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The Soy Connection

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HEALTH AND NUTRITION NEWS ABOUT SOY

Research Updates

By Mark Messina, Ph.D.

How do you spell relief?

Recent media coverage of soy has focused on the role soy might play in pain management. These articles highlighted research presented at this year's meeting of the American Pain Society in Baltimore by Drs. Srinivasa N. Raja and Jill M. Tall from Johns Hopkins University. According to their research, rats fed diets high in defatted soyflour had less swelling when injured and exhibited less response to pain compared to rats on different diets.

The first article to report that rats fed soy-containing diets experienced less pain following partial sciatic ligation (PSL) was published in 1998.¹ PSL is used as a model for studying certain types of pain in humans. Israeli researchers undertook their initial investigation because of reports indicating the rat response to this procedure varied among laboratories. Even in their own laboratory the response varied over time. Consequently, Shir and colleagues compared the effects of two different diets, one of which was high in soy, on the pain response in rats. They found quite convincingly that in general the soy-fed rats experienced less pain in response to ligation, but in particular they were less sen-

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Isoflavone-rich Soy Protein Healthy Addition To Diabetic Diet

By Tammy J. Stephenson, Ph.D. and James W. Anderson, M.D.

Diabetes mellitus is a condition that afflicts people of all ages, genders, and parts of the world.¹ According to the most recent statistics, some 17 million Americans have diabetes, up more than 8 percent than previously estimated. In addition, nearly 16 million Americans have "pre-diabetes" or impaired glucose tolerance.² Interestingly, the American Diabetes Association scientific advisory board recently revised recommendations for diagnosing and classifying diabetes mellitus to account for the large number of people with pre-diabetes who previously did not meet traditional diabetes criteria.³ Of the millions of Americans with diabetes ~ 5 percent have Type 1 diabetes and 90-95 percent have Type 2 diabetes; about 2-5 percent of pregnant women develop gestational diabetes.⁴ While important short-term consequences of diabetes mellitus include hyperglycemia and ketosis, more long-term complications include retinopathy, neuropathy, nephropathy, and blood lipid abnormalities.

Although over a dozen oral medications and insulins are available for the treatment of diabetes, nutrition management remains a cornerstone in diabetes care.⁵ A well-controlled diet in conjunction with regular exercise can improve metabolic control and decrease all risks and complications associated with diabetes. Limited research has also shown that incorporating soy into the diet of a person with diabetes may also be an effective medical nutrition tool. In particular, whole soyfoods may improve blood glucose levels, protect against cardiovascular disease, and prevent nephropathy, diabetic kidney disease.

Effects of Soy on Glycemic Control

In 1917, John Harvey Kellogg first reported on the potential value of soy-

beans in treating blood sugar levels in diabetes.⁶ At that same time, Friedenwald and Ruhrah⁷ testified that patients with diabetes who consumed soybeans had less sugar spilling into their urine. Unfortunately, since these two preliminary reports, there has been very little research on how soyfoods affect glycemic control in diabetes. The effects of soy polysaccharides on glucose tolerance were evaluated in two similarly-designed trials of Type 2 diabetes patients in the 1980s. Mahalko and collaborators⁸ found that soy hull consumption improved markers of glucose tolerance while Tsai et al⁹ showed that administration of soy polysaccharides improved postprandial blood glucose handling and lessened increases in glucagon and pancreatic polypeptide levels following a meal. This finding was then replicated in 1992 when Librenti and colleagues¹⁰ reported that individuals with diabetes who consumed soy fiber had significantly lower postprandial glucose levels than those eating cellulose. In addition, three animal studies^{11,12,13} have found similar results, suggesting that soy protein improves serum glucose and insulin levels, as well as insulin sensitivity in diabetes. Although the exact mechanism has yet to be elucidated, it cannot be overlooked that the soluble fiber component of the soybean may be the most important factor. Indeed, approximately 15 percent of the soybean is insoluble carbohydrates and over 30 percent of the fiber in soy is of the soluble variety.

The Effects of Soy on Diabetic Vascular Disease

Persons with diabetes are at a two to three times higher risk for cardiovascular disease than those without. As

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Soy Protein and Diabetic Kidney Disease

By Sandra R. Teixeira, Ph.D. and John W. Erdman Jr., Ph.D.

Diabetic kidney disease is the single most important factor leading to end-stage renal failure (ESRF) in the United States¹ and Japan², and a similar trend is now emerging in Europe.² Diabetic kidney disease appears to result from an interplay between metabolic and hemodynamic factors³ in patients with a genetic predisposition. In these patients, the kidneys eventually start deteriorating, and protein begins to appear in the urine. This condition, called proteinuria, is a hallmark of diabetic kidney disease and is an indicator of disease progression. If left untreated, kidney function will worsen, as indicated by a decrease in glomerular filtration rate (GFR). Eventually, ESRF sets in, and dialysis or a kidney transplant is required to sustain life.

Soy protein and some of its constituents may interfere with several factors that contribute to kidney disease in diabetics. Presented below is recent research, which has begun to investigate the effect of soy protein on diabetic kidney disease.

Animal Studies

The effects of dietary protein type and quantity on the progression of diabetic kidney disease were examined in a Type 2 diabetes mellitus animal model.⁴ Groups of diabetic and control mice were fed one of four diets, with soy protein or casein at 12 or 20 percent calories, from early diabetes onset to approximately 6 months of age. In diabetic mice, a 20 percent casein diet increased urinary albumin excretion (UAE). Low protein diets (12 percent), independently of protein type, reduced UAE levels. A high soy protein diet (20 percent) maintained UAE at a constant level throughout the study. Thus, while soy protein at 20 percent was not as effective as the low protein diets in decreasing UAE, it prevented the natural increase in UAE known to occur in these animals.^{5,6} These results suggest that soy protein promoted an improvement in glomerular macromolecular permeability and perhaps helped to prevent diabetic kidney disease progression.

Human Studies

Several human studies on diabetic

kidney disease have been published, but no long-term prospective clinical trials have been reported to date. Jibani et al⁷ studied eight Type 1 diabetic patients with marginally elevated UAE and a slightly reduced GFR (45 – 34 ml/min/1.73m²). The patients followed their usual diet (1.4 g/kg/d total protein with 0.9 g animal protein) for eight weeks, and then followed a low animal protein diet (1.0 g/kg/d total protein with 0.7 g vegetable protein) for another eight weeks. Albumin excretion was lower after the low animal protein diet than after the lead-in period. However, since total protein intake was also significantly lower for the vegetable protein diet, the effects of a vegetable protein diet could not be differentiated from the effects of a low protein diet.

In a randomized crossover trial, Kontessis et al.⁸ compared the effects of vegetable protein (0.95 g protein/kg/d) and animal protein (1.1 g protein/kg/d) for four weeks in nine normotensive Type 1 diabetic patients, with normal or marginally elevated UAE, and GFR between 88 – 129 ml/min/1.73m². GFR, renal plasma flow (RPF), and fractional clearance of albumin were lower after the vegetable protein diet.

In 1998, Anderson et al carried out a clinical trial on eight Type 2 diabetic patients being treated with insulin, with urinary protein excretion (UPE) between 50 – 1000 mg/24-h, and serum creatinine below 176.8 μmol/L (2 mg/dl)⁹. Diets during the dietary intervention period (8 weeks) were designed to have 1 g protein/kg/d with 50 percent of the protein from soy protein beverages and meat analogues, or from ground beef and milk. The soy protein diet

led to a significant reduction in serum total cholesterol, triglycerides, and urea nitrogen. However, UPE was significantly higher after the soy protein diet.

We studied fourteen Type 2 diabetic patients previously diagnosed with diabetic kidney disease, with UAE < 2000 mg albumin/g creatinine, serum creatinine < 132.6 μmol/L (1.5 mg/dl), and total cholesterol < 6.2 mmol/L (240 mg/dl).¹⁰ This was a double-blinded trial with a crossover design consisting of a four-week lead-in period, and two eight week intervention periods, each followed by a four week washout period. Total protein intake was ~ 0.9 g/kg/d during the lead-in and washout periods and ~ 1.4 g/kg/d during both interventions with 0.5 g/kg/d of the total dietary protein intake provided in the form of protein powders of soy protein or casein. Soy protein reduced UAE by 9.5 percent, while casein led to an increase of 11.1 percent in UAE.

In summary, the impact of soy protein on diabetes mellitus and its complications has just begun to be explored. Initial results are promising, indicating that consumption of soy protein may reduce risk of several complications of diabetes, including diabetic kidney disease and dyslipidemias. In addition, diets high in plant foods are associated with lower fat and higher fiber intake, both of which constitute a healthful dietary pattern for diabetes. These promising results call for larger and longer clinical trials for both men and women, as well as establishment of the mechanisms of action for soy protein in diabetic kidney disease.

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Isoflavone-rich Soy Protein Healthy Addition To Diabetic Diet *(Continued from Page 1)*

reviewed by Clarkson¹⁴, soy protein and isoflavones are believed to mediate cardiovascular disease through a combination of mechanisms. Reductions in total and LDL-cholesterol, increases in HDL-cholesterol, protection against LDL-oxidation, endothelium-mediated vasodilation, and improvements in arterial compliance all seem to be important in persons with or without diabetes. In a recent finding, Hermansen et al¹⁵ reported that a soy supplement providing soy protein and soy fiber to persons with Type 2 diabetes significantly improved lipid levels. A favorable effect of soy on LDL particle size was found. Our studies at the University of Kentucky in both Type 1 and Type 2 subjects have also shown favorable effects of an isoflavone-rich soy protein based diet on total and LDL-cholesterol and triglycerides. The most recent animal work has concurred with these findings and reported that soy-feeding virtually completely prevented the development of abnormally elevated LDL- and VLDL-cholesterol.¹⁶ Of particular interest in diabetes, is the potential of soy isoflavones to inhibit LDL oxidation, a frequent contributor to vascular disease in this population. Indeed, several investigators have found soy isoflavones prevent oxidative damage.^{17,18,19,20}

Effects of Soy on Development of Diabetic Nephropathy

Approximately 40 percent of all end-stage renal disease cases in the United States are in persons with diabetes. Therefore, dietary interventions to prevent and/or treat diabetic kidney disease are a high priority. Dietary protein intake has been a focal point in the research on nephropathy. Most recently, it has been hypothesized that the quantitative grams of protein consumed may not be as important as once speculated. Rather, it is the type of protein that may be the most important factor in retarding renal damage. Indeed, animal protein intake appears to increase renal blood flow and filtration (beef >

chicken > fish) and, as such, leads to overworking of the kidneys. Soy protein intake does not seem to have such an affect.^{21,22}

As reported previously in this newsletter,²³ two clinical studies investigating the effects of a soy-based diet on renal health in diabetes were presented at the Fourth International Symposium on the Role of Soy in Preventing and Treating Chronic Disease. The first, a study in Type 2 diabetes subjects, showed that urine albumin excretion and total to HDL-cholesterol levels were significantly reduced following a soy diet. The second, a study that we conducted in Type 1 diabetes subjects, found that glomerular filtration rate (GFR), a marker of renal damage, and lipid profiles were significantly improved during an eight-week soyfoods based diet. These results were not duplicated in a previous study that our group²⁴ conducted in Type 2 diabetes subjects with a history of hypertension and proteinuria. We found no effects of a soy diet on protein excretion, but did show a significant reduction in both total cholesterol and triglycerides. Although not specifically looking at soy-based diet, a very recent study²⁵ in 28 patients with Type 2 diabetes and micro- or normo-albuminuria evaluated lipid and renal effects of a chicken-based diet. Both the low protein diet and chicken protein-based diet significantly lowered GFR as compared to the control diet. In addition, only the chicken-based diet reduced urine albumin excretion. Apolipoprotein B, a marker of cardiovascular health, was also lower during the low-protein and chicken-based diet as compared to the control. This research only adds to the hypothesis that protein type, rather than simply amount of protein, is key in the development and progression of diabetic renal disease.

Practical Implications

Although preliminary research evaluating the effects of soyfoods and the treatment of diabetes looks promising, there is much more that

needs to be done. At this time, isoflavone-rich soy protein appears to be a healthy addition to a diabetic diet. Our specific recommendations are to choose fiber-rich soyfoods to replace simple carbohydrates and animal protein. In addition, persons with diabetes should continue to follow a low-fat diet, something that can easily be accomplished through soy-based eating. These small changes may have a significant impact on glycemic control, kidney function, vascular health, and subsequent risk for heart disease.

ABOUT THE AUTHORS

Tammy Stephenson, Ph.D., is an Assistant Professor in the Department of Nutrition and Food Science at the University of Kentucky. She teaches several undergraduate courses at the university and frequently includes soy nutrition in her lectures. Along with Dr. James Anderson and Dr. Paolo Fanti, she is involved in research evaluating the health effects of a soyfoods-rich diet in both diabetic nephropathy and end-stage renal disease.

James W. Anderson, M.D., is professor of Medicine and Clinical Nutrition at the University of Kentucky. He directs the Health Management Resources program and is director of the University of Kentucky Metabolic Research Group. He is founder of the HCF Nutrition Research Foundation and formed the Obesity Research Network, a network of physicians which performs clinical research in the area of obesity.

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Soy Symposium 2002 Set For September

The 10th Annual Soy Symposium will be held September 19-20, 2002 at the DoubleTree Guest Suites Hotel in downtown Chicago.

Sponsored by the United Soybean Board and the Soyfoods Association of North America, this informative event is designed especially for marketing, marketing research, product development, nutrition research and new business development personnel from large and small food companies across the United States. Included will be sessions on allergenicity and biotechnology. Research on soy and human health will be addressed by Dr. Mark Messina.

Economically priced at just \$350 for two days of informative instruction, for the last 10 years the Soy Symposium has provided the highest quality program at the lowest possible cost. The United Soybean Board founded this event primarily to assist American food companies as they compete in the exploding soyfoods market.

For registration information, please call toll-free (888) 772-8454, e-mail us at soy@communiqueinc.com, or go online to www.talksoy.com. ☺

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ABOUT THE AUTHORS

Sandra R Teixeira, Ph.D., is currently involved in research investigating new compounds for the prevention and treatment of diabetes mellitus and obesity and has expertise on the biological effects of soy protein on lipid metabolism and diabetic kidney disease. Formerly a dietitian in the Department of Nephrology at Hospital de Sao Joao, Porto, Portugal, she is a member of the American Society for Nutritional Sciences, the American Society for Clinical Nutrition and the Portuguese Society for Nutritional Sciences.

John Erdman, Ph.D., is professor of Food Science and Human Nutrition; professor of Internal Medicine; and professor of Nutrition in the Division of Nutritional Sciences at the University of Illinois at Urbana. He also holds an endowed chair in Nutrition Research at the university. He currently serves as

president of the American Society for Nutritional Sciences and in 2001 was named a lifetime national associate of the National Academy of Sciences.

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Research Updates (Continued from Page 1)

sitive to noxious heat. A follow up experiment confirmed their initial findings.² Next, researchers attempted to determine whether the soy itself was protective or whether the protein (casein) which replaced soy in the diet made the rats more sensitive to pain. They found that the soy was protective because when neither soy nor casein was present in the diet, the rat response was as if they were on the low-soy diet.³

The next experiment revealed the time frame during which soy must be fed to observe the decreased sensitivity to pain. Typically, rats are fed a

given diet beginning 14 days prior to surgery and for 10 days following. However, by manipulating the times during which soy was fed, Shir et al not only determined that feeding soy after surgery was ineffective, but that if soy-feeding was stopped longer than 15 hours before surgery, the benefits were also lost.³ Thus, the effects of soy are very short-term. As to which component or components of soy are responsible for the suppressed pain response has yet to be determined, although a recent paper found a correlation between the sensitivity to pain and serum isoflavone concentra-

tions.⁴ But somewhat surprisingly, pain relief was lost when serum levels were too high or too low. At this point, all studies have been conducted in rats so the applicability of these findings to humans is unclear. Certainly, though, the preliminary findings are intriguing.

Soy for Hot Flash Relief?

We've discussed the effects of soy on the alleviation of hot flashes several times in this newsletter. Two new studies can now be added to the literature in this area, but unfortunately, they

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The Soy Connection newsletter says "thanks" to its readers who participated in the 2002 Annual Readership Survey. Your input is greatly appreciated. The response we received was overwhelming, diminishing our entire supply of DVDs and CD-ROMs. However, you can download a copy of the ready-made PowerPoint presentation on "Soy and Health."



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MNT Expanded For Patients With Diabetes, Renal Disease

The Center for Medicare & Medicaid Services has expanded coverage of medical nutrition therapy (MNT) for Medicare beneficiaries with diabetes and renal disease. Patients are now allowed to receive this new benefit while also getting dia-

betes self-management (DSMT).

The actual number of hours allowed for coverage of MNT for either diabetes or renal disease is based on evidence cited in protocols for both conditions. In an initial episode, three hours per year are covered, spread over any num-

ber of visits. In follow-up years, two hours per year are covered.

For more information, as well as the text of the entire CMS decision, log on to this Web site: www.hcfa.gov/coverage/8b3-ggg.html.

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don't provide much insight into the effectiveness of soy. In one study, researchers from the Federal University of Sao Paulo gave postmenopausal women either isoflavone supplements (100 mg/day) or a placebo for four months.⁵ The data showed a significant decrease in menopausal symptoms in the isoflavone group compared to the placebo group. However, there was absolutely no improvement in the placebo group. This is quite unusual as essentially all studies show when it comes to hot flashes, women in the placebo or control groups report a reduction in the number of hot flashes per day and/or the severity of hot flashes. Thus, it is hard to know what conclusions to draw from this study. In the other study, Canadian researchers fed breast cancer sur-

vivors either a soy beverage which provided 90 mg isoflavones/day or a rice beverage for 12 weeks. At the end of the study, both groups experienced a reduction in menopausal symptoms of between 30 percent and 40 percent but there were no statistically significant differences between groups. However, although serum genistein (the main soybean isoflavone) levels were higher in the soy-fed group as expected, serum levels in the control group suggest exposure to isoflavones. Thus, the control group may have also been consuming some soy thus confounding interpretation of the study.⁶

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