Does Supplementation with Green Tea Extract Improve Insulin Resistance in Obese Type 2 Diabetics? A Randomized, Double-blind, and Placebo-controlled Clinical Trial

Chung-Hua Hsu, MD, PhD; Ying-Li Liao, MD; Su-Ching Lin, MD; Tung-Hu Tsai, PhD; Chien-Jung Huang, MD; Pesus Chou, DrPH

Chung-Hua Hsu, MD, PhD – Institute of Traditional Medicine, National Yang-Ming University, Taipei; branch of Chinese Medicine and Linsen, Taipei City Hospital, Taipei; Community Medicine Research Center, National Yang-Ming University, Taipei. Correspondence address: Institute of Traditional Medicine, National Yang-Ming University, Taipei, Taiwan, 155, Li-Nong St, Sec 2, Peitou, Taipei, Taiwan. Email: owlherbs@yahoo.com.tw

Ying-Li Liao, MD – Department of Endocrinology, Taipei Hospital, Taipei County, Taiwan

Su-Ching Lin, MD – Department of Endocrinology, Taipei Hospital, Taipei County, Taiwan

Tung-Hu Tsai, PhD – Institute of Traditional Medicine, National Yang-Ming University, Taipei, Taiwan

Chien-Jung Huang, MD – Department of Endocrinology, Branch of Lin-Sen, Taipei City Hospital, Taipei, Taiwan

Pesus Chou, DrPH – Community Medicine Research Center, National Yang-Ming University, Taipei, Taiwan; Institute of Public Health, National Yang-Ming University, Taipei, Taiwan

Abstract

BACKGROUND: Green tea is one of the most popular beverages in the world. It is believed to have beneficial effects in the prevention and treatment of many diseases, one of which is type 2 diabetes. The aim of the study is to examine the effect of a decaffeinated green tea extract (GTE) providing a daily dose of 856 mg of epigallocatechin gallate (EGCG) on obese individuals with type 2 diabetes. MATERIALS AND METHODS: The clinical trial was a randomized, double-blind, placebo-controlled clinical trial conducted from December 2007 through November 2008. The subjects were randomly assigned to either receive 1,500 mg of a decaffeinated GTE or placebo daily for 16 weeks. Sixty-eight of 80 subjects, ages 20-65 years with BMI > 25 kg/m^2 and type 2 diabetes for more than one year, completed this study. Homeostasis model assessment for insulin resistance (HOMA-IR) was used as the major outcome measurement. At baseline and after 16 weeks of treatment, anthropometric measurements, fasting glucose, hemoglobin A1C percent (HbA1C), hormone peptides, and plasma lipoproteins were measured from both groups. RESULTS: No statistically significant differences were detected between the decaffeinated GTE and placebo groups in any measured variable. A statistically significant within-group 0.4-percent reduction in HbA1C (from 8.4 to 8.0%) was observed after GTE treatment compared to baseline. Within-group comparison also revealed that the GTE group had significant reductions in waist circumference (WC), HOMA-IR index, and insulin level, and a significant increase in the level of ghrelin. Within-group comparison of those in the placebo group showed a significant increase in the level of ghrelin. CONCLUSIONS: This study found no statistical difference in any measured variable between the decaffeinated GTE and placebo groups; however, there were some statistically significant within-group changes detected. More research is required to determine whether a decaffeinated GTE standardized for EGCG content will provide any clinical benefits in obese individuals with type 2 diabetes. Clinical Trial Registration NO: NCT00567905. *(Altern Med Rev* 2011;16(2):157-163)

Background

Type 2 diabetes is becoming a global epidemic and common health problem. Diabetes is associated with significant morbidity and mortality.[1-3] Individuals with diabetes are more likely to use complementary and alternative medicine (CAM) than those without diabetes[4] and half of the adult diabetic population uses some form of CAM.[5] However, there is still insufficient evidence on the definitive effect of herbs and supplements for type 2 diabetes.[6]

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, including type 2 diabetes.[7,8] Green tea has been found to improve insulin sensitivity *in vivo*.[9,10] Rat studies report a hypoglycemic effect of green tea extract (GTE).[11,12] Epidemiological studies report that consumption of tea may reduce the risk for type 2 diabetes.[13-15] A human clinical trial reported that supplementation with GTE reduced hemoglobin A1c (HbA1C) in persons with glucose abnormalities.[16] The antidiabetic effects of green tea are mainly attributed to its polyphenol content, in

particular, epigallocatechin gallate (EGCG),[17-20] which is most abundant in green tea and has been found to enhance insulin sensitivity and increase glucose uptake.[21,22]

Excess weight and obesity are associated with the development of type 2 diabetes. Although several human studies have examined the effects of high-EGCG GTE on weight control[23-26] or type 2 diabetes,[16,26] to our knowledge, human studies on overweight subjects with type 2 diabetes are lacking. We hypothesized that a decaffeinated GTE would help improve insulin resistance and other aspects of metabolic function in overweight type 2 diabetic patients. This randomized clinical trial was designed to examine the effect of decaffeinated GTE on overweight individuals with type 2 diabetes.

Materials and Methods

Study Design and Participants

The trial was conducted from December 2007 through November 2008 in Taipei Hospital, Taiwan. Among 736 registered type 2 diabetic patients screened at our outpatient clinic, a total of 80 were enrolled. The inclusion criteria were: (1) ages 20-65 years, (2) BMI >25 kg/m^2, (3) Chinese ethnicity, and (4) diagnosis of type 2 diabetes for more than one year. The exclusion criteria were: (1) alanine aminotransferase (ALT) >80 IU/L, serum creatinine >2.0 mg/dL, (2) lactating or pregnant, (3) diagnosis of heart failure, acute myocardial infarction, stroke, or serious injuries, and (4) any other conditions not suitable for trial as evaluated by the physician in charge.

Patients were randomly allocated to receive a decaffeinated GTE (Group A) or a placebo (cellulose; Group B) for 16 weeks (Figure 1). The protocol was approved by the Human Ethics Committee of our hospital. Informed consent was obtained from all enrolled patients. Subjects were instructed to maintain an isocaloric diet and to continue their previous eating habits during the study period. For the first four weeks, every subject was required to report to the study center for blood draw and compliance assessment. Subjects were free to withdraw at any time. Throughout the study period, subjects were directed to continue taking the same dose of any prescribed hypoglycemic agents unless hypoglycemia occurred, in which case they were directed to reduce their dose immediately.

Randomization and Blinding

Subjects were randomly assigned to one of two groups via computer-generated numbers between 0.0 and 0.99. Subjects with a random number between 0.0 and 0.49 were assigned to the decaffeinated GTE group, while those with a random number between 0.50 and 0.99 were assigned to the placebo group. Both active and placebo treatments were contained in the same opaque capsules. Products were administered by a blinded research assistant.

Preparation of Samples and Treatment

Decaffeinated GTE was obtained from the Tea Research and Extension Station, Taoyuan County, Taiwan. It was extracted from dried leaves of green tea according to pre-set standard procedures and verified with certificate of analysis. The decaffeinated GTE used in this study was standardized for several tea catechins in addition to EGCG (Table 1). The placebo was comprised of pure microcrystalline

Keywords: obesity, green tea extract, green tea, EGCG, type 2 diabetes, ghrelin, HbA1C, weight loss, insulin resistance

Figure 1. Trial Profile and Design

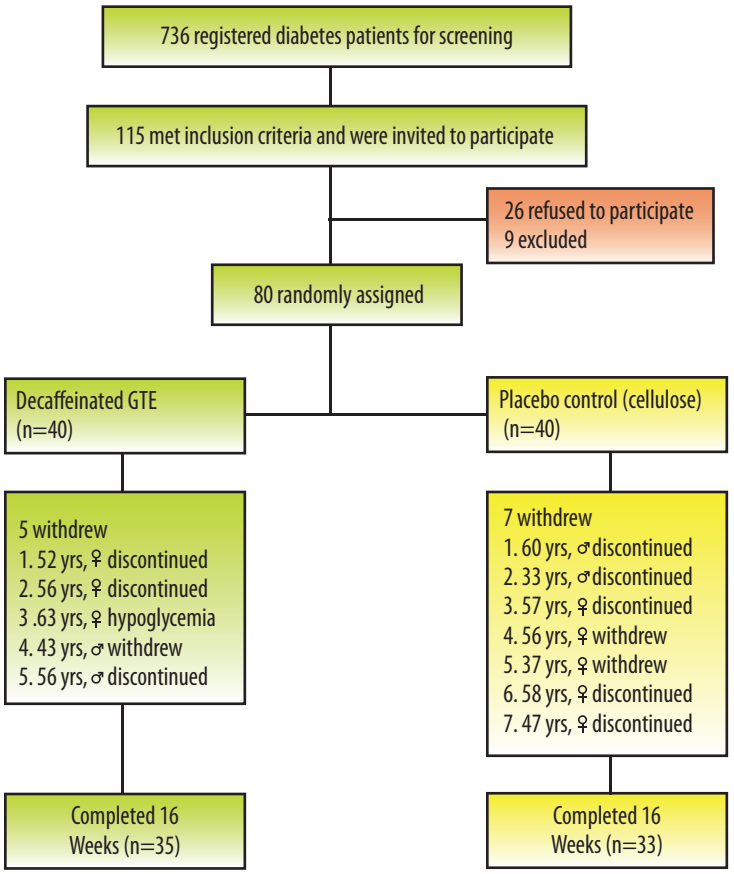

Table 1. Components of Decaffeinated GTE Capsules and Daily Dose (in mg) Received by the Active Treatment Group

Components	% Weight	Daily Dose (in mg)
EGCG (Epigallocatechin gallate)	57.12	856.8
ECG (Epicatechin gallate)	15.74	236.1
EGC (Epigallocatechin)	7.70	115.5
EC (Epicatechin)	4.80	71.9
GCG (Gallocatechin gallate)	4.25	63.7
GC (Gallocatechin)	<0.07	<1.05
Caffeine	<0.07	<1.05
Cellulose	10.33	155.0

cellulose. Capsules contained either 500 mg decaffeinated GTE extract or cellulose. Subjects were asked to take one capsule 30 minutes after meals three times daily for 16 weeks. Total daily dose of tea compounds received by the active group is listed in Table 1.

Outcome Measurements

Homeostasis model assessment for insulin resistance (HOMA-IR) (fasting glucose (mmol/L) × fasting insulin (UI/L)/22.5) was used as the major outcome measurement.[27,28] At baseline and after 16 weeks of treatment the following were assessed for both groups: body mass index (BMI), waist circumference (WC), blood pressure, fasting glucose, HbA1C, fasting insulin, creatinine, ALT, uric acid, hormone peptides (leptin, ghrelin, and adiponectin), and plasma lipoproteins (triglycerides, total cholesterol, HDL-cholesterol, and LDL-cholesterol). The procedures for analyzing hormone peptides and EGCG dose were the same as described in our previous report.[24]

All measurements were made using standardized methods at 0800-0900 after an overnight fast. In the case of anthropometric measurements, subjects were measured in their undergarments while wearing a hospital gown. 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 = weight/height^2 (kg/m^2). WC was measured mid-way between the lateral lower rib margin and the iliac crest. Demographic data was collected during the initial anthropometric assessment.

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 within-group differences at 0 and 16 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 32 subjects.

Results

Demographics and Measurements at Baseline

Among the 736 type 2 diabetic patients screened at our outpatient clinic, 80 fulfilled the inclusion and exclusion criteria and were allocated equally into Groups A and B. The means and the standard deviation (in parenthesis) of age, BMI, WC, years since being diagnosed with type 2 diabetes, and HbA1C were 51.3 (± 9.2) years, 29.7 (± 4.0) kg/m^2, 97.4 (± 10.4) cm, 4.1 (± 4.0) years, and 8.4 (± 2.0), respectively. Five subjects from Group A and seven subjects from Group B withdrew due to personal reasons. In the end, 68 patients completed the study (Figure 1). As shown in Table 2, there were no significant differences in the demographic or clinical profiles between the two groups prior to the study.

Table 2. Baseline Characteristics of Participants

	Decaffeinated GTE (n=35)	Placebo (cellulose) (n=33)
Gender (male/female)	12/23	12/21
Family history of type 2 diabetes, yes (n)	6	4
Age, years	50.5 (±9.2)	52.2 (±9.1)
Time since diagnosis of diabetes, years	4.0 (±4.3)	4.3 (±3.8)
Height, cm	160 (±9.8)	159 (±7.1)
Body weight, kg	77.8 (±13.8)	73.8 (±11.0)

Data expressed as a mean with standard deviation in parenthesis.

Between-Group Comparisons at 16 Weeks

Between-group results are listed in Table 3. There were no statistically significant differences detected for any of the variables assessed after 16 weeks of decaffeinated GTE

Table 3. Within-Group Anthropometric, Blood Pressure, and Lab Data at Baseline and after 16 Weeks

Variables	Baseline			After 16 Weeks			% Reduction		
	Decaffeinated GTE (n=35)	Placebo (cellulose) (n=33)	p-value	Decaffeinated GTE (n=35)	Placebo (cellulose) (n=33)	p-value	Decaffeinated GTE (n=35)	Placebo (cellulose) (n=33)	p-value
Body weight, kg	77.8 (13.8)	73.8 (11.0)	0.17	77.7 (12.1)	74.8 (11.3)	0.35	0.16 (2.01)	0.40 (2.58)	
Body mass index, kg/m²	30.3 (4.3)	29.2 (3.6)	0.25	30.2 (4.3)	29.2 (3.3)	0.26	0.1 (2.4)	0.7 (3.7)	0.43
Waist circumference, cm	99.6 (10.8)	95.0 (9.5)	0.06	96.4 (10.3)*	94.0 (8.4)	0.32	3.2 (3.8)	1.4 (4.1)	0.06
Systolic blood pressure, mmHg	147 (20.6)	150 (17.6)	0.56	146 (20.6)	142 (19.1)	0.42	1.5 (12.7)	0.2 (12.1)	0.68
Diastolic blood pressure, mmHg	88.6 (12.7)	87.6 (2.7)	0.71	88.0 (13.5)	85.9 (10.2)	0.51	-1.2 (12.0)	-0.6(14.5)	0.86
Glucose, mmol/L	9.52 (3.36)	9.71 (3.23)	0.81	8.76 (2.99)	9.17 (3.27)	0.59	0.26 (1.58)	0.15 (1.25)	0.76
HbA1c, %	8.4 (2.1)	8.4 (1.8)	0.98	8.0 (2.0)*	8.2 (1.9)	0.72	4.3 (9.1)	3.0 (9.0)	0.54
Insulin, UI/ L	14.5 (12.0)	11.4 (9.4)	0.21	11.8 (9.3) *	10.8 (9.4)	0.66	11.0 (47.6)	-0.4 (65.1)	0.41
HOMA-IR index	6.2 (5.7)	4.9 (4.0)	0.27	4.7 (4.5)*	3.4 (3.9)	0.74	11.1 (62.2)	2.4 (62.7)	0.57
Leptin, µg/L	11.6 (6.2)	11.2 (10.2)	0.86	11.2 (5.9)	11.8 (10.2)	0.79	0.8 (21.9)	-7.7 (26.7)	0.21
Adiponectin, µg/mL	20.0 (14.6)	18.3 (8.4)	0.55	19.4 (13.3)	17.7 (9.1)	0.53	-2.0 (30.7)	4.0 (19.1)	0.42
Ghrelin, pg/mL	655 (190)	673 (226)	0.73	764 (255)*	787 (237)*	0.71	-18.2 (19.5)	-16.5 (21.1)	0.75
Fasting triglycerides, mmol/L	2.14 (1.41)	2.26 (4.09)	0.73	2.18 (1.27)	2.17 (1.31)	0.99	-0.11 (0.44)	-0.06 (0.46)	0.66
Fasting cholesterol, mmol/L	5.40 (1.00)	5.31 (0.73)	0.68	5.35 (1.08)	5.09 (0.92)	0.29	0.02 (0.25)	0.10 (0.42)	0.39
HDL-cholesterol, mmol/L	1.01 (0.23)	0.97 (0.24)	0.52	1.01 (0.23)	0.99 (0.31)	0.76	-0.03 (0.37)	-0.05 (0.45)	0.78
LDL-cholesterol, mmol/L	3.36 (0.86)	3.07 (0.81)	0.16	3.23 (0.85)	3.08 (0.62)	0.42	0.07 (0.38)	0.54 (29.2)	0.24
Alanine aminotransferase, IU/L	37.0 (27.2)	42.9 (31.3)	0.38	33.9 (14.2)	37.0 (29.9)	0.60	-2.20 (32.95)	10.01 (26.63)	0.10
Creatinine, µmol/L	79.6 (35.4)	88.4 (35.4)	0.08	79.5 (33.6)	88.3 (36.84)	0.07	-0.99 (11.20)	1.01 (10.58)	0.27
Uric acid, µmol/L	333 (101)	351 (83.3)	0.49	327 (107)	345 (89.2)	0.56	-1.32 (18.8)	0.24 (21.4)	0.78

Data expressed as a mean with standard deviation in parenthesis. * $p<0.05$ from baseline to the end (16 weeks) with paired t-tests.

versus placebo treatment. Between-group differences for BMI, WC, blood pressure, fasting glucose, HbA1C, fasting insulin, leptin, adiponectin, ghrelin, plasma lipoproteins, ALT, creatinine, and uric acid all failed to reach statistical significance. There was also no statistically significant difference in HOMA-IR – the major outcome measurement. The average reduction in HOMA-IR index was 11.1 percent (± 62.2%) in the decaffeinated GTE group and 2.4 percent (± 62.7%) in the placebo group after 16 weeks of treatment; this difference was not statistically significant.

Within-Group Comparisons at 16 Weeks

Compared with baseline measurements, 16 weeks of treatment with decaffeinated GTE resulted in significant reductions in WC, HbA1C, HOMA-IR index, and insulin level (Table 3). There were significant increases in ghrelin levels in both the treatment and placebo groups.

Adverse Effects

One subject experienced symptoms of hypoglycemia, two developed mild constipation, and another two had abdominal discomfort after GTE treatment, while one subject had mild constipation and another had abdominal discomfort in the placebo group; all the symptoms were noted in the

first week after treatment. No major adverse effects were noted with either active or placebo treatment.

Conclusions

According to the World Health Organization (WHO), excess weight and obesity are highly associated with type 2 diabetes, insulin resistance, and many other chronic diseases.[29,30] BMI is one of the most popular anthropometric indices. Different ethnic groups have different BMI cut-off points for describing obesity. The optimal cut-off point of obesity among Asian populations remains controversial.[31] In 2000, the WHO defined BMI cut-off points of 23/25/30 kg/m^2 as overweight/obesity class I/obesity class II for people living in the Asia Pacific region.[32] Since subjects in this study were from Taiwan, we used the WHO-defined BMI categorization criteria. All the subjects had BMI >25 kg/m^2 (obesity class 1) and had been diagnosed with type 2 diabetes for more than one year. To our knowledge, this was the first study to explore the effect of decaffeinated GTE on subjects with both obesity and type 2 diabetes.

Some human studies have reported a significant decrease in body weight[25,33,34] after GTE intake. However, most of these studies were of short duration,[33] had no control group,[25] and had small sample sizes.[25,34] Weight loss results with GTE might be complicated by whether or not the extract used contains caffeine. In a meta-analysis, Phung et al concluded that green tea with caffeine produced a small but consistent reduction in BMI, body weight, and WC; however, green tea catechins given without caffeine did not appear to be beneficial for obesity.[35] Stendell-Hollis et al gave decaffeinated green tea to overweight breast cancer survivors for six months. While there was a trend toward weight loss and improvement in HOMA-IR, no statistically significant differences were detected for weight, body composition, or HOMA-IR.[36]

Green tea catechins, especially EGCG, have shown antiobesity and antidiabetic effects *in vitro*.[37] To understand the effect of green tea catechins on diabetes and obesity in humans, and to avoid the potential confounding caused by caffeine in green tea, the GTE used in this study was decaffeinated. Hosoda et al reported a 30-percent decrease in fasting glucose among subjects who drank oolong tea for one month. However, their study was not blinded and the GTE used contained caffeine.[13] In the research conducted by Mackenzie et al using decaffeinated GTE, no beneficial effect on glucose control was observed. They also reported an average increase of 0.4 in HbA1C after three months.[26] Although it was a double-blinded, placebo-controlled, and randomized study, it did not evaluate insulin resistance and hormone peptides, and there were no anthropometric data measured. In contrast to their finding, our study found a within-group reduction of 0.4 in HbA1C after 16 weeks of treatment with decaffeinated GTE.

Despite finding no statistically significant difference between the GTE group and placebo group in any of the anthropometric or lab variables assessed, there were several findings in this study that warrant further exploration.

First, there was significant within-group reduction in the HbA1C level and HOMA-IR index after 16 weeks of treatment in the GTE group, but not in the placebo group. Rat studies have found evidence suggesting that EGCG and other catechins help prevent hyperglycemia by enhancing insulin activity.[9] An epidemiological study conducted in Japan found lower incidence of type 2 diabetes among long-time consumers of green tea.[38]

Second, a significant decrease in WC was observed in both groups, despite there being no significant change in BMI. And the statistical difference in WC between groups ($p=0.06$) just failed to reach the statistical target of $p<0.05$. Although it is possible that changes in body composition or weight distribution occurred, the study was not designed to assess these areas. These results warrant further investigation.

Third, although comparison between groups revealed no statistically significant difference in the level of hormone peptides, within-group data revealed a statistically significant decrease in serum insulin in the decaffeinated GTE group after 16 weeks. Kao et al reported that EGCG significantly reduced insulin levels in an animal study,[20] which is consistent with the within-group findings in the present study. In the present study, within-group statistical analysis also revealed increased serum levels of ghrelin in both the decaffeinated GTE and placebo group. Ghrelin is a novel growth hormone-releasing peptide isolated mainly from the stomach.[39] It has been demonstrated to alter feeding behavior, energy metabolism, and gastrointestinal functions.[40] The increase in ghrelin level found in both groups of this study implies that taking a decaffeinated GTE might increase the secretion of hormone peptides such as ghrelin. Whether an increase in ghrelin would have a

positive or negative effect on patients with metabolic syndrome remains to be determined. More studies are needed to clarify: (1) why both the decaffeinated GTE and placebo group experienced significant increases in ghrelin, (2) whether GTE has any legitimate effects on ghrelin, and (3) what effect GTE-induced changes in ghrelin would have on diabetes control and weight management.

Finally, after 16 weeks of GTE treatment, serum EGCG was detected in only 15 of the 35 subjects receiving active treatment. Why other subjects receiving the active treatment had undetectable serum levels of EGCG after fasting overnight merits more in-depth exploration. Further research on the bioavailability and pharmacokinetics of EGCG in human studies is needed. In addition, whether GTE works in synergy with antidiabetic drugs to reduce the levels of insulin, HbA1C, and HOMA-IR index or whether the different catechins contained in decaffeinated GTE affect peptide hormones, triglycerides, or cholesterol levels also merits more in-depth study.

In summary, the present study showed no statistically significant difference between decaffeinated GTE and placebo in BMI, WC, blood pressure, fasting glucose, HbA1C, fasting glucose, HOMA-IR, hormone peptides, lipids, ALT, creatinine, or uric acid after 16 weeks of treatment. The results of this study suggest that an intake of decaffeinated GTE providing a daily dose of 856 mg EGCG for 16 weeks is safe and free of severe adverse effects. The metabolic effects, bioavailability, and pharmacokinetics of decaffeinated GTE in humans merits continued investigation.

Acknowledgments/Conflicts of Interest

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