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Simultaneous Effect of Resveratrol and Probiotics on Insulin Resistance and Glucagon-Like Peptide (GLP-1) Levels in Diabetic Rats

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ABSTRACT

BACKGROUND AND OBJECTIVE: The main and effective treatment for diabetes is the use of insulin and synthetic drugs and herbal medicines, which may be accompanied by several side effects. Given that GLP-1 secretion is reduced in diabetic patients compared to healthy individuals, the aim of this study was to determine the simultaneous effect of resveratrol and probiotics on insulin secretion and glucagon-like peptide (GLP-1) and to evaluate insulin resistance in diabetic rats.

METHODS: In this experimental study, 40 adult male Wistar rats weighing approximately 250-300 g were used. Animals were randomly divided into 5 groups: control group, diabetic group (using 65 mg/kg streptozotocin and 110 mg/kg nicotinamide intraperitoneally), diabetic group treated with probiotics (50×10^9 bacteria/kg body wt^{-1} daily by dissolving in water), diabetic group treated with resveratrol (10 mg/kg by gavage method) and diabetic group treated with probiotics and resveratrol (co-administration group). After four weeks, the animals were sacrificed and pancreatic tissue and blood samples were isolated for histopathological tests and biochemical tests. Blood glucose, insulin resistance, pancreatic GLP-1 as well as pancreatic histopathology were assessed.

FINDINGS: The co-administration group compared with the diabetic group caused a 42% reduction in serum glucose levels ($p<0.001$) and a 30% reduction in insulin resistance ($p<0.001$). The co-administration group also caused a 23.5% increase in insulin levels ($p<0.001$) and an 88% increase in GLP-1 ($p<0.05$). The co-administration group improved the histology of the pancreas.

CONCLUSION: The results of the study showed that resveratrol and probiotics are effective in controlling diabetes by increasing the levels of GLP-1 and insulin and decreasing insulin resistance.

KEY WORDS: *Probiotics, Resveratrol, Type 2 Diabetes, Glucagon-Like Peptide (GLP-1).*

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Introduction

The prevalence of diabetes is increasing worldwide due to the changes in lifestyle. According to the International Diabetes Federation (IDF), the disease killed 4.2 million people in 2019, and currently about 500 million adults between the ages of 20 and 79 suffer from diabetes, which is likely to increase to 700 million by 2045 (1). Type 2 diabetes is characterized by three types of pathological abnormalities, including peripheral insulin resistance and overproduction of hepatic glucose and impaired insulin secretion (2). Diabetes is considered as an important risk factor for various diseases such as heart, brain, kidney and viral diseases (3-5). Peripheral tissue resistance to insulin can be caused by impaired insulin receptor, disruption of intracellular pathways, and the presence of insulin antagonists (6).

Currently, the main and effective treatment for diabetes is the use of insulin, synthetic drugs and herbal medicines (7-10), which may have several adverse effects (11). Glucagon-like peptide (GLP-1) is one of the most important hormones in the body that is released from enteroendocrine L cells in response to digestion and is the strongest stimulant of glucose-induced insulin secretion (12). In diabetic patients, GLP-1 secretion is reduced compared to healthy individuals and is therefore a suitable target for the development of new antidiabetic drugs (13). GLP-1 increases beta cell mass and also inhibits apoptosis (14).

Increase in this hormone with different compounds can be effective in improving diabetes. Probiotics are living non-pathogenic microorganisms that are one of the most useful methods in the treatment of many diseases (15). Most probiotics belong to the species Bifidobacterium and Lactobacillus. Probiotics can be used as dietary supplements or therapeutic agents (16). Resveratrol, on the other hand, is found as an antioxidant in various species of plants and fruits (17). Resveratrol has anti-inflammatory, anti-cancer, and antioxidant properties and can increase life expectancy in mammals (18, 19).

Therefore, due to the highly effective role of probiotics and resveratrol in type 2 diabetes, it can be suggested as a treatment for diabetics. The aim of this study was to investigate the simultaneous effect of the combination of these two substances on GLP-1 secretion and pancreatic function in diabetic rats.

Methods

This experimental study was performed on 40 healthy male Wistar rats with an average weight of 250-300 g after approval by the ethics committee of Hamadan University of Medical Sciences with the code IR.UMSHA.REC.1397.551. According to the ethical guidelines for working with laboratory animals approved by the Ministry of Health, the animals were kept in constant temperature, 12 hours of darkness and 12 hours of light and without restriction of access to water and food (20).

The animals were randomly divided into 5 groups of 8 and kept in separate cages and divided as follows: Group 1: Healthy control, Group 2: Diabetic (using streptozotocin and nicotinamide intraperitoneally), Group 3: diabetic+probiotics (dissolved in water), group 4: diabetic+resveratrol (by gavage), group 5: diabetic+resveratrol+probiotic; before the beginning of the study (making the rats diabetic) and the start of treatment with probiotics and resveratrol, rats were kept at the center's pet house for one week to adapt to the environment and to reach the study weight.

Induction of type 2 diabetes: Streptozotocin powder was prepared in 0.01 M nicotine amide and sodium citrate buffer with pH=4.5 and kept on ice until intraperitoneal injection. Nicotinamide was injected intraperitoneally at a dose of 110 mg/kg 15 minutes after injection of 65 mg/kg streptozotocin. To confirm the onset of diabetes, 7 days later, blood glucose samples were measured using a glucometer and blood glucose above 250 mg/dl was considered diabetic. At the end of the study, rats were anesthetized with diethyl ether and sacrificed after blood sampling. Pancreatic tissue and blood were isolated for histological tests and biochemical tests. For biochemical analysis, about 100 mg of pancreas was lysed by a homogenizer using a lubricating buffer. The mixture was then centrifuged at 10000×g at 4°C for 20 minutes. The clear supernatant solution was separated and stored in a freezer at -80°C until further testing.

Probiotics Administration: A probiotics supplement containing Bifidobacterium longum, Bifidobacterium breve, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus casei, Lactobacillus bulgaricus was prepared from Genuine Health Company (Canada) and was administered for 4 weeks at a dose of 50×10^9 bacteria/kg body wt^{-1} daily.

Administration of resveratrol: 10 mg/kg resveratrol powder from Natural Fact Company (USA) was weighed daily according to the number of rats in each group and mixed in sterile distilled water for 1 ml per rat and after dissolution, was kept on ice until gavage.

GLP-1 measurement: This hormone was evaluated according to the instructions of the manufacturer (Stabiofarm, China) based on ELISA and sandwich method.

Measurement of insulin and glucose levels and lipid profile: Insulin levels were measured using ELISA kit (Stabiofarm, China). Glucose, total cholesterol and triglyceride levels were measured using Pars Azmoon kit.

Measuring Insulin Resistance: In evaluating the homeostasis model (HOMA), fasting blood glucose and fasting insulin were used to measure insulin resistance according to the following equation:

HOMA-IR= {[(fasting insulin µU/ml)]×[(fasting glucose mmol/l)]} / 22.5

Histological changes assessment: Part of pancreas was fixed in 10% formalin for at least 48 hours. In the next step, paraffin sections were prepared and 5 µm sections were prepared by rotary microtome. The sections were then stained with hematoxylin and eosin and fixed. Histopathological slides were examined by light microscopy. Pathological changes of the pancreas were observed and reported based on structural changes and cellular changes.

Statistical tests: The results were entered in SPSS 16 and analyzed using analysis of variance (ANOVA) and Tukey test, while $p<0.05$ was considered significant. GraphPad Prism version 7.0 was used to draw the diagrams.

Results

Analyses showed that diabetic rats had significantly higher serum glucose levels than the control group ($p<0.001$). Administration of probiotics showed 35% decrease compared to the diabetic group and administration of resveratrol showed 20% decrease compared to the diabetic group separately in diabetic rats and reduced fasting blood sugar (FBS). Simultaneous administration of probiotics+resveratrol in diabetic rats led to a decrease in serum blood sugar levels compared to diabetic rats ($p<0.001$) (42% decrease compared to the diabetic group) (Figure 1). In the diabetic group receiving resveratrol, serum insulin levels increased significantly compared to the diabetic group ($p<0.01$) (23% increase compared to the diabetic group). Furthermore, in the diabetic group receiving resveratrol+probiotics, serum insulin levels increased significantly compared to the diabetic group (23.5% increase compared to the diabetic group) (Figure 2).

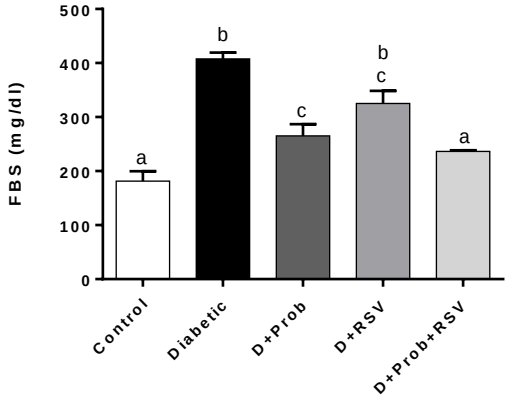

Figure 1. Comparison of serum FBS levels in the study groups. D+Prob: Diabetic group receiving probiotics, D+RSV: Diabetic group receiving resveratrol. GLP-1: Glucagon-like peptide, Prob: Probiotic, RSV: Resveratrol.

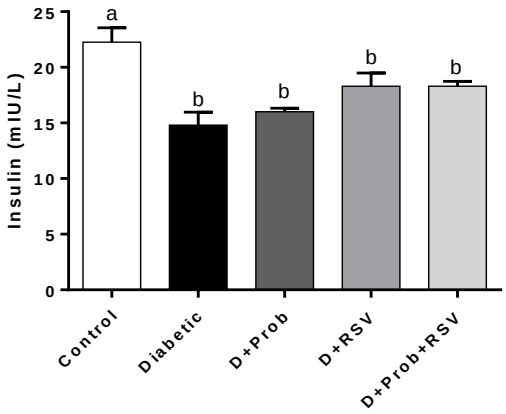

Figure 2. Comparison of serum insulin levels in the study groups. D+Prob: Diabetic group receiving probiotics, D+RSV: Diabetic group receiving resveratrol. GLP-1: Glucagon-like peptide, Prob: Probiotic, RSV: Resveratrol.

The use of probiotics in diabetic rats showed that it significantly reduced the insulin resistance index compared to the diabetic group ($p<0.001$) (28% decrease compared to the diabetic group). In the diabetic group receiving probiotics+resveratrol, insulin resistance index decreased significantly compared to the diabetic group ($p<0.001$) (30% decrease compared to the diabetic group) (Figure 3). Administration of probiotics ($p<0.05$) (10% decrease compared to the diabetic group) and resveratrol ($p<0.05$) (9% decrease compared to the diabetic group) separately in diabetic rats reduced total serum cholesterol levels compared to the control group. Moreover, co-administration of these two supplements in diabetic rats led to a noteworthy reduction in serum cholesterol levels compared to diabetic rats ($p<0.05$) (11% decrease compared to the diabetic group) (Figure 4).

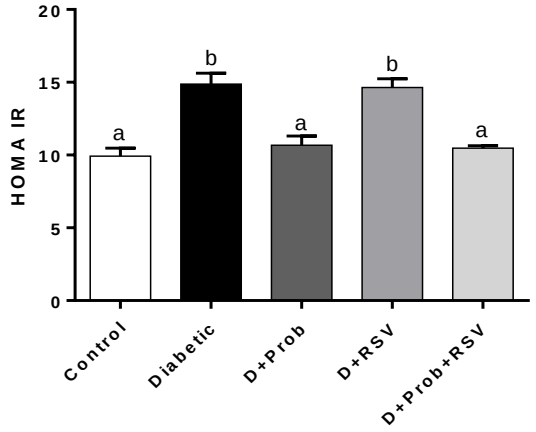

Figure 3. Comparison of HOMA-IR levels in the study groups. **D+Prob: Diabetic group receiving probiotics, D+RSV: Diabetic group receiving resveratrol. GLP-1: Glucagon-like peptide, Prob: Probiotic, RSV: Resveratrol.**

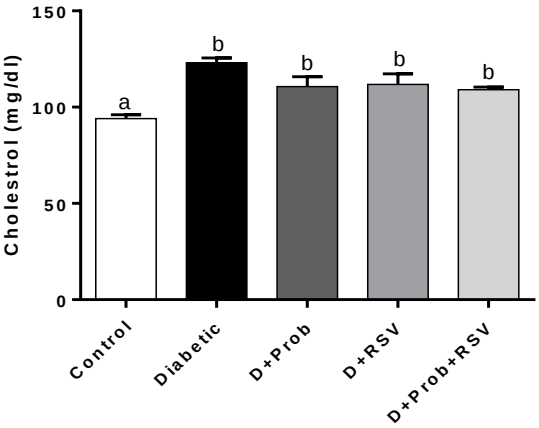

Figure 4. Comparison of serum cholesterol levels in the study groups. **D+Prob: Diabetic group receiving probiotics, D+RSV: Diabetic group receiving resveratrol. GLP-1: Glucagon-like peptide, Prob: Probiotic, RSV: Resveratrol.**

Administration of probiotics (10% decrease compared to the diabetic group) and resveratrol (14% reduction compared to the diabetic group) ($p<0.001$) separately in diabetic rats reduced serum triglyceride levels. Furthermore, co-administration of these two supplements in diabetic rats led to a decrease in serum triglyceride levels compared to diabetic rats ($p<0.001$) (19% decrease compared to the diabetic group) (Figure 5).

The results showed that induction of diabetes in rats led to a decrease in GLP-1 pancreatic tissue compared to the control group ($p<0.001$). Probiotic administration ($p<0.01$) (52% increase compared to the diabetic group) and resveratrol administration ($p<0.001$) (44% increase compared to the diabetic group) separately in diabetic rats prevented the decrease in GLP-1 levels of pancreatic tissue in diabetic rats. On the other hand, the analysis of the results showed that the simultaneous administration of these two supplements in diabetic rats had a greater effect on the GLP-1 levels of pancreatic tissue in diabetic rats ($p<0.001$) (88% increase compared to the diabetic group) (Figure 6).

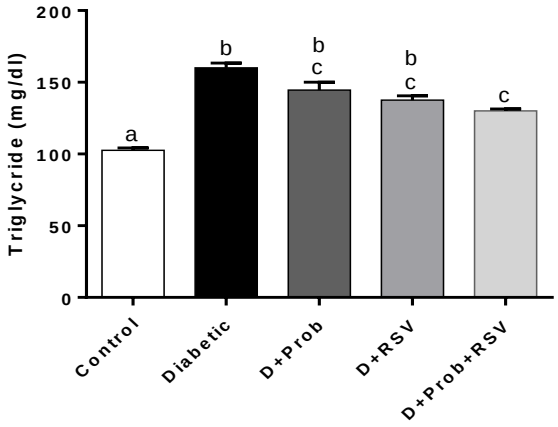

Figure 5. Comparison of serum TG levels in the study groups. **D+Prob: Diabetic group receiving probiotics, D+RSV: Diabetic group receiving resveratrol. GLP-1: Glucagon-like peptide, Prob: Probiotic, RSV: Resveratrol.**

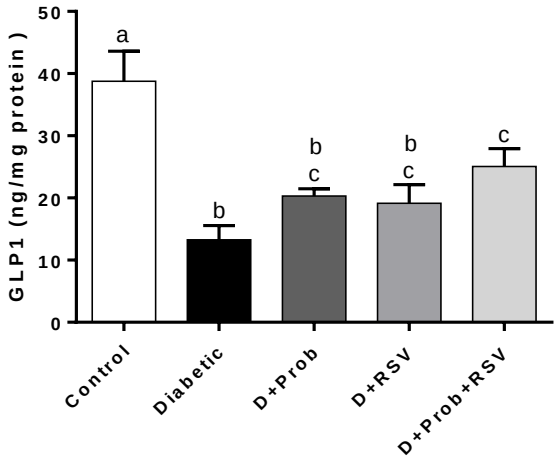

Figure 6. Comparison of GLP-1 levels in pancreatic tissue of the studied groups. **D+Prob: Diabetic group receiving probiotics, D+RSV: Diabetic group receiving resveratrol. GLP-1: Glucagon-like peptide, Prob: Probiotic, RSV: Resveratrol.**

The results of histological analysis of the pancreas show that the control group has a natural appearance without pathologies such as cell death and disruption of cellular order. In diabetic rats, changes such as cell death are clearly present and the number of islets of Langerhans and other islets decreased and severe bleeding in the pancreatic tissue could be observed. On the other hand, the margins of islets of Langerhans are smooth in the control group and the islets have

symmetrical shapes, while in the diabetic group, the margins of the islets are uneven. Administration of probiotics and resveratrol could greatly improve pancreatic tissue changes. Histological changes in the probiotic group and resveratrol group were almost similar (Image 1).

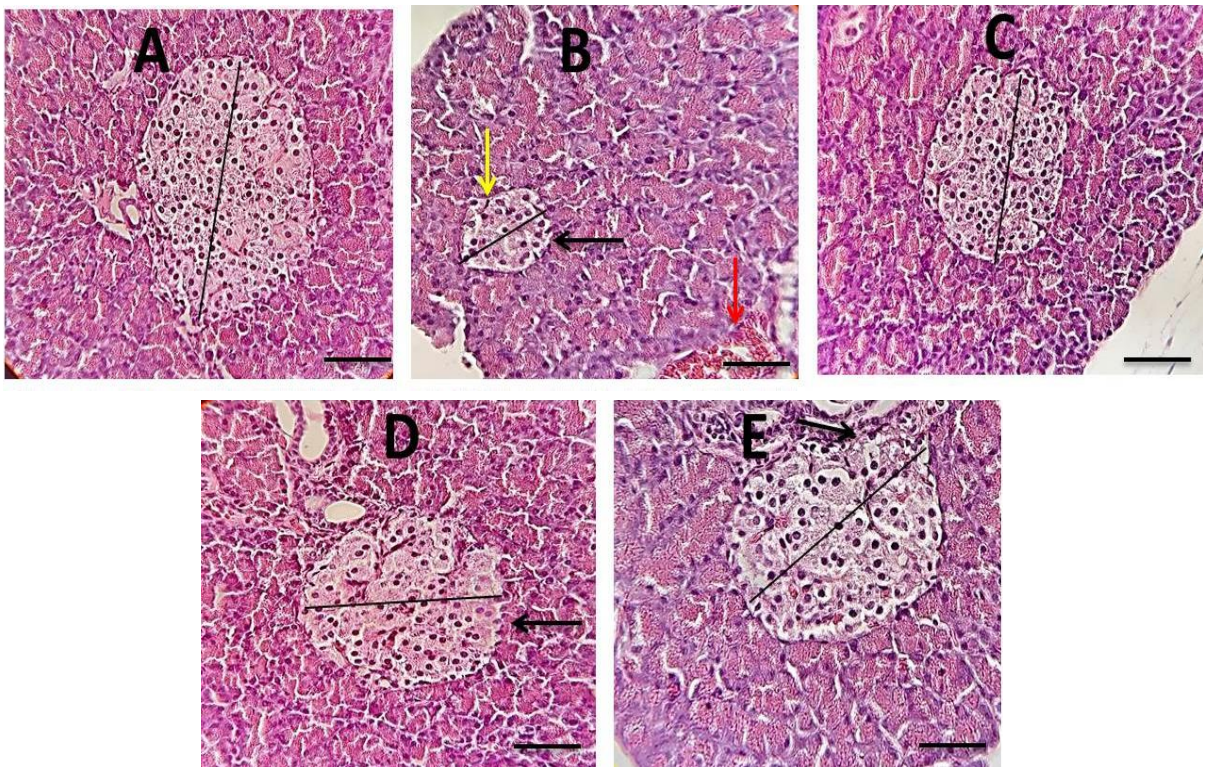

Image 1. Histological findings of the pancreas by hematoxylin and eosin staining. A: Control, B: Diabetic, C: Probiotic, D: Resveratrol E: Combined group (Resveratrol+Probiotics). In diabetic rats, histological changes were observed, including cell death (yellow marker), congestion (red marker), decrease in Langerhans islet cell count and islet size (continuous line) as well as bleeding (red marker). Treatment with probiotics and resveratrol could greatly improve pancreatic tissue changes (400X magnification, 50 µm scale bar).

Discussion

The results of the present study showed that the use of probiotics in diabetic rats can prevent hyperglycemia. Probiotics exert their beneficial effects on diabetes through several main mechanisms: One of the predicted mechanisms is that probiotics improve GLP-1 secretion from the intestine, thereby improving carbohydrate metabolism, lowering glucose levels, and increasing sensitivity to insulin (21). Consistent with our results, a study by Yousaf et al. and Al-Salami et al. showed that the use of probiotics effectively reduced blood glucose levels in diabetic rats (22, 23). Considering the results of blood glucose due to the synergistic effects of resveratrol and probiotics in diabetic rats, their hypoglycemic properties were well observed in the present study when resveratrol and probiotics were administered simultaneously. Resveratrol stimulates insulin secretion by binding to sulfonylurea receptors in beta cells in the pancreas (24). A similar study by Kang et al. showed that the use of resveratrol has an inhibitory effect on the insulin signaling pathway in various cells, which can be a major cause of insulin resistance and reduced sensitivity to it (25). It seems that this inhibitory effect of resveratrol occurs at downstream of the insulin signaling pathway on Insulin Receptor Substrate 1 (IRS-1) factors, suggesting that the therapeutic effects of resveratrol may depend on metabolic conditions, duration of treatment, and the type of tissue involved. The use of probiotics in rats with type 2 diabetes improved insulin resistance, which was more effective than resveratrol. Various beneficial effects of using probiotics to reduce blood glucose levels and improve insulin resistance have been reported (26-28). On the other hand, it seems that the use of probiotics by producing short-chain fatty acids induces the production of incretins such as GLP-1, which due to the insulinotropic properties of these hormones, reduces

insulin resistance in diabetic patients (29). Histological findings confirm the effects of GLP-1, demonstrating that the size and number of beta cells increased in the treatment groups, especially the co-administration group, compared to the diabetic group. Various studies have reported that resveratrol and probiotics are effective in reducing fat. Singh et al. showed that resveratrol can reduce blood sugar, cholesterol and triglyceride levels in patients with type 2 diabetes due to its antioxidant properties (30). This study, like other studies of dyslipidemia in diabetic animals, found that these changes may expose the diabetic patient to the complications of diabetes, including liver damage due to fat accumulation and insulin resistance (31).

The results of this study showed that resveratrol and probiotics in rats with type 2 diabetes effectively increased GLP-1 levels in pancreatic tissue compared with diabetic rats. Consistent with our results, Dao et al. showed that deletion of the GLP-1 gene in diabetic mice eliminates the anti-diabetic effect of resveratrol in these rats, indicating a direct association between resveratrol and GLP-1 in diabetic rats (32). Probiotics play a key role in inducing GLP-1 secretion in diabetic conditions by producing short-chain fatty acid metabolites (33). Consistent with the results of our study, the role of probiotics in increasing GLP-1 in diabetic patients in the human and animal models has been well demonstrated in recent studies (27, 33-35). Co-administration of probiotics and resveratrol showed that GLP-1 levels in pancreatic tissue were significantly increased in diabetic rats.

The results of our observations revealed the beneficial effects of probiotics and resveratrol on increasing GLP-1 and insulin secretion in diabetic rats, and the data clearly show the beneficial effects of combination therapy due to the reduction of hyperglycemia. Further studies are required to determine the mechanism of action of probiotics and resveratrol.

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