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The Effect of Royal Jelly on Irisin in Experimentally Diabetic Rats

Selcen ÇAKIR *1

Abstract

Diabetes Mellitus (DM) is considered a very common health problem today. It causes many acute and chronic complications and negatively affects the quality of life of patients. It is known that diabetes has an impact on many biochemical processes. This study aimed to evaluate the interaction between royal jelly (RJ) and diabetes with irisin, a parameter that has not been investigated before. The study was planned with 3 groups: control group, DM group, DM+350 mg/kg RJ group. In the experiments, 18 female Wistar albino rats were studied. Irisin levels in rat blood serum were determined using the ELISA (Enzyme-Linked Immuno Sorbent Assay) method. Glucose levels in blood taken from the tail vein were determined with a glucometer. As a result of the experimental study, a statistically significant difference was found in the DM+350 mg/kg RJ group compared to the control group ($p<0.05$). The selected dose reduced serum irisin levels in RJ applications. With diabetes, a statistically significant increase was observed in blood glucose levels ($p<0.05$). Although the RJ application caused a numerical decrease, it was not statistically significant. Previous studies have emphasized the effect of RJ on DM and blood biochemical parameters; however, the observation that the relevant dose of RJ reduces irisin levels is recent. The relationship of irisin with energy metabolism is still being investigated. Further studies are required to explain the relationship between irisin and RJ.

Keywords: Diabetes mellitus, Irisin, Royal jelly

1. INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease that is characterized by high fasting blood glucose and causes damage to carbohydrate, lipid, and protein metabolism. In patients with DM, the high level of blood glucose brings the problem of energy homeostasis along [1]. As a concept, energy homeostasis includes energy expenditure, digestion, and energy storage in adipose tissue. Peptide hormones, also known as adipokines, are involved in this hemostasis [2].

Irisin was recently identified by Boström et al. (2012) and is a peptide with 112 amino acids and a weight of 12,587 kDa [2]. Irisin was recognized as an adipokine due to its contribution to the mechanism that causes the browning of white adipose tissue [3-5]. It is also a myokine that is secreted from muscles and is associated with exercise. The presence

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of irisin has been demonstrated in adipose tissue, muscles, cerebrospinal fluid, breast milk, saliva, and Purkinje cells in the cerebellum. Irisin is an anti-diabetic and anti-obesity hormone and achieves this effect by affecting adipose tissue metabolism and maintaining glucose homeostasis [2].

Irisin regulates energy metabolism by inducing the browning of white adipose tissue. It is mainly expressed in muscles as fibronectin type III domain-containing 5 (FNDC5), a type I membrane precursor protein, and then secreted into the circulatory system [4]. The extracellular part of FNDC5 is cleaved and secreted as irisin. FNDC5 is one of the target proteins of the peroxisome proliferator-activated receptor gamma co-activator 1α (PGC-1α) [2,6]. Therefore, irisin has drawn great attention as an attractive target in the fight against obesity and type 2 diabetes mellitus (T2DM). Irisin levels can be increased by PGC-1α overexpression and aerobic exercise training [7]. Irisin modulates glucose metabolism and insulin sensitivity in skeletal muscles and participates in neuroplasticity and satiety in the central nervous system. It also regulates the remodeling of the pancreas, bone tissue, and adipose tissue [3]. It is stated that irisin levels increase in obesity and decrease in T2DM patients. Clinical studies have indicated that irisin may be a predictive marker for insulin resistance, T2DM, or metabolic syndrome [8].

Royal jelly (RJ) is an important food that ensures the development of the queen bee [9]. The unique protein structure of RJ has been subject to many studies. Thanks to its content, this product has positive effects, especially on blood sugar, obesity, and diabetes [10]. RJ is a rich food consisting of proteins, fatty acids, vitamins, carbohydrates, and minerals such as iron, calcium, copper, potassium, magnesium, zinc, and sulfur [11]. Besides hypoglycemic [10], hypotensive [12], and antihypercholesterolemic [13], activities, it has been shown to have high antioxidative and free radical scavenging activity [14].

The drugs used in the treatment of diabetes have high side effects; therefore, alternative treatments have begun to be investigated. For this reason, interest in natural products that lower blood sugar has increased. In a healthy diet, in addition to carbohydrates, macronutrients such as lipids, proteins, and water, micronutrients, vitamins, and minerals are needed. RJ is considered a promising therapeutic product thanks to its rich biological content, but there are not enough studies on it. This study aimed to test the effect of RJ on the irisin parameter, which changes in DM.

2. METHODS

The number of subjects in the study was determined in G*Power 3.1 program. The total sample size was determined as 18 with an effect size of 0.85, an α error of 0.05, and a Power(1-β) of 0.80. Eighteen female Wistar albino rats weighing 200-250 g were divided into 3 groups, resulting in 6 rats in each group. Experiments were carried out in Çanakkale Onsekiz Mart University, Experimental Research Application and Research Center under a temperature of 21 ± 2 °C, a humidity of 50% ± 5%, and a cycle of 12 hours light and 12 hours dark. Groups were formed as in Table 1. To induce diabetes, 50 mg/kg of STZ was administered by intraperitoneal injection. Three days later, blood glucose levels were measured with a glucometer. Rats with a level of 250 mg/dl and above were considered diabetic. RJ was administered by gavage 5 days a week under conditions approved by the ethics committee. Throughout the experiment, animals were given water and pellets ad-libitum.

2.1. Biochemical Analysis

At the end of the experiment, the animals were fasted for 10 hours and anesthetized by administering 70 mg/kg Ketamine and 10 mg/kg Xylazine intraperitoneally (ip). After 30 minutes, blood was taken from their hearts by puncture and the blood was transferred to anticoagulant-free tubes for serum. After the tubes were centrifuged at 1400 g at 4 °C for

10 minutes, the serum was separated and stored in labeled tubes at -80 °C. In the study, Rat Irisin ELISA Kit Cat. No: Elabscience (E-EL-R2514), Biotek ELx800 ELISA Reader, and Biotek ELx50 washer were used. Glucose levels in blood taken from the tail vein were determined with a glucometer.

2.2. Statistical Analysis

The SPSS 23.0 program for Microsoft was used for the statistical evaluation. The difference between the groups was determined by a one-way analysis of variance (ANOVA) ($p<0.05$). The evaluation was made using mean and standard deviation values (M ± SD). The difference between the groups was evaluated with the Tukey post hoc test.

Table 1 Design of groups

Experimental and control groups	Number of animals per group
Control group	6
Diabetes group (DM)	6
Diabetes + 350 mg/kg Royal jelly (DM+RJ)	6

3. RESULTS AND DISCUSSION

Figure 1 shows serum irisin levels. According to the results, there was no statistical difference between the control group and the DM group. After RJ application, serum irisin levels decreased. A statistical difference was found between the control group and the DM-RJ group ($p<0.05$).

Figure 2 shows blood glucose levels. There was a statistically significant increase between the control group and DM and DM+RJ groups ($p<0.05$) whereas no statistically significant difference was determined between the DM and DM+RJ groups.

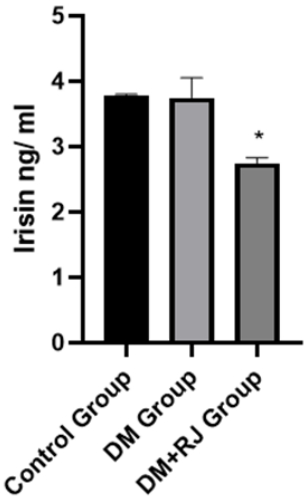

Figure 1 Blood serum irisin ng/ ml. "*" indicates a statistical difference compared to the control group ($P<0.05$, M ± SD)

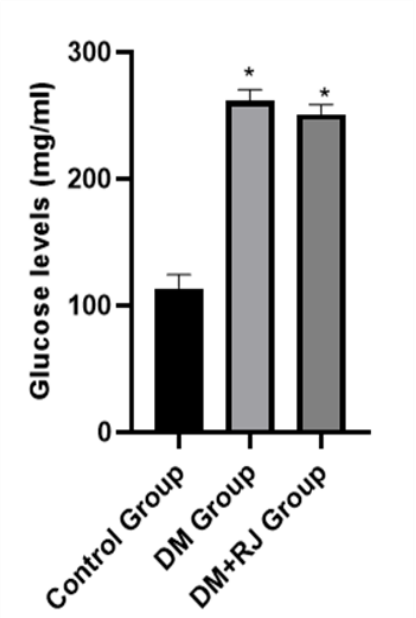

Figure 2 Blood Glucose levels mg/ ml. "*" indicates a statistical difference compared to the control group ($P<0.05$, M ± SD)

Studies on irisin, a recently identified peptide, have mostly focused on exercise, obesity, T2DM, and metabolic syndrome [15, 16]. No sufficient number of studies has examined the relationship between STZ-induced experimental diabetes and irisin. STZ-induced experimental diabetes reduces insulin secretion by causing the destruction of β-cells. It also causes significant body weight loss due to dehydration caused by polyuria [1]. STZ-induced DM causes impairment in

glucose metabolism and also poses a serious risk for energy metabolism.

In the study conducted by Malfitano et al., in which experimental diabetes was induced with 50 mg/kg STZ, it was emphasized that blood glucose level increased whereas body weight and serum insulin level decreased [17]. Moreover, in experimentally diabetic rats induced by 65 mg/kg STZ, firstly the activation of gluconeogenesis for energy production and then the over-mobilization of muscle proteins and lipids were emphasized [18]. Similar to previous studies, in this study, it was observed that STZ-induced DM increased glucose levels.

Although irisin is a member of energy metabolism that has just begun to be investigated, it is emphasized that it may have anti-obesity and anti-hyperglycemic effects [3]. Jiang et al. (2021) investigated the relationship between irisin and FNDC5 in diabetic mice and reported low plasma irisin levels [19]. It was shown that STZ-induced mice have significantly reduced plasma irisin levels as well as low FNDC5 expression in different tissues compared to controls. It was also concluded that the increase in glucose uptake resulted from irisin which induces the expression of Glucose transporter type 4 (GLUT4) in adipocytes [1]. Expression of genes encoding GLUT4 proteins, carnitine palmitoyl transferase, and hormone-sensitive lipase is reported to be significantly increased in adipocyte tissues of irisin-treated individuals [20, 21]. In a study conducted on individuals with normal glucose tolerance who had been newly diagnosed with T2DM, serum irisin levels of individuals with T2DM were found to be lower compared to the control group [21]. Irisin increases glucose uptake and glycogenolysis while decreasing lipid accumulation, adipogenesis, and gluconeogenesis [20]. It is also stated that irisin reduces diabetes-related insulin resistance [22,23]. In addition to studies showing that the irisin level decreases in DM, there are data emphasizing an increase. Norheim et al. (2014) reported that the plasma irisin levels of the prediabetes group were higher compared to the control group [24]. Al-Daghri et al. (2015) similarly reported higher irisin levels in subjects with T2DM than in healthy controls [25]. According to some views, the first increase seen in serum irisin occurs in the obese and diabetic groups. In the second stage, this mechanism is depleted or acclimated, possibly resulting in lower irisin secretion. This can be considered the reason for the contradictory results in the studies [26,27]. In this study, no statistically significant difference was determined between irisin levels in the diabetes group and the control group. The reason for this can be considered as the completion of this study in 4 weeks. Moreover, it has been emphasized that measurement is difficult due to the short half-life of irisin [5].

In a study conducted on serum fasting blood glucose and serum glycosylated hemoglobin levels in women with T2DM, it was reported that RJ significantly decreased serum fasting blood glucose and increased insulin concentration [28]. Furthermore, RJ significantly reduced serum fasting blood glucose, while increasing insulin, albumin, and total protein levels in STZ-induced diabetic rats [9]. In a study conducted with long-term RJ administration, it was reported that irisin inhibited a key enzyme, glucose-6-phosphatase by inducing the expression of protein kinase activated by adiponectin receptor-1 mRNA and phosphorylated AMP in abdominal fat and thus, cured hyperglycemia [10]. 10-hydroxy decanoic acid, the active agent of RJ, has a healing effect on hyperglycemia and insulin resistance [10]. After RJ administration in STZ-induced diabetic rats, there was an improvement in serum biochemical changes and oxidative stress of the liver and pancreas, and an increase in serum insulin level [14]. In this study, serum irisin levels decreased after RJ administration compared to the control group. Due to the antihyperglycemic effect of both RJ and irisin [8,20,29], it has been evaluated that RJ may reduce irisin expression in STZ-induced DM.

It has been reported that irisin is extremely difficult to monitor. Evaluating the data with different techniques will enable us to achieve more comprehensive results. In future studies, the aim is to overcome this limitation with advanced techniques and more studies on dosing for longer periods.

4. CONCLUSION

Recent studies have shown that irisin, an adipomyokine, may play a role in the regulation of thermogenesis, total body energy metabolism, and glucose homeostasis. Therefore, some studies are focusing on the evaluation of irisin as a therapeutic agent. Although studies have shown that recombinant irisin can be given externally, it is possible to try different substances and combinations that balance the circulating irisin level. Especially the short half-life of irisin complicates the external use of this peptide for therapeutic purposes. However, the determination of the auxiliary dose of a product that increases the secretion of this peptide and also supports the treatment of diabetes will contribute to the literature. In this study, it was observed that the relevant dose of RJ decreased blood glucose but did not significantly increase irisin levels. The reason for this may be associated with the selected RJ dose or the duration of administration. Further studies are required to better elucidate the mechanisms of action of both irisin and RJ.

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Authors' Contribution
S.Ç: Conceptualization, literature review, laboratory analysis, data collection, design, and writing, reviewing, and editing.

The Declaration of Conflict of Interest/ Common Interest
No conflict of interest or common interest has been declared by the author.

The Declaration of Ethics Committee Approval
The study was approved by Animal Experiments Local Ethics Committee of Çanakkale Onsekiz Mart University (ÇOMÜ HADYEK 30.06.2020; 2020/06-06).

The Declaration of Research and Publication Ethics
The authors of the paper declare that they comply with the scientific, ethical and quotation rules of SAUJS in all processes of the paper and that they do not make any falsification on the data collected. In addition, they declare that Sakarya University Journal of Science and its editorial board have no responsibility for any ethical violations that may be encountered, and that this study has not been evaluated in any academic publication environment other than Sakarya University Journal of Science.

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