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 slows or prevents development of kidney disease in several different animal models. In healthy humans, substituting soy protein for animal protein decreases renal blood flow and glomerular filtration rate. In humans with diabetic kidney disease (nephropathy), replacing animal protein with soy protein improves renal function and decreases protein loss (proteinuria). 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.

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. Soy peptides—with sizes ranging from four to 20 amino acids—have very important effects on vascular reactivity, blood pressure and blood lipid values. 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.

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. 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. As interest in soy isoflavones increased, most of the hypocholesterolemic effects, for example, were attributed to isoflavones. 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. 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; endothelium-dependent relaxation of arteries; action to regulate the expression of peroxisome proliferator-activator receptor- (PPAR-); and a variety of effects on insulin sensitivity. Recently we suggested that soy isoflavones might affect renal function in these three ways: inhibition of mesangial cell proliferation; alterations in nitric oxide production by
endothelial cells and direct inhibition of the Na-K-Cl co-transporter of the thick ascending limb of the loop of Henle. Some of 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.\

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

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; aging Fischer rat model; rat model of polycystic kidney disease; mouse model of polycystic kidney disease; obese Zucker rat fed high-fat diet; chemically-induced chronic nephrotic syndrome; and mouse model of diabetic nephropathy.

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. 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. 2. ACE inhibitory activity: Because pharmacologic agents that serve as ACE inhibitors have renoprotective effects, it is likely that some of the soy peptides with ACE-inhibitory properties may contribute to this protection. 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. 4. Reduced renal blood flow and glomerular filtration rate. According to the Brenner hypothesis, 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. 5. Inhibition of inflammation: Anti-inflammatory agents, such as methylprednisolone, 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.

Tyrosine kinase inhibition: The important tyrosine kinase inhibitory properties of genistein may also contribute to the protective effect.

PUFA effects: Recent research has focused on the role of fatty acid content of the diet and changes in concentrations of polysaturated fatty acids (PUFAs) in liver and kidney; these PUFAs may mediate important changes in inflammatory and cell-proliferative pathways.

Decreased IGF-1: Soy feeding is associated with a putative risk factor for renal disease insulin-like growth factor-1 (IGF-1). Improved PGE-2 production. Soy protein feeding appears to reverse abnormal reductions in production of prostaglandin E-2 (PGE-2). Decreased 6-keto PGF-1α production: Soy protein also appears to suppress the excessive production of 6-keto prostaglandin-F1α.

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; however, addition of arginine to a low protein diet did not have an observed effect on renal disease in another study. Only limited data are available on effects of soy peptides on renal disease although these peptides have profound hypocholesterolemic effects. Chen and colleagues 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.

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. In addition, the elevated serum cholesterol and triglyceride values may initiate and perpetuate glomerular injury. Schrijvers and colleagues provide an excellent review of the pathophysiology of diabetic nephropathy. Hyperglycemia is central to renal damage and development of nephropathy. 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). 33

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. 5,48 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 development of nephropathy 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


