Original Article

Antihypertensive Effect of Green Coffee Bean Extract on Mildly Hypertensive Subjects

Kazuya KOZUMA, Shigemi TSUCHIYA, Jun KOHORI,
Tadashi HASE, and Ichiro TOKIMITSU

A water-soluble green coffee bean extract (GCE) has been shown to be effective against hypertension in both spontaneously hypertensive rats and humans. This multicenter, randomized, double-blind, placebo-controlled, parallel group study evaluated the dose-response relationship of GCE in 117 male volunteers with mild hypertension. Subjects were randomized into four groups: a placebo and three drug groups that received 46 mg, 93 mg, or 185 mg of GCE once a day. After 28 days, systolic blood pressure (SBP) in the placebo, 46 mg, 93 mg, and 185 mg groups was reduced by −1.3±3.0 mmHg, −3.2±4.6 mmHg, −4.7±4.5 mmHg, and −5.6±4.2 mmHg from the baseline, respectively. The decreases in SBP in the 93 mg group ($p<0.05$) and the 185 mg group ($p<0.01$) were statistically significant compared with the placebo group. Diastolic blood pressure (DBP) in the placebo, 46 mg, 93 mg, and 185 mg groups was reduced by −0.8±3.1 mmHg, −2.9±2.9 mmHg, −3.2±3.2 mmHg, and −3.9±2.8 mmHg from the baseline, respectively, and significant effects were observed in the 93 mg group ($p<0.05$) and the 185 mg group ($p<0.01$) compared with the placebo group. Both blood pressures were significantly reduced in a dose-related manner by GCE ($p<0.001$). Adverse effects caused by GCE were not observed. The results suggested that daily use of GCE has a blood pressure-lowering effect in patients with mild hypertension. (*Hypertens Res* 2005; 28: 711–718)

***Key Words*: hypertension, chlorogenic acid, dose-response, human, randomized controlled study**

Introduction

Hypertension is a primary risk factor for stroke, heart disease, and renal failure, and one of the most critical issues for human health (*1–5*). Hypertension is also a lifestyle-related disease, and modifications in lifestyle are effective for its prevention: *i.e.*, engaging in moderate physical activity; maintaining normal body weight for adults; limiting alcohol consumption; reducing sodium intake; maintaining adequate intake of potassium; and consuming a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat (*4*). Patients with mild hypertension (systolic blood pressure [SBP]/diastolic blood pressure [DBP], 140–159/90–99 mmHg) with no risk factors and with presence of risk factors beside diabetes are classified into low-risk and medium-risk, respectively. In low-risk and medium-risk hypertensive patients, lifestyle changes should be the first therapeutic measure, but if the blood pressure does not decline to an SBP of below 140 mmHg and DBP of below 90 mmHg, then antihypertensive drug treatment should be started (*5*).

As an alternative to drug therapy, it is desirable to use foods or food components for the prevention and/or treatment of hypertension and thereby avoid the adverse effects of organically synthesized drugs as well as the high cost of drug therapy (*6*). Many investigators report that antioxidant vitamins (*7–10*) and supplements (*11*), peptides from milk (*6*, *12*) or fish protein (*13*), polyunsaturated fatty acids (*14*), and many food components (*15–24*) reduce blood pressure in humans and animals. The application of foods or food components is thus expected to be effective as part of the primary therapy for

From Health Care Research Laboratories, Kao Corporation, Tokyo, Japan.
Address for Reprints: Kazuya Kozuma, Ph.D., Health Care Research Laboratories, Kao Corporation, 2−1−3 Bunka, Sumida-ku, Tokyo 131−8501, Japan. E-mail: kouzuma.kazuya@kao.co.jp
Received March 1, 2005; Accepted in revised form June 27, 2005.

Table 1. The Composition of Green Coffee Bean Extract

Component	Content (wt%)
Chlorogenic acids	54
Caffeine	12
Others	34

patients with mild hypertension.

A water-soluble green coffee bean extract (GCE) has been shown to reduce blood pressure in spontaneously hypertensive rats (*25*) and humans (*26*). The GCE used in these reports was a hot-water extract of green coffee beans that contained chlorogenic acid as a major ingredient. Orally administered chlorogenic acid is metabolized to ferulic acid in the liver and/or kidneys (*27*). Ferulic acid, which is a metabolite of GCE containing chlorogenic acid, decreases blood pressure (*25*) and improves vasoreactivity (*28*).

GCE may be considered a novel antihypertensive food component. We conducted a multicenter, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy of antihypertensive treatment with an oral GCE that contained high doses of chlorogenic acid for patients with mild hypertension.

Methods

Study Design

The current study was a randomized, double-blind, placebo-controlled, parallel group, dose-response study conducted for 28 days at 8 centers in Japan. The study was conducted in compliance with the Declaration of Helsinki (1964) and its revised version (2002). The protocol was reviewed and approved by the Clinical Trial Ethics Committee of Isogo Central and Neurosurgical Hospital (Yokohama, Japan) before the start of the study. The nature of the study, the proposal for the study design, and the potential risks of participation in the study were fully explained to each volunteer, and written consent was obtained.

Subjects

Healthy male volunteers, aged 30 to 50 years, with mild hypertension (SBP between 140 and 159 mmHg, and/or DBP between 90 and 99 mmHg) (*5*) were included in this study. Subjects were excluded if they were heavy smokers (>15 cigarettes/day) or hardened drinkers (>30 g alcohol/day), if they had received antihypertensive therapy, or if they exhibited abnormal liver function (aspartate aminotransferase >100 IU/l and/or alanine aminotransferase >100 IU/l) or abnormal renal function (blood urea nitrogen >23 mg/dl and/or serum creatinine >1.3 mg/dl).

Table 2. Nutritional Composition of the Placebo and Test Soup Bases (per 10 g)

	Placebo	Green coffee bean extract		
		46 mg	93 mg	185 mg
Energy (kJ)	45.6	46.9	46.5	48.1
Carbohydrate (g)	1.10	1.14	1.15	1.23
Fat (g)	0	0	0	0
Protein (g)	1.01	1.02	1.02	1.03
Sodium (g)	0.35	0.35	0.35	0.35
Potassium (g)	0.25	0.25	0.25	0.25
Alcohol (g)	0.35	0.36	0.35	0.35
Chlorogenic acid (mg)	0	25	50	100

Table 3. Nutritional Composition of the Ingredients of Soup (per Bag)

	Seaweed	Tofu	Deep-fried tofu
Energy (kJ)	50.4	45.9	52.5
Carbohydrate (g)	1.48	1.28	0.97
Fat (g)	0.10	0.20	0.50
Protein (g)	0.78	0.73	1.03
Sodium (g)	0.15	0.12	0.15
Potassium (g)	0.01	0.02	0.01

Test Diet

The test diet was a soy sauce-flavored instant cup soup containing GCE, which was a hot-water extract of dried, green unroasted coffee beans (flavor folder RC; T. Hasegawa Co., Ltd., Tokyo, Japan). The components of GCE are shown in Table 1. In human clinical trials, GCE was reported to have no adverse effects on hematological parameters and/or blood chemistry (*26*, *28*).

The test diet was eaten at breakfast and consisted of one 10-g pack of soup base (Table 2) and one of three different types of freeze-dried food—"wakame" seaweed, tofu soybean curd, or deep-fried tofu soybean curd—stirred in a cup with 180 ml of hot water (Table 3). The soup base contained 0 mg (placebo), 46 mg, 93 mg, or 185 mg of GCE in 10 g of low-sodium soy sauce (Table 2). The amounts of chlorogenic acid included in these different quantities of GCE were 0 mg, 25 mg, 50 mg, and 100 mg, respectively.

The addition of GCE caused no changes in the color or the taste of the soy soup, and no taste difference was detected between the test diets and the placebo diets. The test diets—*i.e.*, the soup bases and ingredients—included 1.21–1.25 g of salt.

Measurement of Blood Pressure

Blood pressure and pulse were measured 14 days before the trial, at baseline (0 days), and at 14 and 28 days after the start

Table 4. Automated Sphygmomanometers

Center	Model	Manufacturers
Aoba Clinic	HEM-707	Omron Co., Kyoto, Japan
Hikifune Clinic	ES-P2000H	Terumo Co., Tokyo, Japan
Hiratsuka Gastroenterological Hospital	HEM-707	Omron Co., Kyoto, Japan
Hisano Maynds Tower Clinic	BP-203RV	Colin Medical Co., Komaki, Japan
Ishiguro Clinic	GP-303S	Parama-Tech Co., Fukuoka, Japan
Isogo Central and Neurosurgical Hospital	Q9224	Colin Medical Co., Komaki, Japan
Kameido-Minamiguchi Clinic	CH-432B	Japan CBM Co., Tokyo, Japan
Kodama Central Hospital	GP-303S	Parama-Tech Co., Fukuoka, Japan

Table 5. Adverse Events Checklist on Case Report Form

Category	Symptom
Cardiovascular	Edema
	Palpitation
Constitutional symptoms	Fatigue
	Fever
	Hot flush
	Lethargy/drowsiness
	Sweating
Dermatological symptoms	Eruption
	Flushing
	Pruritus
	Rash
Gastrointestinal symptoms	Constipation
	Diarrhea
	Dysgeusia
	Epigastric discomfort
	Heartburn
	Dry mouth
	Nausea
	Salivary gland change
	Stomach discomfort
	Vomiting
Neurological symptoms	Dizziness
	Dysesthesia
	Lightheadedness
	Paresthesia
	Vertigo
Pain	Chest pain
	Headache
	Dull headache
	Abdominal pain
Pulmonary	Cough
Renal/genitourinary	Urinary frequency

Adverse events were checked by physicians' interviews every visit.

of the test period under the morning fasting condition at trough (24±3 h after the last test-diet ingestion). Three measurements were taken in the right arm using automated sphygmomanometers (Table 4) and an appropriate-sized cuff after at least 10 min of rest in the seated position. The median of three measurements was taken as the measured value.

Protocol

Based on the blood pressure measured 14 days before the trial, subjects were randomly assigned to four groups (a placebo or a 46, 93, or 185 mg group). Subjects were also randomized to an approximately equal testing group distribution in each center.

At baseline (0 day) and 28 days, the body weights were measured, and fasting blood samples were collected after the blood pressure measurement and subjected to hematological evaluation (white blood cells, red blood cells, platelets, hematocrit, and hemoglobin) and blood chemistry tests (aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase, alkaline phosphatase, lactate dehydrogenase, blood urea nitrogen, serum creatinine, uric acid, total protein, albumin, total cholesterol, high density lipoprotein cholesterol, and low density lipoprotein cholesterol) at each center. Adverse events (Table 5) were checked by physicians' interview using a case-report form at baseline (0 day), 14 days, and 28 days.

Each subject provided 3 days of food records prior to each visit. The food records were analyzed by a registered dietitian using the Japanese food composition database (Japan Science and Technology Agency, http://food.tokyo.jst.go.jp/) to determine average intakes of energy and salt. Subjects were asked not to change their dietary habits during the study, particularly in regard to their consumption of fat, salt, vegetables, and fruits.

Statistical Analysis

The characteristics of groups at baseline were compared by one-way analysis of variance (ANOVA). The changes in trough blood pressures, pulse, body weight, energy intake, and salt intake were analyzed using one-way repeated measures ANOVA for comparisons with the baseline and two-way repeated measures ANOVA for comparisons of the differences among the four test groups. Values were expressed

Table 6. Baseline Characteristics of Randomized Subjects

	Placebo	Green coffee bean extract			*p* value*
		46 mg	93 mg	185 mg	
n	29	29	28	31	
Age (years)	43.1±9.1	42.9±8.2	43.3±8.3	43.4±8.4	0.99
Weight (kg)	69.9±10.7	73.9±13.6	70.3±8.1	73.6±13.2	0.40
BMI (kg/m^2)	24.0±3.1	25.2±4.0	24.4±2.6	25.1±3.6	0.49
SBP (mmHg)	145.4±5.5	145.9±5.1	145.7±5.0	146.0±5.3	0.89
DBP (mmHg)	91.7±2.5	92.1±2.7	92.5±2.7	92.5±2.9	0.63
Pulse (beats/min)	76.3±8.9	79.6±7.1	75.8±7.7	79.5±6.2	0.23
White blood cells (×10^3/μl)	6.1±1.6	6.2±1.5	6.2±1.2	6.3±1.4	0.96
Red blood cells (×10^4/μl)	486.0±39.1	499.1±35.7	500.4±28.4	490.3±36.5	0.35
Platelets (×10^4/μl)	24.6±5.6	22.6±5.0	23.9±5.0	23.0±5.1	0.47
Hematocrit (%)	45.9±3.4	46.7±4.2	47.7±2.8	46.1±2.7	0.19
Hemoglobin (g/dl)	15.1±1.0	15.5±1.7	15.7±1.0	15.4±1.0	0.25
AST (IU/l)	21.8±5.0	27.3±12.5	25.4±7.1	24.5±6.3	0.15
ALT (IU/l)	25.1±11.4	34.5±24.8	32.5±16.4	30.6±19.8	0.26
γ-GTP (IU/l)	50.3±41.8	45.7±34.2	46.3±32.3	60.1±53.5	0.51
ALP (IU/l)	207.6±54.5	216.7±59.2	201.4±45.1	200.7±59.1	0.66
LDH (IU/l)	181.8±33.0	191.8±39.0	196.5±38.6	193.8±34.2	0.37
Blood urea nitrogen (mg/dl)	13.5±2.9	13.4±2.1	13.6±3.0	13.6±3.0	0.99
Uric acid (mg/dl)	5.8±1.5	6.3±1.1	5.9±1.0	6.1±1.0	0.57
Serum creatinine (mg/dl)	0.8±0.1	0.9±0.2	0.9±0.1	0.8±0.1	0.63
Total protein (g/dl)	7.4±0.4	7.4±0.4	7.4±0.4	7.4±0.4	0.98
Albumin (g/dl)	4.5±0.2	4.5±0.3	4.6±0.3	4.6±0.3	0.61
Triglyceride (mg/dl)	134.0±63.0	129.2±64.3	129.1±69.4	157.7±51.2	0.25
Total cholesterol (mg/dl)	202.9±31.4	205.1±30.4	206.3±31.0	208.8±25.0	0.89
HDL cholesterol (mg/dl)	53.0±11.8	57.2±17.4	55.1±13.2	56.1±14.2	0.72
LDL cholesterol (mg/dl)	125.2±31.7	120.9±27.0	124.9±36.8	126.2±29.9	0.92
Energy intake (kJ/day)	8,066±1,161	8,389±1,600	8,171±942	8,449±1,128	0.60
Salt intake (g/day)	11.4±2.3	11.8±2.1	10.8±1.8	11.4±1.9	0.30

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; HDL, high density lipoprotein; LDL, low density lipoprotein. Values expressed as mean±SD. *One-way ANOVA.

as the mean±SD. Values of $p<0.05$ were considered to indicate statistical significance, and the post hoc Turkey-Kramer method was applied to significant ANOVA results. The relationship between the chlorogenic acid doses and the changes in trough blood pressures after consumption of the test diet for 28 days was analyzed by regression analysis (least squares method). These statistical analyses were performed using the StatView program (version 5.0; SAS Institute Inc., Cary, USA).

Results

One hundred twenty-six applicants were recruited for the study, but 9 were excluded based on the exclusion criteria at recruitment. Thus a total of 117 subjects were randomized, and all completed the study. At baseline in the study, there were no significant differences among the four groups in blood pressure, pulse, age, weight, body mass index (BMI), blood components, dietary energy intake, or dietary salt intake (Table 6). Subjects had a mean compliance of 99.85% as estimated by food records. Three subjects failed to ingest the test diet once, and one subject failed to ingest the test diet twice; thus 113 subjects ingested 100% of the doses of the test diet. Trough SBPs of the placebo group and the testing groups were significantly reduced from baseline ($p=0.018$, $p=0.0002$, $p<0.0001$, and $p<0.0001$ for the placebo group, the 46 mg group, the 93 mg group, and the 185 mg group, respectively), and the reductions in the trough SBPs of the placebo group, the 46 mg group, the 93 mg group, and the 185 mg group after 28 days were −1.3±3.0 mmHg, −3.2±4.6 mmHg, −4.7±4.5 mmHg and −5.6±4.2 mmHg, respectively. There were significant differences between the placebo group and both the 93 mg group ($p<0.05$) and the 185 mg group ($p<0.01$) (Fig. 1). The trough DBP of the placebo group was not reduced significantly ($p=0.296$), whereas those of the testing groups showed significant decreases ($p<0.0001$ for

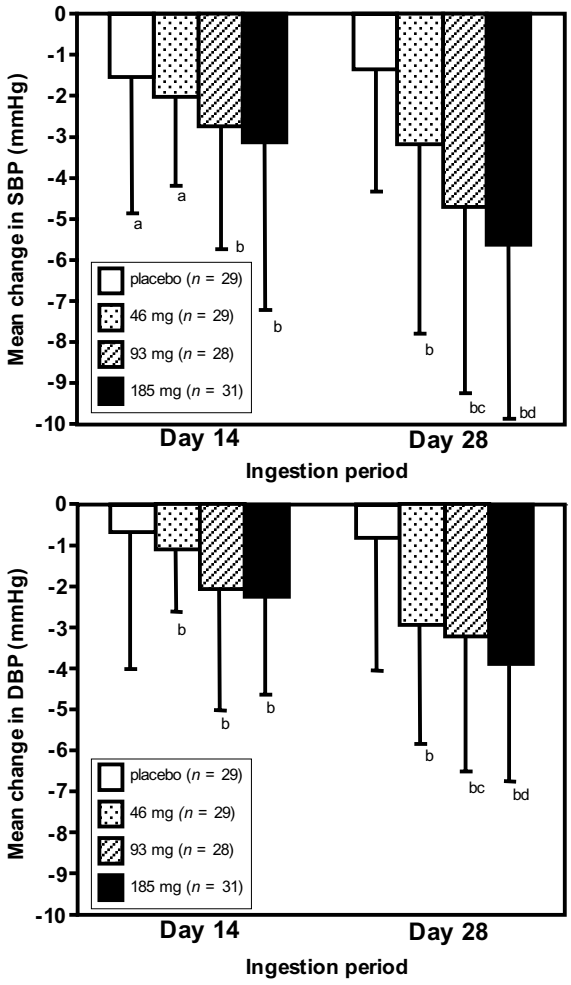

Fig. 1. *Mean (±SD) change in trough SBP and DBP from baseline at 14 and 28 days after ingestion. SBP, systolic blood pressure; DBP, diastolic blood pressure.* [a]$p < 0.05$, [b]$p < 0.01$ *compared with the baseline (one-way ANOVA);* [c]$p < 0.05$, [d]$p < 0.01$ *compared with the placebo (two-way ANOVA);*

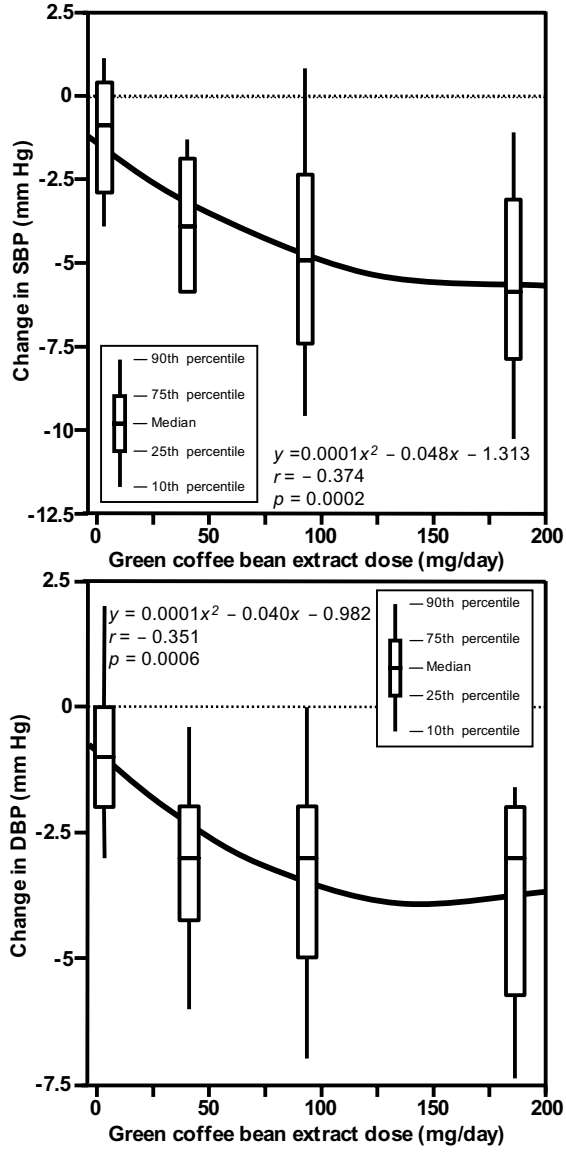

Fig. 2. *Relationship between green coffee bean extract dose and changes in trough SBP and DBP from baseline at 28 days after ingestion. SBP, systolic blood pressure; DBP, diastolic blood pressure.*

the 46 mg group, the 93 mg group, and the 185 mg group). The trough DBP reductions of the placebo group, the 46 mg group, the 93 mg group, and the 185 mg group after 28 days were −0.8±3.1 mmHg, −2.9±2.9 mmHg, −3.2±3.2 mmHg and −3.9±2.8 mmHg, respectively. The reductions observed in the 93 mg group ($p<0.05$) and the 185 mg group ($p<0.01$) were significant compared with the placebo group (Fig. 1).

A significant quadratic trend in the trough BP reduction was evident among GCE doses (SBP: $r=-0.374$, $p=0.0002$; DBP: $r=-0.351$, $p=0.0006$) (Fig. 2).

No significant body weight, energy intake, or pulse changes from baseline were observed in the three test groups or placebo group or among the four test groups (Table 7). The daily salt intake increased significantly from baseline ($p<0.0001$) because the test diets included salts. However, no significant differences in daily salt intake among the four test groups were observed ($p=0.395$; Table 7).

No adverse effects originating in the test or placebo diets were observed in the clinical examination, physical examination, or medical examination/history taking (Table 7).

Discussion

In the present study, we demonstrated for the first time that GCE reduced blood pressure in patients with mild hypertension in a dose-related manner. The main component of GCE is chlorogenic acid (Table 1). Oral administration of chloro-

Table 7. Characteristics of Randomized Subjects after the 28 Days

	Placebo	Green coffee bean extract		
		46 mg	93 mg	185 mg
n	29	29	28	31
Weight (kg)	69.7±10.5	73.8±13.4	70.2±7.9	73.6±13.1
BMI (kg/m^2)	23.9±3.1	25.1±4.0	24.4±2.6	25.1±3.6
Pulse (beats/min)	75.8±1.3	76.7±1.1	77.1±1.4	75.9±1.2
White blood cells (×10^3/μl)	6.1±1.4	6.2±1.4	6.3±1.3	6.5±1.5
Red blood cells (×10^4/μl)	478.7±43.0	498.1±34.7	496.0±34.6	484.1±33.6
Platelets (×10^4/μl)	25.1±5.8	21.6±4.7	23.5±4.9	22.4±4.7
Hematocrit (%)	44.3±5.7	46.6±4.0	47.4±3.1	45.7±2.7
Hemoglobin (g/dl)	14.5±2.1	15.4±1.6	15.6±1.1	15.3±0.9
AST (IU/l)	22.2±6.3	25.5±11.7	24.5±6.9	24.5±6.6
ALT (IU/l)	24.5±13.1	31.6±22.4	30.0±15.0	29.6±18.1
γ-GTP (IU/l)	44.6±25.1	43.2±31.8	44.9±32.2	56.4±44.3
ALP (IU/l)	204.3±50.7	214.9±53.5	206.4±44.7	203.8±59.1
LDH (IU/l)	179.7±31.0	188.6±24.3	191.2±35.0	192.1±43.8
Blood urea nitrogen (mg/dl)	13.2±2.9	14.2±3.1	14.1±2.9	13.2±2.9
Uric acid (mg/dl)	5.6±1.6	6.2±1.2	6.0±1.1	6.1±1.2
Serum creatinine (mg/dl)	0.8±0.2	0.9±0.2	0.9±0.1	0.9±0.1
Total protein (g/dl)	7.5±0.3	7.5±0.4	7.3±0.5	7.4±0.5
Albumin (g/dl)	4.6±0.3	4.6±0.4	4.6±0.3	4.6±0.3
Triglyceride (mg/dl)	138.7±56.8	130.5±63.4	131.4±77.3	163.9±64.9
Total cholesterol (mg/dl)	201.3±31.0	209.4±29.8	199.2±31.4*	201.5±28.2*
HDL cholesterol (mg/dl)	53.0±11.8	57.2±17.4	55.1±13.2	56.1±14.2
LDL cholesterol (mg/dl)	120.7±31.0	123.9±29.5	120.3±27.9	118.0±30.4*
Energy intake (kJ/day)	8,171±1,511	8,785±1,926	8,528±1,273	8,378±1,473
Salt intake (g/day)†	13.0±2.1**	14.3±2.5**	13.9±2.0**	13.6±1.9**

BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; HDL, high density lipoprotein; LDL, low density lipoprotein. Values expressed as mean±SD. *$p<0.05$, **$p<0.01$ compared with baseline. †Including salt from the test diets.

genic acid, as well as the oral administration of GCE, has been shown to reduce blood pressure in spontaneously hypertensive rats (*25*). About one-third of the ingested chlorogenic acid enters into the blood circulation *via* absorption from the small intestine in humans (*29*). The absorbed chlorogenic acids are metabolized to caffeic acid, quinic acid, and ferulic acid, and traces of chlorogenic acid are not metabolized but excreted in urine (*27*). A metabolite of chlorogenic acid, ferulic acid, reduces blood pressure (*25*), acts on NO derived from the vascular endothelium (*30*), and improves vasoreactivity by acting directly on the blood vessels (*28*).

Blood pressure is related to oxidant stress (*31–33*). Oxidant stress is increased, and antioxidant mechanism activities are reduced in hypertensive patients (*34*). Antioxidant vitamins (*i.e.*, ascorbic acid and tocopherol) reduce blood pressure (*8–10*) and improve blood vessel endothelial dysfunction in patients with hypertension (*35*, *36*). Ascorbic acid scavenges oxygen free radicals and improves endothelium-dependent vasodilatation by restoring nitric oxide activity in essential hypertension (*35*, *36*). Chlorogenic acid, caffeic acid, and ferulic acid have antioxidant potencies that are the same as or a little weaker than that of ascorbic acid (*37–42*). The antioxidant property of chlorogenic acid, which is the main component of GCE and of the metabolites of chlorogenic acid, might improve endothelial dysfunction and reduce blood pressure. Further studies are necessary to investigate the mechanism of the antihypertensive effect of GCE and/or chlorogenic acid.

Many studies have reported a correlation between blood pressure and salt intake (*43–48*). In this study, although all the test diets included salt, none of them was found to increase blood pressure.

This study demonstrated that the daily intake of 93 mg of GCE (50 mg of chlorogenic acid) reduced SBP and DBP by 4.7 mmHg and 3.2 mmHg, respectively. A reduction of 5 mmHg in SBP reduces stroke and coronary heart disease mortality by 14% and 9%, respectively (*4*). A reduction of 2 mmHg of DBP could be associated with 14% fewer strokes and 8% less coronary heart disease (*49*). Ochiai *et al*. reported that ingestion of a GCE drink containing 140 mg of chlorogenic acid for 4 months had no adverse or hypotensive effects on normal blood pressure subjects (*28*). In our study, no adverse effects from GCE were observed. Our results indicate

that daily intake of GCE reduces blood pressure in hypertensive subjects and may help to prevent stroke and coronary heart disease.

References

1. Eastern Stroke and Coronary Heart Disease Collaborative Research Group: Blood pressure, cholesterol, and stroke in eastern Asia. *Lancet* 1998; **352**: 1801–1807.
2. Domanski M, Mitchell G, Pfeffer M, *et al*: Pulse pressure and cardiovascular disease-related mortality: follow-up study of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA* 2002; **287**: 2677–2683.
3. Lloyd-Jones DM, Larson MG, Leip EP, *et al*: Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation* 2002; **106**: 3068–3072.
4. Whelton PK, He J, Appel LJ, *et al*, National High Blood Pressure Education Program Coordinating Committee: Primary prevention of hypertension: clinical and public health advisory from the National High Blood Pressure Education Program. *JAMA* 2002; **288**: 1882–1888.
5. Japanese Society of Hypertension Guidelines Subcommittee for the Management of Hypertension: Guidelines for the management of hypertension for general practitioners. *Hypertens Res* 2001; **24**: 613–634.
6. FitzGerald RJ, Murray BA, Walsh DJ: Hypotensive peptides from milk proteins. *J Nutr* 2004; **134**: 980S–988S.
7. Block G, Mangels AR, Norkus EP, Patterson BH, Levander OA, Taylor PR: Ascorbic acid status and subsequent diastolic and systolic blood pressure. *Hypertension* 2001; **37**: 261–267.
8. Noguchi T, Ikeda K, Sasaki Y, *et al*: Effects of vitamin E and sesamin on hypertension and cerebral thrombogenesis in stroke-prone spontaneously hypertensive rats. *Hypertens Res* 2001; **24**: 735–742.
9. Mullan BA, Young IS, Fee H, MaCance DR: Ascorbic acid reduces blood pressure and arterial stiffness in type 2 diabetes. *Hypertension* 2002; **40**: 804–809.
10. Boshtam M, Rafiei M, Sadeghi K, Sarraf-Zadegan N: Vitamin E can reduce blood pressure in mild hypertensives. *Int J Vitam Nutr Res* 2002; **72**: 309–314.
11. Galley HE, Thornton J, Howdle PD, Walker BE, Webster NR: Combination oral antioxidant supplementation reduces blood pressure. *Clin Sci* 1997; **92**: 361–365.
12. Seppo L, Jauhiaine T, Poussa T, Korpela R: A fermented milk high in bioactive peptides has a blood pressure-lowering effect in hypertensive subjects. *Am J Clin Nutr* 2003; **77**: 326–330.
13. Kawasaki T, Seki E, Osajima K, *et al*: Antihypertensive effect of valyl-tyrosine, a short chain peptide derived from sardine muscle hydrolyzate, on mild hypertensive subjects. *J Hum Hypertens* 2000; **14**: 519–523.
14. Das UN: Long-chain polyunsaturated fatty acids interact with nitric oxide, superoxide anion, and transforming growth factor-beta to prevent human essential hypertension. *Eur J Clin Nutr* 2004; **58**: 195–203.
15. Gokce N: L-Arginine and hypertension. *J Nutr* 2004; **134**: 2807S–2811S.
16. Iseki K, Iseki C, Itoh K, *et al*: Estimated protein intake and blood pressure in a screened cohort in Okinawa, Japan. *Hypertens Res* 2003; **26**: 289–294.
17. Hermansen K: Diet, blood pressure and hypertension. *Br J Nutr* 2000; **83**: S113–S119.
18. Saltzman E, Das SK, Lichtenstein AH, *et al*: An oat-containing hypocaloric diet reduces systolic blood pressure and improves lipid profile beyond effects of weight loss in men and women. *J Nutr* 2001; **131**: 1465–1470.
19. Burke V, Hodgson JM, Beilin LJ, Giangiulioi N, Rogers P, Puddey IB: Dietary protein and soluble fiber reduce ambulatory blood pressure in treated hypertensives. *Hypertension* 2001; **38**: 821–826.
20. Kondo S, Tayama K, Tsukamoto Y, Ikeda K, Yamori Y: Antihypertensive effects of acetic acid and vinegar on spontaneously hypertensive rats. *Biosci Biotechnol Biochem* 2001; **65**: 2690–2694.
21. Jenkins DJ, Kendall CW, Jackson CJ, *et al*: Effects of high- and low-isoflavone soyfoods on blood lipids, oxidized LDL, homocysteine, and blood pressure in hyperlipidemic men and women. *Am J Clin Nutr* 2002; **76**: 365–372.
22. Rivas M, Garay RP, Escanero JF, Cia PJ, Cia P, Alda JO: Soy milk lowers blood pressure in men and women with mild to moderate essential hypertension. *J Nutr* 2002; **132**: 1900–1902.
23. Taubert D, Berkels R, Roesen R, Klaus W: Chocolate and blood pressure in elderly individuals with isolated systolic hypertension. *JAMA* 2003; **290**: 1029–1030.
24. Aoki H, Furuya Y, Endo Y, Fujimoto K: Effect of gamma-aminobutyric acid-enriched Tempeh-like fermented soybean (GABA-Tempeh) on the blood pressure of spontaneously hypertensive rats. *Biosci Biotechnol Biochem* 2003; **67**: 1806–1808.
25. Suzuki A, Kagawa D, Ochiai R, Tokimitsu I, Saito I: Green coffee bean extract and its metabolites have a hypotensive effect in spontaneously hypertensive rats. *Hypertens Res* 2002; **25**: 99–107.
26. Saito I, Tsuchida T, Watanabe T, *et al*: Effect of coffee bean extract in essential hypertension. *Jpn J Med Pharm Sci* 2002; **47**: 67–74 (in Japanese).
27. Olthof MR, Hollman PC, Michel N, *et al*: Chlorogenic acid, quercetin-3-rutinoside and black tea phenols are extensively metabolized in humans. *J Nutr* 2003; **133**: 1806–1814.
28. Ochiai R, Jokura H, Suzuki A, *et al*: Green coffee bean extract improves human vasoreactivity. *Hypertens Res* 2004; **27**: 731–737.
29. Olthof MR, Hollman PC, Katan MB: Chlorogenic acid and caffeic acid are absorbed in humans. *J Nutr* 2001; **131**: 66–71.
30. Suzuki A, Kagawa D, Fujii A, Ochiai R, Tokimitsu I, Saito I: Short- and long-term effects of ferulic acid on blood pressure in spontaneously hypertensive rats. *Am J Hypertens* 2002; **15**: 351–357.
31. Nakazono K, Watanabe N, Matsuno K, Sasaki J, Sato T, Inoue M: Dose superoxide underlie the pathogenesis of hypertension? *Proc Natl Acad Sci USA* 1991; **88**: 10045–10048.
32. Romero JC, Reckelhoff JF: Role of angiotensin and oxidative stress in essential hypertension. *Hypertension* 1999; **34**: 943–949.
33. Hozawa A, Ebihara S, Ohmori K, *et al*: Increased plasma 8-

isoprostane levels in hypertensive subjects: the Tsurugaya Project. *Hypertens Res* 2004; **27**: 557–561.
34. Redon J, Oliva MR, Tormos C, *et al*: Antioxidant activities and oxidative stress byproducts in human hypertension. *Hypertension* 2003; **41**: 1096–1101.
35. Taddei S, Virdis A, Ghiadoni L, Magagna A, Salvetti A: Vitamin C improves endothelium-dependent vasodilation by restoring nitric oxide activity in essential hypertension. *Circulation* 1998; **97**: 2222–2229.
36. Hirooka Y, Eshima K, Setoguchi S, *et al*: Vitamin C improves attenuated angiotensin II-induced endothelium-dependent vasodilation in human forearm vessels. *Hypertens Res* 2003; **26**: 953–959.
37. Kono Y, Shibata H, Kodama Y, Ueda A, Sawa Y: Chlorogenic acid as a natural scavenger for hypochlorous acid. *Biochem Biophys Res Commun* 1995; **217**: 972–978.
38. Sawa T, Nakao M, Akaike T, Ono K, Maeda H: Alkylperoxyl radical scavenging activity of various flavonoids and anti-tumor-promoter effect of vegetables. *J Agric Food Chem* 1999; **47**: 397–402.
39. Nakatani N, Kayano S, Kikuzaki H, Sumino K, Katagiri K, Mitani T: Identification, quantitative determination, and antioxidative activities of chlorogenic acid isomers in prune (*Prunus domestica* L). *J Agric Food Chem* 2000; **48**: 5512–5516.
40. Son S, Lewis BA: Free radical scavenging and antioxidative activity of caffeic acid amide and ester analogues: structure-activity relationship. *J Agric Food Chem* 2002; **50**: 468–472.
41. Kikuzaki H, Hisamoto M, Hirose K, Akiyama K, Taniguchi H: Antioxidant properties of ferulic acid and its related compounds. *J Agric Food Chem* 2002; **50**: 2161–2168.
42. Iwai K, Kishimoto N, Kakino Y, Mochida K, Fujita T: *In vitro* antioxidative effects and tyrosinase inhibitory activities of seven hydroxycinnamoyl derivatives in green coffee beans. *J Agric Food Chem* 2004; **52**: 4893–4898.
43. Midgley JP, Matthew AG, Greenwood CM, Logan AG: Effect of reduced dietary sodium on blood pressure: a meta-analysis of randomized controlled trials. *JAMA* 1996; **275**: 1590–1597.
44. Whelton PK, Appel LJ, Espeland MA, *et al*, TONE Collaborative Research Group: Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). *JAMA* 1998; **279**: 839–846.
45. Vollmer WM, Sacks FM, Ard J, *et al*, DASH-Sodium Trial Collaborative Research Group: Effects of diet and sodium intake on blood pressure: subgroup analysis of the DASH-sodium trial. *Ann Intern Med* 2001; **135**: 1019–1028.
46. O'Shaughnessy KM, Karet FE: Salt handling and hypertension. *J Clin Invest* 2004; **113**: 1075–1081.
47. Obarzanek E, Proschan MA, Vollmer WM, *et al*: Individual blood pressure responses to changes in salt intake: results from the DASH-Sodium trial. *Hypertension* 2003; **42**: 459–467.
48. Nishijima K, Tochikubo O: Sodium intake and cardiac sympatho-vagal balance in young men with high blood pressure. *Hypertens Res* 2004; **27**: 393–398.
49. MacMahon S, Peto R, Cutler J, *et al*: Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990; **335**: 765–774.