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Effects of daily quercetin-rich supplementation on cardiometabolic risks in male smokers

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Abstract

Limited information from human studies indicates that dietary quercetin supplementation influences blood lipid profiles, glycemic response, and inflammatory status, collectively termed cardiometabolic risks. We tested the hypothesis that quercetin-rich supplementation, derived from onion peel extract, improves cardiometabolic risk components in healthy male smokers in a randomized, double blinded, placebo-controlled parallel design. Randomly assigned subjects were instructed to take either the placebo (n = 43) or 100 mg quercetin capsules each day (n = 49) for 10 weeks. Anthropometric parameters and blood pressure were measured, and blood lipids, glucose, interleukin-6, and soluble vascular cell adhesion molecule-1 (sVCAM-1) were determined at baseline and after 10 weeks of quercetin supplementation. Quercetin-rich supplementation significantly reduced serum concentrations of total cholesterol ($P < 0.05$) and LDL-cholesterol ($P < 0.01$), whereas these effects were not shown in the placebo group. Furthermore, significant increases were observed in serum concentrations of HDL-cholesterol both in the placebo ($P < 0.005$) and quercetin-rich supplementation group ($P < 0.001$); however, changes in HDL-cholesterol were significantly greater in subjects receiving quercetin-rich supplementation than the placebo. Both systolic ($P < 0.05$) and diastolic blood pressure ($P < 0.01$) decreased significantly in the quercetin-rich supplementation group. Glucose concentrations decreased significantly after 10 weeks of quercetin-rich supplementation ($P < 0.05$). In contrast, no effects of quercetin-rich supplementation were observed for the inflammatory markers-IL-6 and sVCAM-1. Daily quercetin-rich supplementation from onion peel extract improved blood lipid profiles, glucose, and blood pressure, suggesting a beneficial role for quercetin as a preventive measure against cardiovascular risk.

Key Words: Quercetin, onion, cardiometabolic risks, dyslipidemia, inflammation

Introduction

Data from epidemiological and clinical studies have indicated a relationship between dietary intake of flavonoids and reduced risk of cardiovascular disease [1-4], which is mainly ascribed to the compound's *in vitro* antioxidant and anti-inflammatory effects [5]. Onions are a major source of dietary flavonoids including quercetin, rutin, and myricetin. In particular, quercetin has been suggested as the most potent compound displaying antioxidant effects [6]. Quercetin scavenges oxygen free radicals, inhibits lipid peroxidation, and quenches 8-hydroxydeoxyguanosine formation by ultraviolet light irradiation and the Fenton reaction [7], which subsequently protects cellular macromolecules against oxidative damage. Quercetin also inhibits the *ex vivo* resistance of low-density lipoprotein (LDL) to oxidation and resistance to DNA strand breakage induced by hydrogen peroxide in human lymphocytes [8,9].

A number of experimental and *in vitro* studies have reported that quercetin possesses several other beneficial activities, including hypolipidemic [10-12], antihypertensive [13], anti-inflammatory [14,15], and antithrombotic actions [16]. However, as reported in a recent review [17], the effects of dietary quercetin on cardiovascular disease biomarkers in human studies have been inconsistent based on study design, type of compound (pure or food source), study duration, dosage, and the phenotypes of the study subjects. Moreover, limited information is available from human studies as to whether dietary quercetin supplementation influences blood lipid profiles, glycemic response, and inflammatory status, collectively termed cardiometabolic risks.

Therefore, we comprehensively tested the hypothesis that quercetin-rich supplementation, derived from onion peel extract, influences cardiometabolic risk components including blood pressure, blood lipid profiles and the concentrations of glucose and inflammatory cytokines in male smokers who confer relatively higher risks for cardiovascular disease. The results will provide additional information on the effects of dietary quercetin supplementation on cardiometabolic risk components as a preventive measure.

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Subjects and Methods

Study subjects

The total study population consisted of 92 healthy volunteers. The inclusion criteria were male smokers in the age range of 30-60-years. All subjects were healthy, and those with documented type 2 diabetes mellitus, hypertension, thyroid disorders, malabsorption syndrome, or any type of coronary heart disease were excluded. Furthermore, subjects who were taking any medications known to influence the variables to be studied were excluded. Body mass index (BMI) was calculated as weight in kg divided by height in meters squared; waist circumference was also measured. Blood pressure was measured from the left arm in seated patients with an automatic blood pressure monitor (TM-2654, A & D, Tokyo, Japan) after a 20 min rest. Two measurements were taken at least 5 minutes apart, and the mean was used for analysis. The subjects were given written informed consent, and the institutional review board at Hannam University approved the study protocol.

Study protocol and blood collection

This study consisted of 7 days of quercetin depletion followed by a 10-week supplementation period in a randomized, double blinded, placebo-controlled parallel design. During the quercetin depletion period, all subjects were requested to restrict their consumption of quercetin to avoid any influence on the study results. These food ingredients included onions, apples, red wine, tea, biological and freshly pressed fruit juices, berries, grapes, cherries, raisins, parsley, broccoli, cabbage, beans, and tomatoes. Subsequently, the subjects were randomly assigned to either a placebo group (n = 43) or a quercetin-rich supplementation group (n = 49). The subjects were instructed to take either four capsules of placebo (dextrin) or four quercetin capsules per day containing 100 mg quercetin dihydrate and 128 mg other mixed flavonoids (composition unknown). To prepare the quercetin-rich supplementation capsules, onion peels purchased from Nonghyup located in Changnyeong, were washed three times in tap water and extracted with a 60% aqueous ethanol solution (50℃, 3 hrs) in a extractor (1 kL, Hansung F & C Co., Ltd., Seoul, Korea). The extracts were filtered with a filter press (Hankook Industry Co. Ltd., Seoul, Korea), the filtrates were concentrated to 2.4° Brix in a vacuum concentrator (1 kL, Hansung F & C Co), and then the concentrates were processed to powder with a freeze dryer (SFDTS-200 kg Samwon Industry Co., Ltd. Seoul, Korea). Finally, the powder was adjusted to contain 100 mg quercetin/g dextrin (Samyang Co., Seoul, Korea). The subjects were instructed to maintain their usual patterns of dietary intake during the study. Compliance was monitored through biweekly phone calls for capsule counts, and a nutritionist checked for changes in usual dietary patterns at the end of the study. Additionally, the subjects' usual dietary intakes were assessed both at baseline and at 10 weeks after quercetin-rich supplementation using a 24-h recall method. Nutrient intake levels were determined as mean values from a 3-day food record using CAN pro (Korean Nutrition Society, Seoul, Korea) based on the food composition table of the National Rural Living Science Institute in Korea and other published data [18,19]. Venous blood samples were collected from the forearm in EDTA-treated and plain tubes after a fasting period, both at baseline and at 10 weeks after the intervention.

Serum lipid, lipoprotein, and glucose concentrations

Serum cholesterol, LDL cholesterol, and HDL cholesterol were measured with commercially available kits (Choongwae, Seoul, Korea) using enzymatic methods. Serum triglyceride was analyzed using a total glycerol test kit (Roche, Basel, Switzerland). All measurements were performed on a Hitachi 747 autoanalyzer (Hitachi Ltd, Tokyo, Japan). Fasting serum glucose concentrations were measured by the glucose oxidase method using a Beckman glucose analyzer (Beckman Instruments, Irvine, CA, USA).

Plasma IL-6 and sVCAM-1 concentrations

Plasma interleukin-6 (IL-6, R & D Systems, Minneapolis, MN, USA) and soluble vascular cell adhesion molecule-1 (sVCAM-1, R & D Systems) were measured using an enzyme-linked immunoassay, according to the manufacturer's instructions.

Statistical analysis

SPSS 12.0 (SPSS Inc, Chicago, IL, USA) was used for the statistical analysis. The data are presented as means ± SD. Each variable was examined for a normal distribution, and abnormally distributed variables were log-transformed. Pearson's correlation coefficients were used to evaluate relationships between variables. For the within-group test, we conducted paired *t*-tests for the biochemical parameters before and after the 10-week intervention. For the between-group test, differences in clinical parameters between the two groups were analyzed using the Student's *t*-test. P values < 0.05 were considered statistically significant.

Results

Subject characteristics

All 92 male subjects [mean age, 44.3 yrs; placebo group, n = 43; quercetin-rich supplementation group, n = 49] completed the study (Table 1). The mean age of the quercetin-rich supplementation group was greater than that of the placebo group; although the difference was small, it was significant. At the start of the study, BMIs were similar but waist circumferences were different between the two groups. Compliance was high

Table 1. Age and anthropometric measurements in the subjects before and after 10 weeks of quercetin supplementation

	Placebo (n = 43)			Quercetin-rich supplementation (n = 49)			*P*-value[2]
	Baseline	10 wks	*P*-value[1]	Baseline	10 wks	*P*-value[1]	
Age (yrs)	42.4 ± 8.2 [23-55]			46.1 ± 7.1 [32-62]			< 0.05
Body mass index (kg/m^2)	24.9 ± 2.8	24.7 ± 2.9	NS	24.7 ± 3.0	24.8 ± 2.9	NS	NS
Waist circumference (cm)	89.6 ± 5.7	88.1 ± 6.5	< 0.05	80.4 ± 7.2	79.9 ± 6.3	NS	< 0.001

Values are mean ± SD.
[1] *P*-values for the comparison between baseline and the 10 wk intervention were obtained using paired *t*-tests in each group.
[2] *P*-values for comparison between the placebo and quercetin-rich supplementation groups at baseline were made using the Student's *t*-test.

Table 2. Blood lipid profile and glucose measurements before and after 10 weeks of quercetin supplementation

	Placebo (n = 43)			Quercetin-rich supplementation (n = 49)			*P*-value[2]
	Baseline	10 wks	*P*-value[1]	Baseline	10 wks	*P*-value[1]	
Total cholesterol (mg/dL)	194.3 ± 36.4	196.2 ± 37.5	NS	193.5 ± 32.1	185.2 ± 31.3	< 0.05	NS
Triglyceride (mg/dL)	185.0 ± 91.6	171.0 ± 121.1	NS	163.5 ± 87.7	156.9 ± 99.3	NS	NS
HDL-cholesterol (mg/dL)	45.0 ± 5.3	47.3 ± 6.5	< 0.005	44.3 ± 6.9	51.4 ± 6.5	< 0.001	NS
LDL-cholesterol (mg/dL)	115.6 ± 24.7	116.9 ± 25.6	NS	113.2 ± 20.3	106.5 ± 19.1	< 0.01	NS
Glucose (mg/dL)	109.9 ± 28.5	109.4 ± 24.5	NS	108.3 ± 18.1	104.1 ± 17.5	< 0.05	NS

Values are mean ± SD.
[1] *P*-values for comparison between baseline and the 10 wk intervention were obtained using paired *t*-tests in each group.
[2] *P*-values for comparing between the placebo and quercetin-rich supplementation groups at baseline were made using the Student's *t*-test.

Table 3. Blood pressure and inflammatory cytokine concentrations before and after 10 weeks of quercetin supplementation

	Placebo (n = 43)			Quercetin-rich supplementation (n = 49)			*P*-value[2]
	Baseline	10 wks	*P*-value[1]	Baseline	10 wks	*P*-value[1]	
Systolic blood pressure (mmHg)	135.5 ± 11.3	132.5 ± 12.7	NS	132.9 ± 14.9	129.3 ± 13.3	< 0.05	NS
Diastolic blood pressure (mmHg)	86.9 ± 10.4	84.0 ± 9.2	NS	88.7 ± 9.9	85.5 ± 10.0	< 0.01	NS
IL-6 (pg/mL)	1.25 ± 0.44	1.31 ± 0.48	NS	1.26 ± 0.44	1.29 ± 0.44	NS	NS
sVCAM -1 (ng/mL)	4.78 ± 0.34	4.72 ± 0.28	NS	4.85 ± 0.35	4.81 ± 0.29	NS	NS

Values are mean ± SD.
IL-6: interleukin-6; sVCAM -1 : soluble vascular cell adhesion molecule-1
[1] *P*-values for comparison between baseline and 10-wk intervention were made using the paired *t*-test in each group.
[2] *P*-values for comparing the placebo and the quercetin-rich supplementation group were made at baseline using the Student's *t*-test.

and the subjects took 96% of the provided capsules with no differences between the groups. No adverse effects due to quercetin intake were reported. At baseline, the estimated average total caloric intake of all subjects was 2,040 kcal (% CHO:% PRO:% FAT = 55:17:25), and at 10 weeks of intervention it was 2,002 kcal (% CHO:% PRO:% FAT = 54:18:23). As shown in Table 1, a significant change in waist circumference was observed in the placebo group ($P < 0.05$), whereas this result was not shown in the quercetin-rich supplementation group.

Lipid and lipoprotein concentrations

Table 2 describes the changes in lipids and lipoproteins after 10 wk of quercetin supplementation. Serum concentrations of total cholesterol ($P < 0.05$) and LDL-cholesterol ($P < 0.01$) decreased significantly; however, these effects were not shown in the placebo group. Additionally, significant increases in serum concentrations of HDL-cholesterol ($P < 0.001$) were observed after 10 weeks of quercetin-rich supplementation, whereas significant increases in HDL-cholesterol were also observed in the placebo group ($P < 0.005$). However, the changes in HDL-cholesterol in the placebo and quercetin-rich supplementation groups (2.3 ± 4.9 vs. 7.1 ± 5.1 mg/dL, $P < 0.001$) were significantly greater in the quercetin-rich supplementation group than the placebo group. In contrast, no differences were observed in serum TG concentrations in the placebo and the quercetin-rich supplementation groups.

Blood pressure and glucose concentrations

Serum concentrations of glucose decreased significantly ($P < 0.05$) after 10 weeks of supplementation, whereas these effects were not shown in the placebo group (Table 2). Furthermore, both systolic ($P < 0.05$) and diastolic blood pressure ($P < 0.01$) dropped significantly in the quercetin-rich supplementation group (Table 3).

Inflammatory cytokines

No significant changes in the concentrations of IL-6 and sVCAM-1 were observed after 10 weeks of quercetin-rich supplementation (Table 3).

Discussion

Cardiometabolic risks represent a constellation of cardiovascular and metabolic abnormalities that interact to increase the risk for morbidity and mortality from cardiovascular disease and type 2 diabetes mellitus [20,21]. The prevalence of cardiometabolic risks has been increasing and represents a public health concern; thus, therapeutic lifestyle changes and dietary supplements to modify the cardiometabolic risks need to be encouraged. In the present study, we tested whether quercetin-rich supplementation derived from onion peel extract would favorably influence blood lipids, blood pressure, glycemic response, and inflammatory markers. The results showed that blood pressure and glucose concentrations decreased significantly after 10 weeks of intervention. Additionally, quercetin-rich supplementation reduced serum concentrations of total cholesterol and increased serum concentrations of HDL-cholesterol, whereas no effect was observed for serum TG concentrations. Also, quercetin-rich supplementation did not affect the concentrations of the proinflammatory cytokines IL6 and sVCAM-1.

A prospective study reported that the consumption of dietary quercetin is inversely associated with total mortality and cardiovascular mortality [22]. Among the mechanisms explaining these associations include the effects of quercetin on lipid metabolism [10-12], oxidative stress [6], and inflammation [14,15]. Several plausible pathways as to how quercetin affects lipid metabolism have been suggested by animal studies. Quercetin increases fecal excretion of cholesterol and bile acids, thereby, decreasing serum cholesterol levels and total liver cholesterol content in rats [12]. Kamada *et al.* [11] reported that quercetin glucoside significantly reduces the amounts of total cholesterol, triacylglycerol, and total fatty acids in both the plasma and aortas of rats fed a high cholesterol diet. Additionally, recent experimental data further supports the hypolipidemic effect of quercetin. Gnoni *et al.* [23] demonstrated that quercetin induces reductions in both *de novo* fatty acid and TG synthesis and the resulting decreases in VLDL-TG formation in hepatocytes of normal rats suggests a cardioprotective role for dietary quercetin. These results indicate that quercetin may be involved in lipid metabolism in rats by reducing hepatic fatty acid synthesis and by inhibiting cholesterol biosynthesis [24]. However, the hypolipidemic effects of quercetin in human clinical studies have been inconclusive. Supplements of quercetin-rich onion powder [25], grape juice [26], and grape powder [27] favorably influence blood lipid profiles in humans. In addition to the results of controlled clinical studies, epidemiological evidence indicates that dietary quercetin intake is negatively associated with plasma levels of LDL-cholesterol after adjusting for total energy intake, dietary cholesterol intake, age, and BMI [28]. In contrast, as shown by Egert [29], a 2-week supplementation with quercetin did not change blood lipid concentrations in healthy humans. It was also reported that quercetin supplementation increases plasma quercetin concentrations without any effect on blood lipids [30], which is consistent with very recently published data [31]. In the present study, supplementation with quercetin from onion peel extract for 10 weeks significantly reduced serum concentrations of total cholesterol and LDL-cholesterol and significantly increased serum concentrations of HDL-cholesterol in male smokers. These differences can be attributed to the duration of administration, the characteristics of the study subjects, and the amount and/or food sources of ingested quercetin. It is likely that the 10-week study period was long enough to demonstrate such effects of quercetin on the studied parameters. Furthermore, our subjects were all males and current smokers who were at increased cardiovascular risk. Smokers are under a high and sustained free radical load, which may overwhelm the antioxidant defense system, resulting in oxidative damage [32]. Additionally, the associations between chronic cigarette smoking and hypertension and low grade chronic inflammation and endothelial dysfunction are well recognized [33]. While the exact mechanism by which flavonoids, particularly quercetin, influences the cardiometabolic risk components has not been elucidated, a biological smoking interaction may be working to increase quercetin bioavailability in smokers who confer relatively higher risks for cardiovascular disease. Therefore, it would appear that smokers in particular, may benefit from quercetin supplementation. Currently, the prevalence of smoking is estimated at 47.7% in men. Although the prevalence of smoking among Korean men was 64.9% in 1998 and has since declined, it still remains very high [34]. Considering that smoking is one of the major independent risk factors for cardiovascular disease [35], these results indicate that daily quercetin supplementation provides beneficial effects on blood lipid profile measurements, especially in smokers who are exposed to a high degree of oxidative stress and are particularly susceptible to the development of coronary heart disease.

Several studies have demonstrated that quercetin lowers blood pressure in hypertensive animals [13,36,37], which can be primarily attributed to its ability to modulate oxidative stress. Human intervention studies examining the blood lowering effects of quercetin have reported controversial data. While antihypertensive effects of quercetin have been reported [31,38], other interventions failed to show any positive effect of dietary quercetin supplementation [30], suggesting that a certain degree of hypertension may be required for quercetin to exert a blood pressure lowering effect. Although patients with documented hypertension were excluded, 79% of all subjects were classified as prehypertensive or stage 1 hypertensive in the present study. Consistent with earlier studies [31,38], significant reductions in systolic blood pressure by 3.5 mmHg and diastolic blood pressure by 3.2 mmHg were observed following quercetin-rich supplementation, providing additional information on the antihypertensive effects of quercetin in individuals with relatively high blood pressure.

We found that a 10 week quercetin-rich supplementation significantly decreased serum concentrations of glucose. In animal models, quercetin is effective for preventing a total loss

of β-cell mass [39] and may ameliorate the symptoms of streptozotocin-induced diabetes by decreasing oxidative stress [40]. Furthermore, our results agree with a recent experimental report stating that high dose quercetin administration reduces glucose, dyslipidemia, and hypertension in an obese Zucker rat model of metabolic syndrome [41]. The mechanisms by which quercetin displays antidiabetic effects are not yet fully understood, but it is possible that the antioxidant properties of this compound may be involved in this effect.

In contrast to previous *in vitro* results [14,15], no effects of quercetin-rich supplementation were observed for the proinflammatory cytokines IL-6 and sVCAM-1. This may, in part, be explained by the duration of intervention and/or dosage, which were not enough to elicit measurable effects, so further human studies to examine the anti-inflammatory effects of quercetin are needed.

Taken together, quercetin-rich supplementation from onion peel extract improved dyslipidemia, hypertension, and high glucose concentrations in male smokers but showed no effect on inflammation. Our results support the hypothesis that dietary quercetin from onion may play a cardioprotective role by modulating cardiometabolic risk factors.

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