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Quercetin Supplementation has no Synergetic Effect with High-Intensity Interval Training in Ameliorate Lipid Profile in Male Diabetic Rats

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Abstract

Background: In diabetic patients, lipid profile (LP) management is crucial. Quercetin (QUE), as an antioxidant supplement, has received a great deal of attention in improving the LP.

Objectives: The current study aimed to investigate the simultaneous effect of high-intensity interval training (HIIT) and QUE on LP in male diabetic rats.

Methods: Fifty Wistar male rats were randomly assigned to healthy control (HC; n = 10), diabetic control (DC; n = 10), high-intensity interval training (HIIT; n = 10), quercetin supplement (QS; n = 10), high-intensity interval training and quercetin (HIIQ; n = 10). QUE was given (20 mg/kg/d) to the animals daily for six weeks. HIIT has performed five sessions per week for six weeks in 8-10 sets with 85 - 65% of the maximum oxygen consumption (VO2max) on the treadmill. Blood samples were taken directly from the animal's heart 48 hours after the last training session, and high-density lipoprotein (HDL-C), low-density lipoproteins (LDL-C), triglycerides (TG) cholesterol (CHOL), and fasting blood glucose (FBS) were measured in the serum. To analyze the data, two-way analysis of variance (ANOVA) and Tukey's post hoc test were used.

Results: There was no significant difference between HIIQ with HIIT, QS in LDH-C and LDL-C ($P > 0.05$). Also, no significant difference was seen between HIIT, QS, and HIIQ in TG concentration after intervention ($P > 0.05$). CHOL was significantly lower in HIIT than QS ($P = 0.001$), while there was no significant difference between the HIIQ with QS ($P > 0.05$). Also, there was no significant difference between QS and HIIQ in FBS ($P > 0.05$).

Conclusions: It seems that high-intensity interval training and quercetin alone can be effective in improving lipid profile. However, quercetin does not have a synergetic effect with high-intensity interval training in ameliorating lipid profile in diabetic male rats.

Keywords: Exercise Training, Antioxidant, HDL, LDL, Metabolic Disorder

1. Background

Diabetes is the most common progressive metabolic disease in the world, which is responsible for about four million deaths a year (1). The importance of diabetes management is due to its high prevalence and the many complications that occur. Various factors, such as unhealthy lifestyle and genetics, are involved in diabetes development (2), but a sedentary lifestyle is considered the main risk factor for type 2 diabetes and its complications (3). On the other hand, a sedentary lifestyle increases the risk of obesity and type 2 diabetes (4). Diabetes also predisposes patients to many other diseases, such as cardiovascular disease (CVD). In diabetic patients (DP), in addition to the fasting blood sugar (FBS) increment, lipid profile (LP) disorders are also observed (5), which is the main factor in CVD progression (6). Low-density lipoprotein (LDL) and triacylglycerol (TG) increment, as well as total plasma cholesterol (CHOL), are the main factors that affect vascular damage. In contrast, high-density lipoprotein (HDL) has a beneficial effect on vascular wall health (7). However, it has been reported that in DP, the CVD severity due to LP is much higher than in healthy individuals (8). Accordingly, it is necessary for LP management in DP along with FBS. Among the approaches to improve the LP is drug usage and exercise training (ET).

The role of ET and physical activity (PA) in LP regulation

in healthy individuals (HI) is well understood (9). ET and PA level increments have been reported to adequately reduce body fat percentage (BF %) and improve LP (10). However, this mechanism may be slightly different in DP due to metabolic disorders in DP. On the other hand, oxidative stress (OS) in DP is much higher than in HI (11) and leads to increased insulin resistance (IR), exacerbation of LP disorders, and high blood glucose (12). Accordingly, the role of antioxidant supplements (AS) in DP is very important because OS and dysfunction of Redox in DP increase the need to strengthen antioxidant systems (13). Also, the use of AS to manage blood sugar and OS reduction in DP has always been recommended (14).

Quercetin (QUE) is one of the polyphenols and flavonoids found in many fruits, vegetables, leaves, seeds, and grains. It has antioxidant, anti-cancer, anti-viral, and anti-inflammatory properties and can reduce OS by reducing free radicals (15). Nowadays, the use of high-intensity interval training (HIIT) as a systematic training program has received a lot of attention. Intense interval training is effective in improving lipid profiles, improving insulin resistance, and reducing inflammation (16). Despite the positive effect of HIIT, researchers have always considered the use of antioxidant and herbal supplements to enhance the effect of exercise training.

In this regard, Garelnabi et al. (2014) reported that QUE supplementation, along with running on a treadmill for 30 days, could improve cholesterol in mice (17). Also, it has been reported that QUE increased lipolysis after swimming in mice (18). On the contrary, there is evidence that does not suggest any effect of QUE supplementation on plasma lipids (19). Despite such controversies, the effectiveness of HIIT with QUE supplementation on lipid profile has not been studied, and there is no sufficient information.

2. Objectives

The present study aimed to investigate the effect of six weeks of HIIT and QUE supplementation on LP in male diabetic rats and illuminate whether QUE with HIIT has a synergistic effect of improving LP or not in male diabetic rats.

3. Methods

3.1. Animals and Study Procedure

Fifty male Wistar rats aged (10 - 12 weeks, 250 - 350 gr) were procured from the Pasteur Institute of Tehran and, after two weeks of adaptation to the new environment, were randomly assigned to healthy control groups (HC; n=10), diabetic control (DC; n=10), high-intensity interval training (HIIT; n = 10), QUE supplement (QS; n = 10), high-intensity interval training, and QUE (HIIQ; n = 10) groups. All animals in the laboratory were kept in a quiet and non-stressful environment (temperature 23 ± 3°C, 50% humidity, and low noise) and light-dark in the cage for 12 hours. The rats had free access to tap water and compressed food for mice (Pars Livestock Feed Company).

The present study was carried out with the approval of the ethics committee of Islamic Azad University, Sanandaj branch, with the ID number (IR.IAU.SDJ.REC.1400.027), and all the ethical principles of working with laboratory animals were observed.

3.2. Diabetes Induction

It took approximately two weeks for rats to adjust to the laboratory environment. After two weeks, an intraperitoneal injection of low-dose streptozotocin (STZ) 37 mg /kg in 0.1 mM citrate buffer and pH 4.5 was applied after six hours of fasting. Seventy-two hours after STZ injection, blood glucose concentration was measured by glucometer (Boehringer Mannheim UK Ltd), and animals with glucose concentrations between 150 - 350 mg/dl were considered diabetic. Also, the rats' weights were measured before the intervention, and the measurements were repeated at the end of the HIIT protocol by digital scales (Bionic Mobin, Iran).

3.3. Quercetin Supplementation

Rats in the QS and HIIQ group received 20 mg/kg/day QUE (Sigma-Aldrich, St. Louis, USA) by oral gavage for six weeks. QUE was dissolved in dimethyl sulfoxide (DMSO) 2% before the gavage.

3.4. High-Intensity Interval Training

High-intensity interval training (HIIT) was performed five sessions per week for six weeks on a treadmill (Technic Azma Co., Tabriz, Iran). At the beginning of the exercise training (ET) protocol, the animals were familiarized with HIIT for 10 minutes per day for one week at a speed of 10 m/min. After familiarization, the main protocol was developed according to Table 1 (20).

Before the ET, the rats performed a warm-up exercise program for 10 min at a speed of 10 m/min. A 10-minute cool-down program was also included after each session.

The first week of HIIT was done in eight sets at a speed of 25 m/min (65% VO2max) with two min recovery gaps between sets at 10 m/min intensity. For more HIIT program details, see Table 1.

Table 1. High-Intensity Interval Training Details

Weeks	Session/Week	Sets (no)	Speed (m/min)	VO2max (ml/kg.min) (%)	Grade (%)	Rest Interval Between Sets (s)	Speed (m/min) Recovery
1	5	8	25	65	5	120	10
2	5	10	25	65	10	120	10
3	5	10	28	70	10	120	10
4	5	10	28	70	10	120	10
5	5	10	32	75	10	120	10
6	5	10	35	80 - 85	10	120	10

3.5. Laboratory Methods and Biochemical Assays

Two days after the last ET session, 2cc of blood samples were drawn directly from the animals' hearts. Blood samples were centrifuged at 2200 - 2500 rpm for 10 minutes to isolate the serum. The obtained serum was carefully separated by a sampler and stored inside the Eppendorf micropipette tubes until freezing in biochemical tests at -70°C. High-density lipoprotein (HDL-C), low-density lipoproteins (LDL-C), triglycerides (TG), cholesterol (CHOL), and fasting blood sugar (FBS) were measured using spectrophotometry with special kits (Pars Azmoun, Iran). LDL was calculated using the formula (LDL (mg/dl) = TC- (HDL + TG / 5).

3.6. Statistical Analysing

Data were presented as mean ± standard deviation (Mean± SD). The variables' normality distribution was evaluated using the Kolmogorov-Smirnov test. Also, a two-way analysis of variance and Turkey post hoc test were used to test the hypotheses at a significance level of $P \leq 0.05$. Partial eta-squared ($\eta p2$) was used to determine the effect size of HIIT and QUE supplementation. All calculations were performed using SPSS statistical software version 27.

4. Results

Rats' physiological characteristics before intervention are presented in Table 2.

4.1. Fasting Blood Glucose

We found that there was a significant difference between groups in FBS [(F: 47.6; P = 0.001), $\eta p2 = 0.332$, $\eta p2 = 0.521$ for HIIT and QUE, respectively]. FBS levels were significantly higher in the HIIT group than QS (P = 0.001) and HIIQ (P = 0.002) groups. However, there was no significant difference between QS and HIIQ ($P > 0.05$) (Table 3).

4.2. High-Density Lipoprotein

There were significant differences between the groups in HDL-C [(F: 8.8; P = 0.001), $\eta p2 = 0.227$, $\eta p2 = 0.239$ for HIIT and QUE, respectively]. There was no significant difference between the intervention groups ($P > 0.05$).

4.3. Low-Density Lipoproteins

There were significant differences between groups in HDL-C [(F: 6.7; P = 0.001), $\eta p2 = 0.091$, $\eta p2 = 0.072$ for HIIT and QUE, respectively]. No significant difference was seen between the QS, HIIT, and HIIQ groups ($P > 0.05$).

4.4. Triglycerides

There was a significant difference between groups in TG [(F: 8.9; P = 0.001), $\eta p2 = 0.257$, $\eta p2 = 0.143$ for HIIT and QUE, respectively]. There was no significant difference between HIIT, QS, and HIIQ in TG concentration after intervention ($P > 0.05$).

4.5. Cholesterol

Results showed that there were significant differences between groups in CHOL [(F: 9.1; P = 0.001), $\eta p2 = 0.081$, $\eta p2 = 0.189$ for HIIT and QUE, respectively]. There were no significant differences between the HIIQ and QS groups ($P > 0.05$) (Table 3).

5. Discussion

The present study aimed to investigate the synergistic effects of QUE supplementation and HIIT on LP changes and FBS levels.

We found that FBS levels were significantly higher in HIIT than in QS and HIIQ, but there was no significant difference between QS and HIIQ.

This indicates that, firstly, supplementation with quercetin is more effective than HIIT in reducing FBS levels. Secondly, the combination of QUE and HIIT could decrease FBS levels, while there was no advantage in QUE supplementation alone. Mechanisms of quercetin action

Table 2. Rats' Physiological Characteristics Before Intervention [a]

Variables	HC (n = 10)	DC (n = 10)	HIIT (n = 10)	QS (n = 10)	HIIQ (n = 10)
Age (week)	10 - 12	10 - 12	10 - 12	10 - 12	10 - 12
Body weight (gr)	305 ± 45	320 ± 48	312 ± 51	302 ± 41	298 ± 44

Abbreviations: HC, healthy control; DC, diabetic control; HIIT, high-intensity interval training; QS, quercetin supplement; HIIQ, high-intensity interval training and quercetin.
[a] Results are expressed as mean ± SD (n = 10) in each group.

Table 3. Variables Concentration After the Intervention [a, b]

Variables	HC (n = 10)	DC (n = 10)	HIIT (n = 10)	QS (n = 10)	HIIQ (n = 10)
FBS (mg/dl)	85.5 ± 13.5[c]	260 ± 31.4[d]	193.8 ± 41.3[c, d]	136.4 ± 13.5[c, d]	127.8 ± 17.3[c, d]
CHOL (mg/dl)	66.4 ± 3.4	76.5 ± 5.1	65.8 ± 6.3[c]	83.2 ± 8.6[c, d]	67.7 ± 8.4
HDL-C (mg/dl)	39.4 ± 2.4[c]	32.8 ± 2.2	34.1 ± 3	38.2 ± 1.8[c]	42.5 ± 6.2[c]
LDL-C (mg/dl)	16.7 ± 2.8	32.1 ± 6.4[d]	24 ± 8.5	31.7 ± 7.9[d]	21.8 ± 6.4
TG (mg/dl)	51.4 ± 5.8	58 ± 7.9	38.1 ± 7.9[c, d]	44.8 ± 9.7[c]	37.8 ± 6.4[c, d]

Abbreviations: HC, healthy control; DC, diabetic control; HIIT, high-intensity interval training; QS, quercetin supplement; HIIQ, high-intensity interval training and quercetin.
[a] P-value is for ANOVA test.
[b] Results are expressed as mean ± SD.
[c] $P \leq 0.05$ when compared with DC.
[d] $P \leq 0.05$, when compared to HC.

are pleiotropic and involve the inhibition of intestinal glucose absorption, insulin secretory improvement, and insulin-sensitizing activities, as well as improved glucose utilization in peripheral tissues such as skeletal muscles (21). QUE activates adenosine monophosphate kinase (AMPK) in skeletal muscles, which in turn stimulates GLUT4 receptors in the cell membrane (22). Therefore, after the intervention, FBS was expected to decrease due to QUE supplementation. In contrast, exercise training (ET) is a potent stimulator of GLUT4 expression, which improves insulin action (23). Therefore, it seems that effective mechanisms related to blood sugar regulation caused by QUE act better than HIIT (24).

It is unclear why the combination of HIIT and QUE did not improve FBS. However, it seems that the exercise intensity and QUE intestinal absorption also influence its effectiveness (22). These synergetic positive effects of ET and supplements may not always be in the same direction, and sometimes, the adaptive effects might not lead to good results (25, 26). However, the interplay between antioxidants and ET remains poorly understood (26).

The results showed there was no significant difference between the intervention groups (HIIT, QS, and HIIQ) and HC in HDL-C (Table 3). This means that the intervention with QUE and HIIT both were able to improve HDL-C levels close to baseline values in healthy rats (HC), as HDL levels decreased after diabetes induction.

There was no significant difference between HIIQ with HIIT and QS in HDL-C. This shows that, firstly, QUE and HIIT do not have a synergistic effect in improving HDL-C. Secondly, the HIIT effect is not more than QUE in improving HDL-C. Moreover, this indicates that QUE could not increase this lipoprotein better than HIIT, although QUE supplementation with HIIT was as effective as QUE supplementation alone. However, since there was no difference between HIIQ with QS with HIIT, it seems that the synergistic effect of QUE and HIIT was not greater than the effects of HIIT and QUE. To our knowledge, no studies examined the effect of QUE along with HIIT on HDL-C. However, in a similar study, it was reported that HIIT acted synergically with probiotic supplementation to improve HDL-C in ovariectomized rats (27).

The results also showed that there was no significant difference between HIIT, QS, and HIIQ in improving LDL-C. This shows that their combination had no advantage over HIIT or QUE in decreasing LDL-C concentrations.

In general, LDL-C and HDL-C levels were not improved by the simultaneous effect of QUE and HIIT (there was no significant difference between HIIQ than QS/or HIIQ). LP disorders in DP are characterized by an increase in LDL-C and a decrease in HDL-C levels, which is one of the most important causes of CVD. In the present study, HIIT had no effect on changes in LDL-C and HDL-C compared with the DC (Table 3). Contrary to the findings of the present study, it has been reported that 16 weeks of high-intensity interval training can increase HDL-C in both diabetic and

non-diabetic patients; However, LDL-C was not affected by intense interval training (28). We also previously reported that elastic resistance training was able to significantly increase HDL-C in healthy individuals and cause a decrease in LDL-C (9). Basal LDL-C and HDL-C levels appear to be effective in the effect of exercise training, as one study in human samples reported that endurance exercise training, while improving the lipid profile, had the best effect when the HDL-C/LDL-C ratio was low (29).

In the present study, it was observed that the combination of QUE and HIIT did not improve HDL-C and LDL-C. We used 20 mg/kg/body weight/day of the supplement in the supplement groups. In a systematic review and meta-analysis, it is reported that QUE administration did not affect plasma lipid levels in overweight and obese individuals. However, it significantly reduced LDL-cholesterol levels at doses of $\geq$250 mg/day and a total dose of $\geq$14000 mg. This means that QUE doses may influence profile behavior after QUE supplementation (30). It has been reported that high doses of QUE could regulate plasma cholesterol profile and elevate HDL-cholesterol, while low doses are not effective (31).

It has been reported that grape seed extract supplementation as an antioxidant could improve HDL-C and LDL-C in diabetic rats induced by streptozotocin induction (32).

In the current study, we found that only HDL-C was improved by QS (QS vs. DC), and LDL-C could not be affected by QUE and HIIT intervention (Table 3). This suggests that high-intensity interval training and the QUE can only increase HDL-C and do not lower LDL-C. This means that the negative effects of LP disorder in DP are only improved and cannot reduce the adverse effects at the same time. This may be due to the fact that LDL-C is less affected by ET (33).

No significant difference was observed between HIIQ, HIIT, and QS in the TG. This shows that neither intervention method is superior to the other in decreasing TG. However, we found that QUE could ameliorate TG (QS vs. DC: Table 3). It has been shown that QUE can reduce triglyceride synthesis and acetyl-CoA carboxylase activity in rat hepatocytes (34). Therefore, this can be a potential underlying mechanism contributing to hypotriglyceridaemia during QUE supplementation.

It was observed that in the QS, cholesterol levels were significantly higher compared to HIIT and HIIQ.

It was also observed that CHOL in the HIIT was significantly lower than DC. Overall, this indicates there is no additional advantage in QUE supplementation on TG and CHOL improving in diabetic rats. Contrary to the results of the present study, Yang and Kang reported that QUE (30 mg/kg) reduced the serum lipids levels (TC, TG, LDL, and VLDL) (35). It can be argued that the length of the supplementation period and the dose may have been influential in this study. It has been reported that QUE (0.05%) reduced body weight, visceral fat, blood glucose, and insulin in C57BL/6J mice fed a high-fat diet for 20 weeks but not 8 weeks (36). One of the limitations of the current study is that important antioxidant factors such as superoxide dismutase, glutathione peroxidase, and total antioxidant capacity were not measured.

Because QUE is an antioxidant, measuring the changes in the mentioned variables may help interpret the results.

5.1. Conclusions

It seems that HIIT and quercetin supplementation alone can be effective in LP improvement and FBS management in diabetic rats; however, QUE has not had a synergetic effect with high-intensity interval training in ameliorating lipid profiles in diabetic male rats. It is recommended to evaluate inflammatory factors, oxidative stress, and lipid profile variables together to gain a better understanding. Using higher doses of quercetin along with high-intensity interval training can help to understand the synergistic effects of quercetin with intense interval training.

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Footnotes

Authors' Contribution: Esrafil Faraji: Data collection and contribution to the design and implementation of the research; Kamal Azizbeigi: Designing research, writing manuscript, and supervising the research; Khalid Mohammadzadeh Salamat: Statistical analysis; Zaher Etemad: Data collection and implementation of the research.

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