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SHORT COMMUNICATION

No evidence for a thermic effect of the dietary flavonol quercetin: a pilot study in healthy normal-weight women

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Abstract Our objective was to investigate the effect of quercetin supplementation on fasting resting energy expenditure (REE) and respiratory quotient (RQ) in humans. Six healthy, normal-weight women (mean age 25.5 ± 1.6 years, body mass index 21.4 ± 1.5 kg/m^2) participated in a randomized, placebo-controlled, double-blinded crossover study. Treatments were administered as capsules of 150 mg quercetin (aglycone) or placebo. The acute response was measured by indirect calorimetry for 3 h following ingestion. Blood pressure and pulse rate were assessed in 30-min intervals. On the following day, 24 h after capsule intake, a follow-up measurement was performed. Baseline (t_0) REE adjusted for fat-free mass was 4.7 ± 0.26 kJ/min (quercetin) and 4.8 ± 0.35 kJ/min (placebo) and did not significantly change between baseline and end (t_{180}) in either group ($P = 0.992$ for time effect in repeated measures analysis of variance; $P = 0.581$ for time × treatment interaction). Mean RQ was 0.78 ± 0.04 (quercetin) and 0.77 ± 0.04 (placebo). RQ values decreased slowly and to a similar extent during both treatments ($P < 0.001$ for time; quercetin, −0.09 ± 0.05; placebo, −0.08 ± 0.03; $P = 0.877$ for time × treatment interaction). Resting systolic and diastolic blood pressure, pulse pressure as well as resting pulse rate did not significantly change between baseline and end in either treatment group. No significant differences were found between the results of the baseline measurement and 24 h after treatment. In conclusion, the present pilot study provides no evidence for a thermic effect of quercetin in humans.

Keywords Quercetin · Energy expenditure · Respiratory quotient · Indirect calorimetry

Abbreviations

REE	Resting energy expenditure
RQ	Respiratory quotient
FFM	Fat-free mass
FM	Fat mass
SBP	Systolic blood pressure
DBP	Diastolic blood pressure

Introduction

Dietary flavonoids such as catechins as well as flavonols are suggested to have antiobesity effects (Hughes et al. 2008). For example, the administration of green tea catechins with caffeine is associated with significant reductions in body mass index (BMI), body weight, and waist circumference in overweight/obese individuals (Phung et al. 2010). A recent study in mice found that the flavonol quercetin (3,3′,4′,5,7-pentahydroxyflavone) transiently increased energy expenditure measured by indirect calorimetry (Stewart et al. 2008). Quercetin has been proposed to increase cellular energy expenditure by elevating oxygen consumption in human skeletal myocytes. The mechanism

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is thought to involve up-regulation of type 2 deiodinase expression, which has been shown to increase energy expenditure (Silva 2006) by increasing formation of triiodothyronine (thyroid hormone T3) (da Silva et al. 2007). Although these data are promising, studies addressing the influence of quercetin on energy metabolism in humans are limited. Therefore, we conducted a pilot study to investigate the potential acute effects of quercetin on energy expenditure in humans. The quercetin dosage was chosen from our previous study in healthy volunteers (Egert et al. 2008), which showed, although not significant, that fasting resting energy expenditure (REE) tended to increase (+0.10 MJ/24 h) after a continuous (2 weeks) supplementation of 150 mg/day quercetin when compared with baseline values (REE adjusted for fat-free mass at baseline 6.46 ± 0.47 MJ/24 h, at the end of the supplementation period 6.56 ± 0.61 MJ/24 h). We hypothesized that an acute quercetin intake has a thermic effect which was not seen in our previous study.

Materials and methods

Participants

Six healthy normal-weight women, all university students, participated in the study (baseline characteristics presented in Table 1). Inclusion criteria were: non-smoking status, non-athletic, a BMI of 19–25 kg/m^2, 19–30 years of age, weight-stability (±3 kg in last 3 months), and a low-to-moderate intake of caffeine-containing beverages [≤65 to 200 mg/day caffeine, equivalent to, e.g., ≤1 to 3 cups (150 mL per cup) of coffee]. Exclusion criteria were: metabolic and endocrine diseases (e.g., abnormal thyroid function), malabsorption syndromes, alcohol abuse, vegetarian or any other restrictive dietary requirements, use of dietary supplements or any form of medication (with the exception of oral contraceptives), and extreme intake of caffeine (>400 mg/day caffeine, equivalent to, e.g., >6 cups of coffee).

Table 1 Baseline characteristics of the subjects ($n = 6$)

Age (years)	25.5 ± 1.6
Body height (m)	1.63 ± 0.04
Body weight (kg)	57.2 ± 5.3
Body mass index (kg/m^2)	21.4 ± 1.50
Fat mass (kg)	13.2 ± 5.4
Fat mass (%)	22.7 ± 7.2
Fat-free mass (kg)	43.9 ± 1.9
Resting systolic blood pressure (mmHg)	106.2 ± 9.0
Resting diastolic blood pressure (mmHg)	67.2 ± 4.0
Resting pulse pressure (mmHg)	38.0 ± 8.2
Resting pulse rate (beats/min)	60.7 ± 6.9
Resting energy expenditure adj. (MJ/24 h)	6.80 ± 0.35
Respiratory quotient	0.79 ± 0.04

Values are presented as mean ± SD

Resting energy expenditure adj. resting energy expenditure adjusted for fat-free mass

Study design

The study was conducted in a randomized, placebo-controlled, double-blinded crossover design. Subjects ingested six capsules (150 mg quercetin or placebo) with a glass of tap water. The hard gelatine capsules contained quercetin dihydrate (Voigt Global Distribution Inc. Lawrence, KS, USA), mannitol, and the flow-regulating excipient silicium dioxide. A quercetin dosage of 150 mg was selected to represent the 15-fold of the estimated daily quercetin intake in Germany of about 10 mg. Pharmacokinetics of this quercetin dosage was examined previously (Egert et al. 2008). Our data showed that absorption of quercetin occurs within 30 min of ingestion.

One week before the treatment and on treatment day, all subjects ingested a quercetin-low diet to limit the influence of dietary quercetin on the results of the study. Subjects were given a detailed list of foods and beverages rich in quercetin to be avoided, e.g., unpeeled apples, black currents, onions, kale, and red wine.

Subjects completed 4-day dietary records (3 days before treatment and on treatment day). All entries were analyzed using the nutrient calculation program EBISpro (University of Hohenheim, Stuttgart, Germany) based on the German Nutrient Database "Bundeslebensmittelschlüssel" (Max-Rubner Institute, Karlsruhe, Germany).

Resting energy expenditure measurements

On each treatment day, the subjects arrived at the study unit at 0700 h. Body height was measured to the nearest 0.5 cm with a stadiometer. Body composition and body weight were measured on each treatment day after an overnight fast. Body composition (FM, FFM) was determined by air-displacement plethysmography using the BOD–POD Body Composition system (Life Measurements Instruments, Concord, CA, USA) as described (Bosy-Westphal et al. 2005).

REE was measured by the ventilated hood system (Vmax model 29n, Sensor Medics®; Viasys Healthcare, Bilthoven, The Netherlands) after resting for 10 min during calibration of the system in a metabolic ward at constant humidity (55%) and room temperature (22°C). A mass-flow sensor measured volume and airflow. Calibration of flow and gas analysers was done before each measurement. Flow calibration was performed by a 3-l calibration syringe and gas analysers were calibrated using two standard gas concentrations (16% O_2, 4% CO_2; 26% O_2; room air 20.94% O_2, 0.05% CO_2). During the investigation, an

automatic recalibration of gas analysers was made every 5 min. The subjects were awake, and lay quietly and motionless during the measurements. Data were collected every 20 s. Respiratory quotient (RQ) is defined as VCO_2 (carbon dioxide production in liters) divided by VO_2 (oxygen consumption in liters). VO_2 and VCO_2 were converted to REE by using the abbreviated Weir equation (Weir 1949). REE was adjusted for FFM by use of a linear regression analysis according to Ravussin and Bogardus (1989).

The respiratory measurements were of 3.5-h duration, from 0730 to 1105 h. Between 0730 and 0800 h, a baseline measurement was assessed. At 0800 h, the subjects ingested one of the two treatment compounds (quercetin or placebo) together with 200 mL tap water. After 5 min, respiratory measurements were continued for 3 h (post-treatment period). Blood pressure and pulse rate were assessed at 0730, 0800, 0835, 0905, 0935, 1005, 1035, and 1105. Blood pressure measurements were obtained with a standard manual sphygmomanometer under standardized conditions according to the recommendations of the American Heart Association Council on High Blood Pressure Research (Pickering et al. 2005). Pulse pressure was calculated as the pressure difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP). Pulse rate was measured by hand palpation at the radial artery.

On the following day, 24 h after capsule intake, a follow-up respiratory measurement was performed for 30 min between 0800 and 0830. In addition, body weight, body composition, blood pressure and pulse were measured. All measurements were performed by the same trained investigator.

The subjects were instructed to fast, except of water, from 2000 h in the evening prior to the measurements. The subjects abstained from other than habitual medication (contraceptives), and from alcohol and energetic physical activity for 24 h before the respiratory measurements. To limit diurnal variation and inter- and intra-subject variations, all measurements were carried out according to an identical schedule and at the same time of day. The women were measured once every 4 weeks to be sure that they were in the same phase of their menstrual cycle. The subjects were instructed to come to the metabolic ward of the institute by car or bus.

Statistical analysis

Sample size determination ($n = 6$) was based on the pilot study of Boschmann and Thielecke (2007) of similar design aimed to examine the thermogenic potential of the tea catechin epigallocatechin gallate in overweight men. Statistical analyses were performed using SPSS version 17 (SPSS Inc., Chicago, USA). Changes in REE, RQ, BP and pulse rate among the two treatments (quercetin vs. placebo) were tested for significance by repeated measures analysis of variance (RM-ANOVA). Baseline markers were compared between groups using paired t tests. The level of significance was set to $P < 0.05$ (two-tailed). Results are expressed as mean ± standard deviations (SD).

Results

There were no significant differences in mean body weight, fat mass and fat-free mass between quercetin and placebo treatments. Mean intakes of energy (9.4 MJ/day), protein (15.3% of energy intake), carbohydrates (46.1% of energy intake), fat (35.5% of energy intake), fatty acids, antioxidants or dietary fiber were similar between both treatment periods.

REE adjusted for FFM did not significantly change between baseline (t_0) and end (t_{180}) in either treatment group ($P = 0.992$ for time effect in RM-ANOVA; $P = 0.581$ for time × treatment interaction; Fig. 1). All subjects responded similar. Baseline RQ was 0.78 ± 0.04 (quercetin) and 0.77 ± 0.04 (placebo). RQ decreased slowly and to a similar extent during both treatments ($P < 0.001$ for time; quercetin, −0.09 ± 0.05; placebo, −0.08 ± 0.03; $P = 0.877$ for time × treatment interaction; Fig. 1). Resting SBP (quercetin 105.0 ± 10.0 mmHg; placebo 106.0 ± 7.2 mmHg) and DBP (quercetin 64.6 ± 4.8 mmHg; placebo 66.6 ± 7.1 mmHg), pulse pressure (quercetin 40.4 ± 7.2 mmHg; placebo 39.3 ± 6.8 mmHg) as well as resting pulse rate (quercetin 62.6 ± 7.8 beats/min; placebo 61.3 ± 6.5 beats/min) did not significantly change between baseline and end in either group. No significant

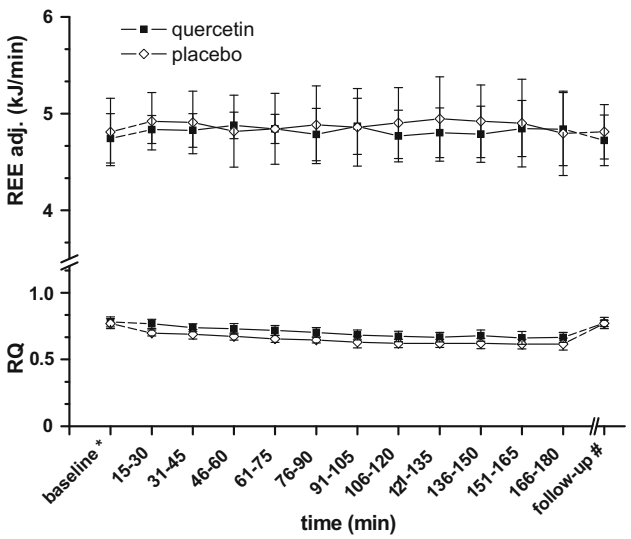

Fig. 1 Effect of supplementation with quercetin or placebo on resting energy expenditure (*REE*) and respiratory quotient (*RQ*) in healthy normal-weight women ($n = 6$ per group). Values are presented as mean ± SD. *Asterisk* baseline measurement before capsule intake, *hash* measurement 24 h after capsule intake, *REE adj.* resting energy expenditure adjusted for fat-free mass. Note that the ordinate is broken and shows different variables

differences in metabolic data were seen between baseline and follow-up (REE at baseline, quercetin 4.7 ± 0.26 kJ/min, placebo 4.8 ± 0.35 kJ/min; REE at follow-up, quercetin 4.7 ± 0.26 kJ/min, placebo 4.8 ± 0.28 kJ/min; RQ at baseline, see above; RQ at follow-up, quercetin 0.77 ± 0.04, placebo 0.77 ± 0.02).

Discussion

Our double-blinded, placebo-controlled study showed that acute ingestion of 150 mg quercetin did not have an effect on fasting REE and substrate oxidation in normal-weight women when compared to placebo. The present findings are consistent with those of our previous studies which showed no significant effects of a long-term quercetin supplementation (150 mg/day for 2 weeks) on fasting REE in healthy normal-weight subjects (Egert et al. 2008), as well as no significant effects of quercetin (150 mg/day for 6 weeks) on body weight, BMI, waist circumference, FM and FFM in overweight/obese patients with metabolic syndrome traits (Egert et al. 2009, 2010).

To the best of our knowledge, no previous research group has examined the effects of dietary quercetin on energy metabolism in humans. Our results are in contrast to the experimental data of Stewart et al. (2008) in C57BL/6J mice, who showed that continuous quercetin ingestion administered as a food admixture (45% kcal fat diet + 0.8% quercetin) significantly enhanced energy expenditure when measured by indirect calorimetry after 3 weeks. However, this effect did not persist for 8 weeks and did not translate into significant quercetin-induced effects on body weight and body composition (e.g., decrease in FM) (Stewart et al. 2008). The loss of an effect on energy expenditure coincided with a significant decrease in plasma concentrations of quercetin between 3 and 8 weeks (Stewart et al. 2008). This decrease was without any decrease in food intake suggesting that adaptive changes in the pharmacokinetics of quercetin may have diminished its metabolic effects. In addition, the data showed that quercetin increased energy expenditure without effects on substrate selection (e.g., fat instead of carbohydrates) (Stewart et al. 2008).

The fact that energy expenditure was increased in response to quercetin supplementation in mice but not in our human studies may be related to differences in the quercetin dosages administered and the plasma quercetin concentrations reached. The high-fat diet used by Stewart et al. (2008) contained 0.8% quercetin, which translates to a daily dose of 20 mg per mouse or 0.8 mg/day per gram body weight for the weight range of mice in their study. In contrast the administered quercetin dosage of our present human study was ~308-times lower (2.6 mg/kg body weight or 2.6×10^{-3} mg/g body weight). Although we did not measure plasma quercetin concentrations, we assume based on the data of our previous pharmacokinetic study (Egert et al. 2008), that the maximum plasma quercetin concentration during our metabolic measurement was ~0.3 μmol/L. It seems likely that this plasma quercetin concentration was below the threshold for an effect on energy metabolism in humans.

Furthermore, it is possible that the time period of our respiratory measurements of 3.5 h was not long enough to detect a possible metabolic effect of quercetin. However, a longer measurement period in the fasting state and under strictly controlled conditions was not reasonable for our subjects.

The underlying molecular mechanisms by which quercetin may affect energy metabolism have yet not been fully elucidated. It has been reported that quercetin upregulated the cAMP-responsive gene for type 2 deiodinase (D2), an intracellular enzyme that activates thyroid hormone (T3) for the nucleus (da Silva et al. 2007). The net effect was a stimulation of D2 activity with a concurrent increase of the rate of T3 production (da Silva et al. 2007). Thyroid hormone is the most potent substance known to rapidly increase oxygen consumption (Silva 2006). It should be noted that the flavonol concentrations that produced such biological effects (2–20 μmol/L) cannot easily be attained via dietary supplementation in humans.

In conclusion, the present pilot study and the results of our previous examinations do not suggest that quercetin in a supra-nutritional dosage of 150 mg significantly affects energy expenditure, fat oxidation, body weight and FM in humans. It will be important in future studies to examine the effects of pharmacological dosages of quercetin on energy expenditure in humans.

The study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the ethical committee of the Medical Faculty of the University of Kiel, Germany. Written informed consent was obtained from all subjects.

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Conflict of interest The authors declare that they have no conflict of interest.

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