.
21. Gibbs BF, Zougman A, Masse R, Mulligan C. Production and characterization of bioactive peptides from soy hydrolysate and soy-fermented foods. Food Research Internatl. 2004;37:123-31.
22. Remuzzi G, Ruggenenti P, Perico N. Chronic renal diseases: renoprotective benefits of renin-angiotensin system inhibition. Ann Intern Med. 2002;136:604-15.
23. Jafar TH, Stark PC, Schmid CH, Landa M, Maschio G, de Jong PE, et al. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. Ann Intern Med. 2003;139:244-52.
24. Hodgson JM, Croft KD and Puddey IB. Soybean isoflavonoids and their metabolites inhibit in vitro lipoprotein oxidation in serum. J Nutr Biochem. 1996;7:664-9.
25. Kanazawa T, Osanai T, Zhang XS, Uemura T, Yin XZ, Onedera K. Protective effects of soy protein on the peroxidizability of lipoproteins in cerebral vascular diseases. J Nutr. 1995;125:639S-46S.
26. Aoki H, Otaka Y, Igarashi K, Takenaka A. Soy protein reduces paraquat-induced oxidative stress in rats. J Nutr. 2002;132:2258-62.
27. Iwasaki K, Gleiser CA, Masoro EJ, McMahan CA, Seo EJ, Yu BP. The influence of dietary protein source on longevity and age-related disease processes of Fischer rats. J Gerontol. 1988;43:B5-12.
28. Ogborn MR, Bankovic-Calic N, Shoesmith C, Buist R, Peeling J. Soy protein modification of rat polycystic kidney disease. Am J Physiol. 1998;274:F541-F549.
29. Tomobe K, Philbrick DJ, Ogborn MR, Takahashi H, Holub BJ. Effect of dietary soy protein and genistein on disease progression in mice with polycystic kidney disease. Am J Kidney Dis. 1998;31:55-61.
30. Tovar AR, Murguía F, Cruz C, Hernández-Pando R, Aguilar-Salinas CA, Pedraza-Chaverri J, Correa-Rotter R, Torres N. A soy protein diet alters hepatic lipid metabolism gene expression and reduces serum lipids and renal fibrogenic cytokines in rats with chronic nephrotic syndrome. J Nutr. 2002;132:2562-9.
31. Torres N, Torre-Villalvazo I, Tovar AR. Regulation of lipid metabolism by soy protein and its implication in diseases mediated by lipid disorders. J Nutr Biochem. 2006;17:365-73.
32. D'Amico G, Gentile MG. Influence of diet on lipid abnormalities in human renal disease. Am J Kidney Dis. 1993;22:151-7.
33. Aukema HM, Housini I, Rawling JM. Dietary soy protein effects on inherited polycystic kidney disease are influenced by gender and protein level. J Am Soc Nephrol. 1999;10:300-8.
34. Brenner BM, Meyer TW, Hostetter TH. Dietary protein restriction and the progressive nature of kidney disease. New Engl J Med. 1982;307:652-9.
35. Williams AJ, Baker F, Walls J. Effect of varying quantity and quality of dietary protein intake in experimental renal disease in rats. Nephron. 1987;46:83-90.
36. Ogborn MR, Nitschmann E, Weiler HA, Bankovic-Calic N. Modification of polycystic kidney disease and fatty acid status by soy protein diet. Kidney Int. 2000;57:159-66.
37. Sankaran D, Lu J, Bankovic-Calic N, Ogborn MR, Aukema HM. Modulation of renal injury in pcy mice by dietary fat containing n-3 fatty acids depends on the level and type of fat. Lipids. 2004;39:207-14.
38. Sankaran D, Bankovic-Calic N, Cahill L, Yu-Chen PC, Ogborn MR, Aukema HM. Late dietary intervention limits benefits of soy protein or flax oil in experimental polycystic kidney disease. Nephron Exp Nephrol. 2007;106:e122-e128.
39. Aukema HM, Housini I. Dietary soy protein effects on disease and IGF-I in male and female Han:SPRD-cy rats. Kidney Int. 2001;59:52-61.
40. Fair DE, Ogborn MR, Weiler HA, Bankovic-Calic N, Nitschmann EP, Fitzpatrick-Wong SC, Aukema HM. Dietary soy protein attenuates renal disease progression after 1 and 3 weeks in Han:SPRD-cy weanling rats. J Nutr. 2004;134:1504-7.
41. Hwang SY, Taylor CG, Zahradka P, Bankovic-Calic N, Ogborn MR, Aukema HM. Dietary soy protein reduces early renal disease progression and alters prostanoid production in obese fa/fa Zucker rats. J Nutr Biochem. 2007;Jul 24[Epub ahead of print]
42. Narita I, Border WA, Ketteler M, Ruoslahti E, Noble NA. L-arginine may mediate the therapeutic effects of low protein diets. Proc Natl Acad Sci U S A. 1995;92:4552-6.
43. Schrijvers BF, de Vriese AS, Flyvbjerg A. From hyperglycemia to diabetic kidney disease: the role of metabolic, hemodynamic, intracellular factors and growth factors/cytokines. Endocr Rev. 2004;25:971-1010.
44. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. New Engl J Med. 1993;329:977-86.
45. Jibani MM, Bloodworth LL, Foden E, Griffiths KD, and Galpin OP. Predominately vegetarian diet in patients with incipient and early clinical diabetic nephropathy: effects on albumin excretion rate and nutritional status. Diabet Med. 1991;8:949-953.

46. Barsotti G, Navalesi R, Giampietro O, Ciardella F, Morelli E, Cupisti A, Mantovanelli A, Giovannetti S. Effects of a vegetarian, supplemented diet on renal function, proteinuria, and glucose metabolism in patients with "overt" diabetic nephropathy and renal insufficiency. Contr Nephrol. 1988;65:87-94.
47. Wheeler ML, Fineberg SE, Fineberg NS, Gibson RG, Hackward LL. Animal versus plant protein meals in individuals with type 2 diabetes and microalbuminuria: effects on renal, glycemic, and lipid parameters. Diabetes Care. 2002;25:1277-82.
48. Teixeira SR, Tappenden KA, Carson L, Jones R, Prabhudesai M, Marshall WP, Erdman JW Jr. 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.