Type 2 Diabetes and Glycemic Response to Grapes or Grape Products¹,²

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Abstract
Type 2 diabetes affects ~7% of the population in the United States and is characterized by decreased disposal of glucose in peripheral tissues due to insulin resistance and overproduction of glucose by the liver, defects in pancreatic β-cell function, and decreased β-cell mass. Obesity, decreased physical exercise, and consumption of foods with a high glycemic index (GI) and load are major predisposing factors in the development of type 2 diabetes. The GI is used to evaluate the rise in blood glucose levels in response to food. The GI provides an indication of the quality of carbohydrate in a food. The glycemic load (GL) is used to provide information about the quantity of carbohydrates in a food and the insulin demand. Individuals with diabetes are advised to maintain a diet of low-GL foods, because low-GL diets improve diabetes symptoms. Grapes have a mean GI and GL in the low range. Little research has been performed with grapes and/or grape products to determine the glycemic response either alone or with a meal. Grapes and other fruits contain numerous polyphenols, including the stilbene resveratrol, the flavanol quercetin, catechins, and anthocyanins that have shown potential for reducing hyperglycemia, improving β-cell function, and protecting against β-cell loss. Therefore, with a low mean GI and GL, grapes or grape products may provide health benefits to type 2 diabetics. J. Nutr. 139: 1794S–1800S, 2009.

Introduction
The American Diabetes Association estimates that ~7% of the population in the United States have type 2 diabetes (1). Type 2 diabetes is characterized by hyperglycemia, peripheral resistance to the action of insulin, and eventual destruction of insulin-producing β-cells in the pancreas (2). Diabetic patients are at increased risk for cardiovascular disease, blindness, nerve and kidney damage, and limb amputations. Diabetics are also at greater risk for developing different cancers due to the immunological disturbances induced by aberrant metabolism. Obesity is a major predisposing factor in the development of diabetes. In obese populations, inflammatory molecules produced by adipose tissue and increased circulation of FFA play an important role in producing peripheral insulin resistance as well as increasing damage to the insulin-producing β-cells. The main treatments for type 2 diabetes include diet, exercise, and medications.

Besides obesity, a number of other risk factors increase the likelihood of developing diabetes. The CDC describes the risk factors for developing diabetes, which include physical inactivity, an immediate relative with diabetes, abnormal cholesterol and triglyceride levels, and high blood pressure (3). As with most diseases, genetics plays an important role in determining development of diabetes. Type 2 diabetes is found more commonly in African Americans, Native Americans, Asian Americans, Pacific Islanders, or individuals of Hispanic American/Latino heritage. The rate for Native Americans is noteworthy, because 20–50% of this population has type 2 diabetes (4).

Regulation of blood glucose by insulin
Under normal physiological conditions, blood glucose levels are tightly regulated by the secretion of insulin and glucagon by specialized cells in the islets of Langerhans of the pancreas (5). High blood glucose promotes insulin release from the β-cells of the islets. Insulin stimulates the uptake of glucose from the blood by different tissues such as muscle, kidney, and adipose, promotes the storage of glucose in the liver as glycogen, and inhibits lipolysis in adipose tissue. Resulting depletion of blood glucose by the action of insulin in turn promotes the secretion of glucagon from the α-cells in the pancreatic islets, which stimulates glycolysis in the liver and release of glucose back into the blood.
Skeletal muscle is a major site of glucose uptake stimulated by insulin. The mechanisms of glucose uptake are similar in skeletal and adipose tissue. Insulin-stimulated uptake of glucose is mediated by the action of glucose transporters on the cell surface (6,7). Glucose transporter-4 (GLUT4) is expressed by muscle, adipose, and kidney cells. Under basal conditions, GLUT4 is sequestered in insulin-responsive storage compartments within the cell. Insulin upregulates the expression of GLUT4 on the cell surface of these cells by stimulating the exocytosis of the stored GLUT4.

Insulin acts to increase glucose uptake by binding to the insulin receptor (IR). The IR is a membrane-bound tyrosine kinase containing 2 extracellular α subunits and 2 intracellular β subunits [reviewed in (6)]. Binding of insulin to the extracellular α subunits results in a change in protein conformation, which then activates the tyrosine kinase domain of the intracellular β subunits. The β subunits undergo a series of autophosphorylation at different tyrosine residues involved in recognizing IR substrates (IRS). Once the IR is stimulated, phosphorylation of IRS proteins generates docking sites for phosphatidylinositol-3-kinase (PI3K) at the cell membrane (8). Activation of PI3K at the IR stimulates the accumulation of phosphatidylinositol-3,4,5-trisphosphate, which acts as a second messenger in mediating insulin-stimulated translocation of GLUT4. Studies have shown that activation of PI3K and subsequent accumulation of phosphatidylinositol-3,4,5-trisphosphate are essential for insulin-stimulated GLUT4 translocation (9-11). Downstream targets of the PI3K signal transduction pathway involved in GLUT4 translocation include protein kinase B, atypical protein kinase Cα, and 3′-phosphoinositide-dependent kinase (6). Although PI3K activation is necessary for insulin-stimulated GLUT4 translocation, a second pathway for stimulating GLUT4 translocation has been proposed. The tyrosine kinase activity of the IR is enhanced by association with caveolae, the caveolin-rich invaginations of the cell membrane that represent a subset of lipid rafts (12). Upon stimulation of the IR by insulin, the proto-oncogene cellular-Casitas B-lineage lymphoma (c-Cbl) is recruited to the caveolae and phosphorylated. Phosphorylated c-Cbl recruits adaptor proteins that are responsible for activating TC10, a Ras homolog-family GTPase, and TC10 has been shown to modulate the exocytosis of GLUT4 (13,14). Both of these signaling pathways lead to insulin-dependent arrangements in the actin cytoskeleton of the cell resulting in exocytosis and docking of stored GLUT4 at the cell membrane (15,16).

One of the major characteristics of type 2 diabetes is the development of insulin resistance (5). Insulin normally prevents lipolysis in the adipose tissue and stimulates storage of glucose in the liver. Type 2 diabetes with insulin resistance often have increased levels of circulating fatty acids and persistant glucose precipitation in the liver due to the inability of insulin to prevent lipolysis and promote storage of glucose. Increased release of fatty acids from adipose tissue, increased glucose production by the liver, and reduced stimulation of glucose uptake in turn promote the insulin-resistant state. Insulin resistance can be caused by desensitization of the IR. There are currently 2 basic mechanisms known to occur for attenuating IR signaling (6). Serine phosphorylation of the IR and/or IRS and dephosphorylation of the activating tyrosine residues of the IR or its substrates contribute to decreased IR function. Several candidate molecules have been investigated for their role in inducing insulin resistance. Enzymes implicated in serine phosphorylation of the IR include PI3K, protein kinase B, glycogen synthase kinase-3, extracellular signal-related kinase, c-Jun N-terminal kinase, and inhibitor of kB kinase β (6). Inhibitor of kB kinase β is notable for its role in mediating downstream signaling by inflammatory cytokines, because chronic inflammation can also promote insulin resistance as well as β-cell dysfunction. Alterations in the IR itself or an IRS can decrease insulin sensitivity. Targeted disruption of the IRS-2 gene in mice produced progressive development of diabetes with peripheral insulin resistance, increased blood insulin, and hyperglycemia (17). Kido et al. (18) developed mice with heterozygous null mutations in the ir, irs-1, and irs-2 genes and these mice exhibited varying degrees of insulin resistance. Taken together, these data indicate that both upstream and downstream effectors in the IR signaling pathway affect insulin sensitivity.

Both reduction in β-cell mass and β-cell dysfunction contribute to the development of type 2 diabetes [reviewed in (19)]. β-Cell mass is normally maintained by proliferation of preexisting β-cells and neogenesis from pancreatic ductal progenitors (20,21). Glucose is a major regulator of β-cell mass and function as determined by animal studies. β-Cells proliferate in response to increased insulin demand brought about by increased blood glucose levels. Studies have shown that infusion of glucose into rats and mice increased β-cell mass in the islets (22-24). However, a 25-50% decrease in β-cell mass has been observed in patients at the time of diagnosis of type 2 diabetes (25,26). High levels of circulating glucose and FFA found in type 2 diabetic patients are toxic to β-cells. Prolonged hyperglycemia in individuals with diabetes causes not only β-cell dysfunction but also decreased β-cell mass due to induction of apoptosis. Furthermore, the increased presence of circulating fatty acids in combination with hyperglycemia has also been implicated in the induction of β-cell apoptosis, resulting in decreased β-cell mass and function. El-Assaad et al. (27) showed that infusion of lipids in diabetic patients caused impaired insulin secretion. In vitro studies used to define the mechanism of β-cell dysfunction showed that exposure of islets or β-cells to fatty acids inhibited insulin gene expression and induced β-cell apoptosis (19). Examination of pancreatic autopsies tissue from overweight and lean diabetic patients showed a 63 and 41% reduction in β-cell volume, respectively, compared with nondiabetic control samples (28). In these tissues, a 3- to 10-fold increase in β-cell apoptosis was observed in tissue from type 2 diabetic patients compared with control tissue, further suggesting that reduction in β-cell mass in diabetic patients is due to increased apoptotic β-cell death.

**Glycemic index and glycemic load**

Dietary changes are often necessary to control type 2 diabetes, whether insulin is required or not. The glycemic index (GI) was developed by Jenkins et al. (29) to measure the rise in blood glucose after eating a particular food. The GI was formulated in an attempt to aid diabetic populations in their food selection with the recommendation that diabetics select foods with a low GI (30). The GI of a test food is typically determined by measuring the blood glucose levels in at least 6 individuals over a 2- to 3-h period after consumption of a food containing 50 g of available carbohydrate [reviewed in (31)]. The blood glucose response to 50 g of ingested glucose (reference) is measured in the same individual on a different day at the identical time points postingestion. The subsequent area under the curve (AUC) for

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3 Abbreviations used: AUC, area under the curve; c-Cbl, cellular-Casitas B-lineage lymphoma; GI, glycemic index; GL, glycemic load; GLUT4, glucose transporter-4; IR, insulin receptor; IRS, insulin receptor substrate; PI3K, phosphatidylinositol 3-kinase; SIRT1, sirtuin.
the blood glucose responses to both the test food and the reference (set at 100) are used to generate the GI using the following equation (32): (AUC of test food ÷ AUC of glucose) × 100. The use of white bread as the reference food instead of glucose for determining GI has been proposed due to concerns of delayed gastric emptying by glucose and because white bread stimulates more insulin than glucose when related to the blood glucose response (30,33). Using glucose as the reference, foods are classified as low (<55), medium (55–69), or high (>70) GI (31). The overall glycemic response can be altered by fat, protein, and fiber in a meal, as well as processing. For example, Henry et al. (34) showed that the GI of bread alone was 71, whereas the GI of bread combined with different types of fats (butter, olive oil, grape seed oil) ranged between 50 and 58.

Whereas the GI provides an indication of the quality of carbohydrate in a food, glycemic load (GL) is used to provide information about the quantity of carbohydrates in a food and the insulin demand. The GL can be determined by direct or indirect methods. The indirect method for assessing the GL of a food uses the following equation (32):

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GL = \left( \frac{GI \text{ value} \times 100}{3} \right) \times g \text{ of available carbohydrate} \\
\times \text{weight of food.}
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The direct method uses a 3rd concept of glycemic equivalence or glycoemic glucose equivalence. For each participant, a standard curve is constructed by measuring the blood glucose response to increasing amounts of glucose (31). The same participant is then given the test food and the blood glucose response to the test food is compared with the standard curve for glucose. The GL classification of a food is low (<10), medium (10 to <20), and high (≥20) (31).

Dietary GI has been used to predict the risk for developing type 2 diabetes, as well as cardiovascular disease. High-GI diets increase the risk of diabetes by chronically increasing insulin demand, which in turn may lead to β-cell exhaustion, dysfunction, and apoptosis (35). Combining a high-GI diet with a genetic predisposition toward diabetes, physical inactivity, or obesity increases the risk of developing insulin resistance and glucose intolerance, resulting in hyperglycemia and high blood levels of fatty acids. Research has suggested that low-GI and -GL diets improve glycemic control in individuals with impaired glucose tolerance and diabetes by lowering fasting blood glucose and glycated proteins and improving insulin sensitivity (36).

**Regulation of diabetes by grapes and grape components**

Most fruits and vegetables have a low GI and GL. The GI and GL of some commonly consumed fruits are shown in Figure 1. The values in Figure 1 represent the means of different studies taken from a comprehensive GI and GL listing compiled by Foster-Powell et al. (37). The mean values for grapes place this fruit in the low-GI and -GL range.

Little research has been performed to identify the benefits of grape intake for type 2 diabetics. Because both the GI and GL fall within the low range, this fruit is appropriate for inclusion in a diet targeting low glycemic foods, such as a diet for a diabetic individual. Grapes contain an abundance of phytochemicals with antioxidant and antiinflammatory activities. A small number of studies have been conducted that suggest grapes or constituents of grapes may have some protective effects against the metabolic disturbances observed in type 2 diabetics. Furthermore, antiinflammatory activities of certain grape components may have positive benefits in reducing inflammation-related complications of type 2 diabetes, such as cardiovascular disease. Banini et al. (38) recently showed that continued consumption of dealcoholized muscadine grape wine altered blood insulin levels in type 2 diabetic subjects. Nondiabetic control and type 2 diabetic participants were instructed to drink 150 mL of juice, wine, or dealcoholized wine prepared from muscadine grapes once per day after dinner for 28 d. Subjects receiving the dealcoholized wine had reduced fasting blood insulin levels and the fasting blood glucose:insulin ratio increased from 8.5 to 13.1 during the 28-d intervention. A low glucose:insulin ratio of <7 is predictive of insulin resistance. The muscadine grape juice and wine did not differ in fasting blood glucose, insulin, or glycated hemoglobin before or after the intervention. This study points toward the possibility that consumption of grapes or grape preparations may be beneficial to individuals with aberrant insulin responses to glucose. Further studies using human participants need to be performed to investigate the potential health benefits of grapes for this disease.

Other studies have been performed to test the health benefits of grapes or grape components using animal models for diabetes, many of which utilized chemically induced models for analyses of metabolic disturbances. Induction of diabetes with the chemicals alloxan or streptozotocin results in loss of β-cell mass often accompanied by infiltration of the islets by activated immune cells (39). Although these models do not completely represent type 2 diabetes and have often been used as models for type 1 diabetes due to the immune cell infiltration, they have been used to analyze metabolic disturbances, β-cell loss, and generation of reactive oxygen species associated with diabetes. There is limited information available that describes the effects of grapes or grape products on peripheral insulin resistance that characterizes type 2 diabetes. Therefore, studies using chemically induced models of diabetes have been included below to provide some information on the potentially protective role grapes and their constituents may play in managing type 2 diabetic complications.

Phytochemicals found in grapes or grape plant-derived products have shown inhibitory effects in the chemically induced
diabetic models. Polyphenol extracts from red wine with or without ethanol were given orally to streptozotocin-treated rats each day for 6 wk (40). Both control and diabetic rats that received the red wine extract without ethanol showed decreased body growth, food intake, and blood glucose levels. Diabetic rats that received ethanol alone or red wine extract with ethanol had partially restored body growth and both groups had reduced hyperglycemia and increased plasma insulin compared with untreated groups. In a separate study, a rat model for insulin resistance was used to study the health benefits of red wine polyphenol extracts, ethanol, and extracts plus ethanol (41). Rats fed red wine polyphenols had reduced hypertension, cardiac hypertrophy, and production of reactive oxygen species in cardiac tissue. In both of these studies, the authors used pharmacological doses of the red wine polyphenols. Grapevine leaves were also assessed for antidiabetic properties by Orhan et al. (42). Subfractions of aqueous extracts from the leaves of Vitis vinifera L. were injected intraperitoneally into streptozotocin-induced diabetic rats. Treatment with the polyphenol-enriched fraction reduced blood glucose in the diabetic rats compared with control animals.

Procyanidins extracted from grape seed were shown to reduce hyperglycemia in streptozotocin-induced diabetic rats (43). A single oral dose of the extract at a concentration of 250 mg/kg body weight significantly decreased blood glucose concentrations that were elevated from the streptozotocin treatment. Furthermore, the procyanidin extract combined with low dose insulin was significantly more effective than the low dose insulin alone in reducing hyperglycemia in these rats. Using differentiated L6E9 myocyte and 3T3-L1 adipocyte cell lines, the authors further showed that the procyanidin extract increased uptake of glucose in these cells, suggesting procyanidins may have an insulin mimetic effect. In another study, El-Alfy et al. (44) found that pretreatment with orally administered proanthocyanidins from red grape seeds significantly inhibited the rise in blood glucose levels after alloxan injection compared with control rats. Repeated daily administration of the proanthocyanidin preparation for 72 h increased insulin levels in the blood back to control levels. The proanthocyanidins decreased lipid peroxidation and increased pancreatic glutathione levels. These data indicate that the grape seed proanthocyanidins protected β-cell function and suggest a protective effect against generation of damaging reactive oxygen species.

Resveratrol is a stilbene that is produced in the skins of grapes and acts as an antifungal agent in the plant. Resveratrol is also found in other types of berry fruits such as blueberries and cranberries. Antihyperglycemia and antilipemic roles for resveratrol in diabetes have been recently shown. In middle-aged mice fed a high-fat diet, the addition of resveratrol to the diet increased insulin sensitivity, prevented development of fatty liver, increased the number of mitochondria in the liver, and increased life span compared with mice receiving a high-fat diet alone (45). In another study, Lagouge et al. (46) found that dietary resveratrol prevented diet-induced obesity, reduced insulin resistance, and improved mitochondrial function in muscle tissue in young mice. The protective activity of resveratrol was attributed to its ability to activate sirtuin 1 (SIRT1), an NAD+-dependent deacetylase that has been linked to increased life span (46, 47). Chi et al. (48) investigated the effects of oral resveratrol on blood glucose in rat models for insulin-dependent diabetes, non-insulin-dependent diabetes, and insulin resistance. They found that resveratrol administration lowered plasma glucose by both insulin-dependent and -independent mechanisms in normal and diabetic animals. However, in these studies, resveratrol was found to stimulate the secretion of insulin from the pancreas of those animals that still had β-cell mass. Further analysis revealed that oral resveratrol increased the expression of GLUT4 in the muscle tissue by activation of the PI3K-Akt pathway. In streptozotocin-treated diabetic rats, resveratrol administered orally for 14 d significantly decreased blood glucose and insulin levels compared with diabetic control animals (49). Furthermore, plasma triglyceride concentrations dropped significantly over the 14-d treatment period compared with control rats. These data suggest an intriguing role for resveratrol in controlling the hyperglycemia and dyslipidemia that characterize type 2 diabetes and cause many of the metabolic complications in this population.

Generation of reactive oxygen species in the pancreatic islets has been observed in experimental animal models of diabetes and oxidative stress may be involved in reducing the β-cell mass by inducing apoptosis (39). Quercetin is a flavonoid antioxidant found in many fruits and vegetables, including grapes. Using streptozotocin to induce diabetes in rats, Coskun et al. (50) found quercetin effective in preventing total loss of the β-cell mass. Quercetin was injected intraperitoneally at a concentration of 15 mg/kg body weight 3 d before and then daily for ~4 wk after the streptozotocin treatment. Using immunohistochemical analysis of pancreatic tissue, the authors showed that quercetin treatment maintained β-cell mass. Several different parameters of oxidative stress were analyzed in the pancreatic tissue of these animals, including malondialdehyde, an indicator of lipid peroxidation, and activity of the antioxidant enzymes superoxide dismutase, glutathione peroxidase, and catalase. Diabetic animals had elevated levels of tissue malondialdehyde and all 3 of the antioxidant enzymes showed increased activities indicative of oxidative stress in the diabetic state. However, the quercetin treatment significantly reduced the level of malondialdehyde and the activities of the antioxidant enzymes in pancreatic tissue, in some cases back to normal levels. Although the quercetin was injected into the rats rather than fed orally, these studies indicate an interesting and potentially important role for quercetin and possibly other flavonoids for reducing the oxidative stress in the pancreas during diabetes and aiding in the preservation of the β-cell mass.

**Regulation of diabetes by other fruits**

Certain other fruits have been tested for antidiabetic activities. Dietary tart cherries were examined in the Dahl salt-sensitive rat, which develops hyperlipidemia and insulin resistance (51). Rats were fed a diet supplemented with 1% freeze-dried cherries for 90 d. In these studies, total blood cholesterol, total blood triglycerides, blood glucose, and insulin were significantly reduced in rats that received the cherry diet compared with control rats. Ginseng berry extract was used in both the ob/ob and db/db mouse models for type 2 diabetes to determine whether this fruit had antidiabetic activities (52, 53). The ob gene encodes the hormone leptin, which signals satiety in healthy individuals, and the db gene encodes the leptin receptor (54). The ob/ob mouse has a mutation in the ob gene that causes a deficiency in leptin, whereas the db/db mouse does not have a functional leptin receptor. Both of these mouse strains develop a severely obese phenotype and hyperglycemia. Although the extract was injected intraperitoneally rather than administered orally, the ginseng berry extract significantly reduced body weight and blood glucose levels in both mouse models. In another study, proanthocyanidins were extracted from persimmon peel and administered orally to C57BL/Ks-l-db/db mice by a stomach tube (55). Mice were orally administered the proan-
thiocyanin preparation daily for 6 wk. Serum glucose, triglyceride, and total cholesterol concentrations and oxidative stress in the liver were measured. Oral administration of the persimmon peel proanthocyanidins decreased hyperglycemia and blood triglyceride and total cholesterol concentrations, and improved the oxidative status of the liver of these mice.

Several exotic fruits have been examined for potential antidiabetic activities. Acerola fruit (*Malpighia emarginata* DC) is found in Central and South America. Diabetic mice were given polyphenol-rich extracts from Acerola fruit in their drinking water or plain water for 8 wk (56). Blood glucose concentrations in fed mice were tested and hyperglycemia was reduced at 5 wk compared with the control diabetic mice. However, this reduction was not maintained through the course of the 8-wk experiment. *Synsepalum dulcificum* is a berry fruit from West Africa known as miracle fruit. Insulin-resistant rats were orally administered lyophilized and redissolved miracle fruit (57). Miracle fruit decreased plasma glucose and insulin compared with control animals receiving vehicle only. The fruit of *Tetrapleura tetraptera* is found in tropical areas of Africa. Using streptozotocin-treated rats, extracts from this fruit were administered orally and blood glucoses were measured over an 8-h period (58). Diabetic rats receiving the fruit extract had a ~50% reduction in blood glucose concentrations over 8 h compared with diabetic control rats.

**Future directions**

There is a paucity of information regarding the health benefits of grapes and grape constituents for management, treatment, or prevention of type 2 diabetes. The published literature thus far suggests a potential regulatory role for grape products in the management of type 2 diabetes and these data are summarized in Table 1. Experiments with other fruits have also shown positive health benefits for reducing some of the metabolic disturbances in type 2 diabetes, such as hyperglycemia and hyperinsulinemia. It is noteworthy that many of the grape studies described in this review have used pharmacological concentrations of extracts and individual polyphenols. Further research is needed to determine whether beneficial effects in the management of type 2 diabetes can be achieved by diets rich in whole grapes, grape products, or individual grape-derived polyphenols. The low range of GI and GL make grapes an acceptable and desirable part of the diet of diabetic individuals. Grapes, especially darkly colored fruits, have an abundance of antioxidant molecules that have the ability to regulate insulin and glucose metabolism and oxidative stress induced in this disease. Extensive human studies are needed to gain insight into the role grapes and grape products can play in regulating hyperglycemia, insulin sensitivity, and relieving oxidative damage to maintain β-cell mass. A standardized grape product would be beneficial for initial analyses of the health benefits of grapes by different investigators. Studies using different grape cultivars would be ideal to determine which cultivars show maximum health benefits. Research with humans should involve long-term study designs to determine whether the consistent addition of grapes or grape products to the diet will have long-term benefits for reducing disease progression. For studies involving healthy subjects and type 2 diabetics, the insulin response will be an important parameter to investigate, because insulin resistance is indeed a major problem exacerbating the hyperglycemic state observed in this population. Plasma triglycerides, cholesterol levels, and inflammatory molecules will also be important parameters to examine in human studies, because type 2 diabetics are at high risk for developing cardiovascular complications.

Other articles in this supplement include (59–65).

**Literature Cited**


