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Original Research

Effect of Royal Jelly Intake on Serum Glucose, Apolipoprotein A-I (ApoA-I), Apolipoprotein B (ApoB) and ApoB/ApoA-I Ratios in Patients with Type 2 Diabetes: A Randomized, Double-Blind Clinical Trial Study

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ABSTRACT

Objectives: Type 2 diabetes is the most common metabolic disorder worldwide. Evidence supports a role for royal jelly (RJ) in reduction of serum glucose and lipids in animals and healthy subjects. The purpose of this study was to determine the effect of RJ intake on serum glucose, apolipoprotein A-I (ApoA-I), apolipoprotein B (ApoB) and ApoB/ApoA-I ratios in patients with type 2 diabetes.
Methods: Fifty patients with type 2 diabetes participated in a double-blind, placebo-controlled study. The participants were randomly divided into RJ and placebo groups and were given doses of 1000 mg royal jelly or placebo 3 times a day for 8 weeks, respectively. Weight, height, fasting blood glucose, ApoA-I and ApoB were measured at baseline and endpoint.
Results: There were no significant differences in baseline characteristics and dietary intakes between groups. The mean difference in glucose concentrations decreased in the RJ group (–9.4 mg/dL vs. 4 mg/dL; p=0.011). The mean difference in ApoA-I concentrations increased in the RJ group (34.4 mg/dL vs. –1.08 mg/dL; p=0.013). There was a significant decrease in mean difference of ApoB/ApoA-I in the RJ group compared with the placebo group (0.008 vs. 0.13; p<0.044), respectively.
Conclusions: These data suggest that RJ intake may have desirable effects on serum glucose, Apo-A-I concentrations and ApoB/ApoA-I ratios in people with type 2 diabetes.

Mots clés :
ApoA–I
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RÉSUMÉ

Objectifs : Le diabète de type 2 est la maladie métabolique la plus fréquente dans le monde. Les données probantes établissent un lien entre la gelée royale (GR) et la réduction du glucose sérique et des lipides chez les animaux et les sujets sains. L'objectif de la présente étude était de déterminer l'effet de l'apport en GR sur le glucose sérique, l'apolipoprotéine A –I (ApoA–I), l'apolipoprotéine B (ApoB) et les ratios ApoB/ApoA –I des patients souffrant du diabète de type 2.
Méthodes : Cinquante patients souffrant du diabète de type 2 ont participé à l'étude comparative contre placebo, à double insu. Nous avons réparti de manière aléatoire les participants en un groupe GR et un groupe placebo, soit des doses respectives de 1000 mg de GR ou du placebo 3 fois par jour durant 8 semaines. Nous avons mesuré le poids, la taille, la glycémie à jeun, l'ApoA–I et l'ApoB au début et à la fin.
Résultats : Nous n'avons observé aucune différence significative dans les caractéristiques initiales et les apports alimentaires entre les groupes. La différence moyenne dans les concentrations de glucose a diminué dans le groupe GR (–9,4 mg/dl *vs* 4 mg/dl; p=0,011). La différence moyenne dans les concentrations d'ApoA –I a diminué dans le groupe GR (34,4 mg/dl *vs* –1,08 mg/dl; p=0,013). Nous avons observé une diminution significative dans la différence moyenne du ratio ApoB/ApoA –I dans le groupe GR par rapport au groupe placebo (0,008 *vs* 0,13; p<0,044), respectivement.

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Conclusions : Ces données suggèrent que l'apport en GR peut avoir des effets bénéfiques sur le glucose sérique, les concentrations d'ApoA –I et les ratios ApoB/ApoA –I chez les personnes souffrant du diabète de type 2.

Introduction

The prevalence of type 2 diabetes is increasing, rising from 171 million in 2000 to an expected level of 366 million in 2030 (1), and up to 90% of diabetes cases are type 2 diabetes (2). Also, this prevalence is reported to be more than 14% in Tehran, Iran, with an estimated incidence of new cases in about 1% of population per year (3).

Type 2 diabetes is one of the major metabolic disorders and is associated with great morbidity and economic cost. Apart from hyperglycemia, type 2 diabetes is also characterized by oxidative stress, inflammation and insulin resistance (4). Dietary intervention has been successfully proven to improve serum lipid levels and glycemic profiles in adults with type 2 diabetes (5).

Royal jelly (RJ) is a traditional product commonly used as a supplement in medical treatments of various diseases. It is secreted from the hypopharyngeal and mandibular glands of young worker bees to feed larvae and the adult queen bee (6). RJ is a unique substance containing a combination of free amino acids, proteins (12% to 15%), sugars (10% to 12%), fatty acids, lipids (3% to 7%), bioactive substances such as 10-hydroxy-trans-2-decenoic acid, vitamins and minerals (7–9).

RJ has been demonstrated to possess several pharmacologic activities in experimental animals and in some human studies, including vasodilator and hypotensive activities (10,11) antioxidative activity (12), antitumour activity (13,14), antihypercholesterolemic activity (15,16) and anti-inflammatory activity (17). To date, most studies have been designed to be used in rats or have been achieved in vitro, and a few of them have been designed for healthy humans.

Therefore, the purpose of the current study was to determine the effects of RJ consumption on serum glucose, ApoA-I, ApoB and ApoB/ApoA-I ratios in people with type 2 diabetes compared with a group receiving placebo.

Methods

This parallel design, randomized double-blind placebo-controlled study was financially supported by Iran University of Medical Sciences (p/1006), Tehran, Iran.

Subjects

All subjects were adult volunteers with type 2 diabetes according to the definition by the American Diabetes Association, which includes serum fasting glucose ≥126 mg/dL, 2-hour plasma glucose levels ≥200 mg/dL and glycated hemoglobin (A1C) levels of 6% to 8%, after 2 tests and confirmation by an endocrinologist. They were recruited mainly among the patients who were referred to the Endocrinology and Metabolism Research Center of Iran University of Medical Sciences, Tehran, Iran. The purpose and expectations of the study were explained to each volunteer. The participants freely volunteered to participate in the present study and could withdraw from the study whenever they wished. Eligible patients were included after we received written informed consent.

Study criteria included patients who had had type 2 diabetes for 5 to 10 years, were between 20 and 65 years of age, had body mass indexes between 20 and 30, had taken glucose-lowering medications for type 2 diabetes (antidiabetic drugs such as metformin, glibenclamide or both) without insulin injection, had no histories of alcohol abuse or smoking, were taking no supplements (including vitamins and minerals and also lipid-lowering drugs) during the 3 months before and during the study, had no hepatic or renal disease, and had no history of cancer or myocardial infarction.

Exclusion criteria were total serum cholesterol and triglyceride levels above 240 and 400 mg/dL, respectively; any sign of sensitivity to RJ at any time during the study; pregnancy or lactation; taking oral contraceptives during the study and starting insulin injection.

The study was approved by the Ethics Committee of Iran University of Medical Sciences, Tehran, Iran (registration #90-01-122-12592) and was registered on the Iranian Registry of Clinical Trials website (IRCT138905102709N8).

Experiment design

Among the 50 volunteers with type 2 diabetes, 46 patients were randomly divided into 2 groups—the RJ group (13 females and 10 males, 51.8±9.7 years) and the placebo group (11 females and 12 males, 53.1±7.5 years). The RJ group was given 3000 mg RJ capsules per day (Natural Life, Frengrove, Australia), and the placebo group received 3 capsules that looked exactly the same but contained glycerin, which could not be distinguished by color, odor or taste (Pars Minoo, Tehran, Iran) for 8 weeks.

The participants were specifically asked to maintain their usual diets, physical activities and medications during the study period. Medical and drug histories were obtained via face-to-face interviews. The dietary intakes of patients were assessed using a 24-hour-recall food questionnaire for 3 days (2 weekdays and 1 weekend day) at the beginning, at week 4 and at the end of 8 weeks. All of the 24-hour-recall questionnaires were analyzed by the Nutritionist IV software program (v. 4.1), and mean intakes of energy, macronutrients and some of the micronutrients were calculated. Physical activity was measured by an International Physical Activity Questionnaire (18) at baseline and at the end of the study. Compliance with the supplementation protocol was supervised by a research technician who contacted the subjects once a week. Each subject was required to return the original bottle of their respective supplement for capsule counts, and compliance was monitored by counting the unconsumed capsules each week.

All subjects were stable because medications had not been modified over the past month, and there was homogeneity regarding their treatments (metformin, glibenclamide or both).

Blood samples (10 mL) were collected from each patient after 12 to 14 hours of fasting, between 8 AM and 10 AM. Fasting blood sugar levels were measured by an autoanalyzer using an enzymatic method (Pars Azmon kit, Tehran, Iran). ApoA-I and ApoB were measured by immunoturbidimetry (Pars Azmon) with a Cobas MIRA analyzer (Roche Diagnostic, Basel, Switzerland).

Statistical analyses

In designing the study, we considered power of 90% with a 2-sided test, with alpha=0.05 (type I error) to detect a 5% difference in serum glucose between the 2 groups. On the basis of standard deviations (SDs) reported in a similar study (16), the number of subjects needed to treat to detect this difference was 20 per group. Given an anticipated dropout rate of 25%, we set the enrollment target at 25 subjects.

Statistical analyses were performed using SPSS (v. 16; SPSS, Chicago, Illinois, USA). Data are presented as mean ± SD or percentage. The normality of variables was tested by the Kolmogorov-Smirnov test. Paired t tests and independent t tests were used to compare the differences within a group or between groups, respectively. A p value less than 0.05 was considered statistically significant.

Results

Of the initially enrolled 50 participants, 4 patients did not complete the study. The reasons they gave it up were incidence of liver cancer (n=1), fear of increasing blood glucose (n=1) and unwillingness to provide blood samples (n=2). Finally, 23 subjects in the RJ group and 23 subjects in the control group were analyzed (Figure 1).

Energy intake and macronutrient and micronutrient composition of the diets did not differ between groups at baseline and did not change in the placebo or RJ group during the intervention period (Table 1). Baseline characteristics did not differ between the 2 groups of the study population (Table 2). All medications were continued as usual.

The mean differences in blood glucose concentrations significantly decreased in the RJ group and increased in the placebo group (–9.4±13.5 mg/dL vs. 4±8.2 mg/dL; p=0.011) (Table 3). Also, RJ supplementation resulted in significant increases in ApoA-I concentrations (mean difference of 34.4±53.3 mg/dL vs. –1.08±32.6 mg/dL in the placebo group; p=0.013). Although Apo B concentrations increased in both the RJ and the placebo groups, there were no significant differences between the 2 groups at the end point (p<0.65).

The results showed that the mean difference in the ApoB/ApoA-I ratio increased in the placebo group (0.13±0.2; p<0.011 vs. 0.008±0.2; p<0.7 in the RJ group). Also, changes in the ApoB/ApoA-I ratio from the baseline were statistically significant in the 2 groups (p<0.044) (Table 3).

No adverse effects were observed. The overall compliance level with supplementation was 90% in this study.

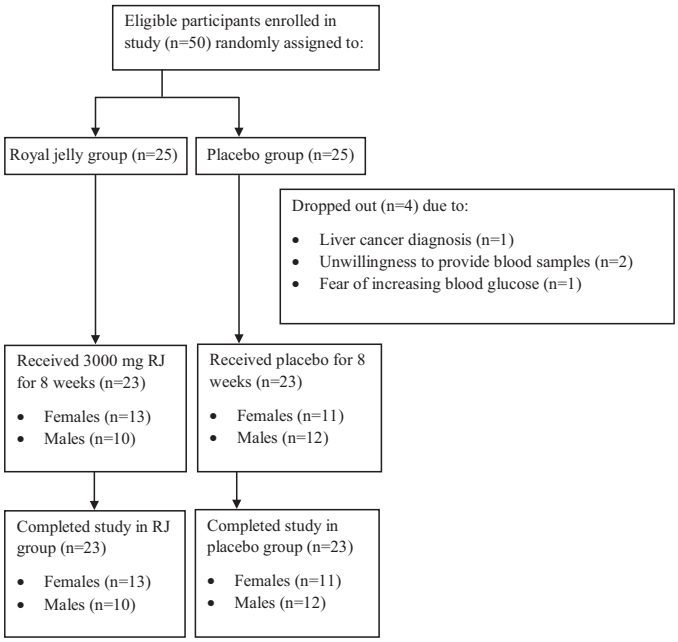

Figure 1. Flowchart of the study participants.

Table 2
Characteristics of participant groups who received royal jelly supplements or placebo before and after the intervention

Characteristics	Placebo group		Royal jelly group	
	After	Before	After	Before
Age (year)	—	53.13±7.45	—	51.78±9.65
Weight (kg)	73.8±11	74±11.3	75.4±10.1	75.6±10.2
BMI (kg/m^2)	27.9±3.6	28.01±3.81	27.9±2.5	27.79±2.65
Duration of diabetes	—	6.74±1.68	—	6.15±1.19
Medications[a]				
Metformin (n, %)	—	8 (34.78)	—	5 (21.74)
Glibenclamide (n, %)	—	11 (47.83)	—	14 (60.87)
Metformin+glibenclamide (n, %)	—	4 (17.39)	—	4 (17.39)
Physical activity level[a]				
Light (n, %)	16 (69.5)	15 (65.2)	14 (60.8)	14 (60.8)
Moderate (n, %)	7 (30.4)	8 (33.4)	9 (39.1)	9 (39.1)
Intensive (n, %)	—	—	—	—

Note: Data are expressed as means ± SD except those marked[a], denoting n, %. All parameters were not significantly different between groups at baseline and did not change in the royal jelly or the placebo group during the intervention period.

Discussion

According to our results, RJ intake (3 grams per day) reduced serum glucose, increased serum ApoA-I and modified the ApoB/ApoA-I ratio after 8 weeks.

Recent studies of the effects of supplementary RJ on glucose metabolism in patients with diabetes and in healthy people have been contradictory. Mobasseri et al reported that RJ does not appear to have significant immediate effects on glycemic factors in patients with type 2 diabetes (19). On the other hand, Pourmoradian et al reported that RJ supplementation resulted in significant reduction in fasting blood glucose and A1C levels in females with type 2 diabetes (20). It has also been reported that supplementation with RJ

Table 1
Daily total energy and dietary intakes before and after the intervention (n=46)

Characteristics	Placebo group			RJ group		
	p value [a]	After	Before	p value[a]	After	Before
Energy (Kcal)	0.306	1730.6±246.9	1770.04±184.28	0.289	1716.9±213.3	1685.69±217.79
Protein (g/day)	0.083	65.2±12.1	69.32±10.26	0.102	69.3±10.2	65.34±8.93
Carbohydrate (g/day)	0.310	242.2±34.5	248.84±28.91	0.566	240.3±29.8	237.49±30.93
Total fat (g/day)	0.083	53.6±7.6	57.56±9.72	0.236	55.8±9.05	53.81±10.76
SFA (g/day)	0.55	24.3±4.9	25.08±4.14	0.114	22.04±4.8	24.04±5.15
MUFA (g/day)	0.301	12.9±2.8	13.56±4.81	0.084	14.7±3.7	13.78±3.69
PUFA (g/day)	0.144	16±3.6	17.82±3.91	0.498	16.5±4.3	15.78±3.46
Vitamin C (mg)	0.107	80.2±18.5	74.22±21.13	0.874	78.2±18.8	77.53±18.48
Vitamin E (mg)	0.117	14.4±5.8	17.93±7.05	0.632	17.6±5.5	18.09±5.09

SFA, Saturated Fatty Acid; *MUFA*, Monounsaturated Fatty Acid; *PUFA*, Polyunsaturated Fatty Acid.
Note: Data are expressed as means ± SD.
[a] p value of significance within groups using the paired t test.

Table 3
Effects of 8 weeks' intake of royal jelly supplements or placebo on biochemical variables in patients with type 2 diabetes

Characteristics	Placebo group		RJ group		p value[a]
	After	Before	After	Before	
Glucose (mmol/L)	8.31±2.2[a]	8.09±2.69	6.60±1.71[b]	7.13±2.47	0.011[c]
ApoA-I (g/L)	1.68±0.24[b]	1.69±0.20	1.91±0.43[b,d]	1.56±0.25	0.013[c]
ApoB (g/L)	1.09±0.25[d]	0.86±0.20	1.08±0.20[d]	0.88±0.22	0.65
ApoB/ApoA-I	0.6±0.1[d]	0.51±0.14	0.58±0.1	0.57±0.17	0.044[a]

Note: Data are means ± SD.
[a] p value denotes the significance of the difference between the change from baseline on royal jelly vs. placebo.
[b] Denotes significant a difference between groups (RJ and placebo) at the end of the study, p<0.05.
[c] Denotes significant mean change of the variable from the baseline between groups (RJ and placebo) using an independent t test.
[d] Denotes significant difference within group (p<0.05) using a paired t test.

may be beneficial in weight management in patients with diabetes (21). In healthy subjects, a clinical study demonstrated that RJ significantly affects serum glucose levels (22). In an animal study, Zamami et al showed that RJ reduced the index of insulin resistance (HOMA-IR) but not blood glucose levels in rats (23). It has been shown that insulin resistance is associated with changes in oxidative stress levels. RJ has protective effects against oxidative stress because of its antioxidant peptides, so RJ can ameliorate insulin resistance via its antioxidant effect (23). It has been supposed that antioxidative peptides derived from RJ proteins hydrolyze with protease N to produce the strong antioxidative activity. In line with another study, which showed the serum glucose-lowering effect of RJ, our results also showed the same results in people with diabetes. It has been shown that RJ contains biologically active substances that cause insulin-like activity (22).

Dietary protein has been shown to affect plasma cholesterol concentrations (16). The large number of proteins in RJ may decrease plasma levels of cholesterol. Kamakura et al showed that RJ reduces the levels of the cholesterol biosynthesis enzyme and influences the activity of the hepatic lipoprotein receptors that regulate very low lipoprotein uptake in mice (15). In addition, RJ has estrogen-like effects that may reduce the concentration of plasma cholesterol and low-density lipoprotein in vitro and in vivo (24). The unsaturated fatty acids in RJ, such as trans-10-hydroxy-2-decenoic acid, essential fatty acids, arachidonic acid and RJ acid probably regulate lipid metabolism (24). However, there was no significant difference in ApoB between the 2 groups at the end of study, but mean differences in ApoB and ApoA-I were lower, and ApoA-I levels were higher in the RJ group than in the placebo group. This could have an impact on lowering the risk for cardiovascular disease in patients with diabetes because plasma concentration of atherogenic lipoprotein particles measured by ApoB is a more strongly predictive factor in the development of coronary heart disease than the cholesterol carried by these particles, which are measured by non-high-density lipoprotein (non-HDL) cholesterol (25). ApoB is significantly higher in people with diabetes than in healthy people (26,27). On the other hand, increases in ApoA-I compared with decreases in ApoB are more important for reducing risks for coronary heart disease; and also, ApoB/ApoA-I is the strongest predictor of cardiovascular disease compared to LDL-c and HDL-c (27). According to our knowledge, no studies have been made of ApoB or ApoA-I and the effects of RJ in people with diabetes.

Limitations

Regarding the limitations of our study, we can point to the duration of supplementation (8 weeks), and it would be better if we could have the possibility of continuing the intervention up to 12 weeks, which was impossible because subjects had time limitations to come to the study centre, and compliance was limited if we extended the time. Further investigations are needed to determine the times and effective dosages of RJ supplementation.

Conclusions

The present study suggests that RJ is a functional food that has benefits for people with type 2 diabetes. The present study suggests that RJ intake may have desirable effects on serum glucose and Apo A-I and may decrease cardiovascular risks in people with type 2 diabetes. More research is needed to find the effects of RJ mechanisms on lipoproteins.

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