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ORIGINAL ARTICLE

Effect of green tea extract on obese women: A randomized, double-blind, placebo-controlled clinical trial

Chung-Hua Hsu [a,b,c], Tung-Hu Tsai [d], Yung-Hsi Kao [e], Kung-Chang Hwang [f], Ting-Yu Tseng [d], Pesus Chou [a,b,*]

[a] *Community Medicine Research Center, National Yang-Ming University, Taipei, Taiwan*
[b] *Institute of Public Health and Department of Public Health, School of Medicine, National Yang-Ming University, Taipei, Taiwan*
[c] *Department of Chinese Medicine, Taipei Hospital, Taipei County, Taiwan*
[d] *Institute of Traditional Medicine, National Yang-Ming University, Taipei, Taiwan*
[e] *Department of Life Science, College of Science, National Central University, Taoyuan County, Taiwan*
[f] *Department of Pediatrics, Taipei Hospital, Taipei County, Taiwan*

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Body weight

Summary
Aims: To examine the effect of green tea extract (GTE) on obese women and to explore the relationship between GTE and obesity-related hormone peptides.
Methods: A randomized, double-blind, placebo-controlled clinical trial was conducted from July 2006 to June 2007 in Taipei Hospital, Taiwan. Seventy-eight of 100 obese women aged between 16 and 60 years with BMI > 27 kg/m^2 and who had not received any other weight control maneuvers within the last 3 months completed this study. The subjects were randomly divided into Groups A and B. Group A ($n = 41$) received GTE while Group B ($n = 37$) took cellulose as a placebo, one capsule (400 mg) three times each day for 12 weeks. The body weight (BW), body mass index (BMI) and waist circumflex (WC) were measured at the beginning of the study and after 12 weeks of treatment with GTE. The data were compared and expressed as % reduction.
Results: There was only a 0.3% reduction in BW (0.15 kg) after 12 weeks of treatment with GTE. There was no statistical difference in % reduction in BW, BMI and WC between the GTE and placebo groups. Within group comparison revealed that the GTE group had significant reduction in LDL-cholesterol and triglyceride, and marked increase in the level of HDL-cholesterol, adiponectin and ghrelin. On the other hand, the placebo group showed significant reduction in

* Corresponding author. Community Medicine Research Center and Institute of Public Health, National Yang-Ming University, Taipei, Taiwan, 155, Li-Nong St, Sec 2, Peitou, Taipei, Taiwan. Tel.: +886 2 2826 7050; fax: +886 2 28201461.
E-mail address: pschou@ym.edu.tw (P. Chou).

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triglyceride only, and a marked increase in the level of ghrelin alone.
Conclusions: This study showed no statistical difference in % reduction in BW, BMI and WC between the GTE and placebo groups after 12 weeks of treatment. The intake of GTE (491 mg catechins containing 302 mg EGCG) for 12 weeks is considered safe as shown by the results.

Introduction

Obesity is becoming a global epidemic and common health problem. More than 50% of Americans have BMI $>$ 27 kg/m^2.[1–4] It has been reported that the prevalence of obesity in the United States increased 50% from 1991 to 1998.[5] The same trend was noted in Taiwan.[6–7] Furthermore, the incidence and prevalence of obesity are increasing worldwide, especially in the developing and newly industrialized nations. Obesity is related to diabetes mellitus, hyperlipidemia and cardiovascular diseases, which are major diseases in Taiwan and other developing countries.[8–9]

Green tea is one of the most popular beverages in the world. It is believed to have beneficial effects in prevention and treatment of many diseases, one of which is obesity.[10–13] An epidemiological human study showed that consumption of tea for more than 10 years led to a lower percentage of total body fat and smaller waist circumfluence.[14] The anti-obesity effects of green tea are mainly attributed to its polyphenol content, in particular, epigallocatechin gallate (EGCG),[15] which is most abundant in green tea and has been found to inhibit adipocyte proliferation and differentiation in *in vitro* studies.[16–18]

Many human studies have been designed to examine the effects of green tea extract (GTE) with high EGCG content on weight and fat control, and most of these studies have found a significant decrease in body weight and body fat when compared with the baseline measurements.[18–24] However, many of these reports lacked a controlled design,[18–19] were of short duration,[20,21] had small sample sizes,[20–23] were combined with other weight control methods[22–24] or had not explored obesity-related hormone peptides.[18–24] We hypothesized that GTE would help reduce body weight by influencing obesity-related hormone peptides. Thus, we conducted this randomized clinical trial to examine the effect of GTE on obese women and to explore the relationship between GTE and obesity-related hormone peptides.

Methods

Study design and participants

The trial was conducted from July 2006 to June 2007 in Taipei Hospital, Taiwan. Among 336 registered obese women screened at our outpatient clinic, a total of 100 were enrolled. The subjects had to be between 16 and 60 years old and with BMI $>$ 27 kg/m^2. The exclusion criteria were: (1) endocrine disease, e.g. thyroid disorder, pituitary disorder, and sex gland disorder; (2) heart disease, e.g. arrhythmia, heart failure, myocardial infarction, and patient with pacemaker; (3) allergy and immunology disease; (4) high aminotransferases (alanine, aspartate $>$ 80 IU/L) or high serum creatinine ($>$2.5 mg/dl); (5) pregnant or lactating women; (6) childbirth within 6 months; (7) stroke or otherwise unable to exercise; (8) management for weight control within 3 months; and (9) any other conditions deemed unsuitable for trial as evaluated by the physician-in-charge. The enrolled patients were randomly allocated to receive GTE (Group A) or a placebo (cellulose; Group B) for 12 weeks (Fig. 1). The protocol was approved by the Human Ethics Committee of our hospital. Informed consent was obtained from all the enrolled patients. In the lead-in period of 2 weeks, the patients should maintain weight and WC within 0.5% and were given detailed explanation of the study design; they were then randomly assigned to one of the two study groups. The subjects were not allowed to receive other obesity management and were asked to keep their former diet during the study period. For 4 weeks, every subject had to come once a week to the hospital for a blood sample to be taken and for us to assess his/her compliance in consuming the amount of GTE prescribed. All subjects were free to withdraw at any time during the course of the study.

Randomization and blindness

All subjects were randomly assigned to one of the two above-mentioned groups. A random number between 0.0 and 0.99 was generated by the computer for each subject. Subjects with a random number between 0.0 and 0.49 were assigned to the group with GTE, while those with a random number between 0.50 and 0.99 were assigned to the placebo group with cellulose. The same opaque capsules containing either dried powdered GTE or placebo (cellulose) were administered to the subjects by a research assistant blinded to the contents in the capsules. All subjects were treated in the same fashion.

Preparation of sample and treatment

Our GTE samples, obtained from the Tea Research and Extension Station, Taiwan, were extracted from dried leaves of green tea according to the pre-set standard procedures with certificate of analysis given. The placebo given to the control group comprised pure microcrystalline cellulose. The subjects were asked to take one capsule containing 400 mg of either GTE or cellulose three times each day for 12 weeks. The above capsule was taken 30 min after meals. Table 1 shows the components of caffeine and polyphenols in the capsules.

Outcome measurements

The outcome was evaluated as % reduction in BW, BMI and WC after 12 weeks of intervention. All measurements were

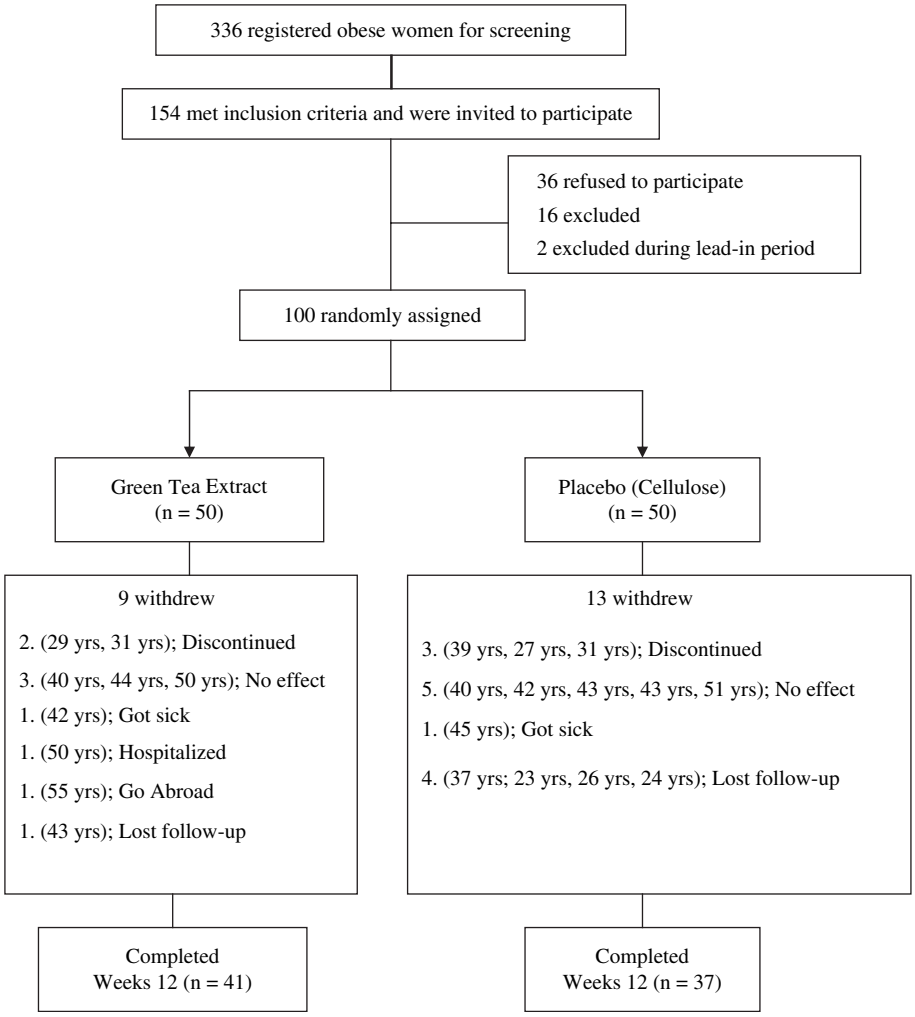

Figure 1 Trial profile and design.

done after an overnight fast using standardized methods and were performed at the beginning of the study and after 12 weeks of treatment. The subjects were measured in their undergarments with a hospital gown on. Height was measured with a wall-mounted stadiometer to the nearest 0.1 cm, weight was measured on a calibrated balance beam scale to the nearest 0.1 kg, and BMI was calculated according to the formula: BMI = body weight (BW)/height (kg/m^2). WC was measured mid-way between the lateral lower rib margin and the iliac crest, and hip circumference (HC) was measured at the levels of the major trochanters through the pubic symphysis, with the scale to the nearest 0.1 cm. We simultaneously collected the demographic data and fasting laboratory data such as blood sugar, creatinine, aminotransferases aspartate, aminotransferases alanine, uric acid, and plasma lipoproteins (triglyceride, cholesterol, HDL-cholesterol (HDL) and LDL-cholesterol (LDL)).

Table 1 Components of caffeine and polyphenols (400 mg each capsule)

Components	% weight	
	Green tea extract	Placebo
Caffeine	2.275	0
Gallocatechine (GC)	5.132	0
Epigallocatechine (EGC)	3.076	0
Catechins	0.690	0
Epicatechine (EC)	5.861	0
Epigallocatechine gallate (EGCG)	31.429	0
Gallocatechine gallate (GCG)	2.290	0
Epicatechine gallate (ECG)	2.647	0
Cellulose	46.60	100

Hormone peptides analysis

At baseline and after 12 weeks of treatment, insulin, adiponectin, leptin and ghrelin of both groups were measured. Homeostasis model assessment for insulin resistance (HOMA-IR) [fasting glucose (mmol/l) × fasting insulin (UI/l)/22.5] was used as insulin resistance measurement.[25–26] All measurements were made using standardized methods at 0800–0900 h after an overnight fast. A sample of whole blood was drawn and centrifuged at 4 °C, and a 1-ml aliquot of serum was rapidly frozen (−80 °C) for subsequent hormone analysis. The plasma adiponectin concentration was measured by a radioimmunoassay kit (Linco Research,

Inc., St. Charles, MO, USA). This kit employs the double-antibody/polyethylene glycol technique using ^{125}I-labeled adiponectin and a multispecies adiponectin rabbit antiserum. Plasma insulin levels were measured using a commercially available radioimmunoassay (Linco Research, Inc., St. Charles, MO, USA). The intra- and inter-assay coefficients of variation were 3.1 and 4.9%, respectively. The limit of sensitivity was 0.5 ng/ml. Plasma ghrelin levels were measured with a commercially available radioimmunoassay (Linco Research, Inc., St. Charles, MO, USA), using ^{125}I-labeled ghrelin as a tracer. The detection limitation for the assay was 10 ng/ml. The intra- and inter-assay coefficients of variation were 6.5 and 9.6%, respectively.

EGCG dose analysis

The sample was extracted with 100 ml of 50% methanol in sonication for 10 min. Then 2 ml of the extract were centrifuged at 10,000 rpm (Eppendorf Centrifuge 5402, MI, USA) for 10 min. The supernatant was filtrated with a 0.22-μm syringe filter (Millipore, Bedford, MA, USA), and 20 μl of the filtrate were injected into the HPLC system. HPLC analysis was performed by a Hitachi 7000 series module equipped with a photodiode array detector and wavelength was set at 273 nm. Catechin, epicatechin and EGCG were separated from the extract using a Merck Purospher STAR C-18 (50 × 4.6 mm i.d., 5 μm). The flow rate of the mobile phase was 0.8 ml/min. All samples were analyzed at room temperature (25 ± 1 °C).

Statistical analysis

The data were analyzed using SPSS software (version 11.5). Student *t*-test was employed to examine the main outcomes, demographic data, and other measurements between group means. Paired *t*-tests were utilized to examine differences within group at 0—12 weeks. All *p* values were two-tailed and the α level of significance was set at 0.05. We estimated in power 0.8 that each group needed 35 subjects.

Results

Demographics and measurements at baseline

Among the 336 obese women screened at our outpatient clinic, 100 fulfilled the inclusion and exclusion criteria and were allocated equally into Groups A and B. The means (SD) of age, height, BW and BMI were 43.4 (11.8) years, 158.2 (5.3) cm, 77.5 (12.5) kg and 30.8 (4.1) kg/m^2, respectively. Nine subjects of Group A and 13 subjects of Group B withdrew due to personal reason. In the end, 78 patients completed the study (Fig. 1). As shown in Table 2, there was no significant difference in the demographic and clinical profiles of both groups prior to the study or in compliance of dosage taken between the two groups.

Comparison between groups at 12 weeks

Table 2 displays the measurement after 12 weeks of intervention. As can be seen, there was no statistical difference in % reduction in BW, BMI and WC between the GTE and placebo groups after 12 weeks of treatment. Comparison between groups also showed no significant differences. The average weight loss was 0.15 kg in the GTE group and 0.03 kg in the placebo group after 12 weeks of treatment.

Table 3 shows the % reduction in anthropometric measures, fasting serum levels and hormone factors. As can be seen, there was no statistical difference in the % reduction between the two groups.

Comparison within group at 12 weeks

After treatment, the GTE group revealed significant reduction in WC, HC and levels of LDL-cholesterol and triglyceride, and marked increase in the levels of HDL-cholesterol, adiponectin and ghrelin. On the other hand, the placebo group showed significant reduction in HC and triglyceride only, and marked increase in the level of ghrelin alone.

Adverse effects

No subjects withdrew from the study because of discomfort or adverse effects associated with the treatment. Three subjects developed mild constipation and two patients had abdominal discomfort after GTE treatment, while two subjects had mild constipation and one patient had abdominal discomfort after cellulose treatment. All the symptoms were noted in the first week after treatment. No major adverse effects were noted.

Discussion

The present initial results showed no statistical difference in % reduction in BW, BMI and WC between the GTE and placebo groups after 12 weeks of treatment. Moreover, comparison between groups displayed no statistical difference in the levels of serum factors and hormone peptides.

This study found no effect of GTE weight reduction in obese women. There was only a 0.3% reduction in BW (0.15 kg) after 12 weeks of treatment with GTE. Chantre and Lairon examined the effect of GTE (375 mg catechins containing 270 mg EGCG; daily) on overweight subjects and found a 4.6% reduction in BW.[19] However, their study was not a controlled one. A randomized, double-blind controlled study was conducted by Kovas et al. They investigated the effect of GTE on maintaining body weight after 4 weeks of very-low-diet BW loss and found no significant difference in BW regain between the GTE (573 mg catechins containing 323 mg EGCG; daily) and placebo groups.[27] In the present study, we used a similar daily dose of GTE (491 mg catechins containing 302 mg EGCG; daily) on obese women without any other weight control maneuvers. Our study showed the same result. Many human studies showed significant decrease in body weight and body fat[18—24] after GTE intake. However, most of these studies were of short duration,[20—21] had small sample sizes,[20—23] or were combined with other weight control methods.

Despite showing no evidence supporting the effect of GTT on weight reduction, the data of this study still revealed the following. First, there were significant

Table 2 Demographic and biochemical characteristics of participants at baseline and after 12 weeks

Variables	Green tea extract ($n = 41$), mean (SD)			Placebo (cellulose)($n = 37$), mean (SD)		
	Baseline (A)	12 weeks (B)	Difference (A − B)	Baseline (A)	12 weeks (B)	Difference (A − B)
Basic data						
Age (years)	43.0 (11.1)			43.9 (12.6)		
Height (cm)	158.6 (4.9)			157.8 (5.7)		
Weight (kg)	78.5 (10.3)	78.3 (10.6)	0.15 (2.0)	76.3 (14.5)	76.2 (14.4)	0.03 (1.9)
Body mass index (kg/m^2)	31.2 (3.5)	31.1 (3.7)	0.06 (2.8)	30.5 (4.6)	30.5 (4.6)	0.006 (0.8)
Waist circumflex (cm)	94.7 (7.7)	93.0 (8.5)	1.7 (4.1)*	93.0 (12.6)	91.7 (11.5)	1.3 (5.8)
Hip circumflex (cm)	110.6 (7.4)	109.4 (7.9)	1.2 (2.7)**	109.7 (10.0)	107.5 (10.1)	2.2 (3.5)**
Systolic blood pressure (mmHg)	134.9 (16.2)	131.3 (13.5)	3.6 (14.9)	135.4 (20.0)	132.5 (16.9)	2.9 (12.3)
Diastolic blood pressure (mmHg)	82.9 (9.3)	81.7 (9.1)	1.2 (10.6)	81.6 (11.5)	79.4 (10.9)	2.3 (10.4)
Fasting serum factors						
Glucose (mg/dl)	113.1 (37.7)	112.6 (34.0)	0.6 (15.6)	104.1 (26.1)	106.7 (30.9)	2.6 (9.8)
Triglyceride (mg/dl)	141.4 (81.7)	135.7 (781)	8.6 (27.4)*	138.1 (88.3)	105.5 (33.5)	32.6 (74.4)*
Cholesterol (mg/dl)	211.3 (35.7)	202.7 (33.1)	5.7 (45.1)	202.7 (33.1)	199.7 (32.0)	2.7 (30.6)
HDL-cholesterol (mg/dl)	42.5 (9.6)	44.1 (10.0)	−1.6 (4.9)*	45.1 (10.9)	44.7 (11.4)	0.5 (10.3)
LDL-cholesterol (mg/dl)	150.6 (33.3)	134.5 (31.8)	16.1 (22.2)***	135.5 (35.8)	129.9 (32.6)	5.6 (31.4)
Creatinine (mg/dl)	0.8 (0.2)	0.8 (0.1)	0.03 (0.2)	0.8 (0.2)	0.8 (0.2)	0.02 (0.1)
Aminotransferases aspartate (IU/L)	25.5 (9.4)	23.2 (8.2)	2.3 (7.6)	30.6 (22.8)	28.1 (19.5)	2.5 (17.1)
Aminotransferases alanine (IU/L)	32.7 (18.8)	29.8 (16.9)		34.2 (33.3)	34.2 (33.0)	2.9 (29.6)
Uric acid (mg/dl)	5.7 (1.4)	5.8 (1.5)	−0.007 (1.0)	5.7 (1.4)	5.6 (1.4)	0.2 (1.1)
Hormone peptides						
Insulin (IU/ml)	16.1 (14.6)	14.7 (8.1)	1.4 (13.5)	13.1 (7.4)	13.4 (8.7)	−0.3 (9.9)
Leptin (ng /ml)	15.4 (5.1)	16.4 (4.3)	−1.0 (3.5)	15.4 (7.7)	16.8 (11.3)	−1.5 (4.7)
Adiponectin (μg/ml)	18.9 (6.7)	21.4 (8.7)	−2.5 (4.2)***	21.4 (8.2)	23.5 (8.8)	−2.0 (5.4)
Ghrelin (pg/ml)	997.0 (257.0)	1088.9 (285.1)	−91.9 (188.2)*	1031.8 (270.8)	1146.8 (341.7)	−115 (190.1)*
HOMA insulin resistance index	5.0 (6.6)	4.3 (3.6)	0.64 (5.4)	3.5 (2.7)	3.6 (2.9)	−0.1 (3.0)

*$p = 0.01$–0.05; **$p = 0.001$–0.01; ***$p < 0.001$.

reductions in the levels of LDL-cholesterol and triglyceride and marked increase in the level of HDL-cholesterol after 12 weeks of treatment in the GTE group. Animal studies showed that GTE intake decreased the absorption of triglycerides and cholesterol.[28–29] Some animal model studies reported that GTE decreased plasma levels of LDL-cholesterol and triglyceride and increased the level of HDL-cholesterol.[30–31] The mechanism accounting for this remains to be determined. An *in vivo* study might partly explain the above finding that there was EGCG dose-dependent inhibition of lipid accumulation in maturing pre-adipocytes.[12] Although the human study of Nagao et al. demonstrated that 12 weeks of GTE (690 mg catechins containing 136 mg EGCG; daily) intake decreased the level of malondialdehyde-modified LDL in men, neither their study nor ours showed any significant difference in serum lipid or blood sugar between the groups in the human studies. This might be attributed to the dose of GTE being too low for any effects to be detected. The optimum dose of GTE intake should be determined in order to detect its effect on serum lipid in future human studies.

Second, the present study also aims to explore the change in obesity-related hormone peptides after 12 weeks of treatment. Although comparison between groups revealed no significant difference in the level of hormone peptides, the initial data showed increase in serum levels of adiponectin and ghrelin in the GTE group after 12 weeks. Adiponectin is a hormone produced in adipocytes. It has been found that circulating adiponectin levels and adiponectin gene expression in adipose tissue are reduced in patients with type 2 diabetes and obese populations.[32–34] Many studies demonstrated that adiponectin has both anti-atherogenic and anti-diabetic properties.[32–37] Some animal studies have demonstrated that EGCG can increase the level of adiponectin, which is a benefit biomarker.[38–39] Kao et al. have reported that EGCG can significantly reduce the level of leptin and insulin in animal studies.[40] However, this study could not obtain the same result. We attributed this to the dose of GTE being too low for any effects to be detected in human studies. The effects of EGCG on changes in hormone level and loss in body weight vary with the route of administration. Oral intake of EGCG

Table 3 % reduction in outcomes after 12 weeks of treatment

Variables	Green tea extract $n = 41$, mean (SD)	Placebo (cellulose) $n = 37$, mean (SD)	p value
Anthropometric measures			
Weight (kg)	0.31 (2.6)	0.05 (2.6)	0.67
Body mass index (kg/m^2)	0.20 (2.7)	0.01 (3.6)	0.72
Waist circumflex (cm)	1.75 (4.4)	1.10 (5.9)	0.58
Hip circumflex (cm)	1.09 (2.5)	1.94 (3.3)	0.21
Systolic blood pressure (mmHg)	1.90 (11.0)	1.5 (8.7)	0.86
Diastolic blood pressure (mmHg)	0.68 (12.3)	1.92 (1.4)	0.66
Fasting serum factors			
Glucose (mg/dl)	−1.0 (12.8)	−2.5 (7.4)	0.52
Triglyceride (mg/dl)	1.5 (28.56)	14.4 (30.1)	0.06
Cholesterol (mg/dl)	3.0 (14.4)	0.1 (15.5)	0.39
HDL-cholesterol (mg/dl)	−4.4 (11.7)	−1.1 (20.3)	0.38
LDL-cholesterol (mg/dl)	9.9 (14.1)	−1.1 (38.8)	0.10
Hormone peptides			
Insulin (IU/ml)	−17.4 (66.0)	−17.3 (58.7)	0.87
Leptin (ng /ml)	−6.9 (26.0)	−5.0 (21.4)	0.72
Adiponectin (μg/ml)	−13.0 (21.0)	−10.6 (26.7)	0.66
Ghrelin (pg/ml)	−10.4 (20.9)	−11.4 (20.0)	0.82
HOMA insulin resistance index	−21.5 (75.6)	−18.9 (58.5)	0.87

in animal studies showed less or no change in hormone level and loss in body weight compared with the same dose of EGCG injected.[40] The bioavailability and pharmacokinetics of EGCG in human studies merit further exploration. Ghrelin is a novel growth hormone-releasing peptide isolated mainly from the stomach.[41] It has been demonstrated to alter feeding behavior, energy metabolism, and gastrointestinal functions.[42] Many studies demonstrated that weight loss was associated with increase in ghrelin level.[43–44] Both groups in our study showed increases in the level of ghrelin. This might imply that taking GTE and cellulose would increase the secretion of hormone peptides such as ghrelin, which might have potential benefits on obese control. Further studies are needed to validate such a possibility.

Finally, after 12 weeks of GTE treatment, serum EGCG was detected in only five of 41 GTE samples. The reason why serum levels of EGCG cannot be easily measured after fasting overnight is worth further exploration. GTE have many biological effects *in vitro*, and general effects are observed in the range of 10—100 μM.[45] Healthy subjects consuming 800 mg EGCG reached a plasma concentration of 0.96 μM. [46] Our GTE subjects had daily oral intakes of 491 mg catechins containing 302 mg EGCG. This might account for the insignificant biological effect and why EGCG was not detected in most of the serum samples. Moreover, in a human study, single oral consumption of 800 mg EGCG might cause mild headache and fatigue.[46] The bioavailability and pharmacokinetics of EGCG in human and animal models have been previously reported[47–52] How to determine the optimum EGCG dosage and achieve less adverse effects is worth more in-depth investigation in future studies.

It is impossible for all subjects to maintain the same food consumption throughout the study period. The subjects were not allowed to receive other obesity management and were asked to keep their former diet during the study. We expected that the randomized design could balance the bias between the two groups. The biochemical data in both groups, such as the triglyceride level, became different after intervention. Whether it is due to the intake of GTE and cellulose, or the change in eating habits of the subjects during the study period merits further exploration.

Besides the trivial side effects, we had some interesting observations, including the improvement of mild diarrhea (two in the GTE group and one in the placebo group), and insomnia (two in the GTE group). This might be verified with larger samples and longer follow-up in the future.

Conclusions

This study showed no statistical difference in % reduction in BW, BMI and WC between the GTE and placebo groups after 12 weeks of treatment. The intake of GTE (491 mg catechins containing 302 mg EGCG) for 12 weeks is considered safe in this study. The bioavailability and pharmacokinetics of EGCG in human studies are worth more in-depth investigation.

Conflict of interest statement

None to declare.

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References

1. Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults. Clinical guidelines on the identification, evaluation, and obesity in adults: executive summary. *Am J Clin Nutr* 1998;**68**:899–917.
2. Sturm R. Increases in clinically severe obesity in the United States, 1986–2000. *Arch Intern Med* 2003;**163**:2146–8.
3. Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors. *JAMA* 2001;**2003**(289):76–9.
4. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999–2000. *JAMA* 2002; **288**:1723–7.
5. Mokdad AH, Serdula MK, Dietz WH, et al. The spread of the obesity epidemic in the United States. 1991–1998. *JAMA* 1999;**282**:1519–22.
6. Lin YC, Yen LL, Chen SU, et al. Prevalence of overweight and obesity and its associated factors: findings from national nutrition and health survey in Taiwan, 1993–1996. *Prev Med* 2003; **37**:233–41.
7. Kou MD. *The national survey of the changes in nutritional and health status from 1992 to 1997 in Taiwan: anthropometric index and obesity. Final report of the Department of Health*. Taipei: Taiwan: Department of Health; 1998.
8. Must A, Spadano J, Cokley EH, Field AE, Colditz AE, Dietz WH. The disease burden associated with overweight and obesity. *JAMA* 1999;**282**:1523–9.
9. Tsai WL, Yang CY, Lin SF, Fang FM. Impact of obesity on medical problems and quality of life in Taiwan. *Am J Epidemiol* 2004; **160**:557–65.
10. Kao YH, Chang HH, Lee MJ, Chen CC. Tea, obesity, and diabetes. *Mol Nutr Food Res* 2006;**50**:188–210.
11. Wolfram S, Wang Y, Thielecke F. Anti-obesity effects of green tea: from bedside to bench. *Mol Nutr Food Res* 2006;**50**: 176–87.
12. Lin JK, Lin-Shiau SY. Mechanisms of hypolipidemic and anti-obesity effects of tea and tea polyphenols. *Mol Nutr Food Res* 2006;**50**:211–7.
13. Moyers SB, Kumar NB. Green tea polyphenols and cancer chemoprevention: multiple mechanisms and endpoints for phase II trials. *Nutr Rev* 2004;**62**:204–11.
14. Wu CH, Lu FH, Chang CS, Chang TC, Wang RH, Chang CJ. Relationship among habitual tea consumption, percent body fat, and body fat distribution. *Obes Res* 2003;**11**:1088–95.
15. Balentine DA, Wiseman SA, Bouwens LC. The chemistry of tea flavonoids. *Crit Rev Food Sci Nutr* 1997;**37**:693–704.
16. Lin J, Della-Fera MA, Baile CA. Green tea polyphenol epigallocatechin gallate inhibits adipogenesis and induces apoptosis in 3T3-L1 adipocytes. *Obes Res* 2005;**13**:982–90.
17. Wu BT, Hung PF, Chen HC, Huang RN, Chang HH, Kao YH. The apoptotic effect of green tea (−)-epigallocatechin gallate on 3T3-L1 preadipocytes depends on the Cdk2 pathway. *J Agric Food Chem* 2005;**53**:5695–701.
18. Furuyashiki T, Nagayasu H, Aoki Y, Bessho H, Hashimoto T, Kanazawa K, et al. Tea catechin suppresses adipocyte differentiation accompanied by down-regulation of PPARgamma2 and C/EBPalpha in 3T3-L1 cells. *Biosci Biotechnol Biochem* 2004; **68**:2353–9.
19. Chantre P, Lairon D. Recent findings of green tea extract AR25 (Exolise) and its activity for the treatment of obesity. *Phytomedicine* 2002;**9**:3–8.
20. Dulloo AG, Duret C, Rohrer D, Girardier L, Mensi N, Fathi M, et al. Efficacy of a green tea extract rich in catechin polyphenols and caffeine in increasing 24-h energy expenditure and fat oxidation in humans. *Am J Clin Nutr* 1999;**70**: 1040–5.
21. Rumpler W, Seale J, Clevidence B, Judd J, Wiley E, Yamamoto S, et al. Oolong tea increases metabolic rate and fat oxidation in men. *J Nutr* 2001;**131**:2848–52.
22. Komatsu T, Nakamori M, Komatsu K, Hosoda K, Okamura M, Toyama K, et al. Oolong tea increases energy metabolism in Japanese females. *J Med Invest* 2003;**50**:170–5.
23. Westerterp-Plantenga MS, Lejeune MP, Kovacs EM. Body weight loss and weight maintenance in relation to habitual caffeine intake and green tea supplementation. *Obes Res* 2005;**13**: 1195–204.
24. Nagao T, Komine Y, Soga S, Meguro S, Hase T, Tanaka Y, et al. Ingestion of a tea rich in catechins leads to a reduction in body fat and malondialdehyde-modified LDL in men. *Am J Clin Nutr* 2005;**81**:122–9.
25. Matthews D, Hosker J, Rudenski A, Naylor B, Treacher D, Turner R. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;**28**:412–9.
26. Onora E, Formentini G, Calcaterra F, Lombardi S, Marini F, Zenari L, et al. HOMA-estimated insulin resistance is an independent predictor of cardiovascular disease in Type 2 diabetic subjects: prospective data from the Verona diabetes complications study. *Diabetes Care* 2002;**25**:1135–41.
27. Kovacs EM, Lejeune MP, Nijs I, Westerterp-Plantenga MS. Effects of green tea on weight maintenance after body-weight loss. *Br J Nutr* 2004;**91**:431–7.
28. Raederstorff DG, Schlachter MF, Elste V, Weber P. Effect of EGCG on lipid absorption and plasma lipid levels in rats. *J Nutr Biochem* 2003;**14**:326–32.
29. Löest HB, Noh SK, Koo SI. Green tea extract inhibits the lymphatic absorption of cholesterol and alpha-tocopherol in ovariectomized rats. *J Nutr* 2002;**132**:1282–8.
30. Yokozawa T, Nakagawa T, Kitani K. Antioxidative activity of green tea polyphenol in cholesterol-fed rats. *J Agric Food Chem* 2002;**50**:3549–52.
31. Miura Y, Chiba T, Tomita I, Koizumi H, Miura S, Umegaki K, et al. Tea catechins prevent the development of atherosclerosis in apoprotein E-deficient mice. *J Nutr* 2001;**131**:27–32.
32. Hotta K, Funahashi T, Arita Y, et al. Plasma concentrations of an oval, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler Thromb Vasc Biol* 2000;**20**: 1595–9.
33. Weyer C, Funahashi T, Tanaka S, et al. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. *J Clin Endocrinol Metab* 2001; **86**:1930–5.
34. Statnick MA, Beavers LS, Conner LJ, et al. Decreased expression of apM 1in omental and subcutaneous adipose tissue of human with type 2 diabetes. *Int J Exp Diabetes Res* 2000;**1**:81–8.
35. Singhal A, Jamieson N, Fewtrell M, Deanfield J, Lucas A, Sattar N. Adiponectin predicts insulin resistance but not endothelial function in young, healthy adolescents. *J Clin Endocrinol Metab* 2005;**90**. 4615–4521.
36. Fernandez-Real JM, Castro A, Vazquez G, Casamitjana R, Lopez-Bermejo A, Penarroja G, et al. Adiponectin is associated with vascular function independent of insulin sensitivity. *Diabetes Care* 2004;**27**:739–45.
37. Farvid MS, Ng TW, Chan DC, Barrett PH, Watts GF. Association of adiponectin and resistin with adipose tissue compartments, insulin resistance and dyslipidaemia. *Diabetes Obes Metab* 2005;**7**:406–13.
38. Shimada M, Mochizuki K, Sakurai N, Goda T. Dietary supplementation with epigallocatechin gallate elevates levels of circulating adiponectin in non-obese Type-2 diabetic Goto–Kakizaki rats. *Biosci Biotechnol Biochem* 2007;**71**:2079–82.
39. Potenza MA, Marasciulo FL, Tarquinio M, Tiravanti E, Colantuono G, Federici A, et al. EGCG, a green tea polyphenol,

improves endothelial function and insulin sensitivity, reduces blood pressure, and protects against myocardial I/R injury in SHR. *Am J Physiol Endocrinol Metab* 2007;**292**:1378—87.
40. Kao YH, Hiipakka RA, Liao S. Modulation of endocrine systems and food intake by green tea epigallocatechin gallate. *Endocrinology* 2000;**141**:980—7.
41. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature* 1999;**402**:656—60.
42. Nakazato M, Murakami N, Date Y, Kojima M, Matsuo H, Kangawa K, et al. A role for ghrelin in the central regulation of feeding. *Nature* 2001;**409**:194—8.
43. Mäestu J, Jürimäe J, Valter I, Jürimäe T. Increases in ghrelin and decreases in leptin without altering adiponectin during extreme weight loss in male competitive bodybuilders. *Metabolism* 2008;**57**(2):221—5.
44. Reinehr T, Roth CL, Alexy U, Kersting M, Kiess W, Andler W. Ghrelin levels before and after reduction of overweight due to a low-fat high-carbohydrate diet in obese children and adolescents. *Int J Obes (Lond)* 2005;**29**(4):362—8.
45. Liao S, Kao YH, Hiipakka RA. Green tea: biochemical and biological basis for health benefits. *Vitam Horm* 2001;**62**:1—94.
46. Chow HHS, Cai Y, Alberts DS, Hakim I, et al. Phase I pharmacokinetics study of tea polyphenols following single-dose administration of epigallocatechin gallate and polyphenol. *Cancer Epidemiol Biomarkers Prev* 2001;**10**:53—8.
47. Henning SM, Niu Y, Lee NH, Thames GD, Minutti RR, Wang H, et al. Bioavailability and antioxidant activity of tea flavanols after consumption of green tea, black tea, or a green tea extract supplement. *Am J Clin Nutr* 2004;**80**:1558—64.
48. Chow HH, Cai Y, Hakim IA, Crowell JA, Shahi F, Brooks CA, et al. Pharmacokinetics and safety of green tea polyphenols after multiple-dose administration of epigallocatechin gallate and polyphenon E in healthy individuals. *Clin Cancer Res* 2003;**9**:3312—9.
49. Lin LC, Hung LC, Tsai TH. Determination of (−)-epigallocatechin gallate in rat blood by microdialysis coupled with liquid chromatography. *J Chromatogr A* 2004;**1032**(1-2):125—8.
50. Fang JY, Tsai TH, Lin YY, Wong WW, Wang MN, Huang JF. Transdermal delivery of tea catechins and theophylline enhanced by terpenes: a mechanistic study. *Biol Pharm Bull* 2007;**30**:343—9.
51. Lin LC, Wang MN, Tseng TY, Sung JS, Tsai TH. Pharmacokinetics of (−)-epigallocatechin-3-gallate in conscious and freely moving rats and its brain regional distribution. *J Agric Food Chem* 2007;**55**:1517—24.
52. Warden BA, Smith LS, Beecher GR, Balentine DA, Clevidence BA. Catechins are bioavailable in men and women drinking black tea throughout the day. *J Nutr* 2001;**131**:1731—7.