Effect of quercetin supplementation on blood pressure in patients with a history of ischemic stroke

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ABSTRACT: Cerebrovascular disease including ischemic and hemorrhagic stroke is one of the most prevalent and destructive disease. Accompanying Hypertension with cardiovascular disease will increase the risk of coronary heart disease and stroke. A few studies examined the effects of quercetin supplementation showing its protective effect on endothelial function. Animal studies have shown that quercetin supplementation increases nitric oxide bioavailability and therefore helping the blood vessels to dilate. Quercetin supplementation has favorable effects in patients with stroke. Our objective was to examine the effect of quercetin supplementation on blood pressure in patients with a history of ischemic stroke. Seventy-two patients aged 50-75 years with a history of ischemic stroke including men and women with 25<BMI<35 kg/m² have been selected. Subjects were randomized into quercetin supplementation and placebo group. These patients received 1000 mg quercetin/d or placebo for 8 weeks. Weight, height and systolic and diastolic blood pressure were measured before and after the intervention. Also the daily intakes of food were evaluated by 24-hour questionnaire. Significant changes of systolic (13.7±2.33 mmHg vs 12.88±1.89 mmHg, p=0.04) and diastolic blood pressure (8.66±1.45 mmHg vs 8.26±0.98 mmHg, p=0.02) were observed by taking quercetin. There were no significant changes in weight and the daily intakes of energy and macronutrients between 2 groups and dietary intake of quercetin was not different after intervention. According to the results, quercetin supplementation might improve endothelial function by lowering blood pressure in patients with a history of ischemic stroke.

Keywords: diastolic blood pressure; Ischemic stroke; quercetin; systolic blood pressure

Abbreviations: ACE- angiotensin converting enzyme; BMI- body mass index; DBP- diastolic blood pressure; NO- nitric oxide; RAAS- rennin-angiotensin-aldosterone system; SBP- systolic blood pressure; SPSS- software package used for statistical analysis; USDA- U.S. department of agriculture

INTRODUCTION

Quercetin is one of the flavonoids found in fruits and vegetables (Boots et al, 2008). The main sources are apples, onions, tea, berries and red wine (Prior, 2006). Quercetin has an antioxidant property which can neutralize the free radicals and decrease cell damage (Boots et al, 2008). According to the previous studies, quercetin has a reduced effect on coronary heart disease and stroke (Lee et al, 2011; Leone et al, 1992; Takizawa et al, 2003; Ishisaka et al, 2011). The other activities such as antithrombotic, vasodilatory, anti-inflammatory and anti-carcinogenic are associated with its scavenging activity (Knekt et al, 2002; Egert et al, 2009). One of the interventional studies on rats indicated increased production of nitric oxide (NO) by quercetin supplementation...
In regards to pathophysiology of ischemic stroke analysis, the constricting effects on the blood vessels can be stabilized (Wade et al, 2008). High blood pressure is defined as systolic blood pressure over 140 mmHg and diastolic blood pressure more than 90 mmHg (Larson et al, 2012). Hypertension is one of the risk factors of ischemic stroke and sometimes it can develop after the stroke (Soler et al, 2010). The results of animal-based studies have indicated that quercetin supplementation can decrease the symptoms of stroke, cell death and improve endothelial dysfunction (Lee et al, 2011; Montenegro et al, 2010; Cho et al, 2006). There are a few studies that have examined the effects of quercetin on blood pressure but the duration of intervention and its dosage were different (Egert et al, 2009; Edwards et al, 2007; Knab et al, 2011). Thus more studies are needed to clarify the results. This study was a double-blind, placebo-controlled study to examine the effects of quercetin supplementation on blood pressure in patients with a history of stroke.

**METHODS AND SUBJECTS**

Seventy-two patients with a history of stroke (6 month – 2 years) were selected. The patients were men and women aged 50-75 years with a Body Mass Index (BMI) between 25-35 kg/m². Exclusion criteria were: any recent change of their medication, history of renal and liver disease, metabolic disorders including thyroid or adrenal disease, hemorrhagic stroke, hormone therapy, treatment with warfarin or heparin and simultaneous medication of aspirin and clopidogrel.

This randomized, double-blind and placebo-controlled study was conducted between February and December 2012. This study was approved by the Ethics Committee of Tehran University of Medical Sciences and written informed consent was given to each patient. Excluded participants were the subjects who did not complete the intervention period, not take more than 12 capsules, and those who altered the dosage of their blood pressure-lowering medications.

The main capsules have 500mg quercetin and the placebo contained rice flour. Patients were randomly divided into treatment or placebo groups and they had two capsules to consume per day for 8 weeks. Daily intake of food was collected by24-hour recall questionnaire. Two three-day food records at the beginning and end of the intervention were obtained from each patient. These questionnaires were analyzed with nutrition 4 and USDA database (Bhagwat et al, 2011) in order to estimate the intake of energy, proteins, carbohydrates, total fat and quercetin.

Height was measured by a stadiometer at the beginning of the intervention, with bared feet. And, also weight was measured by a Seca scale. Calculation of BMI was with its formula: weight (kg)/ height (m²).

Blood pressure measured with a mercury sphygmomanometer under standard conditions which the American Heart Association Council on high blood pressure recommends (Pickering et al, 2005). Patients sat comfortably for 5-10 minutes. Each patient asked to remove the clothes which cover cuff location on arm. The arm was placed at the level of the right atrium and blood pressure (SBP and DBP) were measured while the patient was seated with no talking. If there were different in blood pressure measurements (>10 mmHg), another measurement was required after 5 minutes. The average of the measurements was considered as SBP or DBP. The trained individual was responsible for the measurements.

All data were analyzed by SPSS (version 11.5) and results were reported as mean±SD, Using Independent-Sample t-test to compare the differences in placebo and treatment groups at the beginning of the study. Paired-Samples t-test was also used to compare the differences between the two groups. Regression analyses (ANCOVA) was required to detect the variables between two groups before and after treatment. Pvalue <0.05 was considered significant (sig 2-tailed).

**RESULTS**

Seventy–two patients including 43 men and 29 women participated in this study. There were 36 patients: 13 women and 23 men - in placebo group with a mean age of 62.08±11.2 years. Also, thirty-six subjects were in intervention group including 16 women and 20 men with a mean age of 63.39±9.84.

Three-day food record before and after treatment indicated no significant changes in mean intake of energy, protein, carbohydrate, total fat and quercetin between groups and within groups. No significant changes were seen in body weight and BMI with quercetin supplementation (table 1). There were no significant changes in systolic and diastolic blood pressure in the placebo group, whereas significant decrease in SBP and DBP were observed in intervention group (P<0.05). The blood pressure data are in table 2.
DISCUSSION

The present study indicated that 1000 mg/d quercetin supplementation in 8 weeks in patients with a history of stroke can reduce blood pressure.

Flavonoids such as quercetin is generate by plant metabolism with various phenolic structures and have an antioxidant property, so they can scavenge free radicals and chelate metal ions. Other biological activities include antithrombotic, anti-inflammatory and vasodilatory effects (Knekt et al, 2002). As mentioned previously, quercetin is found in tea, onions, apples, berries and red wine (Prior, 2006; Larson et al, 2012; Edwards et al, 2007). Quercetin can reduce blood pressure through several mechanisms. Increased oxidative stress produces free radicals which are responsible for destruction of cell membrane and finally cell death (Ishisaka et al, 2011). Oxidative stress can be decreased by quercetin through the reactive hydroxyl group of quercetin neutralizing free radicals by bounding to the reactive sites of them (Saleh, 2011). So impaired vasodilation improves which can be the result of free radicals and increased oxidative stress (Larson et al, 2012). In addition, in an animal-based study has been shown that quercetin supplementation may decrease plasma malondialdehyde and urinary isoprostanes which are involved in oxidative stress (Larson et al, 2012; Edwards et al, 2007).

The inner layer of blood vessel (endothelium) synthesizes vascular dilator (nitric oxide) or vascular constrictor (endothelin-1). These factors are important to regulate blood pressure. When endothelial dysfunction occurs, bioavailability of NO decreases and causes the vessel to constrict by releasing endothelin-1. Quercetin is shown to improve endothelial dysfunction by increasing NO production or bioavailability (Larson et al, 2012; Perticone et al, 2001). The other mechanism which the blood pressure is regulated is rennin-angiotensin-aldosterone system (RAAS). Increased activation of RAAS can cause endothelium dysfunction leading to hypertension. Angiotensin converting enzyme (ACE) converts angiotensin 1 to angiotensin 2 which its inhibition can lead to lower blood pressure (Cohn, 2010). Quercetin has an inhibitory effect on ACE in cell culture medium (Loizzo et al, 2007) through the reactive hydroxyl group of quercetin binding with the active site of ACE consist of zinc ion (Ke Chen et al, 1996; Carretero, 2005). Also, increases in urine volume and urinary excretion of sodium may occur by quercetin supplementation promoting reduction in the blood pressure.

Based on the above evidence, quercetin might work as an ACE inhibitor (Larson et al, 2012). In addition, Ca++-sensitizing mechanism which is involved in contraction of smooth muscle is shown to be inhibited by quercetin (Pérez-Vizcaíno et al, 2002).

Two human studies are in line with our study and indicated a reduction in SBP and DBP by quercetin supplementation (Edwards et al, 2007; Knab et al, 2011) but one of the other studies showed the SBP reduction (Egert et al, 2009) which incorporated the lower dose of 150 mg/d quercetin for 6 weeks.
CONCLUSION

The results in this study indicated that 1000 mg/d quercetin supplementation in patients with a history of stroke significantly reduced blood pressure and could have a protective role in stroke.

AKNOWLEDGEMENT

This study was financially supported by Tehran University of Medical Sciences and international campus of Tehran University of Medical Sciences. The authors thank all the patients, the personnel of Imam Hussein and Firoozgar hospital who collaborate in this study.

REFERENCES