Body Weight Loss and Weight Maintenance in Relation to Habitual Caffeine Intake and Green Tea Supplementation

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Abstract

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Objective: Investigation of the effect of a green tea-caffeine mixture on weight maintenance after body weight loss in moderately obese subjects in relation to habitual caffeine intake.

Research Methods and Procedures: A randomized placebo-controlled double blind parallel trial in 76 overweight and moderately obese subjects, (BMI, 27.5 $\pm$ 2.7 kg/m^2) matched for sex, age, BMI, height, body mass, and habitual caffeine intake was conducted. A very low energy diet intervention during 4 weeks was followed by 3 months of weight maintenance (WM); during the WM period, the subjects received a green tea-caffeine mixture (270 mg epigallocatechin gallate + 150 mg caffeine per day) or placebo.

Results: Subjects lost 5.9 $\pm$1.8 (SD) kg (7.0 $\pm$ 2.1%) of body weight ($p < 0.001$). At baseline, satiety was positively, and in women, leptin was inversely, related to subjects' habitual caffeine consumption ($p < 0.01$). High caffeine consumers reduced weight, fat mass, and waist circumference more than low caffeine consumers; resting energy expenditure was reduced less and respiratory quotient was reduced more during weight loss ($p < 0.01$). In the low caffeine consumers, during WM, green tea still reduced body weight, waist, respiratory quotient and body fat, whereas resting energy expenditure was increased compared with a restoration of these variables with placebo ($p < 0.01$). In the high caffeine consumers, no effects of the green tea-caffeine mixture were observed during WM.

Discussion: High caffeine intake was associated with weight loss through thermogenesis and fat oxidation and with suppressed leptin in women. In habitual low caffeine consumers, the green tea-caffeine mixture improved WM, partly through thermogenesis and fat oxidation.

Introduction

The increasing incidence of obesity is a recognized medical problem in developed countries (1). Obesity is a major factor in a number of diseases, including coronary heart diseases, hypertension, non–insulin-dependent diabetes, pulmonary dysfunction, osteoarthritis, and certain types of cancer (2–4).

Factors related to the development of obesity are decreased physical activity and increased energy intake. Weight loss and loss of body fat can, thus, be achieved by reducing energy intake and/or increasing energy expenditure.

Treatment of obesity is beneficial in that weight loss reduces the risk for mortality and morbidity. Even modest weight loss, 5% to 10% of the initial body weight, already leads to beneficial health effects (5–7). Modest weight loss is a realistic goal for most subjects (5,7).

However, long-term maintenance of the body weight lost can be described as unsuccessful. Most studies on weight maintenance show an undesired weight regain (8–12), indicating that subjects did not change their eating and activity behavior adequately (13). Interventions to improve long-term weight maintenance are needed to treat obesity effectively. The limited long-term effectiveness of conventional weight management (dietary intervention, physical activity, and behavioral therapy) leads to the development of alternative weight reduction strategies.

A rapidly growing therapeutic area is the use of natural herbal supplements. One of these agents is a green tea-

caffeine mixture (epigallocatechin gallate plus caffeine), whose claimed antiobesity properties have been ascribed to increased thermogenesis and fat oxidation (14–19). A green tea-caffeine mixture contains caffeine that may stimulate thermogenesis and fat oxidation through inhibition of phosphodiesterase, an enzyme that degrades intracellular cyclic AMP and through antagonism of the negative modulatory effect of adenosine on increased noradrenaline release (14). Human studies have shown that caffeine stimulates thermogenesis and fat oxidation (15–17). In addition, green tea-caffeine mixtures contain large amounts of tea catechins, which have been shown to inhibit catechol O-methyl-transferase (18). Also in humans, a green tea-caffeine mixture has been shown to stimulate thermogenesis and fat oxidation in the short-term (19–21). Dulloo et al. (19) showed that the effect of a green tea-caffeine mixture was greater than could be attributed to its caffeine content.

Based on these studies in humans, we hypothesized that a green tea-caffeine mixture would reduce body weight regain in humans after weight loss, possibly through a thermogenic effect (19–21).

However, as seen in our previous study, a possible effect may partly depend on habitual caffeine intake. There we found posthoc, after the subjects were divided into habitually low caffeine consumers (<300 mg/d) and habitually high caffeine consumers (>300 mg/d), a stronger body weight maintenance after body weight loss, i.e., 16% body weight regain vs. 39% body weight regain ($p < 0.05$), in the habitually low caffeine consumers (149 ± 90 mg/d) compared with the high caffeine consumers (511 ± 167 mg/d) (22).

Therefore, we executed a follow-up study on body weight maintenance with the aim of investigating whether the same green tea-caffeine mixture may improve weight maintenance by preventing or limiting weight regain after weight loss of 5% to 10% in moderately obese subjects with a low or high habitual caffeine intake.

Research Methods and Procedures

Subjects

Ninety male and female overweight and moderately obese subjects, 18 to 60 years of age and with BMI between 25 and 35 kg/m², were recruited from the local population. They underwent a medical screening. Selection was based on being in good health, a nonsmoker, not using medication, and, at most, a moderate alcohol user. Seventy-six subjects were eligible for participation in the study. They were divided into two stratified groups according to sex, BMI, age, dietary restraint (factor 1 of the Three-Factor Eating Questionnaire, indicating cognitively restrained eating behavior), resting energy expenditure (REE),[1] and being either

habitual low caffeine consumers ($n = 38$; caffeine consumption < 300 mg/d) or habitual high caffeine consumers ($n = 38$; caffeine consumption > 300 mg/d). [Caffeine consumption was asked using individual dietary anamneses including all possible caffeine-containing drinks or foods (coffee, tea, chocolate, Coca Cola, Red Bull); the main source of caffeine intake was coffee.] The cut-off point was based on our previous study (22). All subjects gave their written informed consent. The Medical Ethics Committee of the Academic Hospital in Maastricht approved of the study. Subsequently, within the low or high habitual caffeine consumption groups, subjects were further stratified according to the characteristics mentioned above and randomized to a prospective green tea-caffeine mixture treatment group and a placebo group for the weight maintenance phase (Table 1). During this weight maintenance phase, the subjects received a green tea-caffeine mixture [45 mg epigallocatechin gallate + 25 mg caffeine + 380 mg placebo (vegetable oil)/capsule; 6 capsules/d; 2 capsules before each meal] or placebo [450 mg placebo (vegetable oil)/capsule; 6 capsules/d; 2 capsules before each meal]. The dosage of epigallocatechin gallate was the same as used by Dulloo et al. (19); the dosage of caffeine was lower to avoid a dosage >1000 mg/d, because of the habitually high caffeine consumption of 100 to 1000 mg/d in The Netherlands (23).

The capsules were manufactured by Novartis CH, Nyon, Basel, Switzerland.

Measurements

The following measurements were executed at baseline, after body weight loss, and after 3 months of weight maintenance.

Anthropometry

Body weight was measured with a digital balance (model 707; Seca, Hamburg Germany; weighing accuracy of 0.1 kg) with subjects in underwear, in a fasted state, and after voiding their bladder. Height was measured using a wall-mounted stadiometer (model 220; Seca). BMI was calculated as weight (kilograms) divided by height (meters) squared.

The distribution of fat was studied by measuring the waist circumference at the site of the smallest circumference between the rib cage and the ileac crest, with the subjects in standing position.

Body Composition

Total body water (TBW) was measured using the deuterium (^2H_2O) dilution technique (24). In the evening, after collection of a background urine sample, the subjects ingested a dose of deuterium enriched water (^2H_2O). After consumption of the ^2H_2O, no fluid or food was consumed. The following morning, a urine sample from the second voiding was collected between 8:00 AM and 10:00 AM. Deuterium concentration in the urine samples was measured

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[1] Nonstandard abbreviations: REE, resting energy expenditure; TBW, total body water; FFM, fat-free mass; FM, fat mass; RQ, respiratory quotient; FFA, free fatty acid; PAL, physical activity level; TEE, total energy expenditure; VLED, very low energy diet.

Table 1. Baseline characteristics of the subjects ($n = 76$) divided over habitual high and low caffeine intake groups and prospective treatment groups (green tea vs. placebo)

	Green tea ($n = 38$)		Placebo ($n = 38$)	
	Low caffeine ($n = 19$)	High caffeine ($n = 19$)	Low caffeine ($n = 19$)	High caffeine ($n = 19$)
BM (kg)	85.1 ± 9.5	85.0 ± 8.5	85.1 ± 9.6	85.0 ± 8.3
Height (m)	1.70 ± 0.12	1.70 ± 0.11	1.70 ± 0.10	1.70 ± 0.12
BMI (kg/m^2)	29.6 ± 2.6	29.5 ± 2.4	29.6 ± 2.7	29.5 ± 2.2
Waist (cm)	94.2 ± 7.7	94.0 ± 7.1	94.0 ± 7.3	94.0 ± 7.0
FFM (kg)	53.4 ± 9.1	53.3 ± 9.2	53.4 ± 9.2	53.3 ± 9.0
FM (kg)	31.7 ± 6.9	31.7 ± 5.8	31.7 ± 7.0	31.7 ± 5.6
Percent body fat	37.3 ± 5.4	37.3 ± 4.7	37.3 ± 5.1	37.7 ± 4.9
F1	7.0 ± 2.7	7.5 ± 3.1	7.0 ± 2.8	7.4 ± 3.3
F2	5.7 ± 2.1	6.0 ± 2.2	5.6 ± 2.4	6.1 ± 2.3
F3	4.9 ± 3.0	4.9 ± 3.1	4.9 ± 3.1	4.9 ± 3.2
HP	16.1 ± 3.7	16.3 ± 3.2	16.2 ± 3.6	16.2 ± 3.1
Hunger (mm VAS)	38.2 ± 24.0	32.5 ± 26.2	37.6 ± 25.0	32.7 ± 25.2
Satiety (mm VAS)	25.9 ± 20.2	$35.3 \pm 21.8*$	26.9 ± 21.4	$36.3 \pm 22.9*$
REE (MJ/d)	6.9 ± 0.9	7.0 ± 1.0	6.9 ± 1.0	7.1 ± 1.1
RQ	0.84 ± 0.03	0.83 ± 0.04	0.84 ± 0.02	0.83 ± 0.03
PAL	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1
TEE (MJ/d)	11.0 ± 1.3	11.4 ± 1.5	11.0 ± 1.2	11.4 ± 1.6
Glucose (mM/L)	5.5 ± 0.8	5.6 ± 0.5	5.6 ± 0.7	5.7 ± 0.6
Insulin (mUnits/mL)	10.4 ± 4.3	10.5 ± 3.6	10.5 ± 5.3	10.6 ± 4.6
BHB (mM/L)	250.0 ± 78.6	264.4 ± 103.7	256.0 ± 84.7	266.4 ± 93.2
Glycerol (mM/L)	96.4 ± 34.0	99.2 ± 38.6	97.4 ± 35.0	98.2 ± 39.7
FFA (mM/L)	324.1 ± 131.0	322.9 ± 122.5	323.7 ± 132.0	322.1 ± 120.8
Triglycerides (mM/L)	1286.9 ± 633.2	1262.9 ± 626.1	1363.9 ± 605.9	1313.9 ± 600.9
Leptin (ng/L)	26.3 ± 8.6	$19.0 \pm 7.9*$	26.0 ± 6.8	$18.8 \pm 6.9*$

Values are mean $\pm$ SD.
* $p < 0.05$, pooled high caffeine intake groups compared with the pooled low caffeine groups (factorial ANOVA).
Scores on the Three-Factor Eating Questionnaire (25): F1, cognitive restraint; F2, disinhibition; F3, hunger.
HP, Herman-Polivy restraint (26); VAS, visual analogue scale; BHB, β-hydroxy-butyrate.

using an isotope ratio mass spectrometer (Micromass Optima, Manchester, United Kingdom). TBW was obtained by dividing the measured deuterium dilution space by 1.04 (24). Fat-free mass (FFM) was calculated by dividing the TBW by the hydration factor of 0.73. By subtracting FFM from body weight, fat mass (FM) was obtained. FM expressed as a percentage of body weight gives percentage of body fat.

Attitude Toward Eating

To determine whether attitude toward food intake changed during the experiment, the Three-Factor Eating Questionnaire was used (25). Factor 1 indicates cognitive dietary restraint, factor 2 indicates disinhibition of eating, and factor 3 indicates general hunger feelings. In addition, the Herman Polivy questionnaire (26) was used to determine the frequency of previous dieting.

In addition to these questionnaires, subjects' baseline caffeine intake was estimated during a food anamnesis specific for caffeine-containing products.

Postabsorptive Appetite Profile

To determine the postabsorptive appetite profile, hunger and satiety were rated on anchored 100-mm visual analog scales in the morning before breakfast. This time-point was chosen because, in previous studies (22,27), we found significant relationships of body weight maintenance with

changes in postabsorptive hunger or satiety ratings, i.e., in the fasting state before breakfast.

Blood Parameters

A fasted blood sample of 10 mL was taken and mixed with EDTA to prevent clotting. Plasma was obtained by centrifugation, frozen in liquid nitrogen, and stored at $-80\,°C$ until further analysis. Plasma glucose concentrations were determined using the hexokinase method (Glucose HK 125 kit; ABX diagnostics, Montpellier, France). The Wako NEFA C-kit (Wako Chemicals, Neuss, Germany) was used to determine free fatty acid (FFA) concentrations. Insulin concentrations was measured using the radioimmunoassay kit (Insulin RIA-100; Kabi Pharmacia, Piscataway, NJ). The glycerokinase method was used to determine glycerol concentrations (Boehringer Mannheim, Mannheim, Germany). Triacylglycerol was measured using the GPO-trinder kit (Sigma Diagnostics, St. Louis, MO). Concentrations of triacylglycerol were corrected for glycerol.

The β-hydroxybutyrate dehydrogenase method (Sigma Diagnostics) was used to determine β-hydroxybutyrate concentrations. Leptin concentrations were measured using the human leptin radioimmunoassay kit (Linco Research, St. Charles, MO).

Adverse Events

Frequency and intensity of adverse events during treatment were recorded.

REE and Substrate Oxidation

REE and substrate oxidation were measured by means of an open circuit ventilated hood system. REE was measured in the morning with subjects in a fasted state and lying supine for 30 minutes. Gas analyses were performed by a paramagnetic oxygen analyzer (type 500A; Servomex, Crowborough Sussex, United Kingdom) and an infrared carbon dioxide analyzer (Servomex type 500A) (28). Calculation of REE was based on the formula of Weir (29). Respiratory quotient (RQ) was calculated as CO_2 produced divided by O_2 consumed.

Physical Activity

Physical activity was determined during 1 week partly using a Computer Science Applications (CSA) accelerometer (30) and partly with a triaxial accelerometer for movement registration (Tracmor, Maastricht, The Netherlands). The Tracmor is a small device ($7 \times 2 \times 0.8$ cm, 30 grams) that measures accelerations in the anteroposterior, mediolateral, and vertical directions of the trunk (31). Subjects were wearing the same type of accelerometer during waking hours in a belt at the back of the waist during three different phases of the study.

Physical activity level (PAL) was calculated using the following equations:

$$\text{CSA: PAL} = [0.000001379 \times (\text{counts/d} \times 5)]$$
$$+ 1.113 \text{ (30)}$$

$$\text{Tracmor: TEE} = -1.259 + (1.552 \times \text{REE}) + (0.076$$
$$\times \text{counts/min) (31)}$$

$$\text{PAL} = \text{TEE/REE}$$

in which total energy expenditure (TEE) and REE are expressed in megajoules per day.

Energy Expenditure

For subjects who were wearing the CSA, TEE was calculated by multiplying REE by PAL. For those subjects who were wearing the Tracmor, TEE was calculated as indicated above.

Weight Loss Period

After baseline measurements were determined, the subjects followed a very low energy diet (VLED; 2.1MJ/d) for 4 weeks to lose weight. The diet (Modifast) was supplied in three packets daily, to be dissolved in water to obtain a milkshake, pudding, soup, or muesli. This diet provided 2.1 MJ/d and was a protein-enriched formula diet, containing 50 grams of carbohydrates, 52 grams of protein, 7 grams of fat, and a micronutrient content that met the Dutch recommended daily allowance. Vegetables and fruit were allowed in addition to Modifast. The aim was a body weight loss of at least 4 kg over 4 weeks.

After this weight loss period, the measurements described above were repeated.

Weight Maintenance

During the weight maintenance phase, the subjects received a green tea-caffeine mixture (45 mg epigallocatechin gallate + 25 mg caffeine + 380 mg placebo/capsule; 6 capsules/d) or placebo (450 mg placebo/capsule; 6 capsules/d).

Within the low or high caffeine intake group, subjects were stratified according to sex, BMI, age, dietary restraint (Three-Factor Eating Questionnaire, factor 1), and REE and divided into two groups. A double-blind administration of the supplementation (green tea-caffeine mixture or placebo) was carried out. Thus, from each group, the high caffeine consumers as well as the low caffeine consumers, 19 subjects were allocated to the green tea-caffeine mixture group, and 19 subjects were allocated to the placebo group, resulting in four different groups (Table 1).

Repeated Measurements

Measurements as described under baseline measurements were executed again 3 months after the start of the weight maintenance period. In addition, body weight was determined 1 and 2 months after the start of the weight maintenance phase.
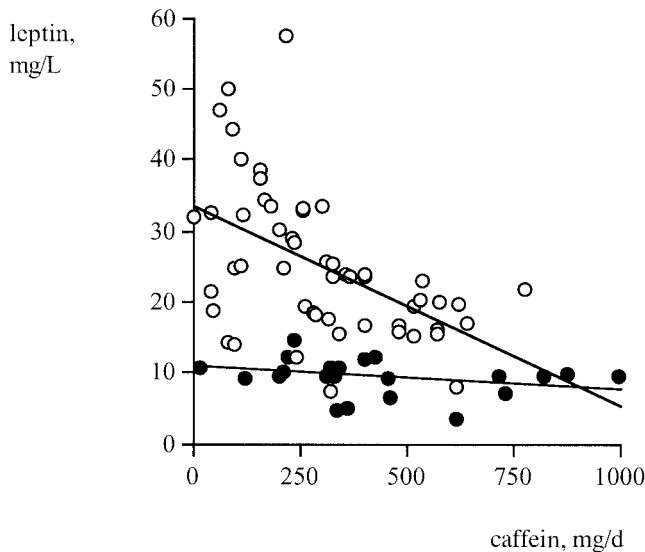
Figure 1: Leptin concentration as a function of habitual caffeine intake. Women (○; $n = 53$): $y = -0.3x + 33.6$; $r^2 = 0.3$, $p < 0.001$. Men (●; $n = 23$): $y = -0.003x + 10.8$; $r^2 = 0.003$, $p > 0.1$.
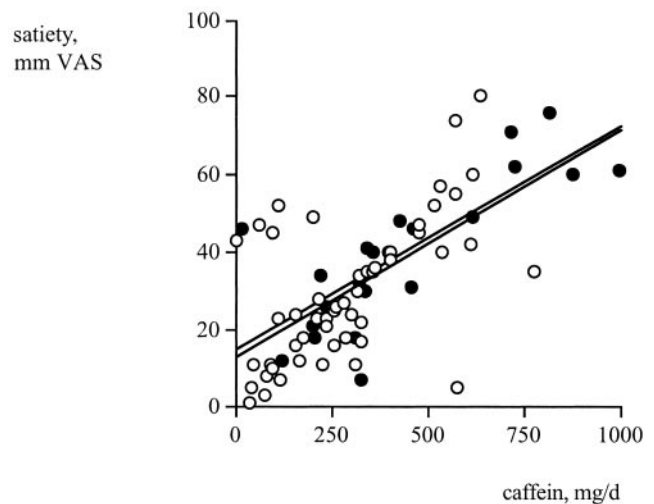

Figure 2: Satiety as a function of habitual caffeine intake in men and women. Women (○; $n = 53$): $y = 0.06x + 13.0$; $r^2 = 0.4$; $p < 0.001$. Men (●; $n = 23$): $y = 0.06x + 14.5$; $r^2 = 0.6$; $p < 0.001$. VAS, visual analogue scale.

Body weight maintenance was expressed as rate of regain over the first 3 months after weight loss. The 3-month period to measure weight maintenance was based on the stable rate of regain (0.67 kg/mo) that we showed before over the first 3 months and on the strong relationship of rates of regain between 3 and 8 or 14 months ($r = 0.9$; $p < 0.0001$) (10–12).

Data Analysis

The two groups were stratified according to the number of men/women, BMI, age, eating behavior (Three-Factor Eating Questionnaire, factor 1), REE, and caffeine consumption, and the differences between these groups were checked using a factorial ANOVA. Stratification was successful when the p values of this comparison were high, indicating very small differences. p values for these differences were >0.9 for sex distribution and BMI, >0.8 for age, >0.6 for dietary restraint, and >0.5 for REE and caffeine consumption.

The effect of treatment with a green tea-caffeine mixture over time was compared with placebo, using two- or four-factor ANOVA repeated measures. Posthoc, a Scheffe *F* test was applied. Relationships based on individual differences were tested using regression analysis. When appropriate, differences between groups were analyzed using a factorial ANOVA or a Student's *t* test. The software used was Statview SE+Graphics (Abacus Concepts, Berkeley, CA). Statistical significance was set at $p < 0.05$.

Results

General

No adverse events occurred. Almost no different effects for men or women were observed; therefore, these data were

pooled where possible. The low caffeine intake groups consumed statistically significant less caffeine/d, i.e., 151 ± 87 mg/d, than the high caffeine intake groups, i.e., 524 ± 158 mg/d (pooled groups; $p < 0.001$). Habitual caffeine intake was sustained during the study.

Baseline

At baseline, high caffeine intake seemed to imply a higher satiety and a lower leptin concentration (Table 1). Regression analyses showed that satiety was positively related to caffeine intake in both sexes (women: $r^2 = 0.4$; men: $r^2 = 0.6$; $p < 0.001$) and that leptin was inversely related to caffeine intake in women ($r^2 = 0.3$; $p < 0.001$) but not in men ($r^2 = 0.003$; $p > 0.1$), because of the small range of leptin concentrations in these men (Figures 1 and 2).

Weight Loss

During the VLED intervention, subjects lost a significant amount of their original body weight ($p < 0.001$). Weight loss was significantly higher (6.7 ± 1.4 kg) in the high caffeine intake groups than in the low caffeine intake groups (pooled groups; 5.1 ± 1.2 kg; $p < 0.01$). This also implied greater reductions in BMI, waist circumference, fat mass, and percentage body fat ($p < 0.01$; (Figures 3 and 4). During weight loss, the high caffeine intake groups decreased REE less and sustained fat oxidation more (Figures 5 and 6). Body weight loss did not differ between the two prospective treatment groups.

Attitude toward eating did not change significantly during weight loss, nor did Herman Polivy restraint scores or PAL; these were not different between prospective treat-
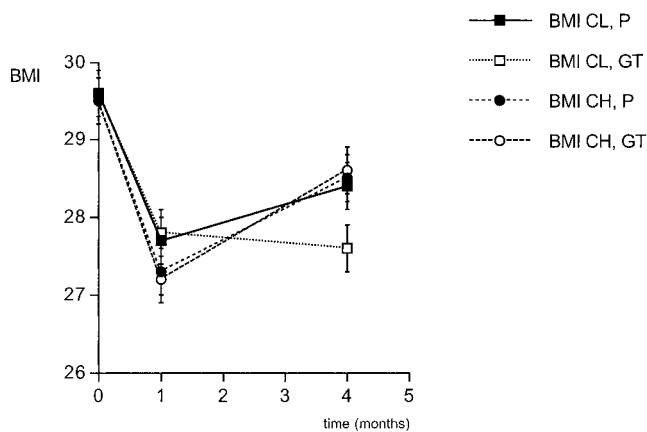
Figure 3: BMI of men ($n = 23$) and women ($n = 53$) over time. Month 1: after the VLED; month 4: after 3-month follow-up; CL, habitual low caffeine intake; CH, habitual high caffeine intake; GT, green tea during follow-up; P, placebo during follow-up. * $p < 0.01$, at month 1: group (pooled high caffeine intake groups vs. pooled low caffeine intake groups) $\times$ time (two-factor repeated measures ANOVA). * $p < 0.01$, at month 4: group (low caffeine intake group receiving green tea vs. all other groups) $\times$ time (four-factor repeated measures ANOVA).

ment groups. Satiety in the fasted state before breakfast increased significantly during the VLED in the low caffeine intake groups; it did not differ between prospective treatment groups (Table 2).

The blood parameters glucose, insulin, triacylglycerol, and leptin decreased during weight loss, whereas glycerol, FFA, and β-hydroxybutyrate increased, without differences in changes between prospective treatment groups (Table 2).

Weight Maintenance

During the weight maintenance period, the percentage of body weight regained was significantly smaller in the low caffeine intake group that received the green tea-caffeine mixture ($-11.1 \pm 24.3\%$), and, in fact, the group continued to lose weight, compared with the low caffeine group receiving placebo ($40.8 \pm 28.9\%$; time $\times$ treatment interaction; $p < 0.01$). This was also the case when the low-caffeine intake group that received the green tea-caffeine mixture was compared with the high caffeine group receiving the green tea-caffeine mixture, who regained $24.4 \pm 18.7\%$ of the body weight lost (time $\times$ treatment interaction; $p < 0.01$). This also implied a smaller increase in body mass, BMI, waist circumference, and FM over time in the low caffeine intake group that received the green tea-caf-
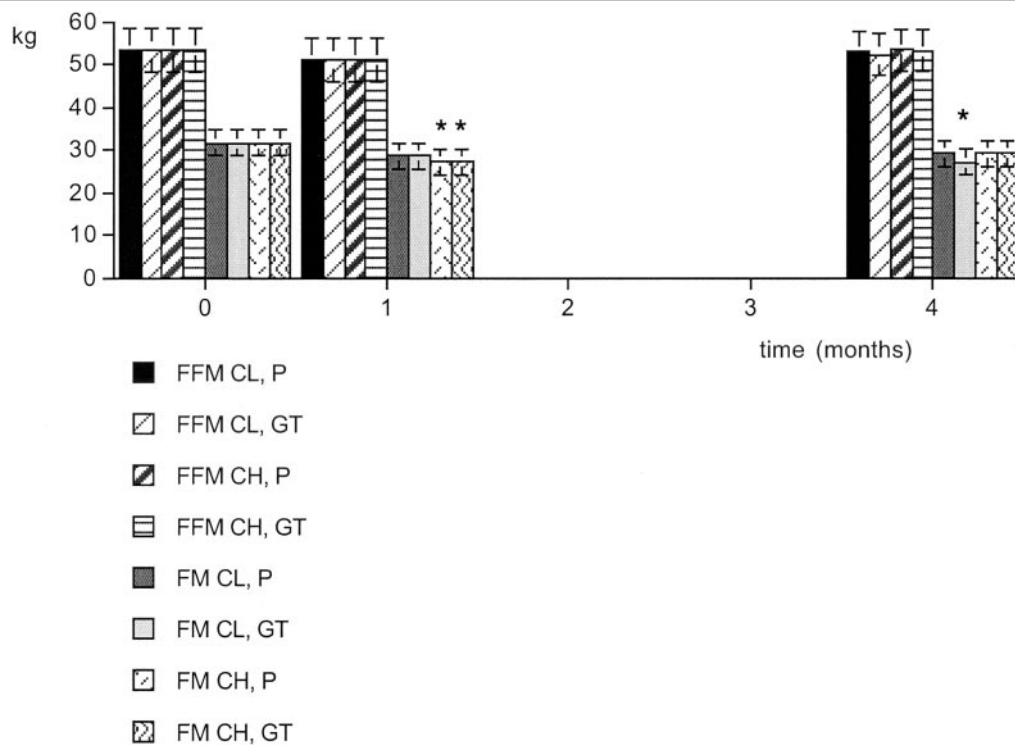

Figure 4: Body composition of men ($n = 23$) and women ($n = 53$) over time. FFM, fat-free mass (kilograms); FM, fat mass (kilograms). Month 1, after the VLED; month 4, after 3-month follow-up; CL, habitual low caffeine intake; CH, habitual high caffeine intake; GT, green tea during follow-up; P, placebo during follow-up. * $p < 0.01$, at month 1: group (pooled high caffeine intake groups vs. pooled low caffeine intake groups) $\times$ time (two-factor repeated measures ANOVA). * $p < 0.01$, at month 4: group (low caffeine intake group receiving green tea vs. all other groups) $\times$ time (four-factor repeated measures ANOVA).
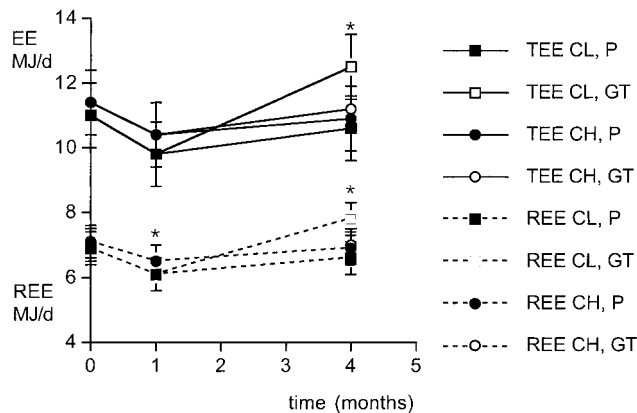
Figure 5: Total energy expenditure (EE; megajoules per day) and REE (megajoules per day) of men ($n = 23$) and women ($n = 53$) over time. Month 1, after the VLED; month 4, after 3-month follow-up; CL, habitual low caffeine intake; CH, habitual high caffeine intake; GT, green tea during follow-up; P, placebo during follow-up. * $p < 0.01$, at month 1: group (pooled high caffeine intake groups vs. pooled low caffeine intake groups) $\times$ time (two-factor repeated measures ANOVA). * $p < 0.01$, at month 4: group (low caffeine intake group receiving green tea vs. all other groups) $\times$ time (four-factor repeated measures ANOVA).
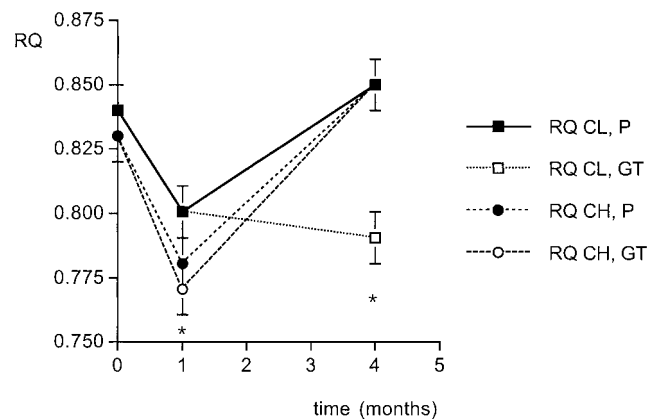

Figure 6: RQ of men ($n = 23$) and women ($n = 53$) over time. Month 1, after the VLED; month 4, after 3-month follow-up; CL, habitual low caffeine intake; CH, habitual high caffeine intake; GT, green tea during follow-up; P, placebo during follow-up. * $p < 0.01$, at month 1: group (pooled high caffeine intake groups vs. pooled low caffeine intake groups) $\times$ time (two-factor repeated measures ANOVA). * $p < 0.01$, at month 4: group (low caffeine intake group receiving green tea vs. all other groups) $\times$ time (four-factor repeated measures ANOVA).

feine mixture. In fact, in this group, body weight was still reduced, whereas in the other groups, regain took place. Despite no increase in body weight, REE was increased significantly more in the low caffeine consumers receiving the green tea-caffeine mixture than in the other groups (Figure 5); RQ was also significantly lower over time than in the other groups, indicating a higher fat oxidation (Figure 6). The concentration of leptin was lower in the low and high caffeine intake groups receiving the green tea-caffeine mixture and in the high caffeine intake group that received placebo. Only the low caffeine intake group that received placebo had a higher leptin concentration (Table 2). In the low caffeine intake group that received the green tea-caffeine mixture, the concentrations of insulin and triacylglycerol were lower during weight maintenance than in the other three groups, whereas the concentrations of β-hydroxybutyrate, glycerol, and FFAs were higher ($p < 0.05$; group $\times$ time interaction; Table 2).

Discussion

During the body weight loss phase when all subjects used a VLED, an association between body weight loss and habitual caffeine intake appeared. Body weight loss during the VLED was greater in the group with a habitual high caffeine intake (>300 mg/d). Furthermore, at baseline, satiety was positively related to habitual caffeine intake in both sexes, and leptin was inversely related to habitual caffeine intake in women. Absence of this relationship in

men was obviously caused by the lower range of leptin concentrations in men. Leptin production in white adipose tissue is regulated by the sympathetic nervous system through $\beta3$ adrenoceptors (32). The stimulating effect of caffeine on the sympathetic nervous system may lead to down-regulation of leptin release (33).

A larger body weight loss during the VLED may be associated with a lower energy intake or higher energy expenditure. Here, thermogenesis in the pooled high vs. low caffeine intake groups was reduced significantly less during the VLED, whereas fat oxidation was increased; therefore, we conclude that thermogenesis and fat oxidation played a role in the greater body weight loss. An effective role of relatively increased thermogenesis and fat oxidation through caffeine intake has been shown before in short- and long-term experiments (15–17,34,35).

Food and energy intake were not known, because no food intake diaries were used because reported energy intake data in a free-living situation are reliable from only a minority of subjects (31). However, it seems unlikely that, during the VLED, food intake was more reduced in the high caffeine intake groups, because there was no difference in the scores on the Three-Factor Eating Questionnaire, (dietary restraint, disinhibition, or hunger) that would show influences on food intake between the high and low caffeine intake groups. Moreover, the original difference in satiety between these groups had disappeared after weight loss, so this could not have affected possible differences in food intake either. The disappearance of the previous difference in satiety is

Table 2. Changes in characteristics of the subjects ($n = 76$) divided over habitual high and low caffeine intake groups and prospective treatment groups (green tea vs. placebo)

| | Green tea ($n = 38$) | | | | | |
| Habitual caffeine intake | Low caffeine ($n = 19$) | | | High caffeine ($n = 19$) | | |
Time point	1	2	3	1	2	3
F1	7.0 ± 2.7	7.3 ± 3.5	8.9 ± 10.6	7.5 ± 3.1	7.5 ± 3.9	10.6 ± 4.8
F2	5.7 ± 2.1	6.1 ± 2.2	5.3 ± 2.9	6.0 ± 2.2	6.2 ± 2.1	5.2 ± 2.5
F3	4.9 ± 3.5	4.9 ± 3.5	3.6 ± 3.1	4.9 ± 3.1	5.0 ± 2.9	3.7 ± 3.4
HP	16.1 ± 3.7	16.0 ± 4.2	16.4 ± 3.7	16.3 ± 3.2	16.4 ± 4.8	17.5 ± 3.4
Hunger (mm VAS)	38.2 ± 24	35.2 ± 23	29.7 ± 17	32.5 ± 26	33.0 ± 22	34.0 ± 21
Satiety (mm VAS)	25.9 ± 20	35.5 ± 25†	40.8 ± 21	35.3 ± 21	37.7 ± 24	40.6 ± 21
PAL	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.2	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1
glucose (mM/L)	5.5 ± 0.8	5.3 ± 0.7	5.1 ± 0.8	5.6 ± 0.5	5.0 ± 0.5	5.4 ± 0.4
insulin (mUnits/mL)	10.4 ± 4.3	7.6 ± 3.3	7.6 ± 6.8*	10.5 ± 3.6	6.3 ± 2.6	9.6 ± 3.0
BHB (mM/L)	250.0 ± 78	449.6 ± 98	442.8 ± 95*	264.4 ± 93	554.4 ± 63	261.1 ± 96
Glycerol (mM/L)	96.4 ± 34	106.4 ± 42	104.1 ± 41*	99.2 ± 38	119.2 ± 48	93.2 ± 47
FFA (mM/L)	324.1 ± 131	409.1 ± 141	402.6 ± 122*	322.9 ± 122	422.9 ± 133	358.7 ± 190
TG (mM/L)	1286 ± 633	966 ± 333	952 ± 269*	1363 ± 606	953 ± 305	1258 ± 602
Leptin (mg/L)	26.3 ± 8.6	11.9 ± 4.6	11.4 ± 8.7*	19.0 ± 7.9	8.0 ± 3.9‡	17.2 ± 11.6

Values are mean ± SD.
Time points: 1, baseline data; 2, data after 4 weeks VLED using Modifast; 3, data after 13 weeks of weight maintenance.
Scores on the Three-Factor Eating Questionnaire: F1, cognitive restraint; F2, disinhibition; F3, hunger.
HP, Herman-Polivy restraint questionnaire; VAS, visual analogue scale; BHB, β-hydroxy-butyrate; TG, triacylglycerol.
* $p < 0.01$, group × time (ANOVA 4-factor repeated measures; Scheffe F, post hoc).
† $p < 0.05$, group × time interaction during 4 weeks VLED.
‡ $p < 0.05$, difference between pooled high and low caffeine intake groups.

probably caused by the high protein diet that the subjects received as a VLED, which does sustain satiety (27,36). However, we cannot draw firm conclusions with respect to food and energy intake. Surprisingly, in the low caffeine intake group who consumed the green tea-caffeine mixture of 270 mg epigallocatechin gallate + 150 mg caffeine per day, body weight maintenance after body weight loss was considerably greater. Weight loss was prolonged in the low caffeine intake group that received the green tea caffeine mixture, whereas in the placebo group, body weight regain over time was significant. Thermogenesis must have contributed to this difference because REE was increased significantly more in the low caffeine intake group receiving the green tea-caffeine mixture than in the other groups. In this successful weight maintenance group, REE must have increased because of the ingestion of the green tea-caffeine mixture, whereas the increase in REE in the placebo group was caused by increase in body weight. Also, in the successful weight maintenance group, FFM was still increased during weight maintenance; body weight loss was loss of only FM, caused by a higher fat oxidation.

We cannot draw firm conclusions on food and energy intake during the weight maintenance period either, because these can be collected reliably for only a minority of subjects in a field study (31). However, Kao et al. (37) reported a 50% to 60% reduced food intake in Sprague-Dawley rats as well as in lean and obese male Zucker rats when epigallocatechin gallate was injected intraperitoneally. Therefore, it is of interest to estimate whether, in addition to the thermogenic effect of our green tea-caffeine mixture, the pure green tea catechins may have affected food intake. During weight maintenance, the increase in body weight in the placebo group (low caffeine users receiving placebo) was 2.2 kg over 90 days, representing 66 MJ or 0.8 MJ/d. Thus, energy expenditure was increased from 9.8 to 10.6 MJ/d in this group. This means that food intake was increased to 10.6 MJ/d also. However, in the group of low caffeine users receiving the green tea-caffeine mixture, the further reduction of body weight with 0.6 kg equals a negative energy balance of 0.2 MJ/d. This is due partly to the increased energy expenditure by 2.7 MJ/d; thus energy intake must have increased by 2.5 MJ/d. Therefore, it is

Placebo (n = 38)					
Low caffeine (n = 19)			High caffeine (n = 19)		
1	2	3	1	2	3
7.0 ± 2.8	7.6 ± 4.0	9.6 ± 5.1	7.4 ± 3.3	7.4 ± 3.2	9.2 ± 3.7
5.6 ± 2.4	6.3 ± 2.0	5.3 ± 2.7	6.1 ± 2.3	6.0 ± 1.9	5.4 ± 2.9
4.9 ± 3.1	5.4 ± 3.6	3.5 ± 3.6	4.9 ± 3.2	5.2 ± 3.2	3.6 ± 3.9
16.2 ± 3.6	16.7 ± 3.1	17.4 ± 2.7	16.2 ± 3.1	16.3 ± 3.1	17.0 ± 3.0
37.6 ± 25	36.9 ± 23	33.2 ± 22	32.7 ± 25	34.8 ± 24	34.8 ± 23
26.9 ± 21	34.1 ± 24†	39.2 ± 23	36.3 ± 22	36.3 ± 22	39.1 ± 21
1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.2
5.6 ± 0.7	5.2 ± 0.6	5.5 ± 0.4	5.7 ± 0.6	5.0 ± 0.6	5.4 ± 0.3
10.5 ± 5.3	7.3 ± 3.4	8.6 ± 3.0	10.6 ± 4.6	6.6 ± 3.6	9.5 ± 3.0
256.0 ± 84	465.0 ± 84	266.0 ± 94	266.4 ± 93	526.4 ± 73	267.9 ± 86
97.4 ± 35	107.4 ± 45	90.2 ± 37	98.2 ± 39	118.2 ± 39	91.2 ± 53
323.7 ± 132	403.7 ± 132	362.3 ± 159	322.1 ± 121	403.7 ± 132	360.9 ± 176
1262 ± 626	962 ± 326	1276 ± 566	1313 ± 601	953 ± 301	1269 ± 586
26.0 ± 6.8	10.8 ± 4.9	23.3 ± 4.2	18.8 ± 6.9	8.2 ± 3.8‡	17.1 ± 6.4

unlikely that possible reduced food intake would cause the weight maintenance in the group of low caffeine users receiving the green tea-caffeine mixture. Practically, we showed evidence suggesting that overweight subjects who lose 5 to 6 kg weight in 4 weeks and who hardly drink coffee or tea or other caffeine-containing products may profit from a regular intake of a green tea-caffeine mixture of 270 mg epigallocatechin gallate + 150 mg caffeine per day.

Leptin concentration was low in the successful weight maintenance group, probably because of sustained body weight loss, as we have shown before (38).

It is remarkable that the high caffeine intake group receiving the green tea-caffeine mixture did not show greater body weight maintenance after body weight loss than the high caffeine intake group that received placebo. Here the sensitivity to caffeine may be lost, perhaps because of saturation of the enzyme system. The high caffeine intake group had become nonresponders to the green tea-caffeine mixture, probably because of a ceiling effect. Also, the very low leptin concentrations may have caused a homeostatic restoration of body weight regain (39).

The fasting blood parameters glucose, insulin, triacylglycerol, and leptin showed a decrease with weight loss, and β-hydroxybutyrate, glycerol, and FFAs showed an increase with weight loss; these parameters returned to almost baseline values during weight regain. Only during further weight loss, such as in the low-caffeine group that received the green tea mixture, did these parameters not return to baseline values.

Taken together, we conclude that habitual high caffeine intake was associated with a greater weight loss and rela-

tively higher thermogenesis and fat oxidation. A mixture of green tea (epigallocatechin gallate) with caffeine was associated with greater weight maintenance in habitual low caffeine consumers, supported by relatively greater thermogenesis and fat oxidation.

Acknowledgments

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