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Lycopene Partially Reverses Symptoms of Diabetes in Rats with Streptozotocin-Induced Diabetes

Aysegul Bayramoglu,[1] Gokhan Bayramoglu,[1] and Hakan Senturk[2]

[1]*Department of Biology, Science and Arts Faculty, Artvin Coruh University, Artvin, Turkey.*
[2]*Department of Biology, Science and Arts Faculty, Eskisehir Osmangazi University, Eskisehir, Turkey.*

ABSTRACT In the present study, we describe the effects of lycopene on the symptoms of streptozotocin (STZ)–induced diabetes in rats. Lycopene at the dose of 2.5 mg/kg body weight (bw) per day was orally administered to STZ-induced diabetic rats for a period of 7 days after onset of diabetes. At the same time, food–water intake and body weight change were recorded daily. Upon sacrifice, biochemical parameters, such as the serum glucose, insulin, total cholesterol (TC), triglyceride (TG), alanine aminotransferase (ALT), and aspartate aminotransferase (AST), were measured in all experimental groups. Administration of lycopene at the dose of 2.5 mg/kg bw per day significantly reduced serum glucose, TC, TG, ALT, and AST levels, and increased serum insulin levels, but there were no improvements in food–water intake and body weight change parameters in lycopene-treated diabetic rats. The results suggest that orally administrated lycopene exhibits a potent hypoglycemic effect in STZ-induced diabetic rats and that lycopene may be useful for the management of diabetes mellitus.

KEY WORDS: • ***antioxidants*** • ***diabetes*** • ***liver*** • ***lycopene*** • ***pancreas*** • ***rat*** • ***streptozotocin***

INTRODUCTION

DIABETES IS A SEVERE DISEASE caused by an autoimmune destruction of pancreatic β-cells (type 1) or insulin resistance (type 2). The concomitant hyperglycemia and/or hypoinsulinemia have serious detrimental health effects and often compromise the quality of life.[1] Also, diabetes is associated with disturbances in carbohydrate, protein, and fat metabolism that occurs secondary to an absolute or relative lack of insulin (hypoinsulinemia).[2]

The goals of managing diabetes mellitus are to optimize the control of blood glucose, to decrease the effects of oxidative stress, and to normalize disturbances in lipid metabolism.[3]

Synthetic antidiabetic agents used in the treatment of diabetes can produce serious side effects, including hypoglycemic coma and impaired liver and kidney functions. Therefore, the search for more effective and safer antidiabetic agents continues to be an important area for research.[4]

For centuries, folk medicine has employed plants for their medicinal and protective abilities. Recent epidemiologic studies show that consumption of fruits, vegetables, grains, and legumes prevents chronic illnesses. This has prompted further research into herbal products with antidiabetic activity possessing fewer side effects.[5]

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Address correspondence to: Aysegul Bayramoglu, PhD, Department of Biology, Science and Arts Faculty, Artvin Coruh University, Artvin 08000, Turkey, E-mail: abayramoglu@artvin.edu.tr

Lycopene, a 40-carbon acyclic carotenoid with 11 linearly arranged conjugated double bonds,[6] is a dietary carotenoid found in fruits, such as fresh ripe tomato, watermelon, papaya, guava, and grapefruit, and is one of the primary carotenoid components that accumulates in human tissues and fluids, such as the prostate and serum, after absorption.[7] Lycopene is a potent neuroprotective, antiproliferative, anticancer, antiinflammatory, cognition enhancer, and hypocholesterolemic agent.[8] It has been ranked as being most potent among the following antioxidants: lycopene > α-tocopherol > α-carotene > β-cryptoxanthin > zeaxanthin = β-carotene > lutein. Moreover, several studies suggest that lycopene is a more potent scavenger of oxygen radicals than any other major dietary carotenoids.[9] Lycopene, because of its high number of conjugated double bonds, has been reported to exhibit higher singlet-oxygen-quenching ability compared with β-carotene or α-tocopherol and to act as a potent antioxidant, preventing the oxidative damage of critical biomolecules, including lipids, low-density lipoproteins, proteins, and DNA.[10,11] Lycopene has been under considerable investigation for its antioxidant benefits in treating various chronic human diseases, like cancer, cardiovascular diseases, osteoporosis, and diabetes.[8]

There is little information regarding the effects of lycopene on diabetes. Therefore, in the present study, the effects of lycopene, at a dose of 2.5 mg/kg body weight (bw), were investigated in nondiabetic, diabetic, and lycopene-treated diabetic rats. Accordingly, body weight changes, daily food–water intake values, and serum glucose, insulin, total

cholesterol (TC), triglyceride (TG), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels were measured and compared statically.

MATERIALS AND METHODS

Animals

Twenty-four adult Sprague–Dawley rats (weighing 190–210 g) were obtained from TICAM (Medical and Surgical Experimental Research Center, Eskisehir Osmangazi University) and housed in polycarbonate cages in an air-conditioned room (22°C ± 2°C) with a 12-h light/12-h dark cycle (7:00 a.m. on; 7:00 p.m. off). Standard rat feed and water were provided *ad libitum*. The rats were allowed to acclimatize to the laboratory environment for 7 days before the start of the experiment.

All procedures were conducted in conformity with the Institutional Ethical Committee for Animal Care and Use at Eskisehir Osmangazi University (protocol no. 26/158) and the international guidelines on the ethical use of animals (NIH publication no. 80-23).

Drug and reagents

Streptozotocin (STZ) and lycopene (catalogue nos. S0130-1G and L9879-1 MG, respectively) were purchased from Sigma.

Experimental induction of diabetes

Diabetes was induced following overnight fasting of the rats by an intramuscular injection of STZ in a single dose of 50 mg/kg bw. STZ was dissolved in a freshly prepared 0.01 M citrate buffer (pH 4.5) whereas the control rats were injected with buffer alone. Five days after STZ administration, a diabetic state was confirmed by the positive response to glucose presence in urine (urinalysis strips; Arkray).[12]

Experimental design

The rats were randomly divided into three groups as follows ($n = 8$ per group): Group 1 (NC): nondiabetic control rats; Group 2 (DC): diabetic control rats received vehicle solution (olive oil, volume = 1 mL/kg bw); and Group 3 (LYCO): diabetic rats treated with lycopene 2.5 mg/kg bw in vehicle solution.

The vehicle (olive oil, volume = 1 mL/kg bw) and the lycopene solutions (dissolved in olive oil, volume = 1 mL/kg bw) were administered orally using an intragastric tube daily for 7 days. At the same time, food–water intake and body weight changes were recorded daily. After 7 days of treatment, the rats were fasted overnight and then under ether anesthesia, the blood samples from rats were intracardiacly collected in polystyrene tubes without anticoagulant. The rats were then immediately sacrificed by cervical decapitation.

Biochemical analysis

The serum samples were separated by centrifugation at 1600 *g* at 4°C for 15 min using a cooling centrifuge (Hermle ZK510) and analyzed for the serum glucose, insulin, TC, TG, ALT, AST.

The serum glucose, TC, TG, ALT, and AST levels were immediately measured with a commercial kit (Biolabo) using an autoanalyzer (Airone 200-RA; Crony Instruments). The serum glucose, TC, and TG were expressed in mg/dL, and ALT and AST were expressed in U/L.

Insulin assay

The serum insulin level of each blood sample was measured by an enzyme-linked immunosorbent assay using a commercial kit (Ultrasensitive Rat Insulin Enzyme-Linked Immunosorbent Assay; Mercodia), based on the direct sandwich technique in which two monoclonal antibodies are directed against separate antigenic determinants on the insulin molecule. The serum insulin levels were expressed as μg/L.

Statistical analyses

Results were expressed as mean ± standard deviation. The intergroup variations were measured by one-way analysis of variance followed by Tukey's test to assess the significance. Statistical significance was considered at $P < .05$. The statistical analyses were performed using the SPSS Statistical Software version 12.

RESULTS

Body weight (initial and final) and daily food and water intake values

Table 1 shows the initial and final body weights and the daily food and water intakes of all groups during the experimental period. There was slight decrease between initial and final body weights in the DC and LYCO groups.

Table 1. Initial and Final Body Weight and Daily Food and Water Intake Values in Groups

Groups	*Initial body weight (g)*	*Final body weight (g)*	*Daily food intake (g/100 g body weight)*	*Daily water intake (mL/100 g body weight)*
NC	197.75 ± 3.45	204.50 ± 2.77	7.23 ± 0.42	16.63 ± 1.79
DC	206.00 ± 3.02	201.25 ± 2.81	12.39 ± 2.65[a]	47.12 ± 2.94[a]
LYCO	204.00 ± 2.61	201.50 ± 5.83	11.09 ± 2.50[a]	44.33 ± 3.32[a]

Data are mean ± standard deviation values ($n = 8$). For group descriptions, see "Materials and Methods" section.

[a]$P < .05$, significantly different from NC group by Tukey's multiple range tests.

NC, nondiabetic control; DC, diabetic control; LYCO, diabetic treated with lycopene.

Table 2. Serum Glucose, Insulin, Total Cholesterol, Triglyceride, Alanine Aminotransferase, and Aspartate Aminotransferase Values in Groups

Groups	*Glucose (mg/dL)*	*Insulin (μg/L)*	*TC (mg/dL)*	*TG (mg/dL)*	*ALT (U/L)*	*AST (U/L)*
NC	104.30 ± 13.07	6.94 ± 0.39	88.68 ± 3.58	47.96 ± 5.76	44.50 ± 3.29	69.62 ± 5.04
DC	505.87 ± 19.88[a]	2.38 ± 0.41[a]	142.98 ± 10.66[a]	80.02 ± 3.47[a]	87.07 ± 9.33[a]	129.87 ± 12.62[a]
LYCO	413.75 ± 16.77[ab]	3.55 ± 0.43[ab]	105.30 ± 4.15[ab]	61.55 ± 5.15[ab]	59.83 ± 4.31[ab]	96.55 ± 6.85[ab]

Data are mean ± standard deviation values ($n = 8$).

$P < .05$, significantly different from [a]NC group and [b]DC group by Tukey's multiple range tests.

TC, total cholesterol; TG, triglyceride; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

The food and water intakes in the DC and LYCO groups were significantly higher than in the NC group ($P < .05$). On the other hand, food and water intakes were slightly, but not significantly, higher in the lycopene-treated group as compared with diabetic control group rats (Table 1).

Changes in serum glucose, insulin, TC, TG, ALT, and AST

STZ treatment caused significant increases in serum glucose (485.01%), TC (61.23%), TG (66.84%), ALT (95.66%), and AST (86.54%) and decreases in serum insulin (291.59%) when compared with nondiabetic control group ($P < .05$). In the LYCO-treated diabetic group, glucose, insulin, TC, TG, ALT, and AST values were found to be preserved ($P < .05$) compared with DC group. Although administration of lycopene at the dose of 2.5 mg/kg bw per day significantly reduced the serum glucose (18.21%), TC (26.35%), TG (23.08%), ALT (31.28%), and AST (25.65%) levels and increased the serum insulin level (49.15%), the values were not restored to the same levels as those of the normal control group after 7 days of treatment (Table 2).

DISCUSSION

In research investigations, type 1 diabetes is usually induced by an STZ injection and the animals often display typical characteristics of diabetes, that is, polyuria, polydipsia, increased water intake, dehydration, weight loss, and increased food intake.[1,13] The weight loss is associated with abnormalities due to osmotic diuresis and glucose intolerance, resulting from inadequate insulin secretion or hyperlipidemia in diabetes mellitus. Prolonged osmotic diuresis may cause excessive urinary electrolyte loss. Disturbances in renal function are associated with several abnormalities, including proteinuria and progressive renal failure.[14] The present study is consistent with our earlier studies on diabetes with regard to body weight change and food–water intake correlation between the nondiabetic and diabetic control group.[12,15,16] Generally, the body weights are reduced in STZ-induced diabetic rats and restored when subjected to hypoglycemic treatment.[17] In the present study, unfortunately, there was no improvement in symptoms of diabetes (body weight change and food–water intake) as a result of treatment with lycopene (Table 1).

The mechanism by which STZ brings about its diabetic state includes selective destruction of pancreatic β-cells that makes cells less active, leading to poor sensitivity of insulin for glucose uptake by tissues.[18] Effective control of blood glucose levels is a key step in preventing or reversing diabetic complications.[15] Our findings clearly suggest that lycopene decreased the serum glucose and increased insulin levels in STZ-induced diabetic rats (Table 2). Briefly, the hypoglycemic effect of the lycopene can be explained by the fact that it might have increased glucose utilization in diabetic rats by promoting insulin secretion in the pancreas. Therefore, lycopene may have potential as an oral hypoglycemic agent in the control of diabetes mellitus.

Generally, following STZ treatment, the plasma AST and ALT levels increase as a result of metabolic changes in the liver, such as administration of toxin, cirrhosis of the liver, hepatitis, and liver cancer. Thus, they can be used as markers to assess the extent of liver damage.[17] Epidemiological studies show that diabetic patients are at higher risk of chronic liver disease and hepatocellular carcinoma. Diabetes and insulin resistance were also identified as important factors associated with an increased risk of advanced liver fibrosis in patients with normal ALT.[19] In diabetes, several authors have reported increases in AST and ALT activities as well as changes in lipid concentration in the serum of diabetic patients.[20] Moreover, AST (a nonspecific marker for hepatic injury) and especially ALT (a specific marker for hepatic parenchymal injury) are used in the evaluation of hepatic disorders.[20–22] An increase in these enzyme activities reflects active liver damage[18] and the increase in the activities of plasma ALT and AST indicated liver dysfunction. Ohaeri also found that liver was necrotized in STZ-induced diabetic rats.[23] Therefore, an increase in the activities of AST and ALT in plasma might be mainly due to the leakage of these enzymes from the liver cytosol into the blood stream.[24] Injury to the hepatocytes alters their transport function and membrane permeability, leading to leakage of enzymes from the cells. Therefore, the marked release of AST and ALT from liver cytosol into circulation indicates severe damage to hepatic tissue membranes associated with diabetes.[25] Therefore, increased activities of AST and ALT found in this study may be interpreted as a result of the liver cell destruction or changes in the membrane permeability, indicating that severe hepatocellular damage is induced by diabetes.[2] In the present study, treatment with lycopene at the dose of 2.5 mg/kg bw per day was able to protect against the increase in the activity of these enzymes in diabetic rats (Table 2), demonstrating the

protective effect of lycopene against diabetes-induced hepatic damage, and suggesting it has potential as a hepatoprotective drug.

The liver and some other tissues participate in the uptake, oxidation, and metabolic conversion of free fatty acids; synthesis of cholesterol and phospholipids; and secretion of specific classes of plasma lipoproteins, and the liver is regarded as one of the central metabolic organs in the body, regulating and maintaining lipid homeostasis.[26] It has been demonstrated that insulin deficiency in diabetes leads to a variety of derangements in metabolic and regulatory processes, which in turn lead to accumulation of lipids in hepatic tissue.[3] Also, it is known that diabetes is usually associated with abnormally high levels of serum lipids and it is associated with profound alterations in the plasma lipid and lipoprotein profile.[2] Accumulation of lipids in diabetes is mediated through a variety of derangements in metabolic and regulatory processes, especially insulin deficiency, thereby rendering the diabetic patient more prone to hypercholesterolemia.[27] In diabetes, hypercholesterolemia is associated with the consequences of hyperinsulinemia, insulin resistance, and glucose intolerance.[28] Hypercholesterolemia and hypertriglyceridemia in STZ-induced diabetic rats are well documented. Excess production of serum fatty acids by STZ-induced diabetics promotes the conversion of excess fatty acids into phospholipids and cholesterol in liver.[3] In addition, plasma TC and TG levels are also strongly related to the degree of diabetic control rats. The increased TC and TG levels observed in diabetic rats may be the result of impaired liver function, caused by the damage done by STZ, which acts either directly or indirectly by enhancing the plasma glucose levels.[17] Generally, according to literature, improvements in cholesterol and TG levels in the blood are dependent upon the recovery of liver function. Further, the recovery of liver function is dependent upon restoration of blood glucose and insulin to more normal levels by treatment of diabetes. These relationships explain our findings clearly (Table 2) and our results suggest that lycopene could be used as a drug to bring about both hypoglycemic and hypolipidemic effects.

In conclusion, our results suggest that lycopene partially reverses some diabetic complications. But, lycopene does not show the expected impact on body weight change and food–water intake after 7 days of treatment. However, Zhu *et al*.[29] reported that different doses of lycopene [10, 30, and 60 mg/(kg·day^{-1}), p.o.] are only expected to have an effect on some STZ-induced diabetic symptoms after 30 days of treatment. As might be expected from the study by Zhu *et al*.,[29] we believe that an increase in drug dose and/or especially treatment duration might result in positive effect of lycopene on body weight change and food–water intake ratio. In accordance with the other parameters obtained in the present study, we believe the data support that oral administration of lycopene may have a potential benefit in preventing diabetes, since pancreatic damage induced by environmental chemicals and other factors is a cause of diabetes.

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AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

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