American Dietetic Association

RESEARCH

Original Research

Influence of Quercetin Supplementation on Disease Risk Factors in Community-Dwelling Adults

AMY M. KNAB, PhD; R. ANDREW SHANELY, PhD; DRU A. HENSON, PhD; FUXIA JIN, PhD; SERENA A. HEINZ; MELANIE D. AUSTIN, MS; DAVID C. NIEMAN, DrPH

ABSTRACT

Background In vitro data indicate quercetin has antioxidative and anti-inflammatory functions with the potential to lower disease risk factors, but data in human beings are limited.

Objective The objective of this study was to investigate the effect of quercetin, vitamin C, and niacin supplements (500 mg quercetin, 125 mg vitamin C, and 5 mg niacin [Q-500]; 1,000 mg quercetin, 250 mg vitamin C, and 10 mg niacin [Q-1,000]), on disease risk factors in a large group of community adults (n=1,002, 60% women) varying widely in age and body mass index.

Design Subjects were randomized into one of three groups (placebo, Q-500, or Q-1,000) and ingested supplements for 12 weeks. Blood samples were taken pre- and postsupplementation, and plasma quercetin, inflammatory markers (ie, C-reactive protein and five cytokines), diagnostic blood chemistries, blood pressure, and blood lipid profiles were measured.

Results Plasma quercetin increased in the Q-500 and Q-1,000 groups. No differences in blood chemistries were found except for a small decrease in serum creatinine and increase in glomerular filtration rate in Q-500 and Q-1,000 groups. A small decrease in mean arterial blood pressure was measured for Q-500 and Q-1,000 groups compared to placebo. A difference in serum total cholesterol was measured between Q-500 and placebo groups, and there was small decrease in high-density lipoprotein cholesterol levels in the Q-1,000 group. Change in inflammatory measures did not differ between groups except for a slight decrease in interleukin-6 for the Q-1,000 group.

Conclusions Q-500 or Q-1,000 supplementation for 12 weeks had a negligible influence on disease risk factors.

J Am Diet Assoc. 2011;111:542-549.

A. M. Knab, R. A. Shanely, and F. Jin are assistant professors with Appalachian State University at the Human Performance Lab within the North Carolina Research Campus (NCRC), Kannapolis. D. C. Nieman is a professor, Appalachian State University, and director of the Human Performance Lab at the NCRC, Kannapolis. M. D. Austin is the laboratory research manager, Department of Health, Leisure and Exercise Science, Appalachian State University, Boone, NC. D. A. Henson is a professor and associate dean, College of Arts and Sciences, Appalachian State University, and S. A. Heinz is a graduate student, Department of Biology, Appalachian State University, Boone, NC.

Address correspondence to: David C. Nieman, DrPH, North Carolina Research Campus, Human Performance Laboratory, 600 Laureate Way, Kannapolis, NC 28081. E-mail: niemandc@appstate.edu

Manuscript accepted: October 26, 2010.

0002-8223/$36.00

doi: 10.1016/j.jada.2011.01.013

Flavonoids, a group of naturally occurring polyphenolic compounds found in plants, are associated with antioxidative (1), anti-inflammatory (2), antipathogenic (3,4), cardioprotective (5), and anticarcinogenic (6) activities. Inflammation and oxidative stress are key mechanisms in the pathogenesis of certain disease states, supporting the strategy of increased flavonoid intake either through diet or supplementation for prevention of cardiovascular disease (CVD). Indeed, epidemiologic studies indicate that high consumption of foods rich in flavonoids is associated with a decrease in CVD risk factors (7-9), and risk of CVD (5). Flavonoid supplementation as a therapeutic method for reducing disease risk factors is receiving increasing attention.

In vitro and animal studies support the notion that quercetin, the major flavonoid consumed by human beings, reduces disease risk factors (10). For example, in mice fed a high-fat diet, quercetin lowered circulating plasma cytokines (interferon-γ, interleukin [IL]-1, and IL-4), without a change in body composition or weight (11). In addition, quercetin significantly decreased serum total cholesterol and phospholipid levels, and liver enzyme activity involved with fatty acid synthesis in mice fed quercetin for 15 days (12). In rats, quercetin inhibits nuclear factor-kappaB, cytokine expression, and cytokine-inducible nitric oxide synthase expression (13,14), and decreases blood pressure (15,16).

Data on the effects of supplemental isolated flavonoids, specifically quercetin, on lowering disease risk factors in humans is limited with conflicting results (17). Egert and colleagues (18) reported no effect of 2 weeks of quercetin supplementation (50, 100, or 150 mg/day) on inflammatory markers, lipid profile, or body composition in 35 healthy subjects. In a subsequent crossover trial of 93 overweight subjects, Egert and colleagues (19) reported a decrease in both systolic blood pressure and high-density lipoprotein (HDL) cholesterol after 6 weeks of ingesting

quercetin at a dose of 150 mg/day. Conquer and colleagues (20) reported no change in serum lipoproteins or blood pressure in 27 healthy subjects ingesting 1,000 mg/day quercetin for 1 month. Another study found that 730 mg quercetin/day for 1 month decreased blood pressure in overweight subjects with mild hypertension (21). Egert and colleagues (19) proposed that quercetin may provide protection against CVD, especially in those at high risk.

Quercetin-related benefits on CVD risk factors are unclear given inconsistencies in dosing regimens and low subject numbers in previous trials in human beings. Our study investigated two doses of quercetin combined with vitamin C and niacin (500 mg quercetin, 125 mg vitamin C, and 5 mg niacin [Q-500]) or 1,000 mg quercetin, 250 mg vitamin C, and 10 mg niacin [Q-1,000], for 12 weeks on disease risk factors (eg, blood pressure, blood lipid levels, and inflammatory cytokines) in a large community group (n=1,002) varying widely in age and body mass index (BMI). Doses were based on prior studies of human beings conducted in our lab (22). The mixture was based on unpublished animal studies showing increased bioavailability of quercetin when mixed with vitamin C (1:1 ratio) and niacin (Quercegen Pharma, personal communication, September 2006). Our hypothesis was that a quercetin-vitamin C-niacin supplement (Q-500 or Q-1000) would improve disease risk factors compared to placebo.

METHODS

Subjects

Male and female noninstitutionalized subjects (N=1,023), 18 to 85 years of age, were recruited via mass advertising from the community. Approximately half of subjects were studied during a 12-week period from January to April 2008, and the second half from August to November 2008. Women who were pregnant or lactating were excluded from the study, but no other exclusion criteria were employed. Both diseased and nondiseased subjects were allowed to participate, and during recruitment, subjects were stratified by sex (40% men), age (40% young adults aged 18 to 40 years, 40% middle-aged adults aged 41 to 65, and 20% elderly adults, aged 65 and older), and BMI (45% normal or 18.5 to 24.9, 30% overweight or 25 to 29.9, and 25% obese or ≥30) to ensure representation of these various subgroups. Thirty-seven percent of subjects reported past or current history for one or more chronic diseases: hypertension (19%), arthritis (16%), cancer (6%), cardiovascular disease (4%), and/or diabetes (4%). Where noted, subjects taking medication for a chronic disease were excluded from analysis. During the study, subjects agreed to avoid any other supplements containing quercetin; no other restrictions were placed on diet, supplement use, or medications. All experimental procedures were approved by the Appalachian State University Institutional Review Board, and written informed consent was obtained from each subject.

Research Design

Subjects were randomized to one of three groups: Q-500 (500 mg quercetin, 125 mg vitamin C, 5 mg niacin/day), Q-1,000 (1,000 mg quercetin, 250 mg vitamin C, 10 mg niacin/day), or placebo. Supplements were administered utilizing double-blind procedures. Subjects ingested two soft chew supplements twice daily (upon awakening, and between 2 PM and the last meal of the day) during the 12-week study period. Supplements were prepared by Nutravail Technologies (Chantilly, VA) with Quercegen Pharma (Newton, MA), and were soft, individually wrapped chews (5.3 g/piece) that contained either 125 or 250 mg quercetin, 125 or 250 mg vitamin C (ascorbic acid and sodium ascorbate), 5 or 10 mg niacin, and 20 kcal sugars in a carnauba wax, soy lecithin, corn starch, glycerin, and palm oil base colored with FD&C Yellow No. 5 and No. 6. Placebo supplements were prepared exactly the same way minus the quercetin, ascorbic acid and sodium ascorbate, and niacin. Data from Quercegen Pharma (unpublished data, personal communication, September 2006) indicate that the bioavailability of quercetin is enhanced with vitamin C and niacin, and thus this study tested whether the combination of quercetin, vitamin C, and niacin had an influence on the outcome measures.

Following the first blood sample, subjects began supplementing with the chews and continued this for 12 weeks. The following information was also reported via monthly logs by each subject: adherence to the supplementation regimen; physical activity and diet status; change in disease status and medication use; and gastrointestinal (constipation, heartburn, bloating, diarrhea, nausea, and vomiting), skin (rash, dryness, and flushing), allergy, and mental (energy, headache, stress, and focus/concentration) symptoms.

Outcome Measures

To obtain lifestyle habit information, subjects were asked to complete a lifestyle habit survey 2 weeks before the first lab visit for the study. Height was measured using a stadiometer, whereas body mass and body composition were measured using a Tanita bioelectrical impedance scale (Tanita, Arlington Heights, IL). Following an overnight fast, and a 15-minute seated rest, resting blood pressure was measured. Blood samples were obtained following the overnight fast (between 7 and 9 AM) before and after the 12-week supplementation period. These blood samples were then analyzed for outcome measures as described below. Unless otherwise specified all chemicals were purchased from Sigma Aldrich (St Louis, MO).

Plasma Quercetin. Plasma quercetin was measured as previously described (22). Briefly, total plasma quercetin (quercetin and its primary conjugates) from heparin-treated blood was measured following solid-phase extraction via reversed-phase high-performance liquid chromatography with ultraviolet detection. Quercetin conjugates were hydrolyzed by incubating 500-μL plasma aliquots with 10 μL 10% DL-dithiothreitol solution, 50 μL 0.58 mol/L acetic acid, 50 μL of a mixture of β-glucuronidase/arylsulfatase, and crude extract from Helix pomatia (Roche Diagnostics Corporation, Indianapolis, IN) for 2 hours at 37°C. Chromatographic analysis was performed using the Ultimate 3000 HPLC-PDA system (Dionex Corporation, Sunnyvale, CA) with a Gemini C18 column (Phenomenex, Torrance, CA).