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Royal Jelly Decreases Blood Pressure, Serum Glucose, and Interleukin-6 in Patients with Type 2 Diabetes on an Iso-caloric Diet

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ABSTRACT

Background: Royal Jelly (RJ) is a mixture of protein, glucose, lipid, vitamins, and minerals that is widely used as a commercial medical product. Previous studies have shown that RJ has physiological effects such as anti-inflammatory, anti-tumor, anti-allergic, and antioxidant. In the present study, the effects of RJ on some cardiovascular disease risk factors were investigated in patients with type 2 diabetes on an iso-caloric diet. **Methods:** In this randomized controlled trial, patients with type 2 diabetes aged 25-65 years with body mass index (BMI) of 26-30 kg/m2 and hemoglobin A1c (HbA1c) of 7-9% were included. The patients were randomly assigned to receive 1000 mg of RJ supplement or the placebo three times daily for 8 wks. Weight, fasting blood glucose (FBG), HbA1c, blood pressure, and inteleukin-6 levels were measured. **Results:** In comparison to the placebo, FBG (P = 0.006), interleukin-6 (P = 0.017), and systolic blood pressure (P = 0.02) were significantly decreased in the RJ group at the end of the study. There were significant differences in the mean changes of systolic blood pressure at the baseline to the endpoint of systolic blood pressure between the two groups (P = 0.006). **Conclusions:** Royal Jelly may reduce incidence of cardiovascular disease by lowering effects on FBG, inteleukin-6, and systolic blood pressure in patients with type 2 diabetes.

Keywords: *Royal jelly; Interleukin-6; Blood pressure; Type 2 diabetes*

Introduction

Diabetes mellitus (DM), defined by elevated glycemic markers, is a major risk factor for cardiovascular diseases (CVDs). Cardiovascular diseases are the most common cause of death

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among adults with DM underscoring the need for aggressive CVDs risk factor management (Go *et al.*, 2013). Insulin resistance occurs in several tissues. Hyperglycemia increases the risk of atherothombosis through several potential mechanisms (Laakso, 1999). Low-grade inflammation is linked to insulin resistance and involved in the pathogenesis of type 2 diabetes mellitus (T2DM) (Dandona *et al.*, 2003). The signaling pathways of inflammation and insulin are tightly linked so that presence of defects in both of them leads to insulin resistance, endothelial dysfunction, and finally cardiovascular complications. Obesity, as a common feature of diabetic patients is associated with more generalized systemic inflammation involving circulating inflammatory proteins such as C-reactive protein (CRP), Interleukin-6 (IL-6), plasminogen activator inhibitor (PAI-1), P-selection, vascular cell adhesion molecule (VCAM-1), and fibrinogen. Adhesion molecule expression is induced by pro-inflammatory cytokines such as IL-1β, tumor necrosis factor (TNF-α), and CRP produced by the liver in response to IL-6 (Van Gaal *et al.*, 2006). Insulin resistance and type 2 diabetes are associated with several changes in lipids and lipoproteins (Garvey *et al.*, 2003).

Totally, high blood pressure, insulin resistance, and inflammation are the most important risk factors of CVDs in patients with T2DM. Therefore, it is important to recognize and treat these conditions to postpone or even prevent from CVDs incidence in T2DM patients.

More diabetic patients use complementary and alternative medicine (CAM). Royal jelly (RJ) as a bee product is secreted from the hypopharingeal and mandibular glands of the worker bees. It is a popular traditional food containing proteins, sugar, and fatty acids (10-hy-droxy-2-decenoic acid) (Tokunaga *et al.*, 2004). Hypotensive activity, insulin-like action, antitumor activity, and vasodilation are some pharmacological functions of RJ (Tokunaga *et al.*, 2004).

One study indicated that peptides consuming RJ can reduce blood pressure by inhibiting the activity of angiotensin converting enzyme (ACE) (Maruyama *et al.*, 2005). In one study, researchers showed the anti-inflammatory actions of RJ at the cytokine level. Furthermore, it was represented that it can reduce the production of pro-inflammatory cytokines (TNF-α, IL-6, and IL-1) in a dose-response manner.

Some factors in RJ can inhibit secretion of pro-inflammatory cytokines (Kohno *et al.*, 2004). In another study, researchers assessed the effects of RJ consumption on blood glucose levels in healthy participants. Blood glucose and area under the curve were significantly reduced after RJ supplementation (Münstedt *et al.*, 2009). Hyperglycemia is an initiation of tissue destruction in DM and high blood pressure can worse the blood glucose levels (Brownlee, 2005). To the best of our knowledge, this is the first human study in which the effect of RJ supplementation is evaluated on serum glucose, IL-6, glycosylated hemoglobin (HbA1c), and blood pressure in T2DM patients. It is hypothesized that RJ supplementation improves serum glucose, IL-6, HbA1c, systolic, and diastolic blood pressure (SBP and DBP) in T2DM patients through decrease of insulin resistance.

Materials and Methods

Study design and participants: In designing the study, power of 90% with a two-sided test and α = 0.05 (type I error) were considered to detect a 5% difference in serum glucose between the two groups. On the basis of SDs, the values reported in a similar study were used (Hang *et al.*, 2007). The number of participants needed to detect this difference was 20 in each group. Given an anticipated drop-out rate of 25 %, the enrollment target was set at 25 individuals. The double-blinded randomized controlled trial (RCT) was conducted in the Endocrine and Metabolism Institute of Iran University of Medical Sciences to assess the RJ effects on serum glucose, IL-6, SBP, DBP, and HbA1c in T2DM patients The inclusion criteria consisted of: (1) being in the age range of 25-65 years, (2) having BMI of 26-30 kg/m^2, (3) Iranian ethnicity, (4) diagnosed type 2 diabetes for 5-10 years, (5) HbA1c of 7-9%, and (6) receiving oral hypoglycemic drugs. The exclusion criteria included: (1) serum triglyceride level (TG) > 400 mg/dL, serum cholesterol level > 240 mg/dL, (2) lactating or pregnancy, (3)

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diagnosis of heart, liver, and renal failure, cancer, acute myocardial infarction, stroke, or serious injuries, (4) receiving multivitamin or antioxidant supplements at least 3 months, (5) smoking/alcohol consumption, (6) taking oral contraceptive or lipid lowering drugs, (7) insulin infusion, (8) allergy to RJ, (9) any mal-absorption diseases such as celiac or steatorrhea, and (10) athletes. The study was approved by the Bioethics Committee of Iran University of Medical Sciences. Totally, 46 patients were randomly assigned into two groups; Group RJ (RJG) received 1000 mg of the RJ supplements (Natural life. Frengrove Co. Australia) three times daily and placebo group (PG) received1000 mg of exactly the same placebo (as glycerin) (Pars Minoo Inc. Tehran Iran) three times daily for up to 8 weeks. Shape, color, and package of the placebo were similar to the RJ. Products were administered by a blinded researcher assistant to the patients. First, RJ and placebo were divided into similar packages for one week intake. Then, residuals of each package were assessed to determine the compliance of the patients. In this regard, participants with the compliance rate below 80% were excluded from the study. Those who entered the study were randomly assigned to one of the two groups via computer-generated numbers. Both active and placebo treatments were contained in the same opaque capsules and side effects of supplements were recorded.

Participants were instructed to maintain an isocaloric diet, continue their previous eating habits under the supervision of an experienced nutritionist, and not to change their routine physical activities during the study period. Throughout the study period, individuals were directed to continue taking the same dose of any prescribed hypoglycemic agents unless hypoglycemia occurred; in this case they were directed to reduce their dose immediately.

Measurements: Daily food intake was obtained by a 24-hour dietary recall questionnaire and physical activity level by International Physical Activity Questionnaire (IPAQ) questionnaire in three days (two regular days and one holiday) at the beginning and end of the study. These dietary intake data were analyzed by the Nutritionist 4 (N4) software (Nutritionist 4, First Data Bank, San Bruno, CA, USA).

Fasting blood samples were collected at the baseline and 8 wk after the intervention. Serum glucose was used as the major outcome measurement. Moreover, SBP, DBP, HbA1c, and IL-6 levels were assessed for both groups at the baseline and end of the study. Serum glucose was measured by an enzymatic method (Pars Azmon Co. kit, Tehran, Iran) using Liasys autoanalyzer. Later, HbA1c was measured by HPLC and IL-6 by ELISA method (BD bio science Co. kit, USA). Nutritional data were obtained via 24 hour diet recall. Participants' weight was also measured on a calibrated balance Seca scale to the nearest 0.5 kg, followed by the demographic data collected at the initiation of the study.

Data analysis: Statistical analyses were performed through $SPSS_{16}$ software (version 16; IBM Corp., USA). Normal distribution of variables was checked by Kolmogorov Smirnov Test; independent samples *t-test* was then used to test whether the differences between the mean values of the items studied in both groups were significant or not. Paired sample t-test was applied to evaluate differences before and after the intervention in each group. All data were expressed by means ± SD. The level of significance was determined at P-value < 0.05.

Ethical consideration: All experiments were conducted in accordance with the Declaration of Helsinki and all procedures were carried out while participants were totally aware of them and signed written consents. This study has also been registered at the Iranian registry of clinical trials (www.irct.ir) with IRCT number: IRCT201103012709N18**)**.

Results

Demographic and anthropometric measurements at the baseline: The participants' demographic information through the intervention is shown in **figure 1**. There were 45.4% and 48% male participants in the RJ and placebo groups, respectively. Participants' gender was not significantly different between the two groups.

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Mean weight of participants was neither significantly different between the RJP and PG at the baseline (75.6 ± 10.2 kg vs. 74.1 ± 11.3 kg, respectively), nor at the end of the study (75.4 ± 10.1 kg vs. 73.9 ± 11.02 kg, respectively). Changes of weight mean from the baseline to the end were not significantly different between the two groups. Weight of participants was also not significantly different in each group before and after the intervention. Mean and standard deviation of nutrients' intake data are shown in **Table 1**.

There was no significant difference within and between the two groups for intake of energy and nutrient before and after the intervention. The level of physical activity and lipid lowering drugs were not different between the two groups at the baseline. No side effects were observed from supplements in the participants.

Laboratory analysis measurements: As it is shown in **Table 2**, there was no significant difference in serum glucose, IL-6, HbA1c, SBP, DBP, and IL-6 between the two groups before the intervention. Serum glucose (P = 0.006), SBP (P = 0.02), and IL-6 (P = 0.017) decreased compared with the initial values at the end of the study in RJG. There were significant differences in mean changes from the baseline to endpoint of SBP (P = 0.006) between the two groups. There was no significant difference after RJ supplementation compared to previous values in serum glucose, HbA1c, and DBP.

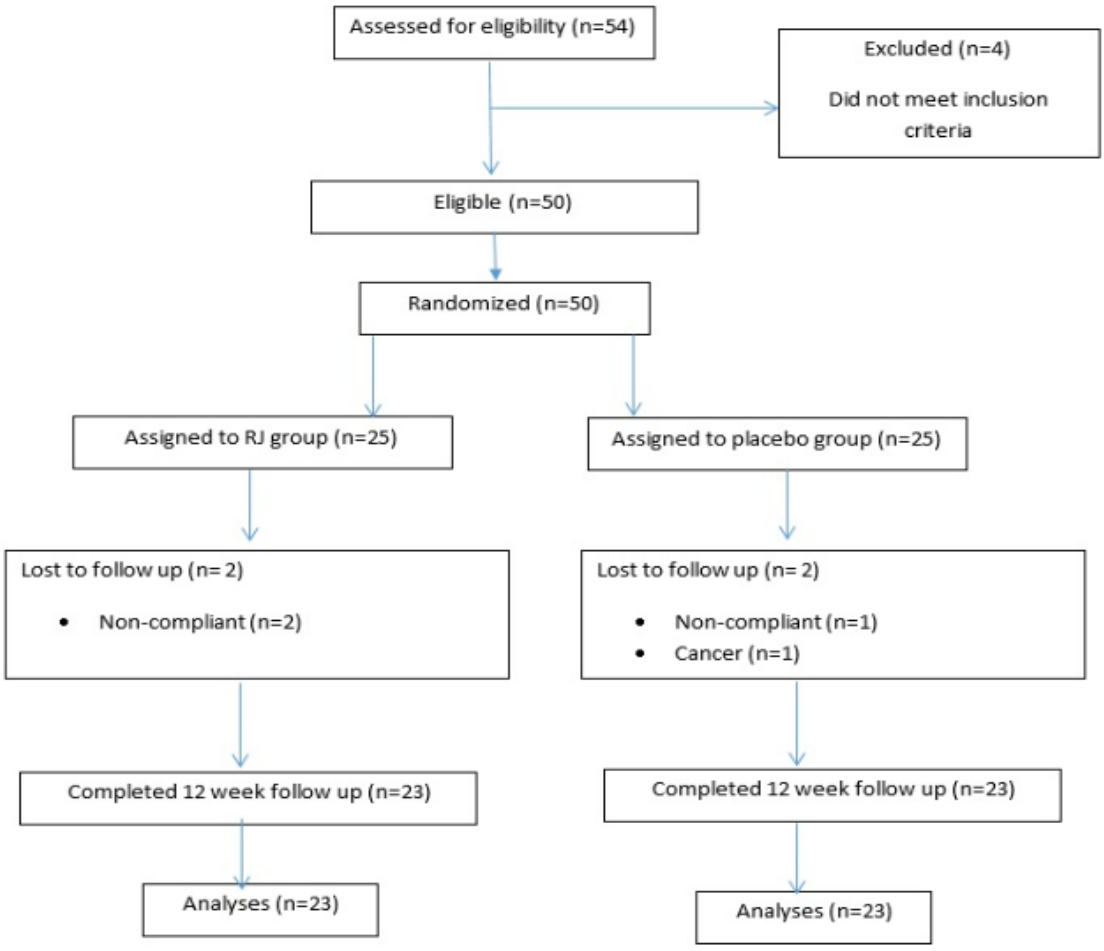

Figure 1. Follow of participants through the intervention

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Table 1. Comparison of dietary intake of energy, macronutrients and some micronutrients between the two groups

Dietary intake	RJ group (n=23)	Placebo group (n=23)	*P*-value[a]
Total energy (Kcal/day)			
Before	1685.69 ± 217.79	1770.04 ± 184.28	0.28
After	1716.95 ± 213.37	1730.65 ± 246.94	0.30
Total protein (g/day)			
Before	65.34 ± 8.93	69.32 ± 10.26	0.10
After	69.32 ± 10.26	65.25 ± 12.10	0.08
Total carbohydrate (g/day)			
Before	237.49 ± 30.93	248.84 ± 28.91	0.56
After	240.37 ± 29.87	242.29 ± 34.57	0.31
Total fat (g/day)			
Before	53.81 ± 10.76	57.56 ± 9.72	0.23
After	55.84 ± 9.05	53.65 ± 7.65	0.08
Saturated fat (g/day)			
Before	24.04 ± 5.15	25.08 ± 4.14	0.11
After	22.04 ± 4.85	24.30 ± 4.95	0.55
Mono unsaturated fat (g/day)			
Before	13.78 ± 3.69	13.56 ± 4.81	0.08
After	14.73 ± 3.76	12.95 ± 2.89	0.30
Poly unsaturated fat (g/day)			
Before	15.78 ± 3.46	17.82 ± 3.91	0.49
After	16.56 ± 4.31	16.06 ± 3.69	0.14
Vitamin C (mg/day)			
Before	77.53 ± 18.48	74.22 ± 21.13	0.87
After	78.28 ± 18.81	80.27 ± 18.51	0.10
Vitamin E (mg/day)			
Before	18.09 ± 5.09	17.93 ± 7.05	0.63
After	17.67 ± 5.59	14.43 ± 5.81	0.11

[a]: Student *t-test*, [a:] Paired *t-test*; [b]: Student *t-test*

Table2. Camparison of mean (±SD) some cardiovascular disease risk factors within and between groups

Variables	Group	Before	After	Change	P-value [b]
Glucose (mg/dL)	RJ	128.4 ± 44.4	119.0 ± 30.9	-9.4 ± 26.0	0.09
	Placebo	145.7 ± 48.4	149.7 ± 40.2	4.0±30.4	0.53
	P-value[a]	0.2	0.006	0.11	
Hmoglobin bA1c (%)	RJ	8.1 ± 4.1	6.7 ± 2.2	-1.45 ± 4.1	0.33
	Placebo	7.4 ± 6.2	8.6 ± 4.9	1.16 ± 5.1	0.95
	p value	0.6	0.11	0.48	
Systolic blood pressure (mmHg)	RJ	131.4 ± 10.2	126.8 ±13.8	-4.5 ± 8.0	0.01
	Placebo	136.1 ± 14.4	136.7 ± 14.1	0.6 ± 2.8	0.31
	p value	0.2	0.02	0.006	
Dystolic blood pressure (mmHg)	RJ	86.5 ± 8.5	83.6 ± 3.9	-2.9 ± 8.1	0.09
	Placebo	86.1± 6.1	86.2 ± 5.8	0.13 ± 1.2	0.6
	p value	0.83	0.08	0.07	
Interleukin-6 (pg/ml)	RJ	6.6 ± 3.3	4.8 ± 1.4	-1.79 ± 3.4	0.02
	Placebo	6.6 ± 3.2	6.1± 1.9	-0.51 ± 2.8	0.39
	p value	0.99	0.017	0.18	

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Discussion

To the best of our knowledge, this is the first RCT conducted to assess the effects of RJ supplementation on the incidence of cardiovascular risk via measurement of serum glucose, IL-6, HbA1c, and blood pressure in T2DM patients. In this study, intake of RJ significantly reduced serum glucose, SBP, and IL-6 after the intervention but there were no significant differences before and after RJ supplementation in HbA1c and DBP. Some tests were carried out to confirm that RJ reduced the effects of diabetes on animals. The simultaneous administration of RJ and a fructose solution for 8 weeks to insulin-resistant rats significantly reduced plasmatic concentration of insulin, triglycerides, and SBP, without affecting the blood levels of glucose or total cholesterol. These results suggest that RJ can be a functional dietary treatment to prevent from insulin resistance associated with developing hypertension in diabetic patients (Nomura *et al.*, 2007, Zamami *et al.*, 2008). One clinical study demonstrated that RJ significantly affects serum glucose levels in healthy participants (Munstedt et al. 2009). It was reported in another study that RJ reduced the index of insulin resistance (HOMA-IR) but did not reduce blood glucose levels in rats (Zamami *et al.*, 2008). In a recent study, researchers showed that RJ increased catalase activity and antioxidant power, while it decreased malondialdehyde levels in the kidney tissue homogenates of streptozotocin induced diabetic rats (Ghanbari *et al.*, 2015). It has also been shown that RJ contains biologically active substances which causes insulin-like activity (Kramer *et al.*, 1982). Elevated blood glucose level contributes to the proteins and lipid glycation, resulting in the formation of advanced glycation end-products (AGEs) (Pickup, 2004). Receptors for AGEs (RAGE) are expressed in many different tissues and cell types, including endothelial cells, vascular smooth muscle cells, and macrophages (Basta *et al.*, 2004) that lead to the intracellular generation of ROS which activates NF-kB (Wendt *et al.*, 2002). Then, the expression of TNF, IL 1, 6, 8, and 18 as well as interferon-γ (IFN-γ) are increased (Wautier *et al.*, 2001). A clinical study suggests that acute hyperglycaemia can result in elevated levels of circulating inflammatory cytokines, in particular TNF-α, IL-6 and IL-18 (Basta *et al.*, 2002). In one study, the anti-inflammatory actions of RJ at a cytokine level were examined. Supernatants of RJ suspensions were added to a culture of mouse peritoneal macrophages stimulated with lipopolysaccharide and IFN-γ. The production of proinflammatory cytokines such as TNF-α, IL-6, and IL-1 were efficiently inhibited in a dose-dependent manner without having cytotoxic effects on macrophages. This suggests that RJ contains factor(s) responsible for the suppression of proinflammatory cytokines secretion.

Researchers named the factor for honey-bees, RJ-derived anti-inflammatory factor (HBRJ11AIF) and further investigated its molecular aspects. Size fractionation study showed that HBRJ-AIF is composed of substances of low (< 5 kDa) and high (> 30 kDa) molecular weights; the former is a major component. Chromatographic analysis showed that MRJP3 is one candidate for the HBRJ-AIF with high molecular weights. Thus, these results suggest that RJ has anti-inflammatory actions through inhibiting pro-inflammatory cytokine production by activated macrophages (Kohno *et al.*, 2004). One study indicated that Protease N treated RJ (Pro-RJ) and peptides (IY, VY, IVY) from Pro-RJ, inhibited ACE activity and they have an antihypertensive effect in repeated oral administration for 28 days in spontaneously hypertensive rats (Tokunaga et al. 2004). Another study suggested that the trans-2-octenoic acid and the hydroxydecanoic acid from RJ may be responsible for the anti-hypertensive action, with different RJ fractions exercising bigger or smaller effects on the duration of the action (Librowski and Czarnecki, 2000).

Researchers investigated the anti-inflammatory effects of RJ in formalin-induced rat paw edema; they administered 25, 50, and 100 mg/kg, intera-peritoneal of RJ to these rats. The highest anti-inflammatory effect was observed in doses of 50 and 100 mg/kg (Arzi *et al.*, 2015).

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In one human study, researchers determined the effects of RJ supplementation on diabetic females. A single dose of 1000 mg RJ was used in this study. Means of fasting blood glucose remarkably decreased after supplementation of RJ. In the current study, however, 1000 mg RJ was used 3 times daily. Serum glucose was reduced significantly but HbA1c level was neither significantly different between the two groups, nor before and after the supplementation. In comparison to the placebo group, SBP and IL-6 were significantly reduced after 8 weeks of supplementation (Pourmoradian *et al.*, 2014).

To our knowledge, this is the first randomized controlled trial on RJ supplementation in DM patients. However, the small sample size and short duration of the study can be mentioned as its limitations. Studies with bigger sample size and longer duration are recommended and needed before reaching final conclusions. Further studies are suggested to investigate the effect of RJ on other diseases with inflammatory pathogenesis.

Conclusion

High blood pressure, insulin resistance, and inflammation are the most important risk factors of cardiovascular complications in type 2 diabetic patients. In the present study, supplementation of RJ decreased serum glucose level, SBP, and IL-6. So, RJ may be an effective supplement for decreasing CVDs risk factors in T2DM patients.

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Author's contribution

Shidfar F and Khoshpay B designed the study. Khoshpay B and Mousavi SN carried out the study. Malek M informed the patients and Hosseini F analyzed the data. Hosseini SH with the biochemical analysis. Mousavi SN and Shidfar F designed the manuscript and all authors studied and approved the final version of the manuscript.

Conflict of interest

Authors declare that there is no conflict of interest.

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