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Original Article

Effects of Quercetin Supplementation on Oxidative Stress, Blood Pressure, Aerobic Power, Concentric Pathologic Hypertrophy and Cardiac Function in Men with Hypertension and Coronary Artery Disease After Percutaneous Coronary Intervention: a Randomized, Double-Blind Placebo-Controlled Trial

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ABSTRACT

Background and Objectives: The aim of this study was to investigate possible effects of quercetin supplementation on oxidative stress, blood pressure, aerobic power, concentric pathologic hypertrophy and cardiac function in men with hypertension and coronary artery disease (CAD) after percutaneous coronary intervention (PCI).

Materials and Methods: The present study was a randomized, double-blind clinical trial; in which, 24 men with hypertension and CAD after PCI (aged 40–60 years) were participated. Patients were prescribed quercetin (250 mg/day) or placebo for two months. Plasma total antioxidant capacity (TAC) and malondialdehyde (MDA) were assessed using colorimetric methods as well as left ventricular diastolic dysfunction (LVDD), p wave depression (PWD), ejection fraction (EF) and E/A using echocardiography and WRp using Storer-Davise cycle test. Systolic and diastolic blood pressures were measured before and after the intervention. Data were analyzed using ANCOVA and paired-sample T-test.

Results: Supplementation resulted in a significant improvement in oxidative stress reduction (TAC increased and MDA decreased), systolic and diastolic blood pressures, systolic (EF) and diastolic (E/A) functions and aerobic power, compared to pretest and placebo groups following eight weeks of treatment ($p < 0.05$). A small decrease in RWT was seen in quercetin group at the end of intervention with no statistical significance ($p > 0.05$). The RWT was not significantly different between the quercetin and placebo groups ($p > 0.05$).

Conclusions: Quercetin supplementation can improve oxidative stress, blood pressure, left ventricular function and aerobic power in men with hypertension and CAD after PCI. However, this includes no effects on concentric pathologic hypertrophy. Further studies are necessary to verify effects of quercetin supplementation on left ventricular hypertrophy in humans.

Keywords: Quercetin, Oxidative stress, concentric pathologic hypertrophy, Left ventricular function, blood pressure, CAD

Introduction

Cardiovascular disease (CVD) is the leading cause of mortality in world [1]. Coronary artery disease (CAD) or coronary heart disease (CHD) and hypertension are the most prevalent CVDs [1]. Risk factors of CAD (including hypertension) increase oxidative stress [2]. Oxidative stress occurs from an excessive production of ROS that surpasses the antioxidant system [3]. Oxidative stress that causes vascular inflammation initiates the first stage of CAD and leads to pro-atherogenic events such as LDL oxidation, endothelial dysfunction, proliferation and migration of the vascular smooth muscle cells and eventually coronary artery stenosis [2]. Angioplasty or percutaneous coronary intervention (PCI) is a method used to reopen obstructed coronary arteries caused by CADs [1]. Patients experiencing PCI

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typically need minimum preparation, improve within hours and can usually be discharged on the day of intervention [4]. Although procedural death associated with PCI is low (0.1%), many cases experience growing re-narrowing or sudden blockage of the stent [1]. Studies have shown that oxidative stress increases in patients after PCI [5, 6]. Coronary interventions, consisting of balloon angioplasty and coronary stent implantation, are correlated with enhanced vascular levels of reactive oxygen species (ROS) as well as altered endothelial cell and smooth muscle cell functions. Those alter-actions potentially cause thrombosis, restenosis or endothelial dysfunction in treated arteries [5]. Based on the previous studies, levels of oxidative stress and lipid peroxidation in patients with hypertension [7, 8] and coronary stenosis [2, 9–11] and patients after PCI [5, 6] are high and their antioxidant defense enzyme activity is relatively low. Generally, ROS cause CVDs, including hypertension, cardiac hypertrophy, atherosclerosis and heart failure [12]. Furthermore, oxidative stress negatively affects cardiac muscle function and exercise performance through molecular alterations in heart muscles [13] in these patients [7, 8, 14]. Therefore, use of antioxidant supplements with medications may be beneficial in these patients. Bioflavonoids are reported as important antioxidants. In fact, these molecules are phenolic compounds that naturally exist in fruits and vegetables [15]. Nowadays, the value of bioflavonoids in preventing chronic diseases such as CVDs and atherosclerosis is well addressed [1, 3, 15, 16]. Quercetin is one of the most famous bioflavonoids, which is more abundant, compared to other flavonoids [1, 3, 15].

Quercetin has shown antioxidant properties in several studies [3, 17, 18]. Moreover, this compound has shown useful effects on blood pressure in humans and animals [18, 19]. Quercetin is effective in decreasing cardiovascular risk through various approaches such as diminishing oxidative stress and limiting platelet adhesion [15, 16]. Due to antioxidant properties of quercetin and recommendations by pioneer researches to assess effects of this supplement in diseases with high oxidative conditions, use of quercetin is suggested in patients with hypertension and coronary stenosis and patients after PCI [17, 20]. Previous studies have shown that quercetin prescription of 1 g daily is well tolerated by humans [3, 15]. In numerous studies (humans and animals), quercetin supplementation has been reported safe with no adverse symptoms or harmful physiological effects [1, 3, 21, 22]. To the best of the authors' knowledge, effects of quercetin on oxidative stress in patients post PCI has not been studied previously. Although a study has investigated effects of quercetin in patients with CAD, effects of quercetin on oxidative stress have not been investigated in these patients [16]. Therefore, the present study was carried out to investigate effects of quercetin on oxidative stress, blood pressure, aerobic power, concentric pathologic hypertrophy and cardiac function in men with hypertension and CAD after PCI.

Materials and Methods

Subjects: The present study was a randomized, double-blind clinical trial; in which, 24 men with hypertension and CAD after PCI were participated from Bahman Hospital Cardiac Rehabilitation Center, Zanjan, Iran, 2019. The minimum sample size per subgroup was ten during the empirical investigation. In this study, the smallest example size was selected due to the small number of available subjects (n = 60) based on the inclusion criteria. Another reason included difficulties in access to people with hypertension and CAD after PCI. Before commencing the study, written informed consents were received from the participants. Furthermore, study was approved by the Ethics Committee of Sport Sciences Research Institute of Iran and registered in Iranian Registry of Clinical Trials (registration no. IRCT20160927030023N3). Inclusion criteria for the participants were men, aged 40–60 year old, with hypertension (systolic blood pressure/diastolic blood pressure higher than 135/85 mm Hg), concentric myocardial hypertrophy [wall thickness to diastolic end dimension greater than 0.42 (RWT > 0.42)], EF above 30, PCI within the past month and approximately similar drug uses (unchanged types and doses of medications from the last month). The participants were excluded from the study if changing the highlighted criteria, having other diseases that might require special treatments, smoking, having acute illnesses and unwilling to continue the study. The participants continued their treatments during the intervention with the same type and dose of medications.

Design: Participants were categorized into two major groups of quercetin supplement and placebo groups using blocked randomization method. The supplement group used 250 mg/day of quercetin (Solaray, USA) and the placebo group used an identical placebo capsule containing lactose (Daroupakhsh, Iran) for eight weeks. Participants were advised not to change their diets and physical activities during the study. At the beginning of the intervention, participant characteristics, types and doses of medications and histories of past diseases were asked. Weight and height of the participants were measured using standard protocol with light clothes with no shoes to the nearest 0.5 kg and 0.5 cm and then body mass indices (BMI) were calculated. The body fat proportion was calculated using bioelectrical

impedance analysis (X-Contact 356; Jawon Medical, Republic of Korea). Blood pressure was measured twice at sitting position and after 5–10 min using analog sphygmomanometer (Omron Random Zero Blood Pressure Analyzer, Japan) and the average of the two stages was recorded. Data of dietaries were collected using 24-h recall procedure within two days, including one normal day and one holiday. Two-day mean values of the energy and nutrient intakes of the participants were calculated using Nutritionist IV Software v.4.1 (First Databank Division, Hearst, USA).

Biochemical analysis: Before and after the intervention, venous blood samples were collected after at least 8–10 h of fasting. Blood plasmas were separated using 10 min of centrifuging at 2000 g and stored at -80 ºC until biochemical analyses. During the intervention, participants were regularly monitored using phone calls. At the end of the study, compliance was assessed by counting the number of capsules. Participants who used less than 80 percent of quercetin and placebo capsules were excluded from the study. The TAC of plasma was measured using colorimetric method and antioxidant assay kit (Novin Salamat, Iran) with an assay range of 0.044–0.33 mmol/L according to the manufacturer's instructions. Malondialdehyde (MDA) was assessed using colorimetric method and thiobarbituric acid reactive substances (TBARS) assay kit (Novin Salamat, Iran) with a dynamic range of 0–50 µmol/L for the colorimetric method at standard conditions according to the manufacturer's instructions.

Echocardiography: All participants were subjected detailed echocardiographic analyses with images reviewed by an expert cardiologist. Echocardiography was carried out in primary care settings using portable VIVID I Machine (GE Healthcare, UK). The LV end-diastolic diameter (LVEDD), posterior wall thickness (PWT), LV ejection fraction and diastolic function parameter (E/A ratio of the mitral valve) were measured following current recommendations [23]. The relative wall thickness (RWT) was calculated as 2 × PWT / LVEDD (concentric hypertrophy if RWT was ≤ 0.42) [24].

RWT = 2 × posterior wall / left ventricular diastolic diameter

Peak work rate (WRp)/peak aerobic power measurement: Each participant carried out a ramp-incremental exercise test, using Storer-Davise cycle test [25]. To carry out Storer-Davise cycle test, the participant initially pedaled with no resistance (0W) for a 4-min warmup. A constant pedaling cadence of 60 rev/min was programmed during the test. After the warmup, the work rate increased at 0.30 kP/min (15 W/min) until the participant was unable to generally continue or to continue on the constant pedaling cadence of 60 rev/min. The peak work rate (WRp) was calculated as the highest work rate (WR) reached and maintained at a pedaling frequency of no less than 60 rpm for 30 s. Supervisions by exercise physiologists, physicians and physical therapists were carried out during the exercise sessions and further included periodical blood pressure measurement, ECG continuous recording, Borg evaluation scale and peripheral oxygen saturation monitoring.

Statistical methods: All values were reported as mean ±SD (standard deviation). Kolmogorov-Smirnov test was used to check if distribution of the quantitative variables was normal. Independent t-test and analysis of covariance (ANCOVA) were used to compare between the two groups at the beginning and the end of the interventions, respectively. Paired t-test was used to compare the mean values before and after the interventions. The SPSS Statistical Software v.15 (IBM Analytics, USA) was used for data analysis. The level of $p \leq 0.05$ was considered statistically significant.

Results

Totally, 24 participants (12 participants in each group) completed the study and then per-protocol statistical analyses were carried out. Independent t-test showed that weight, BMI, age, height and body fat proportion were not significantly different between the quercetin and placebo groups (Table 1).

The daily energy and nutrient intakes are shown in Table 2.

Table 1. Baseline characteristics of the participants

Variable	Quercetin group (*n*=12)	Placebo group (*n*=12)	*P* value†
Age (years)	57.18±4.25	56.23±4.38	0/65
Height (cm)	169.8±7.21	170.6±3.83	0/76
Weight (kg)	74.86±10.46	77.32±7.12	0.29
BMI¶ (kg/m2)	25.96±3.58	26.56±2.16	0.44
Body fat (percentage)	23.95±5.79	23.42±2.78	0.78

Values are expressed as mean ±SD (standard deviation); ¶BMI, body mass index; †independent t test

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Table 2. Daily energy, macronutrient and micronutrient intakes in the two groups

	Quercetin group (*n*=12)	Placebo group (*n*=12)	*P* value†
Energy (kcal/d)	2081.4±244.2	2151.3±302.4	0.53
Carbohydrate (g/d)	320.3±46.7	335. 5±53.4	0.48
Protein (g/d)	81.6±41	83.5±42	0.55
Lipid (g/d)	55.5±14	53.6±16	0.30
Vitamin A (RAE/d)	724.24±421.91	708.26±621.10	0.49
Vitamin E (mg/d)	2.97±2	2.71±2.21	0.78
Vitamin C (mg/d)	76.81±48.86	79.73±53.18	0.56
Vitamin D (µg/d)	1.19±1.64	1.09±1.20	0.75
Fe (mg/d)	13.08±3.95	12.99±4.01	0.67
Zn (mg/d)	6.62±4.32	6.80±3.95	0.85

Values are expressed as mean ±SD (standard deviation); †independent t test

As shown in Table 3, ANCOVA analysis and paired t test showed that quercetin supplementation significantly improved oxidative stress decreases (TAC increased and MDA decreased), systolic and diastolic blood pressures (both decreased), systolic (EF) and diastolic (E/A) functions (both increased) and aerobic power (increased significantly), compared to pretest and placebo groups following eight weeks of treatments ($p < 0.05$). A little decrease in RWT was seen in quercetin group at the end of intervention with no statistical significance ($p > 0.05$). The RWT values were not significantly different between the quercetin and placebo groups after eight weeks ($p>0.05$). Paired t test showed no statistically significant differences for the mean placebo group values ($p > 0.05$).

Table 3. Biochemical and echocardiographic parameters, aerobic power and blood pressure of the participants before and after eight weeks of supplementation

	Quercetin group (*n*=12)	Placebo group (*n*=12)	*P* value
TAC(mmol Fe^{+2}/L)			
Before	0.914±0.27	0.923±0.26	0.938†
After	1.075±0.33	0.934±0.21	0.032‡
P *value*¶	0.028	0.339	
MDA(nmol/ml)			
Before	27.10±2.15	28.85±5.46	0.574†
After	23.40±5.2	28.09±5.27	0/042‡
P *value*¶	0/038	0.341	
Systolic blood pressure (mmHg)			
Before	143.7±10.23	144.4±10.58	0.861†
After	135.5±9.96	143.2±10.25	0/002‡
P *value*¶	0/002	0.186	
Diastolic blood pressure(mmHg)			
Before	86.54±4.82	87.55±4.80	0.632†
After	80.09±5.00	86.36±4.10	0/004‡
P *value*¶	0/005	0.351	
LVPWd(mm)			
Before	11.66±0.64	12.14±0.67	0.101†
After	11.63±0.55	12.15±0.74	0.067‡
P *value*¶	0.341	0.670	
LVEDd(mm)			
Before	47.45±2.39	47.68±2.50	0.830†
After	47.81±2.48	47.60±2.74	0.890‡
P *value*¶	0.340	0.298	
RWT(percentage)			
Before	0.50±0.034	0.51±0.050	0.694†
After	0.49±0.038	0.51±0.55	0.520‡
P *value*¶	0.132	0.381	
LVEF(percentage)			
Before	51.00±5.21	50.18±3.81	0.702†
After	53.27±5.62	50.50±4.41	0/032‡
P *value*¶	0/030	0.586	
E/A ratio			
Before	0.780±0.124	0.767±0.88	0.782†
After	0.812±0.127	0.760±0.87	0/023‡
P *value*¶	0/021	0.314	
WRp(watts)			
Before	98.18±26.29	100.25±18.60	0.402†
After	109.09±22.34	100.50±18.60	0/002‡
P *value*¶	0/000	0.166	

Values are expressed as mean ±SD (standard deviation); TAC, total antioxidant capacity; MDA, malondialdehyde; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVPWd, LV posterior wall thickness; LVEDd, LV end diastolic diameter; RWT, relative wall thickness; LVEF, LV ejection fraction**;** E/A ratio, peak early filling (E wave) and late diastolic filling (A wave) velocity ratio; WRp, peak work rate; ‡ANCOVA was used to compare differences between the two groups after eight weeks (adjusted for baseline values); †independent t test; ¶paired t test

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Discussion

Based on the current knowledge, this study is the first study to investigate effects of quercetin supplement (250 mg/day) on oxidative stress in patients with CAD. In this study, quercetin supplementation resulted in significant decreases in plasma levels of MDA as well as significant increases in plasma TAC. These results are similar to results from other studies such as those by Chiodo et al. [26], Monteiro et al. (36), Kandhare et al [27], Kumar et al. [28], Duarte et al. [20], Galisteo et al. [29] and Boots et al. [17]; in which, ROS and MDA levels decreased and activities of antioxidant enzymes of SOD, CAT and TAC increased following supplementation with quercetin. A previous study by the authors showed similar results from six weeks of quercetin supplementation [3]. Of flavonoids, quercetin includes the strongest antioxidant characteristic due to the presence of OH group in B and C-rings [3]. Quercetin represses free radicals in three stages, including generation of hydroxyl radicals in Fenton reaction, formation of lipid peroxy radicals and formation of superoxide ions [30, 31]. In contrast, Cammerer et al. [32] showed that a flavonoid-based antioxidant-rich diet included no effects on oxidative stress, six months after PCI. Furthermore, Kammer et al. used a flavonoid-rich diet contrary to the pure quercetin used in the present study. In a study by Javadi et al. [15], quercetin did not affect plasma TAC and MDA levels in patients with RA. However, participants of the current study were different from those of Javadi's study. moreover, blood concentration of quercetin might be different. Various doses of 730 mg supplementation (for 28 days) in prehypertensive patients [33], 150 mg per day (for two weeks) in obese patients with metabolic syndrome [19] and 1000 mg per day (for three weeks) in athletes after sports matches [34] showed no significant effects on antioxidant capacity of the plasma. Duration of the intervention in these studies was much less than that in the present study.

In the present study, a significant effect was reported on blood pressure, which was similar to that reported by Egert et al. [19]. Egert et al. [19] found that quercetin led to a significant decrease in systolic blood pressure of all participants with obesity and hypertension. Whereas, Edwards et al. [33] reported that quercetin included no significant effects on blood pressure in pre-hypertensive patients. Only patients in Stage 1 of hypertension showed significant decreases in systolic and diastolic blood pressures. In the current study, quercetin showed an effect on blood pressure, possibly because patients suffered from hypertension. Researchers have investigated antihypertensive effects of quercetin in animal models of essential hypertension. Quercetin in hypertensive rats decreased blood pressure. In contrast, quercetin did not affect normotensive rats. Additionally, quercetin decreased cardiac hypertrophy. These effects were associated with a decreased oxidant status due to the antioxidant properties of quercetin [20]. In another study, quercetin (0.1 g/kg) demonstrated both antihypertensive and antioxidant properties in hypertensive rat models. Quercetin also inhibited cardiac hypertrophy [29]. In a study by Garcia-Saura et al., quercetin supplementation decreased systolic blood pressure of Goldblatt hypertensive rats [35]. The compound decreased cardiac hypertrophy developed in Goldblatt hypertensive rats. In the current study, eight weeks of quercetin supplementation significantly improved left ventricular systolic (EF) and diastolic (E/A) functions. In contrast, quercetin showed no significant effects on concentric pathologic hypertrophy (RWT). Up to date, only two studies have investigated effects of quercetin on structure and function of the heart in humans [16, 36]. Results of these two studies are similar to results of the present study. Effects of quercetin on oxidative stress in these studies have not been investigated. In the current study, quercetin increased LV systolic and diastolic functions by decreasing oxidative stress and increasing antioxidant defense system. In a study of Castillo et al. [37], quercetin prevented cardiac diastolic dysfunction in the same blood vein. Furthermore, quercetin decreased oxidative stress. Therefore, mechanisms that support cardioprotective effects of quercetin might be mediated by the upregulation of antioxidant mechanisms on the heart. In human studies, quercetin included no significant effects on heart structure and hypertrophy [16, 36]. In the present study, a little decrease in RWT was seen in quercetin group at the end of the intervention with no significance. Whereas, quercetin supplementation decreased cardiac hypertrophy induced by pressure overload in rats [20, 28, 29, 38–40]. In these animal studies, daily quercetin doses were much more than those in the current study.

Findings of this study have suggested that eight-week supplementation with quercetin improves the endurance performance. This has been shown in several studies [3, 21, 41–44]. It is possible that quercetin improves mitochondrial biogenesis in humans; therefore, improves aerobic capacity [21, 45]. Furthermore, decrease of oxidative stress and improvement of heart function can be the mechanism; through which, quercetin develops aerobic capacity [3, 45]. For the first time in this study, dietary supplementation with quercetin (250 mg daily for 56 days) increased endurance capacity in men with heart diseases. However, findings were not similar to those

reported by some other researchers [46, 47]. Ganio et al. Showed that five days of quercetin supplementation did not increase aerobic capacity in untrained individuals [47]. Cureton et al. found that 1 g/day of quercetin supplementation (7–16 days) included no significant effects on VO_2 peak and perception of efforts or metabolic responses during submaximal cycling [46]. Period of quercetin supplementation in this study (eight weeks) was much longer than that in Ganio et al. study (five days) and Cureton et al. (9–16 days). Although this study was the first randomized, double-blind placebo-controlled trial to assess effects of quercetin on oxidative stress, blood pressure, aerobic power, concentric pathologic hypertrophy in patients with hypertension and CAD after PCI, it included limitations. These limitations included the short-term intervention period and the little sample size. Lack plasma quercetin measurement due to the lack of laboratory capacity was another limitation. Similarly, information bias that might occur due to the self-reported dietary intake was a limitation within this study.

CONCLUSIONS

In general, this study showed that quercetin supplementation improved oxidative stress indices, blood pressure, aerobic power and cardiac function in men with hypertension and CAD after PCI. However, quercetin did not affect levels of concentric pathologic hypertrophy (a little decrease in RWT was seen with no significance). Greater sample sizes, longer intervention periods and higher doses of quercetin are suggested in future studies to establish the effectiveness of quercetin on levels of concentric pathologic hypertrophy.

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