Beneficial role of dietary phytoestrogens in obesity and diabetes[1,2]

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ABSTRACT

Evidence is emerging that dietary phytoestrogens play a beneficial role in obesity and diabetes. Nutritional intervention studies performed in animals and humans suggest that the ingestion of soy protein associated with isoflavones and flaxseed rich in lignans improves glucose control and insulin resistance. In animal models of obesity and diabetes, soy protein has been shown to reduce serum insulin and insulin resistance. In studies of human subjects with or without diabetes, soy protein also appears to moderate hyperglycemia and reduce body weight, hyperlipidemia, and hyperinsulinemia, supporting its beneficial effects on obesity and diabetes. However, most of these clinical trials were relatively short and involved a small number of patients. Furthermore, it is not clear whether the beneficial effects of soy protein and flaxseed are due to isoflavones (daidzein and genistein), lignans (matairesinol and secoisolariciresinol), or some other component. Isoflavones and lignans appear to act through various mechanisms that modulate pancreatic insulin secretion or through antioxidative actions. They may also act via estrogen receptor–mediated mechanisms. Some of these actions have been shown in vitro, but the relevance of these studies to in vivo disease is not known. The diversity of cellular actions of isoflavones and lignans supports their possible beneficial effects on various chronic diseases. Further investigations are needed to evaluate the long-term effects of phytoestrogens on obesity and diabetes mellitus and their associated possible complications. *Am J Clin Nutr* 2002;76:1191–1201.

KEY WORDS Obesity, diabetes mellitus, diet, soybean, soy protein, phytoestrogens, isoflavones, flaxseed, lignans, glucose, insulin resistance, antioxidative actions, hyperlipidemia, pancreatic β cells

INTRODUCTION

In recent years, phytoestrogens have attracted increased attention among the public and in the medical community because of accumulated evidence from a large body of literature (1–8) suggesting that consumption of plant-based foods rich in these phytochemicals may benefit human health. Substantial data from epidemiologic surveys and nutritional intervention studies in humans and animals suggest that dietary phytoestrogens have protective effects against menopausal symptoms and a variety of disorders, including cardiovascular disease, cancer, hyperlipidemia, osteoporosis, and various forms of chronic renal disease (1–8). The Food and Drug Administration authorized the use on food labels of health claims associated with soy protein and the reduced risk of cardiovascular disease (9). Several studies in humans and animals have shown that soy protein reduces plasma total cholesterol and LDL cholesterol. Evidence is also emerging that consumption or supplementation of foods rich in phytoestrogens may have a beneficial effect on diabetes mellitus and obesity in animals and humans.

This review examines the evidence for a possible role of dietary phytoestrogens in diabetes mellitus and obesity and discusses various mechanisms by which this class of phytochemicals may affect glucose and lipid metabolism and improve the control of body weight and glucose homeostasis.

BIOCHEMISTRY OF PHYTOESTROGENS

Phytoestrogens are a group of biologically active plant substances with a chemical structure that is similar to that of estradiol, an endogenous estrogen (**Figure 1**). This structural similarity accounts for the ability of these compounds to bind to estrogen receptors in various cells (10–13) and exert estrogenic or antiestrogenic effects. The 3 major classes of phytoestrogens are isoflavones, lignans, and coumestans. The major bioactive isoflavones are genistein and daidzein, which are derived from the precursors biochanin A and formononetin, respectively. Lignans are constituents of many plants and form the building blocks for the formation of lignin in the plant cell wall (14). They are more prevalent in the plant kingdom than are isoflavones. The 2 major lignans, enterolactone and enterodiol, are produced from matairesinol and secoisolariciresinol, respectively. Coumestrol is the most important form of coumestan consumed by humans.

FOOD SOURCES OF PHYTOESTROGENS

Phytoestrogens are found in various plants consumed by humans, including legumes, seeds, and whole grains. The most abundant food sources of isoflavones are soybean and soybean products (**Table 1**). Other beans, lentil, peas, and clover contain a very small quantity of isoflavones. The amount of isoflavone in soybean varies according to the type of soybean, geographic area

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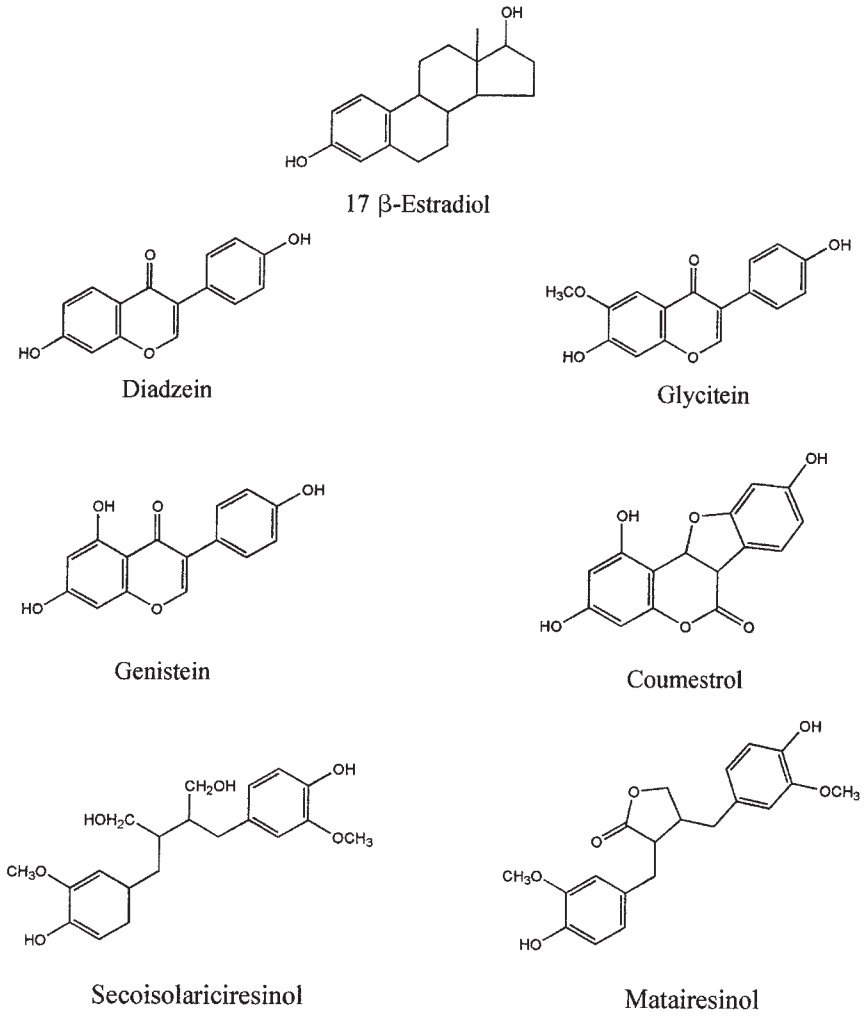

FIGURE 1. Structures of 17 β-estradiol, isoflavones (daidzein, glycitein, and genistein), coumestrol, and lignans (secoisolariciresinol and matairesinol).

of cultivation, and harvest year (15, 17, 18). In addition, the isoflavone content of different soy products varies substantially as a result of differences in processing methods (19). In soybean, the isoflavones are tightly associated with protein. The protein content of soybeans is ≈36% by weight (20). The nutritional value of soy protein is roughly equivalent to that of animal protein of high biological value. For example, isolated soy protein has a protein digestibility–corrected amino acid score of 1.0, which is the same as that of casein and egg protein (21). Processed soybean proteins and foods provide various amounts of genistein and daidzein, as either the conjugated glycones or as the aglycone forms. Mature and roasted soybeans and commercially available soy products (soy flour and textured protein) contain 0.1–5 mg isoflavones/g protein. Green soybeans and tempeh are intermediate sources of isoflavones, providing 0.3 mg/g soy protein. One serving of traditional soy foods provides 0.25–40 mg isoflavones (15, 18). Tofu, isolated soy protein, and some soymilk preparations provide 0.1–2 mg isoflavones/g soy protein. Alcohol extraction dissociates isoflavones bound to soy protein; therefore, alcohol-denatured soy protein is devoid of significant amounts of isoflavones.

Common food sources of lignans include seeds, whole grains, legumes, and vegetables (**Table 2**). The highest concentrations of lignans are found in flaxseed. The concentration of lignans isolated from flaxseed is ≈100 times that produced from most other foods (24). Values obtained from food samples range from 800

TABLE 1
Isoflavone contents of soy products[1]

Soy products	Total isoflavones	Genistein	Daidzein	Glycitein
		μg/g		
Roasted soybeans	2661	1426	941	294
Soy-protein isolate	987	640	191	156
Tempeh	865	422	405	38
Tofu	532	245	238	49
Protein concentrate[2]	73	19	0	54
Soy drink	28	21	7	—

[1] Adapted from Wang and Murphy (15). For the isoflavone contents of other foods, *see* reference 16.
[2] Alcohol extracted.

TABLE 2
Lignans in selected foods[1]

Food and food group	Secoisolariciresinol	Matairesinol
	μg/g	
Seeds		
Flaxseed	3699	10.9
Sunflower	6.1	0
Caraway	2.21	0.06
Pumpkin	213.7	0
Legumes		
Soybean	2.73	Trace
Peanut	3.33	Trace
Pigeon pea	0.5	0
Urid dahl bean	2.4	0.79
Nuts		
Walnut	1.63	0.05
Almond	1.07	Trace
Berries		
Blackberry	37.1	0.23
Lingonberry	15.1	0
Strawberry	12.1	0.05
Cranberry	15.1	0
Red currant	1.6	0
Cereals		
Oatmeal	0.1	0
Oat bran	0.24	1.55
Rye meal, whole grain	0.5	0.65
Rye bran	1.32	1.67
Vegetables		
Broccoli	4.14	0.23
Garlic	3.79	0.04
Carrots	1.92	0.03
Coffee and tea		
Arabica coffee (instant)	7.16	0
Green tea	24.6	1.86
Black tea	15.9	1.97

[1] Adapted from Mazur (22) and Mazur et al (23).

to 3700 μg/g. Other major sources of plant lignans include cereals, cereal brans, oil seeds, and fruit. Modern processing techniques tend to deplete grains of their lignan content because they remove the outer fiber layer, which has the highest concentration of lignan precursors. The major food sources of coumestrol are clover sprouts, alfalfa sprouts, dry round split peas, and other legumes (25).

ABSORPTION AND METABOLISM OF PHYTOESTROGENS

Isoflavones exist primarily in plants in the inactive form as glycosides. Once ingested, isoflavone glycosides (genistin and daidzin) are hydrolyzed in the intestines by bacterial β-glucosidases and are converted to corresponding bioactive aglycones (genistein and daidzein). Further fermentation proceeds in the distal intestine with the formation of specific metabolites. The aglycones are then absorbed from the intestinal tract and conjugated mainly in the liver to glucuronides, which are either reexcreted through the bile and reabsorbed by enterohepatic recycling or excreted unchanged in the urine. Daidzein may be further metabolized to equol, dihydrodaidzein, or *O*-desmethylangolensin, whereas genistein may be metabolized to *p*-ethylphenol in the colon. Daidzein, genistein, equol, and *O*-demethylangolensin are the major isoflavones that have been detected in the blood and urine of animals and humans. Dihydrodaidzein, *p*-ethylphenol, and glycetin have also been detected in human plasma.

Plant lignans, like isoflavones, also undergo intestinal hydrolysis by bacterial β-glucosidases. The lignan glycosides matairesinol and secoisolariciresinol are converted to their corresponding metabolites, enterolactone and enterodiol, by the action of colonic bacteria; enterodiol is readily oxidized to enterolactone (24). These metabolites are then absorbed in the colon and conjugated with glucuronic acid or sulfate in the liver. Some of the metabolites may also undergo enterohepatic circulation. Lignans are excreted in bile and urine as conjugated glucuronides and in feces in the unconjugated form. The major metabolites, enterolactone and enterodiol, are excreted in the urine.

Concentrations of phytoestrogens and their metabolites in plasma and urine have been reported in several studies of humans and animals. In healthy humans consuming diets without soy, plasma concentrations of isoflavones are usually in the nanomolar range (eg, < 40 nmol/L) (26). In contrast, plasma isoflavone concentrations increase markedly in the micromolar range after ingestion of isoflavones from soybean milk (27), soy meal (28), or baked soybean powder (29). Plasma isoflavone concentrations of 1–4 μmol/L have been reported in various population groups consuming foods rich in isoflavones (26, 30–32). Similarly, urinary excretion of isoflavones increases markedly after ingestion of isoflavone-rich diets (32). In healthy young women consuming diets supplemented with flaxseed, plasma lignan concentrations increased from a baseline concentration of 29 to 52 nmol/L after ingestion of flaxseed (26). Urinary lignan excretion also increased with increasing dietary intake of lignan precursors (33–35). In a study of women consuming various habitual diets, the urinary excretion of lignans ranged from 1.5 to 3.3 μmol/24 h in omnivorous women; 2- to 3-fold higher excretion rates were found in vegetarian women (34). A study in rats showed that urinary lignan excretion increases linearly with ingestion of increasing amounts of ground flaxseed or supplementation of the diet with secoisolariciresinol diglycoside (36).

Effects of dietary soy on glucose and lipid metabolism

Metabolism of glucose and lipids is a complex process highly regulated by both peptides and steroid hormones and is influenced by diet. Many studies in humans and experimental animals have examined whether the consumption of soy-containing diets have an effect on glucose and lipid metabolism and on hormones controlling their metabolism. Early studies in healthy human subjects showed that soy polysaccharides reduce postprandial glucose and triacylglycerol concentrations (37, 38), suggesting that polysaccharides in soy may provide potential benefits in conditions of impaired glucose tolerance and hyperlipidemia. The beneficial effect of soy may also be due to proteins in soy. In one study, soy protein induced a lower postprandial insulin-glucagon ratio in healthy and hypercholesterolemic subjects than did casein (39). Soy proteins are rich in arginine and glycine, which are involved in insulin and glucagon secretion from the pancreas. Decreased plasma insulin by soy protein may be due to decreased release from the pancreas or increased hepatic removal. Thus, the decrease in cholesterol seen with soy protein may be due to the decreased insulin-glucagon ratio caused by arginine and glycine (40). In healthy subjects, Lang et al (41, 42) observed no effect of protein source (soy, other vegetable proteins, and animal proteins) on plasma glucose, insulin, or glucagon, but the kinetics of glucose,

insulin, and glucagon were different after ingestion of different sources of protein in a mixed meal (41).

In an early study in gerbils, feeding soy protein in place of casein increased plasma concentrations of insulin, thyroxine, and thyroid-stimulating hormone (43). In healthy pigs, soy-protein feeding compared with casein decreased postprandial serum concentrations of insulin and glucose with a significant reduction in serum total cholesterol, LDL-cholesterol, and triacylglycerol concentrations (44). In another study in minipigs, soy protein and casein affected insulin, glucagon, hydrocortisone, and triiodothyronine similarly, but soy-protein feeding led to increased total and free thyronine and postprandially increased growth hormone (45). The variable hormonal responses to soy feeding in these early studies are difficult to interpret but may be related in part to differences in the basal nutritional state of the animals and in the timing of the observations. However, these hormonal changes may be partly responsible for the effect of soy protein on cholesterol concentrations.

More recently, Lavigne et al (46) evaluated the effects of controlled feeding with various types of dietary proteins on glucose tolerance and insulin sensitivity in healthy male Wistar rats. The rats were fed isoenergetic diets containing casein, cod protein, or soy protein for 28 d. Rats fed cod and soy proteins had lower fasting plasma glucose and insulin concentrations than did the rats fed casein. After an intravenous glucose load (1.5 mL/kg body wt of 85% glucose in saline), the rats fed cod and soy proteins had lower incremental areas under the curves for glucose than did rats fed casein, suggesting that cod and soy proteins improve glucose tolerance. Additionally, higher glucose disposal rates were observed in the rats fed cod and soy proteins than in the rats fed casein, indicating an improvement in peripheral insulin sensitivity. However, in the postprandial state, the lower plasma insulin concentrations observed in the animals fed cod and soy proteins may have been due to decreased pancreatic insulin release, increased hepatic insulin removal, or both. In a study in ovariectomized cynomolgus monkeys, soy protein significantly improved insulin sensitivity and glucose effectiveness compared with casein (47). Furthermore, the animals fed soy protein showed a decrease in aortic cholesterol ester content, suggesting that dietary soy protein may provide additional cardiovascular benefits. Thus, it appears from these studies that soy-based diets may provide potential benefits in conditions associated with impaired glucose tolerance, hyperlipidemia, and reduced insulin sensitivity.

OBESITY AND DIABETES MELLITUS

Obesity and diabetes mellitus are 2 nutritional disorders that have become major public health concerns in industrialized countries, not only because of their increasing prevalence in epidemic proportions but also because of their frequent association with major cardiovascular risk factors (dyslipidemia, atherosclerosis, and coronary artery disease), which are responsible for excess morbidity and mortality. Obesity is a disorder of energy balance and is associated with hyperinsulinemia, insulin resistance, and abnormalities in lipid metabolism. Lipid abnormalities include increased overall production of lipids with increased concentrations of fatty acids, triacylglycerols, and VLDLs. Hyperinsulinemia and associated lipid disorders are well-known independent risk factors for atherosclerosis and cardiovascular disease. Diabetes mellitus is a complex metabolic disorder that involves abnormalities in insulin secretion and insulin action, an altered endocrine system, and endogenous glucose production that leads to progressive deterioration of glucose tolerance and hyperglycemia. Many individuals with type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes also have abnormalities in lipid metabolism, which further increase the risk of premature cardiovascular disease. Insulin resistance is a common feature of obesity and diabetes and is affected by the nature of dietary fat (48). Interventions to control obesity and diabetes should target these abnormalities.

Various dietary interventions to control excess body weight, hyperglycemia, and dyslipidemia have included low-energy and low-fat diets and the consumption of vegetables, fruit, and grains; foods with a high fiber content; and antioxidants. Such interventions have focused on the manipulation of the amount and nature of dietary energy and fat intakes (48). In recent years, increased attention has been directed toward the role of dietary protein intake in obesity and diabetes. Phytoestrogens have been shown to have a beneficial effect by improving serum lipids and modifying LDL oxidation, the basal metabolic rate, and insulin-stimulated glucose oxidation. Isoflavones and lignans also affect energy metabolism. These observations suggest that the consumption of foods rich in phytoestrogens has a beneficial effect on obesity and diabetes.

Effect of soy on obesity

Several studies in obese humans and animals suggest that soy as a source of dietary protein has significant antiobesity effects (**Table 3**). Bosello et al (49) evaluated the short- and long-term effects of hypoenergetic diets containing proteins from different sources in 24 adult humans with obesity (60% above ideal body weight). In this study the subjects were divided into 2 groups and were provided a very-low-energy (375 kcal/d) diet that contained the same amount of protein as casein or soy protein for 15 d followed by 60 d of a higher-energy diet (425 kcal/d). All subjects lost weight, but the reduction was similar in both groups. Total cholesterol, LDL cholesterol, VLDL cholesterol, and triacylglycerol decreased more with soy than with casein. Thus, the reduction in excess body weight appeared to be due to a low energy intake rather than to the source of protein. Similarly, Yamashita et al (50) did not observe any difference in weight loss with very-low-energy diets containing either lean meat or soy protein in obese women. Furthermore, Jenkins et al (51) observed only a marginally greater weight loss in obese subjects after consumption of a low-energy diet with soy protein than after a low-energy diet with casein as the protein source. Fisler et al (56) observed that in obese men fed low-energy diets containing either soy or collagen protein for 40 d, plasma essential amino acids were better maintained by the soy diet than by the collagen protein diet. These findings suggest that long-term substitution of vegetable protein for animal protein in a low-energy diet may provide an additional benefit for weight reduction in obese subjects. In a randomized crossover study in 12 overweight male subjects, 24-h energy expenditure was greater with animal protein than with soy protein (52).

It is not clear from all these studies whether the favorable effects of soy protein are related to its isoflavone content. However, a recent study by Goodman-Gruen and Kritz-Silverstein (57) in presumably normal-weight, postmenopausal women showed that the consumption of isoflavones, genistein, and daidzein was associated with lower body mass indexes and fasting insulin concentrations and higher HDL cholesterol. Genistein and daidzein

TABLE 3
Effects of dietary soy in obese animals and humans

Model	Diet	Amount and duration	Effects	Reference
Humans				
Obese subjects	Very-low-energy diet with soy protein compared with low-energy-diet with casein	375–425 kcal/d for 60–70 d	Decreased body weight but a greater reduction in cholesterol and triacylglycerol	49
Obese women	Low-energy diets with soy protein or lean meat	Low-energy-diets for 16 wk	Similar decrease (9%) in body weight with both diets	50
Obese women	Soy-based liquid formula compared with milk-based liquid formula	1000 kcal/d for 4 wk	No significant difference in body weight decrease between the 2 diets	51
Mildly obese subjects	Soy protein compared with animal protein	28–29% of energy as protein for 4 d	Decreased 24-h energy expenditure	52
Animals				
Genetically obese mice	Soy-protein isolate and hydrolysate compared with casein-protein isolate and hydrolysate	35% protein for 2 wk at 60% of energy	Decreased body weight, plasma glucose, and perirenal fat pad weight	53
Obese yellow mice	Soy-protein isolate and hydrolysate compared with casein-protein isolate and hydrolysate	35% protein for 4 wk at 60% of energy	Decreased body fat and plasma glucose	54
Gold thioglucose-induced obese mice	Soy saponin plus casein	15% casein with total saponin (10–100 mg·d^{-1}·kg body wt^{-1})	Decreased body fat	55

also lowered the insulin response to an oral glucose load. These results indicate the beneficial effects of isoflavones on excess body weight, hyperinsulinemia, and hyperlipidemia, which are the major cardiovascular risk factors commonly associated with obesity. Long-term controlled feeding studies with soy protein or soy isoflavones in obese humans will provide definitive answers. It is important to note that, in healthy subjects, there is no difference in satiety between dietary soy protein, other vegetable proteins, and animal protein (41, 42).

In a study in genetically obese mice, Aoyama et al (58) reported that soy-protein isolate and its hydrolysate were more effective than was whey-protein isolate and its hydrolysate in weight reduction and acts by lowering the perirenal fat pad weight and plasma glucose concentrations. This effect may be due to an active tetrapeptide present in soy (59). The reduction in fat weight may be due to increasing energy production and the activity of uncoupling protein 1 in brown adipose tissue (53). The tetrapeptide from soy also decreased visceral fat weight in mice during a swimming exercise (60). The reduction in body fat by soy-protein isolate and its hydrolysate compared with casein was also observed in genetically obese yellow KK mice and in rats made obese by being fed a high-fat diet (54); plasma glucose decreased more with the soy-protein isolate and its hydrolysate than with casein. Kawano-Takahashi et al (55) reported that the saponins in soy had an antiobesity effect on obesity induced by gold thioglucose in mice.

Several studies reported increased insulin sensitivity (lower plasma and hepatic lipids, plasma glucose, and plasma insulin concentrations) in rats fed isolated soy proteins compared with rats fed casein (61–63). A 37-kDa protein in soy appears to modulate insulin action on fat decomposition in vitro (64). The active proteins are the A1 and A2 subunits of glycinin (65). Iritani et al (66) studied the interaction between dietary fat and protein in lean and genetically obese Wistar fatty rats. Obese Wistar fatty rats have type 2 diabetes mellitus. The source of protein was either casein or soy, and the dietary fats were either saturated fat, beef tallow, or polyunsaturated fat (corn oil or fish oil). Iritani et al observed higher concentrations of insulin receptor messenger RNA in liver and adipose tissue in rats fed soy protein with saturated fats than in rats fed soy with unsaturated fat or casein with any of the fats. Thus, soy protein appears to reduce insulin resistance when a diet low in polyunsaturated fatty acids is consumed. No significant difference was noted for soy protein compared with casein on plasma glucose concentrations, regardless of dietary fat.

Hurley et al (67) studied the interaction between dietary protein and carbohydrate on energy metabolism in rats. They fed casein, soy protein, or cod protein with either starch or sucrose. Soy-protein isolate fed with starch was the most effective combination for reducing total body fat gains. Soy-protein isolate and starch also lowered plasma glucose and insulin concentrations. Decreased total dissectible fat without significant loss of weight gain was observed in another study in rats when casein was substituted isoenergetically with soy protein in a starch-based diet (63). These studies indicate that the type of macronutrient (protein, carbohydrate, or fat) is also important in energy metabolism and weight reduction.

Role of soy in diabetes mellitus

Many studies in humans and animals suggest that soy has beneficial effects on diabetes mellitus (**Table 4**). Thus far, most studies on the effect of soy on type I diabetes have been done in experimental animals. Taha and Wasif (73) studied the effect of soy flour added to whole-durum meal in alloxan-diabetic hypercholesterolemic rats. The addition of soy flour with or without methionine lowered the elevated plasma glucose, cholesterol, and lipid concentrations. It is not clear whether the beneficial effects were due to the nature of the protein or to the high-fiber content of the diet, because high fiber has similar beneficial effects. Interestingly, in a study of BioBreeding rats prone to type 1 diabetes, Atkinson et al (75) reported that, compared with a diet containing a mixture of animal and plant protein, a diet containing soy

TABLE 4
Effects of dietary soy in animals and humans with diabetes mellitus

Model	Diet	Amount and duration	Effects	Reference
Humans				
Type 2 diabetic subjects	Soy protein and fiber compared with casein with cellulose	50 g protein/d, 20 g fiber/d, and 150 mg isoflavones/d for 6 wk	Decreased LDL cholesterol, triacylglycerol, and apolipoprotein B-100; no change in HDL cholesterol and hemoglobin A_{1c}	68
Type 2 diabetic subjects with obesity and hypertension	Soy protein diet compared with animal-protein diet	1 g protein/kg body wt for 8 wk	Decreased total cholesterol and triacylglycerol	69
Obese type 2 diabetic subjects	Soy polysaccharide compared with low fiber	10 g fiber as single meal	Decreased postprandial hyperglycemia and triacylglycerol; no effect on serum insulin	70
Type 2 diabetic subjects	Soy hull	26–52 g fiber/d for 2–4 wk	Improved glucose intolerance and decreased VLDL cholesterol, triacylglycerol, and glycated hemoglobin	71
Animals				
Nonobese diabetic mice	Soy protein with nicotinamide	40–200 d	Inhibited pancreatic insulitis	72
Alloxan-diabetic rats	Defatted soy flour added to whole-durum meal	7–12% soy flour (9% protein) for 28 d	Decreased hyperglycemia and hyperlipidemia	73
Streptozotocin-induced diabetic rats	Soy compared with casein	20% protein for 2–3 wk	Decreased eicosapentaenoic acid and increased arachidonic acid	74
Diabetes-prone BioBreeding rats	Soy protein compared with animal and nonanimal protein	20–23.4% protein for 160 d	Decreased frequency and delayed onset of type 1 diabetes	75
Wistar fatty rats with type 2 diabetes	Soy protein compared with casein with either saturated or polyunsaturated fat	18% protein and 10% fat (tallow, corn, or fish oil) for 3 wk	Increased insulin receptor messenger RNA concentrations in liver and adipose tissue with soy protein	66

protein reduced the frequency of and delayed the onset of diabetes. This finding suggests that the development of type 1 diabetes depends on the nature of the dietary protein. Similarly, in nonobese diabetic mice, soy protein with or without nicotinamide inhibited insulitis, thereby preventing the occurrence of diabetes (72). However, different results were observed in children. Fort et al (76) reported an increased incidence of type 1 diabetes in infants fed a formula diet containing soy compared with breast-fed infants. Similar observations were made in experimental animals given soy protein or cow milk (77). It is possible that this observation may not have been due to soy or its components but to the absence of breast-feeding.

Ikeda and Sugano (74) studied the effect of the interaction between the type of dietary protein and fat in rats with streptozotocin-induced diabetes. They observed significantly different interactions between type of dietary protein (casein compared with soy) and fatty acid saturation in healthy and streptozotocin-diabetic rats. In healthy rats, the linoleic acid desaturation index in liver microsomal phospholipids was significantly lower in rats fed soy than in those fed casein, but the reverse was true in diabetic rats. Soy protein also lowered eicosapentaenoic acid and increased arachidonic acid in diabetic rats compared with casein, which resulted in a decreased ratio of aortic prostacyclin production to platelet thromboxane A_2. Demonty et al (78) studied how the interaction between dietary protein and fat affected lipid metabolism in rats. Menhaden oil with soy protein lowered serum triacylglycerol compared with soy protein and coconut oil. In rats with experimentally induced pancreatitis, soybean trypsin inhibitor was reported to accelerate pancreatic regeneration (79).

Mahalko et al (71) fed different sources of fiber to type 2 diabetic subjects for 2–4 wk and observed a beneficial effect of soy hull on glucose tolerance, lipid indexes, and glycated hemoglobin. The effect may have been due to polysaccharide, a nongel-forming fiber, in general rather than to other constituents of soy. In another study, Tsai et al (70) observed that in obese subjects with type 2 diabetes, soy polysaccharide significantly reduced the increase in postprandial serum glucose and triacylglycerol concentrations. This effect appears to have been due to smaller increases in glucagon and pancreatic polypeptide and larger increases in somatostatin concentrations (70). There was no significant effect on serum insulin concentrations. Anderson et al (69) studied the effect of soy protein in type 2 diabetic subjects with obesity, hypertension, and proteinuria. They observed no beneficial effect on renal function or proteinuria in these subjects when soy protein was one-half of the daily protein intake. However, they did observe a reduction in hyperlipidemia and in cholesterol and triacylglycerol concentrations. In a recent study by Hermansen et al (68) in type 2 diabetic subjects, soy protein with its associated isoflavones and fiber reduced LDL cholesterol, apolipoprotein B-100, and triacylglycerol as compared with a casein diet with cellulose but had no effect on glucose metabolism, as shown by the lack of change in hemoglobin A_{1c}.

Thus, soybean and its components have beneficial effects on lipid concentrations in healthy and type 2 diabetic subjects. However, it is not clear whether this beneficial effect on lipids was due to soy protein, isoflavones, or cotyledon fiber, because high-fiber diets are known to have beneficial effects on lipid metabolism. Vedavanam et al (80) suggested that soy isoflavones may be beneficial for diabetic

subjects because of their estrogenic activity and their ability to prevent glucose-induced lipid peroxidation and inhibit intestinal glucose uptake by decreasing sodium-dependent glucose transporter, which results in a reduction in postprandial hyperglycemia.

Role of flaxseed in obesity and diabetes

The studies on the role of flaxseed and its components in obesity and diabetes in humans are few. In healthy females, 50 g carbohydrate from flaxseed or 25 g flaxseed mucilage (soluble fiber) lowered postprandial glucose by 27% (81). In healthy and hyperlipidemic subjects, ingestion of whole flaxseed lowers serum cholesterol (81–83). This effect may be due to the presence of n−3 α-linolenic acid in flaxseed oil. Indeed, Nestel et al (84) compared the effect of α-linolenic acid from flaxseed oil with oleic acid and saturated fat on arterial compliance (an index of cardiovascular risk) in obese human subjects. Flaxseed oil significantly increased arterial compliance compared with saturated fat. It also improved insulin sensitivity, increased HDL cholesterol, and decreased LDL oxidation (84). Kaminskas et al (85) studied the effect of flaxseed oil in diabetic subjects and noted an increase in HDL cholesterol but only a small decrease in total cholesterol. They attributed this lack of a major effect of n−3 fatty acid from flaxseed oil to the deficiency of Δ^6-desaturase (EC 1.14.99.25) activity in diabetic subjects.

However, Jenkins et al (86) reported that in nonobese, nondiabetic, hypercholesterolemic subjects, diets supplemented with partially defatted flaxseed lowered total and LDL cholesterol but had no effect on serum HDL cholesterol, possibly a result of the fiber present in defatted flaxseed. Because partially defatted flaxseed is low in α-linolenic acid, the hypocholesterolemic effect may be due to other ingredients in flaxseed. Similar results were obtained by Prasad et al (87) in hypercholesterolemic rabbits. They fed rabbits CDC-flaxseed (type II flaxseed) with a very-low α-linolenic acid content for 4–8 wk and observed lower serum total cholesterol and LDL-cholesterol concentrations but no effect on HDL cholesterol. Prasad (88) further showed that secoisolariciresinol diglucoside, a lignan present in flaxseed, also lowers serum total cholesterol and LDL cholesterol and reduces hypercholesterolemic atherosclerosis in rabbits.

Like soy isoflavones, lignans have antioxidant activity (89). However, whole flaxseed had no significant effect on markers of lipid peroxidation in humans (81, 82), but partially defatted flaxseed lowered serum protein thiol groups, indicating increased oxidation (86). This discrepancy needs to be evaluated further. Secoisolariciresinol diglucoside (90), the lignan present in flaxseed, and its mammalian metabolites secoisolariciresinol, enterodiol, and enterolactone (91) have been shown to have antioxidant activity. The antioxidant activity of secoisolariciresinol and enterodiol is higher than that of vitamin E or the parent glucoside present in flaxseed (91). Oxidative stress has been shown to be one of the causes of both type 1 and type 2 diabetes. Secoisolariciresinol diglucoside reduces the incidence of diabetes in streptozotocin-induced diabetic rats (92); diabetes-prone Biobreeding rats, a model for type 1 diabetes (93); and Zucker rats, a model for type 2 diabetes (94).

POSSIBLE MECHANISMS OF ACTIONS FOR PHYTOESTROGENS

The mechanisms by which phytoestrogens exert their beneficial effects on diabetes and obesity are unclear. As a result of their structural similarities to endogenous estrogens, phytoestrogens act as weak estrogens and compete with 17β-estradiol for binding to the intranuclear estrogen receptor protein to modulate gene transcription (10, 95). At least 2 distinct estrogen receptors— estrogen receptor α and estrogen receptor β—have been described and found to be expressed in various tissues (10), including adipose tissue (96). Phytoestrogens have been shown to bind to both estrogen receptors but bind more strongly to estrogen receptor β (12). Phytoestrogens may also exert their biological effects via non-estrogen receptor–mediated mechanisms by inhibiting the activity of several enzymes, including protein tyrosine kinases (97), DNA topoisomerase I (EC 5.99.1.2) and DNA topoisomerase II (EC 5.99.1.3) (98, 99), and ribosomal S6 kinase (100), which are involved in cell-signaling mechanisms and nuclear events such as cell proliferation and differentiation. Additionally, phytoestrogens are known to have potent antioxidative activity. Some of the cellular and metabolic effects of soy (isoflavones) and flaxseed (lignans) on obesity and diabetes may be through both estrogen receptor– and non-estrogen receptor–mediated mechanisms.

Several lines of evidence suggest that phytoestrogens may favorably affect glucose homeostasis, insulin secretion, and lipid metabolism (**Table 5**). In vitro studies have shown that a soybean phytochemical extract containing the isoflavones genistein and daidzein inhibits glucose uptake into rabbit intestinal brush border membrane vesicles in a dose-dependent manner and also protects against glucose-induced oxidation of human LDL (80). This action may be directly relevant to intestinal glucose absorption in vivo because intestinal sodium-dependent glucose transporter 1 and facilitated glucose transporter 2 are increased in experimental diabetes (108, 109). These increases cause increased absorption of glucose from the gut leading to postprandial hyperglycemia, a common phenomenon seen in the diabetic state. An inhibitory effect of soy isoflavones on intestinal glucose transport, if operative in vivo, may help reduce postprandial hyperglycemia in diabetes.

Experimental evidence suggests that protein tyrosine kinases play a permissive role in the regulation of insulin secretion from pancreatic β cells. Several in vitro studies using the isoflavone genistein as a protein tyrosine kinase inhibitor have shown that this compound exerts multiple actions on insulin release from pancreatic islet cells (110–114). For example, in cultured islets of Langerhans, genistein (at a concentration of 100 μmol/L) was shown to increase basal insulin secretion, but this dose of genistein also reduced islet cell proliferation (101). In additional studies, genistein was shown to inhibit islet tyrosine kinase activities and glucose- and sulfonylurea-stimulated insulin release without affecting glucose metabolism (101). However, other groups have reported that genistein inhibits glucose-stimulated insulin secretion (104). Daidzein, which has no effect on tyrosine kinases, also increases insulin secretion from mouse islets (110).

Genistein has also been shown to have a direct effect on lipid metabolism in the liver and adipose tissue. For example, in an isolated perfused liver preparation, genistein reduced the incorporation of [^{14}C]glucose into lipids and increased the output of fatty acids into the medium (102). These changes were accompanied by a decrease in hepatic triacylglycerol content. Genistein was also reported to decrease the number of high-affinity insulin receptors in the livers of ovariectomized rats (103). Similarly, incubation of isolated rat adipocytes with increasing doses of genistein (0.01, 0.3, 0.6, and 1 mmol/L) resulted in inhibition of glucose conversion to total lipids in the absence and presence of insulin (104). A similar antilipogenic effect in adipocytes was observed when acetate was used as the substrate for lipogenesis.

TABLE 5
Metabolic effects of phytoestrogens at the cellular level

Isoflavone	Cell type	Action	Reference
Soybean extract (daidzein and genistein)	Intestinal cells	Inhibits glucose uptake into brush border membrane vesicles	80
Genistein	Pancreatic islet cells	Increases basal insulin secretion but reduces islet cell proliferation and inhibits glucose- and sulfonylurea-stimulated insulin receptors	101
Genistein	Hepatocytes	Decreases incorporation of glucose into lipids and the number of insulin receptors	102, 103
Genistein	Adipocytes	Inhibits glucose conversion into total lipids, stimulates basal lipolysis and epinephrine-induced lipolysis, and inhibits insulin-stimulated glucose oxidation in a dose-dependent manner but has no effects on insulin's stimulation of pyruvate dehydrogenase and glycogen synthase activities or tyrosine autophosphorylation of insulin receptors	104, 105
Genistein	Skeletal muscle cells	Inhibits glucose uptake stimulated by uncoupling protein 3	106
Coumestrol	Skeletal muscle	Decreases glycogen and inhibits insulin binding to membranes	107

In similar experiments, genistein (0.1 and 1 mmol/L) augmented basal lipolysis, and at the lowest concentration (0.01) it further increased lipolysis stimulated by epinephrine in adipocytes. In isolated adipocytes, genistein decreased basal and insulin-induced lipid synthesis from glucose and inhibited insulin-stimulated glucose oxidation and the lipolytic effect of insulin but had no effect on insulin-stimulated pyruvate dehydrogenase (EC 1.2.4.1) or glycogen synthase (EC 2.4.1.11) (105). In another study in isolated rat adipocytes, genistein inhibited de novo lipid synthesis from acetate and glucose but stimulated lipolysis (104). Thus, genistein appears to have direct effects on lipid metabolism in liver and adipose tissue by affecting both lipogenesis and lipolysis. In skeletal muscle cells, genistein was recently shown to inhibit glucose uptake stimulated by uncoupling protein 3 (106). Nogowski et al (115) studied the effect of coumestrol on carbohydrate metabolism in ovariectomized rats. Coumestrol had no significant effect on plasma insulin or glucagon concentrations, but it decreased muscle glycogen and inhibited insulin binding to muscle membrane. Thus, the effect of coumestrol on carbohydrate metabolism appears to be via changes in insulin receptors. Whether these actions of phytoestrogens on skeletal muscle have an effect on overall glucose disposal in vivo is not known. Coumestrol also affects lipid metabolism. In chicks, dietary coumestrol decreased plasma cholesterol concentrations in a dose-dependent manner (107). Thus, phytoestrogens appear to have favorable biological actions on glucose and lipid metabolism that may explain their potential to benefit obesity and diabetes.

SUMMARY AND CONCLUSIONS

Emerging evidence suggests that diets rich in phytoestrogens (isoflavones and lignans), namely soy protein and flaxseed, can have beneficial effects on many aspects of diabetes and obesity. The beneficial effects of dietary soy and flaxseed are observed in both healthy and experimental animals and in healthy humans and those who are obese or have diabetes mellitus. The dietary components responsible for the beneficial effects of soy protein and flaxseed in diabetes and obesity have yet to be determined. However, the studies described above indicate that the beneficial effects may be due to phytoestrogens (isoflavones and lignans), saponins, and trypsin inhibitor in soybean; the nature and amount of fiber consumed; the nature of the protein and protein hydrolysate consumed; the amino acid composition of the protein consumed; and the fatty acid composition of soy and flaxseed oil. In obesity and diabetes, one or more components may have a beneficial effect singly, synergistically, or additively with other active components. Definitive studies should shed more light in this area.

Soy proteins may improve obesity and diabetes by reducing insulin resistance and reduce adiposity by inhibiting insulin secretion from the pancreatic β cells or by inhibiting lipogenesis and enhancing lipolysis in liver and adipocytes. Isoflavones and lignans may also exert beneficial effects on tissue lipids through their antioxidative actions. Some of these mechanisms have been suggested by in vivo studies but most have been shown in vitro. Additional studies are needed to further elucidate the biological and physiologic mechanisms by which isoflavones and lignans improve glucose tolerance and insulin sensitivity.

Studies on the role of flaxseed and its components in obesity and diabetes in humans are few, and studies of the effect of the phytoestrogen coumestrol on obesity and diabetes are needed. Most of the clinical trials that have been conducted have been observational only, have been of relatively short duration, and have involved a small number of patients. Long-term controlled trials on the safety and effectiveness of dietary soy and flaxseed on the development and progression of diabetes and obesity and their complications in patients with diabetes mellitus and obesity are overdue.

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