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Quercetin Reduces Blood Pressure in Hypertensive Subjects[1,2]

Randi L. Edwards,[3] Tiffany Lyon,[3] Sheldon E. Litwin,[4] Alexander Rabovsky,[6] J. David Symons,[3,5] and Thunder Jalili[3]*

[3]Division of Nutrition, [4]Division of Cardiology, and [5]Department of Exercise and Sports Science, University of Utah, Salt Lake City, UT 84112 and [6]USANA Health Sciences, Salt Lake City, UT 84120

Abstract

Epidemiological studies report that quercetin, an antioxidant flavonol found in apples, berries, and onions, is associated with reduced risk of coronary heart disease and stroke. Quercetin supplementation also reduces blood pressure in hypertensive rodents. The efficacy of quercetin supplementation to lower blood pressure in hypertensive humans has never been evaluated. We tested the hypothesis that quercetin supplementation reduces blood pressure in hypertensive patients. We then determined whether the antihypertensive effect of quercetin is associated with reductions in systemic oxidant stress. Men and women with prehypertension ($n = 19$) and stage 1 hypertension ($n = 22$) were enrolled in a randomized, double-blind, placebo-controlled, crossover study to test the efficacy of 730 mg quercetin/d for 28 d vs. placebo. Blood pressure (mm Hg, systolic/diastolic) at enrollment was 137 ± 2/86 ± 1 in prehypertensives and 148 ± 2/96 ± 1 in stage 1 hypertensive subjects. Blood pressure was not altered in prehypertensive patients after quercetin supplementation. In contrast, reductions in ($P < 0.01$) systolic (−7 ± 2 mm Hg), diastolic (−5 ± 2 mm Hg), and mean arterial pressures (−5 ± 2 mm Hg) were observed in stage 1 hypertensive patients after quercetin treatment. However, indices of oxidant stress measured in the plasma and urine were not affected by quercetin. These data are the first to our knowledge to show that quercetin supplementation reduces blood pressure in hypertensive subjects. Contrary to animal-based studies, there was no quercetin-evoked reduction in systemic markers of oxidative stress. J. Nutr. 137: 2405–2411, 2007.

Introduction

Quercetin is a flavonol that belongs to a group of polyphenolic compounds known as flavonoids (1). Widespread epidemiological evidence indicates that quercetin contained in onions, apples, berries, and red wine aids in preventing cardiovascular disease and stroke (2–8). Along with these promising data, recent laboratory studies have demonstrated that quercetin has important vasorelaxant properties on isolated arteries and lowers blood pressure in the spontaneously hypertensive rat (9,10). In addition, we have shown that quercetin administered to rats prevents the development of hypertension and cardiac hypertrophy in response to pressure overload created by abdominal aortic constriction (11). The beneficial effects of quercetin concerning vasorelaxation and blood pressure in rodents have been attributed at least in part to the ability of this flavonoid to decrease indices of oxidative stress (9,11,12).

Despite existing epidemiological and animal-based research concerning quercetin and cardiovascular disease, no studies have evaluated whether quercetin supplementation lowers blood pressure in hypertensive humans. Therefore, we performed a randomized, placebo-controlled crossover trial to test the hypothesis that quercetin reduces blood pressure in prehypertensive and stage 1 hypertensive subjects. Systemic markers of oxidant load also were examined as secondary outcomes to determine whether reductions in blood pressure were associated with lower indices of oxidative stress.

Materials and Methods

Participants and recruitment criteria

This study was approved by the University of Utah Human Use Review Committee, University of Utah Institutional Review Board, and written informed consent was obtained from each participant. Recruitment efforts in the greater Salt Lake City area targeted males and females with prehypertension (120–139 mm Hg systolic/80–89 mm Hg diastolic) and stage 1 hypertension (140–159 mm Hg systolic/90–99 mm Hg diastolic) as defined by the 7th Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (13). **Figure 1** summarizes the number of subjects screened, recruited, and enrolled in this study. Initial screening consisted of asking volunteers if they had a history of high blood pressure, followed by a single blood pressure measurement using an Omron random zero blood pressure analyzer. If blood pressure criteria were met during the initial screening, subjects were referred to the Nutrition Clinic for further

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* To whom correspondence should be addressed. E-mail: thunder.jalili@utah.edu.

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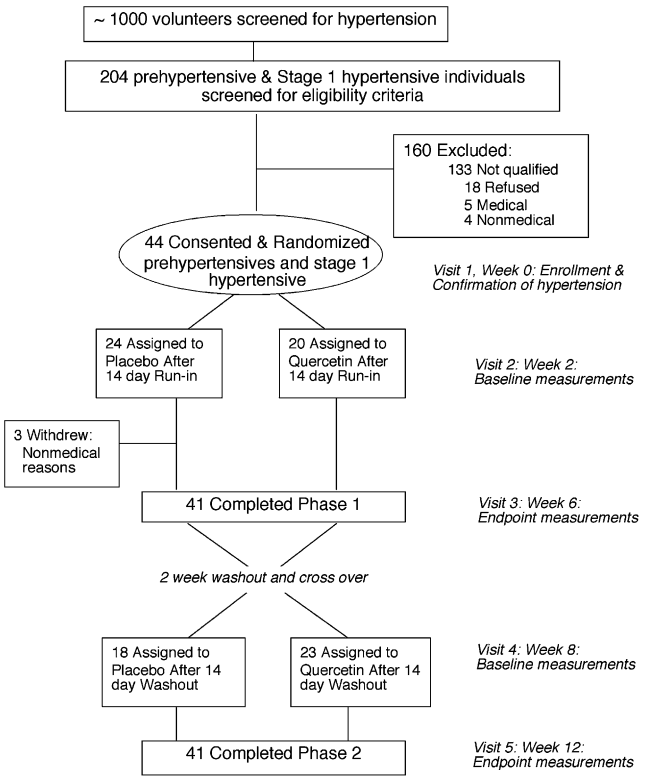

FIGURE 1 Summary of subject recruitment and experimental design.

evaluation of blood pressure and confirmation of eligibility criteria. Subjects who met blood pressure guidelines and eligibility criteria after the clinical evaluation were enrolled in the study. We recruited participants from October 2004 to June 2005. Forty-four patients who met study criteria consented and were enrolled, 21 prehypertensive and 23 stage 1 hypertensive. Forty-one subjects completed the entire protocol and 3 withdrew (1 male and 1 female from the prehypertensive group and 1 male from the stage 1 hypertensive group).

Subjects were excluded based on their current use of antihypertensive medication. Major exclusion criteria for hypertensive subjects included current smoking, history of a prior cardiovascular event, diabetes, renal insufficiency, hyperlipidemia (total cholesterol >240 mg/dL), pregnancy, lactation, any chronic disease that might interfere with study participation, BMI above 35 kg/m^2, consumption of >12 alcoholic drinks weekly, or unwillingness to stop current supplement intake or use of calcium/magnesium antacids. All subjects who met exclusion criteria agreed to maintain their typical diet and exercise habits.

Objectives, interventions, and outcomes

The primary hypothesis to be tested was that 365 mg quercetin aglycone taken twice per day reduces blood pressure in prehypertensive and stage 1 hypertensive subjects. The secondary hypothesis was that quercetin-induced reductions in blood pressure would be associated with lower indices of systemic oxidant stress. Participants chosen from the initial screening process were scheduled for a familiarization visit to the clinic at the University of Utah Nutrition Laboratory. During that visit participant responsibilities were explained, consent was obtained, and blood pressure status was verified. Subjects were then instructed to discontinue any existing supplement use and complete a 14-d run-in period (Fig. 1). After the run-in period, they were enrolled in a double blind, placebo-controlled, crossover trial consisting of a 4-wk quercetin supplementation phase and a 4-wk placebo phase. A 14-d washout period separated the 2 phases. To validate that a 2-wk washout period was sufficient to reduce plasma quercetin to baseline, 5 subjects consumed quercetin supplements for 1 wk, followed by a 1-wk washout period. We then measured plasma quercetin concentrations to determine whether quercetin levels were similar to those who had not taken quercetin.

Subjects were randomly assigned to begin either the quercetin or the placebo phase first. Four-week treatment phases were chosen because this duration has been shown to be efficacious concerning dietary interventions (14). Clinic visits were conducted on overnight-fasted subjects in the morning hours at the beginning and end of the placebo and quercetin supplementation phases. Subjects were instructed not to exercise prior to their appointments. Compliance was confirmed by a tablet count at the completion of each phase of the study and by quantifying plasma quercetin concentrations.

Because no human studies have examined whether quercetin reduces blood pressure in hypertensive humans, the dose of quercetin used in this trial was based on efficacious results we and others have obtained using animal models of hypertension (9,12,15). Tablets containing placebo or quercetin were manufactured by USANA Health Sciences (**Table 1**).

Blood pressure measurement

Blood pressure was a primary outcome variable and was obtained at each clinic visit by a trained observer using an Omron random zero automatic blood pressure analyzer as previously described (16). Each participant sat quietly for 5–10 min, after which their arm was placed at heart level and blood pressure and pulse rate were measured at least 3 times in 3- to 5-min intervals. If blood pressure varied in these determinations by >10 mm Hg, 3 additional trials were performed to measure systolic and diastolic blood pressure. The accumulated measurements then were averaged to determine overall systolic and diastolic pressure and pulse rate for each subject.

Venous blood collection

Blood samples were collected after blood pressure was measured. We collected blood by antecubital venipuncture from fasting subjects into sodium heparin tubes (Becton Dickinson). Collected blood was immediately stored on ice and centrifuged within 10 min at 2500 × *g*; 15 min at 4°C as previously described (17). Plasma was separated and stored at −80°C until it was analyzed for quercetin concentration, plasma antioxidant reserve (PAR), and ferric reducing antioxidant power (FRAP).

Blood lipid, glucose, and urine collection

During each patient visit, whole blood (~50 μL) was obtained from a digit puncture to determine blood lipid concentrations (triglycerides; LDL, VLDL, HDL, and total lipoprotein concentrations) and glucose using a clinical Cholestech LDX blood analyzer (18). These outcomes were quantified because earlier studies have reported beneficial changes in the blood lipid profile of quercetin-supplemented rats that consumed a cholesterol-rich diet (19). Prior to each patient visit, first morning urine was collected, brought to the laboratory, and stored at −80°C for later analysis of isoprostane concentrations.

Quercetin analysis

Plasma quercetin was analyzed as previously described (20) with slight modifications; 250 μL samples were hydrolyzed with 100 μL and 500 μL of 6 mol/L HCl. Supernatants then were extracted with ethyl acetate and injected into an HPLC Discovery C18 column. The mobile phase was 1% acetic acid (solvent A) and 95% acetonitrile in 1% phosphoric

TABLE 1 Composition of quercetin and placebo tablets

	Placebo	Quercetin
	mg/tablet	
Quercetin with corn starch	0	364
Microcrystalline cellulose	564	192
Dicalcium phosphate	312	312
Colloidal silicon dioxide	6	6
Ascorbyl palmitate	6	14
Croscarmellose sodium	12	12

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acid (solvent B). The gradient elution used was solvent B from 10 to 85% over 20 min, and then held for 5 min before returning back to 10% for conditioning. A visible detector with 365 nm was used and quercetin was quantified by peak height ratio method.

Indices of oxidative stress

PAR. Ex vivo amplification of isoprostanes was accomplished by introducing a source of free radicals (3-morpholinosydnonimine) into the blood plasma to induce oxidation of lipoproteins (21). Uric acid, a major water soluble antioxidant present in plasma, was removed using uricase prior to introduction of 3-morpholinosydnonimine so that any protection provided by other antioxidants could be measured. Therefore, PAR measures the non-urate antioxidant capacity, or antioxidant power, of blood. It has been previously demonstrated that supplementing antioxidants can increase the antioxidant capacity of the blood as determined by PAR (21).

FRAP. FRAP measures the ability of an antioxidant to reduce Fe^{3+} to Fe^{2+} (22) and is an index of plasma antioxidant potential in hypertensive patients (23–26). This assay was done as previously described (21). Briefly, plasma samples were diluted 1:2 with PBS, followed by addition of a reagent solution containing 0.8 mmol/L 2,4,6-tri-(2-pyridyl)-s-tirazine and 1.7 mmol/L $FeCl_3 \cdot 6\text{-}H_2O$. Samples were then incubated at 37°C for 15 min and the absorbance at 593 nm was recorded in a plate reader (Molecular Devices, Spectramax 340 pc).

Urinary isoprostane measurement. Urine 8-isoprostane F2α is a measure of lipid peroxidation and can be used to estimate oxidative stress in hypertensive humans (27–29). Quantification of 8-isoprostane F2α (also known as 8-epi-PGF2α or 8-iso-PGF2α) in urine samples was performed using a competitive enzyme-linked immunoassay kit (Cayman Chemical) according to the manufacturer's instructions.

Dietary analysis

Three-day dietary records were obtained from each subject during the last 14 d of both placebo and quercetin treatment. All records were analyzed using the Food Processor dietary analysis program (ESHA Research) (30).

Statistical analyses

All data are reported as means ± SEM. All variables were analyzed using paired *t* tests to detect differences within the placebo and quercetin treatment phases (i.e. baseline vs. endpoint) (SPSS v.11.0.3). Dietary intake data and plasma quercetin concentrations were examined using paired *t* tests comparing placebo vs. quercetin phases. Regression analyses using age, gender, BMI, PAR, FRAP, and urinary isoprostane F2α concentration as independent variables and systolic blood pressure as the dependent variable were performed. Systolic pressure was selected as the dependent variable, because it has been identified as a better predictor of cardiovascular disease than diastolic pressure (13). Differences were considered significant at $P < 0.05$.

Results

Patient characteristics. Nearly 1000 patients were interviewed and screened for eligibility. The majority (i.e. ~800) were not considered further for participation because they met 1 or more of the exclusion criteria or did not have blood pressure within study limits. From this initial screening, 204 individuals were evaluated in more detail at a subsequent clinic visit to determine whether all inclusion/exclusion criteria were met and if blood pressure was within the study limits (Fig. 1). Forty-four subjects were initially enrolled and 41 completed the entire 12-wk study. The age of prehypertensive ($n = 19$, $n = 13$ males) and stage 1 hypertensive ($n = 22$, $n = 13$ males) subjects was 47.8 ± 3.5 and 49.2 ± 2.9 y old, respectively. No adverse effects of quercetin or placebo treatment were reported during the course of the study. Weight and BMI did not change between treatments in either group (**Table 2**). Heart rate was unchanged throughout the study (data not shown).

Plasma quercetin was 695 ± 103 nmol/L after placebo treatment and increased to 1419 ± 189 nmol/L after quercetin treatment. Our preliminary experiments indicated that a 1-wk washout period was sufficient to bring plasma quercetin concentrations to 562 ± 27 nmol/L. These values are similar to those obtained from subjects who consumed placebo but had not yet been exposed to quercetin. There was also no effect of treatment order on the observed changes in blood pressure ($r = 0.194$; $P = 0.388$), indicating that the antihypertensive effect of quercetin did not persist in those who received quercetin supplements before placebo.

Blood pressure. Placebo treatment did not alter blood pressure in either group of hypertensive subjects. Blood pressure was

TABLE 2 Body mass and biomarkers of oxidative stress in prehypertensive and stage 1 hypertensive subjects before and after supplementation with quercetin and placebo[1]

	Weight	BMI	Urinary isoprostane	Plasma FRAP	Plasma PAR
Prehypertensive–placebo	*kg*	*kg/m²*	*nmol/mol creatine*	*μmol/L*	*ng/L*
n	19	19	8	8	8
Baseline	91.6 ± 5.3	29.8 ± 1.3	1.53 ± 0.21	1180 ± 59	346 ± 32
Endpoint	91.6 ± 5.4	29.7 ± 1.3	1.69 ± 0.26	1028 ± 62	321 ± 58
Prehypertensive–quercetin					
n	19	19	8	8	8
Baseline	91.6 ± 5.3	29.6 ± 1.3	1.46 ± 0.16	1089 ± 56	308 ± 55
Endpoint	91.6 ± 5.2	29.7 ± 1.2	1.47 ± 0.21	1072 ± 68	280 ± 37
Stage 1 hypertensive–placebo					
n	22	22	8	8	8
Baseline	88.7 ± 4.4	29.5 ± 1.4	1.67 ± 0.42	1096 ± 70	285 ± 60
Endpoint	88.0 ± 4.4	29.4 ± 1.4	2.57 ± 1.00	1086 ± 66	238 ± 52
Stage 1 hypertensive–quercetin					
n	22	22	8	8	8
Baseline	88.7 ± 5.5	29.3 ± 1.3	2.32 ± 0.70	1056 ± 59	258 ± 55
Endpoint	88.2 ± 5.5	29.5 ± 1.4	1.55 ± 0.17	1152 ± 69	281 ± 74

[1] Values are means ± SEM. There were no changes in either group during either phase of the study.

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similar in prehypertensive subjects compared with placebo after quercetin treatment. In contrast, quercetin supplementation reduced systolic, diastolic, and mean arterial pressure in stage 1 hypertensive subjects (**Fig. 2***A*,*B*; **Table 3**). The antihypertensive effect of quercetin was independent of gender ($r = 0.343$; $P = 0.118$), age ($r = 0.202$; $P = 0.381$), and BMI ($r = 0.061$; $P = 0.788$) in stage 1 hypertensive subjects.

Indices of oxidative stress and antioxidant capacity. Measurements of antioxidant capacity (fasting plasma FRAP and PAR) and oxidative stress (fasting urinary 8-isoprostane F2α concentration) within either placebo or quercetin supplementation phases were not altered (Table 2). The antihypertensive effect of quercetin was independent of PAR ($r = 0.367$; $P = 0.093$), FRAP ($r = 0.02$; $P = 0.930$), and urinary 8-isoprostane F2α ($r = 0.353$; $P = 0.437$) in stage 1 hypertensives.

Dietary analyses. Three-day diet record analysis indicated that there was lower vitamin K intake during the quercetin phase vs. placebo in prehypertensive patients (**Table 4**). Stage 1 hypertensive subjects had reductions in potassium intake during the quercetin supplementation vs. placebo phase (Table 4). All other nutrients evaluated were similar in placebo vs. quercetin phases in both groups of hypertensive subjects.

Fasting plasma lipids and glucose. Concentrations of plasma triglycerides and total, LDL, VLDL, and HDL cholesterol, and fasting blood glucose concentrations did not change after quercetin supplementation or after placebo treatment in prehypertensive or stage 1 hypertensive patients (**Table 5**). The total cholesterol:HDL cholesterol ratio was also unchanged (data not shown).

Discussion

Results from this investigation support our primary hypothesis and are the first to our knowledge to demonstrate that daily supplementation with 730 mg quercetin for 28 d reduces systolic, diastolic, and mean arterial pressure in subjects with stage 1 hypertension. These findings are an important extension of previous studies showing that quercetin lowers blood pressure in hypertensive animals (9,11,12,31,32) and prevents the onset of hypertension in response to mechanical overload in rodents (11). The antihypertensive effect of quercetin in our subjects may also explain at least in part why previous epidemiological reports show an inverse relationship between dietary flavonoid intake and heart disease risk (1–8,33–37). In contrast to results obtained from in vitro experiments and animal models (9,11,12,31,32,38), we did not observe a quercetin-evoked reduction in oxidative stress as determined by plasma PAR, FRAP, and urinary isoprostanes.

To our knowledge, only 1 other study has examined the effect of quercetin supplementation in humans (39). In that investigation, Conquer et al. (39) reported no changes in blood pressure when normotensive individuals (i.e. <120 mm Hg systolic/< 80 mm Hg diastolic) were supplemented with 1000 mg/d of quercetin for 8 wk, despite similar plasma quercetin concentrations (1262 ± 263 nmol/L) compared with our study (1419 ± 189 nmol/L). These data indicate a certain degree of hypertension might be required for quercetin to exert a blood pressure-lowering effect. This possibility is supported by data from the present study wherein quercetin reduced systolic, diastolic, and mean arterial pressure in stage 1 hypertensive subjects but not in those with prehypertension. Likewise, animal-based studies have demonstrated that quercetin is efficacious in lowering blood pressure in hypertensive but not normotensive rats (9,11).

Three-day diet records were used to evaluate whether changes in nutrient intake influenced blood pressure during the quercetin treatment phase. Though stage 1 hypertensive subjects had decreased intake of potassium and prehypertensives consumed less vitamin K during the quercetin phase, it is unlikely that these changes led to reduced blood pressure. With regard to dietary intake of polyphenolic compounds, it is not possible to

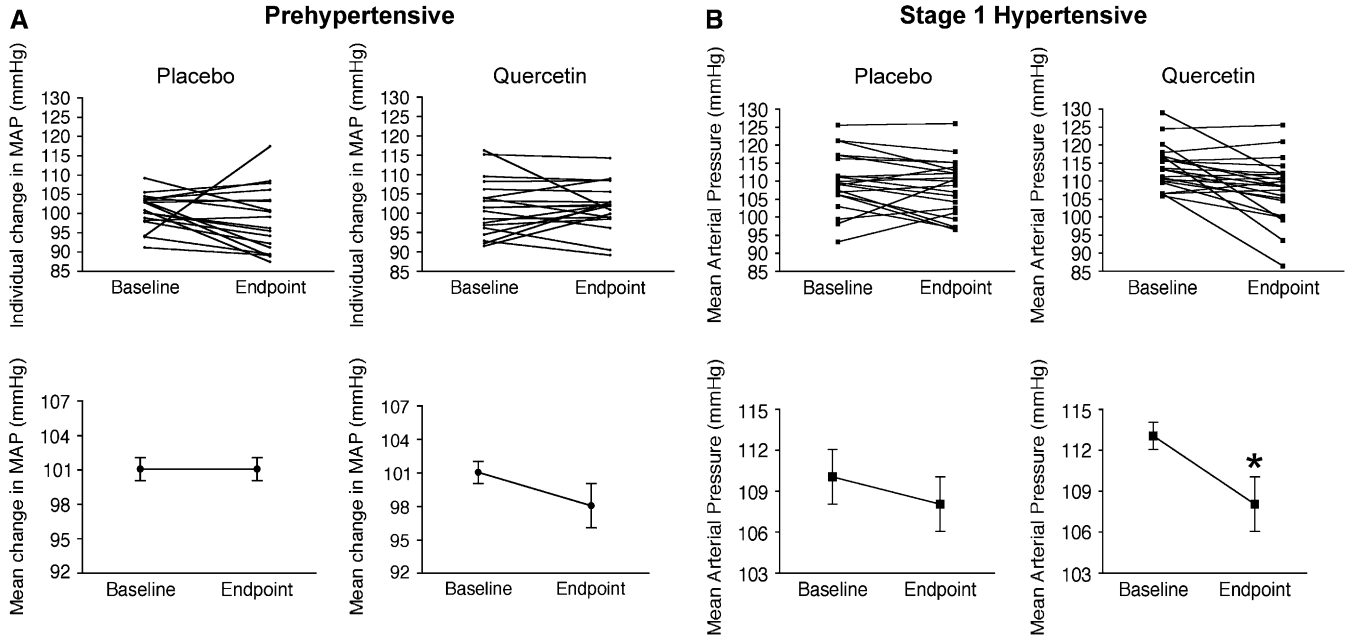

FIGURE 2 Mean arterial blood pressure at baseline and after quercetin and placebo treatments in prehypertensive (*A*, $n = 19$) and stage 1 hypertensive (*B*, $n = 22$) subjects. Upper graphs illustrate individual subject responses during each supplementation phase; the lower graphs show means ± SEM. *Different from baseline, $P < 0.05$. MAP, Mean arterial pressure.

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TABLE 3 Blood pressure in prehypertensive and stage 1 hypertensive subjects before and after supplementation with quercetin and placebo[1]

	Prehypertensive, $n = 19$		Stage 1 Hypertensive, $n = 22$	
	Systolic	Diastolic	Systolic	Diastolic
	mm Hg			
Blood pressure at enrollment	137 ± 2	86 ± 1	148 ± 2	96 ± 1
Placebo				
Baseline	135 ± 3	84 ± 1	141 ± 2	94 ± 2
Endpoint	131 ± 3	87 ± 1	138 ± 2	93 ± 2
Quercetin				
Baseline	132 ± 1	85 ± 1	145 ± 2	97 ± 1
Endpoint	128 ± 3	84 ± 2	138 ± 2*	92 ± 2*

[1] Values are means ± SEM. *Different from quercetin baseline, $P < 0.01$ (paired *t* test).

determine intake of items such as quercetin, because there are no suitable databases available for such an analysis. The lack of databases likely can be attributed to the variation in chemical composition of fruits and vegetables, coupled with the lack of sufficiently accurate analytical tools (33). Despite these limitations, it has been estimated that average dietary intake of quercetin from Western diets is 28–42 mg/d (33,35,36). Intake of polyphenolic compounds in individual diets is likely dependent on fruit, vegetable, and whole grain consumption and variations in these foods would be reflected in the vitamin, mineral, and fiber content reported. Because these dietary variables were generally similar in subjects during the placebo and quercetin phases of the study, we believe that intake of polyphenolic compounds did not differ in participants in our investigation.

TABLE 4 Analysis of 3-d dietary records from prehypertensive and stage 1 hypertensive subjects after supplementation with quercetin and placebo[1]

	Prehypertensive, $n = 18$[2]		Stage 1 hypertensive, $n = 21$[2]	
	Placebo	Quercetin	Placebo	Quercetin
Energy, *kJ/d*	9043 ± 553	9663 ± 829	8776 ± 645	8156 ± 620
Protein, *g/d*	91 ± 5	89 ± 8	87 ± 5	83 ± 6
Fat, *g/d*	74 ± 7	84 ± 9	80 ± 6	72 ± 6
Saturated fat, *g/d*	24 ± 3	27 ± 3	24 ± 2	22 ± 2
Polyunsaturated fat, *g/d*	9 ± 1	9 ± 1	12 ± 2	10 ± 2
Monounsaturated fat, *g/d*	20 ± 2	18 ± 2	19 ± 2	18 ± 2
Fiber, *g/d*	21 ± 1	24 ± 2	22 ± 3	22 ± 4
Carbohydrate, *g/d*	292 ± 19	309 ± 27	252 ± 27	244 ± 23
Cholesterol, *mg/d*	267 ± 34	265 ± 35	232 ± 28	221 ± 28
Vitamin C, *mg/d*	172 ± 28	146 ± 18	164 ± 56	103 ± 16
Vitamin E, *mg/d*	13 ± 2	17 ± 3	15 ± 4	14 ± 3
Vitamin K, *μg/d*	55 ± 13	114 ± 32*	64 ± 22	43 ± 8
Calcium, *mg/d*	1075 ± 101	1015 ± 136	1039 ± 95	966 ± 128
Magnesium, *mg/d*	288 ± 39	271 ± 41	276 ± 24	261 ± 29
Sodium, *mg/d*	2942 ± 303	3482 ± 464	2794 ± 253	3153 ± 238
Potassium, *mg/d*	3035 ± 185	2580 ± 200	2465 ± 239	2195 ± 234*
Selenium, *μg/d*	79 ± 8	65 ± 9	86 ± 12	79 ± 12
Zinc, *mg/d*	10 ± 1	9 ± 1	9 ± 1	8 ± 1

[1] Values are means ± SEM. *Different from placebo, $P < 0.05$ (paired *t* test).
[2] Diet records from 1 patient in the prehypertensive group and from 1 in the stage 1 hypertensive group were not collected.

Recent AHA statistics estimate that over 50 million Americans suffer from hypertension (38). There is a linear relationship between blood pressure and mortality from stroke and ischemic heart disease that emphasizes the importance of blood pressure control (40). Based on risk assessment summarized in the 7th Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, the risk of death from ischemic heart disease and stroke in prehypertensive patients used in the present study is double that of individuals with blood pressure of 115/75 mm Hg and nearly 4 times greater in stage 1 hypertensive patients (13). The quercetin-induced lowering of systolic blood pressure observed in stage 1 hypertensive subjects (−7.2 mm Hg) is clinically relevant because reductions of this magnitude are associated with a decrease in mortality of ~14% from stroke and ~9% from coronary heart disease (40). These findings are noteworthy in light of the emergence of systolic blood pressure as a more important risk factor than diastolic pressure with regard to mortality from cardiovascular disease, particularly in individuals aged >50 y (13).

Lifestyle modification has been emphasized in prehypertensive and hypertensive individuals as an initial intervention to control blood pressure (13). Interestingly, the reduction of blood pressure we observed in stage 1 hypertensive subjects after quercetin supplementation is similar to those experienced following sodium reduction, weight reduction, increased physical activity, or alcohol reduction (41). Other proven lifestyle modifications such as the Dietary Approaches to Stop Hypertension diet result in similar or slightly greater blood pressure reduction (41). Thus, it appears that the effects of quercetin supplementation are consistent with current recommended lifestyle modifications used to reduce blood pressure.

Our secondary hypothesis was that the antihypertensive effect of quercetin would be associated with a reduction of systemic oxidant stress. Rationale for this hypothesis was based on studies showing that quercetin lowers indices of oxidative stress in a dose-dependent manner in spontaneously hypertensive rats (e.g. lower urinary isoprostanes and plasma malondialdehyde) (9) and nitric oxide-deficient rats (e.g. reduced plasma malondialdehyde and glutathione peroxidase activity) (12). Instead, we observed that plasma antioxidant potential (FRAP and PAR analyses) and urinary 8-isoprostane F2α were similar in prehypertensive and stage 1 hypertensive subjects regardless of quercetin or placebo treatment. We do not think that the lack of an antioxidant effect by quercetin treatment was due to the dose we used, because it was similar (730 mg/d, ~8.5 mg/kg) to the concentration used in previous animal studies (10 mg/kg) wherein antioxidant effects were demonstrated (9,12,15). Nevertheless, species-dependent differences in metabolism of quercetin (human vs. rat) may exist. Because local increased vascular and renal oxidative stress have been reported in hypertensive animals (42,43), it is possible that humans in our studies also had elevated oxidative stress in these compartments despite our observation that urinary isoprostanes were unchanged. Vascular and renal oxidative stress are difficult to assess in humans and, as such, we cannot rule out the possibility that quercetin might have produced local effects that were not detected using our global measures of oxidative stress (i.e. urinary isoprostanes).

An important consideration for the present study is the severity of oxidant stress in our hypertensive subjects. In this regard, plasma FRAP was similar between both groups of

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TABLE 5 Plasma lipid and fasting blood glucose concentrations in prehypertensive and stage 1 hypertensive subjects before and after supplementation with quercetin and placebo[1]

	Total cholesterol	LDL	HDL	VLDL	Triglycerides	Glucose
Prehypertensive, $n = 19$			*mmol/L*			
Placebo						
Baseline	5.12 ± 0.24	3.03 ± 0.17	1.24 ± 0.12	0.83 ± 0.11	1.82 ± 0.24	5.68 ± 0.18
Endpoint	5.38 ± 0.22	3.17 ± 0.17	1.31 ± 0.12	0.87 ± 0.10	1.93 ± 0.21	5.89 ± 0.20
Quercetin						
Baseline	5.13 ± 0.23	3.00 ± 0.20	1.24 ± 0.13	0.91 ± 0.13	2.00 ± 0.24	5.99 ± 0.25
Endpoint	5.15 ± 0.24	3.04 ± 0.17	1.25 ± 0.11	0.80 ± 0.06	1.76 ± 0.12	5.89 ± 0.14
Stage 1 hypertensive, $n = 22$						
Placebo						
Baseline	5.32 ± 0.21	2.98 ± 0.21	1.27 ± 0.08	1.08 ± 0.15	2.37 ± 0.34	6.37 ± 0.28
Endpoint	5.33 ± 0.18	3.09 ± 0.17	1.31 ± 0.09	1.00 ± 0.13	2.20 ± 0.29	6.11 ± 0.18
Quercetin						
Baseline	5.34 ± 0.22	3.23 ± 0.24	1.23 ± 0.09	1.05 ± 0.18	2.32 ± 0.39	6.00 ± 0.20
Endpoint	5.22 ± 0.24	3.09 ± 0.26	1.25 ± 0.11	1.10 ± 0.15	2.43 ± 0.34	6.12 ± 0.24

[1] Values are means ± SEM. There were no changes in either group during either phase of the study.

hypertensive subjects (1065–1130 μmol/L) from our present trial and normotensive subjects (973–1064 μmol/L) that were evaluated in a previous study using identical methods (21). These data indicate that the cohort evaluated in the present investigation did not have elevated oxidant stress, at least in terms of FRAP. As such, the ability of quercetin to further reduce markers of oxidative stress may be limited. Evidence does exist, however, for a mechanism involving angiotensin converting enzyme. For example, 30 mg/kg quercetin (p.o.) in rats significantly blunted the hypertensive response to i.v. administration of angiotensin I (44). Although it is possible that higher systemic concentrations of quercetin, as observed in our study, could limit angiotensin II production and lower blood pressure, further investigation would be required to confirm this speculation.

Our study is, to our knowledge, the first to show that quercetin reduces blood pressure in stage I hypertensive individuals. Though we used a powerful experimental design (double blinded, placebo-controlled, crossover) and found quercetin supplementation to be efficacious in reducing blood pressure, extrapolation of our results to the general population should be done with caution given the homogeneous cohort (middle-aged, Caucasian men and women) and modest sample size. Nevertheless, our data indicate that potential exists for this polyphenolic compound to be used as adjunct therapy in diet/lifestyle interventions to help control blood pressure in hypertensive individuals.

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