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Effect of onion peel extract on endothelial function and endothelial progenitor cells in overweight and obese individuals

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ABSTRACT

Objectives: Acute or chronic intake of polyphenol-rich foods has been reported to improve endothelial function. Quercetin, found abundantly in onion, is a potent antioxidant flavonoid. The aim of this study was to investigate whether consumption of onion peel extract (OPE) improves endothelial function in healthy overweight and obese individuals.
Methods: This was a randomized double-blind, placebo-controlled study. Seventy-two healthy overweight and obese participants were randomly assigned to receive a red, soft capsule of OPE (100 mg quercetin/d, 50 mg quercetin twice daily; n = 36 participants) or an identical placebo capsule (n = 36) for 12 wk. Endothelial function, defined by flow-mediated dilation (FMD), circulating endothelial progenitor cells (EPCs) by flow cytometry, and laboratory test were determined at baseline and after treatment.
Results: Baseline characteristics and laboratory findings did not significantly differ between the two groups. Compared with baseline values, the OPE group showed significantly improved FMD at 12 wk (from 12.5 ± 5.2 to 15.2 ± 6.1; $P = 0.002$), whereas the placebo group showed no difference. Nitroglycerin-mediated dilation did not change in either group. EPC counts (44.2 ± 25.6 versus 52.3 ± 18.6; $P = 0.005$) and the percentage of EPCs were significantly increased in the OPE group. When FMD was divided into quartiles, rate of patients with endothelial dysfunction defined as lowest quartile (cutoff value, 8.6%) of FMD improved from 26% to 9% by OPE.
Conclusion: Medium-term administration of OPE an improvement in FMD and circulating EPCs.

Introduction

Overweight and obesity are closely related to the development and progression of cardiovascular disease (CVD) and are currently considered an important public health problem [1]. Epidemiologic studies have shown a rapid increase in the prevalence of overweight and obesity, in adults as well as in children and adolescents, thus increasing the risk for early development of CVD. Currently, nearly 70% of adults are classified as either overweight or obese, compared with <40% just 40 y ago [1].

Endothelial function, as assessed by flow-mediated endothelium-dependent vasodilation (FMD), is an important predictor of cardiovascular events [2,3]. It is well known that a high concentration of adipocytokines is associated with

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inflammation, endothelial dysfunction, and ultimately the onset of atherosclerogenic characteristics in obesity [4]. Alterations in endothelial function precede the development of morphologic atherosclerotic changes and can also contribute to lesion development and later clinical complications [5,6].

Large epidemiologic studies have shown an inverse correlation between dietary flavonol intake and mortality from CVD, risk for stroke, or both [7,8]. Acute or chronic intake of tea, cocoa, wine, and other polyphenol-rich foods have been reported to improve endothelial function, and these effects were attributed to a reduction in plasma oxidative stress by antioxidant polyphenolic compounds [9]. Quercetin, which is found in many kinds of fruits and vegetables but is particularly abundant in onion, is known to be a potent antioxidant flavonoid [10]. Quercetin prevents the induction of endothelial dysfunction, superoxide production, and overexpression by angiotensin II in the rat aorta [11]. Furthermore, a previous study demonstrated that supplementation with quercetin-rich onion peel extract (OPE) influenced adipokine expression, thus addressing its modulatory effect on obesity-induced inflammation, and improved insulin resistance by alleviating the metabolic dysregulation of free fatty acids, suppressing oxidative stress, upregulating glucose uptake, and downregulating inflammatory gene expression [12,13]. There are limited studies on the relationship between quercetin supplementation and endothelial dysfunction in humans. The aim of this study was to determine whether intake of OPE containing quercetin for 12 wk would improve endothelial function in healthy overweight and obese individuals.

Methods

Participants and study design

This was a randomized double-blind, placebo-controlled trial. We recruited 72 healthy Korean volunteers (mean age 43.1 ± 6.7 y; 51 women). The Kyung Hee University Hospital Ethics Committee approved this study and informed consent was obtained from all participants. Inclusion criteria were age 20 to 60 y, body mass index (BMI) >23 kg/m^2, and abdominal circumference >90 cm in men or >85 cm in women. Exclusion criteria were stage II uncontrolled hypertension (>160/100 mm Hg), diabetes, CVD, kidney disease, thyroid disease, cerebrovascular disease, or pregnancy. Individuals with depression, schizophrenia, or a history of alcohol or other drug intoxication were also excluded. None of the participants used herbal medications or vitamins during the study period; no further dietary restrictions were imposed. Dietary intake was measured at baseline, inter-visit, and final visit for maintaining the usual diet of the participants. The intake of functional foods including onion extracts, diet control product, or vitamin was checked because it could affect the result. The study was registered at www.clinicaltrial.gov; identifier: NCT02180022.

After obtaining informed consent, participants were randomly assigned to receive OPE or placebo using a computerized random-allocation sequence with a permutable block design. Based on the random group assignment, 36 individuals received a red, soft capsule of OPE (100 mg quercetin/d, 50 mg quercetin twice daily), whereas the other 36 received an identical placebo capsule for 12 wk.

FMD for assessment of endothelial function, blood sampling for EPC analysis by flow cytometry, and laboratory tests were performed at two time points (before and after the 12-wk treatment). Supine blood pressure (BP) and heart rate were recorded at seven time points. The study diagram is summarized in Figure 1. All examinations were performed in the morning at 0800 h under identical conditions in a temperature-controlled room (23°C–25°C) after individuals had fasted for 12 h since their last consumption of OPE.

Onion peel extract preparation

OPEs were prepared with onion peels purchased from Newfood Co. (Changnyeong, Korea). Peels were washed twice in tap water, extracted with 60% aqueous ethanol solution (50°C, 3 h) in an extractor (1 kL, Hansung F&C Co. Ltd, Korea), and then filtered with a filter press (Hankook Industry Co. Ltd., Korea). The filtrates were concentrated to 1.5 Brix as a percentage of soluble solid, which was measured using a refractometer (Atago Co. Ltd., Tokyo, Japan) in a vacuum concentrator (1 kL, Hansung F&C Co., Ltd., Korea). The concentrates were processed with a freeze dryer (SFDTS- 200 kg, Samwon Industry Co. Ltd., Korea) to give a powder that contained quercetin 100 mg/g [14].

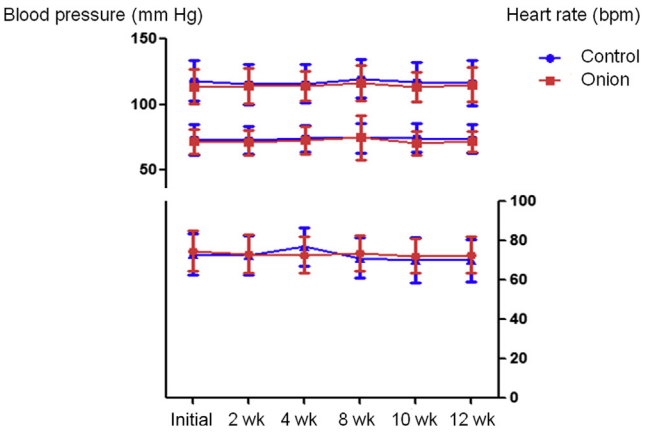

Fig. 1. Hemodynamic effects of onion peel extracts. There were no significant changes in either group.

Endothelial function assessment

Brachial artery FMD was examined using a commercially available system (Vivid 7, GE Vingmed, Horten, Norway) equipped with a 14-MHz linear array transducer as described previously [15,16]. Briefly, the electrocardiographic-gated, end-diastolic, longitudinal, B-mode images were digitally stored on the hard disk of the instrument for on- and offline analysis. After a 10-min rest in the supine position, the right brachial artery was scanned over a longitudinal section located 3 to 5 cm above the right elbow. The baseline brachial artery diameter was averaged from six separate images taken at 5-sec intervals. Subsequently, a pneumatic cuff placed at the level of the upper arm (i.e., distal to the site of brachial artery measurement) was inflated to 250 mm Hg for 5 min. After upper arm-cuff deflation, brachial artery diameter was reexamined at 5-sec intervals for 90 sec. Maximal vasodilation was observed 45 to 60 sec after cuff release. The diameter during peak dilation was averaged from six consecutive frames. FMD was calculated as the percent maximum increase in arterial diameter. Brachial artery diameter was calculated from the trailing edge of the intima-blood interface to the leading edge semiautomatically using a modified version of Image J software (Version 1.47 t, National Institutes of Health, Bethesda, MD, USA) as well as custom-designed software. The brachial artery FMD was calculated as the percent change in brachial artery diameter from baseline [brachial artery FMD = 100 × (diameter, peak–diameter, baseline)/(diameter, baseline)]. The reproducibility of this method in our laboratory was previously reported [15].

Characterization of endothelial progenitor cells by FACS

Based on cell-surface antigen expression, circulating CD45^{low} CD34$^+$ VEGFR2$^+$ mononuclear cells were defined as putative EPCs [15,17]. White blood cells were stained with allophycocyanin-conjugated anti-CD45 monoclonal antibody (mAb), FITC-conjugated anti-CD34 mAb, and phycoerythrin-conjugated anti-VEGFR2 mAb, and further incubated in the dark for 20 min. After appropriate gating based on low cytoplasmic granularity and low expression of CD45, CD34$^+$VEGFR2$^+$ cells were counted and expressed as the number of cells/10^6 total events or number of cells/100 μL of blood.

Laboratory assays

Whole blood was collected into tubes with no preservative or ethylenediaminetetraacetic acid, and centrifuged at 1500g for 15 min and 4°C, and serum or plasma was promptly allotted into storage tubes and frozen at –80°C. Samples were thawed only once for analysis and all samples for a given participant were evaluated in the same analytical run. A standardized method was used to measure glucose and cholesterol levels.

Sample size calculation and statistical analysis

The hypothesis of the present study was that OPE consumption improves endothelial function. In a previous study [18], OPE consumption provided ~30% protection against postprandial endothelial dysfunction in healthy men. Based on previous data showing that the FMD of healthy volunteers is 12.3 ± 4.5 [16], we