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Supplementation of *Cheonggukjang* and Red Ginseng *Cheonggukjang* Can Improve Plasma Lipid Profile and Fasting Blood Glucose Concentration in Subjects with Impaired Fasting Glucose

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ABSTRACT This study was conducted to investigate the plasma lipid profile and blood glucose-lowering effects of *cheonggukjang* (CH) and red ginseng CH (RGCH) in 45 subjects (men:women = 27:18; mean age, 44.9 ± 3.1 years) with impaired fasting glucose (IFG). Subjects were randomly divided into three groups: control (starch, 2 g/day), CH (20 g/day), and RGCH (20 g/day). Each volunteer received his or her daily doses for 8 weeks. The supplementation with CH and RGCH significantly decreased the plasma total cholesterol about 30.0 mg/mL and 37.7 mg/mL, respectively, compared to the initial value. The plasma low-density lipoprotein-cholesterol concentration was also significantly reduced by 29.66% and 23.42% in the CH and RGCH groups, respectively, compared to the initial value. The concentration of plasma non–high-density lipoprotein-cholesterol (107.9 mg/mL) was significantly lowered in the RGCH group compared to the initial value (139.1 mg/mL). The level of erythrocyte thiobarbituric acid-reactive substances was significantly lowered in the CH (6.5 nmol/mL) and RGCH (6.6 nmol/mL) groups compared to the initial value (7.9 nmol/mL and 8.0 nmol/mL, respectively). The ratio of apolipoprotein B and apolipoprotein A-1 concentrations (2.5) was significantly reduced in the CH group compared to the initial value (3.0). The concentration of fasting blood glucose (FBG) was significantly lower in the CH- and RGCH-supplemented groups compared to the initial value. These results suggest that CH and RGCH can lower the FBG concentration and improve the plasma lipid profile in subjects with IFG.

KEY WORDS: • ***fermented foods*** • ***human*** • ***lipids***

INTRODUCTION

IMPAIRED FASTING GLUCOSE (IFG), also called prediabetes, is a condition in which a blood glucose test, taken after an 8–12-hour fast, shows a level of glucose higher than normal but not high enough for a diagnosis of diabetes, a level of 100–125 mg/dL.[1] In 2003, 314 million people (8.2% of the adult population) had prediabetes; however, the number of people with prediabetes is projected to increase to 472 million (9.0% of the adult population) by 2025.[2] Hyperglycemia is widely recognized as the pathogenesis of diabetes and diabetic complications, and it increases the formation and accumulation of advanced glycation end products as well as oxidative stress.[3] Among those with prediabetes about 40–50% of people have been reported to develop type 2 diabetes within 10 years.[2] It is accompanied by an increased risk of cardiovascular disease and microvascular complications with low high-density lipoprotein-cholesterol (HDL-C), high low-density lipoprotein-cholesterol (LDL-C), and high glucose levels.[2]

In recent years, the importance of biologically active substances in foods has been recognized, and many physiologic effects of foods have been reported. In particular, the consumption of soy protein reduces the risks of chronic diseases, including type 2 diabetes.[4] In Korea, there are several traditional fermented soybean products such as *cheonggukjang* (CH), *doenjang*, *kochujang*, and soy sauce. CH has distinct characteristics when compared to other fermented soybean products; for instance, CH is fermented predominantly with *Bacillus subtilis* for short periods without salts and other seasonings. During fermentation, isoflavones are converted from glucosides into the corresponding aglycones, while most proteins are degraded into peptides and amino acids.[5] These are responsible for the unique sensory and functional properties of the final products[6] and may enhance the antidiabetic actions of unfermented soybeans. To fortify CH, another phytochemical food source can be considered. Among ginseng products, Korean red ginseng is produced by steaming white ginseng (*Panax ginseng*), and its bioactivity is superior to the unprocessed white ginseng roots.[7] Most ginseng species contain ginsenosides, polysaccharides, peptides,

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polyacetylenic alcohols, and fatty acids. In particular, ginsenosides (ginseng saponins) have been known as the main active components in ginseng.[8]

Functional studies regarding red ginseng CH (RGCH) in which steamed soybean and red ginseng water extract are mixed prior to fermentation have never been reported. This study compared the possible antidiabetic and antihyperlipidemic effects of CH and RGCH in subjects with IFG for the first time.

SUBJECTS AND METHODS

Subjects

Volunteers were adult males and females who were 25–60 years old subjects with IFG (100 mg/dL < fasting glucose level < 125 mg/dL) who had not been diagnosed with diabetes and treated with drugs. This study was designed under double-blind conditions and using a placebo control. Forty-five subjects who exhibited a mild hyperglycemia were randomly divided into three groups: control (starch, 2 g/day), CH (20 g/day), and RGCH (20 g/day). The average ages were 41.7 ± 3.9, 45.9 ± 2.7, and 47.1 ± 2.8 years, respectively, for the control (nine men and six women), CH (10 men and five women), and RGCH (eight men and seven women) groups. The concentrations of baseline fasting blood glucose (FBG) in the control, CH, and RGCH subjects were 114.50 ± 3.35, 110.75 ± 4.23, and 120.50 ± 4.21 mg/dL, respectively. Each volunteer received his or her daily doses for 8 weeks. Subjects were instructed to take 2 g/day placebo or 20 g/day experimental supplements, which were taken by one-third the total dose three times a day, after every meal. Because these individual doses were sealed into dark-brown pouches, subjects could not recognize which supplement they had been given. This study was performed according to the *International Ethical Guideline for Biomedical Research Involving Human Subjects*.[9]

Materials

CH and RGCH were made by Keimyung Foodex Co. (Daegu, Republic of Korea) as follows: soybeans were sorted, washed, and soaked in water for 24 hours at 4°C and then autoclaved for 45 minutes at 121°C after dehydrating for 30 minutes. The steamed soybeans were cooled to 50°C, inoculated with *B. subtilis* in a 3% (vol/wt) N_2 culture solution, and fermented for 20 hours at 40°C. For RGCH, the steamed soybeans were cooled to 50°C and inoculated with *B. subtilis* in a 3% (vol/wt) N_2 culture solution and 4% (vol/wt) concentrated red ginseng extract. After freeze-drying, the powdered CH (moisture, 6.79%; protein, 50.45%; fat, 23.47%; ash, 4.66%; carbohydrate, 14.63%) and RGCH (moisture, 4.94%; protein, 45.51%; fat, 22.79%; ash, 4.97%; carbohydrate, 21.79%)[10] were provided to the subjects.

The samples (CH and RGCH) used were characterized by comparing their components and activities as described in previous reports;[10,11] total free sugar (in mg%) are 622.47 (CH) and 698.31 (RGCH), total essential amino acids (in mg%) are 533.10 (CH) and 312.96 (RGCH), total free sugars (in mg%) are 622.47 (CH) and 698.31 (RGCH), crude saponins (in mg/g) are 15.90 (CH) and 22.90 (RGCH), viscous substances (in %) are 6.02 (CH) and 6.19 (RGCH), angiotensin converting enzyme activities (in %) are 94.63 (CH) and 96.28 (RGCH), superoxide radical scavenging activities (in %) are 24.01 (CH) and 22.12 (RGCH), and fibrinolytic activities (in units) are 257.25 (CH) and 299.00 (RGCH), respectively.

Analytical methods

Before and after the experiment, blood was taken from the antecubital vein and placed in a heparin-coated tube. Blood samples were drawn after fasting for 12 hours. FBG level was measured by a blood analyzer (Cholestech LDX system, Wilburn Medical, Kernersville, NC, USA). Plasma lipids were measured by means of commercially available kits: total cholesterol (total-C) and HDL-C from Asan Pharmaceutical Co., Ltd. (Seoul, Republic of Korea) and apolipoprotein (apo) A-1 and apo B from Nitto Boseki Co. (Tokyo, Japan). LDL-C was calculated according to Friedewald *et al.*[12] Non–HDL-C was calculated by subtracting HDL-C from total-C. An enzyme-linked immunosorbent assay kit (ALerCHEK, Inc., Portland, ME, USA) was used for the measurement of plasma lipoprotein (a) [Lp(a)] concentration. Apo A-1 and apo B were measured by commercially available kits. The erythrocyte thiobarbituric acid-reactive substances (TBARS) level was measured using the method of Tarladgis *et al.*[13] Erythrocyte samples were mixed with 5% trichloroacetic acid and 60 mmol/L thiobarbituric acid. After incubation at 80°C for 90 minutes, the supernatants were centrifuged at 1,000 *g* for 15 minutes at 4°C, and the absorbance was recorded at 535 nm using tetramethoxypropane (Sigma Chemical Co., St. Louis, MO, USA) as the standard.

Nutrient intake data of subjects were collected by the method of 24-hour dietary recall. The dietary interviewer solicited detailed information about everything the subject had to eat and drink from midnight to midnight of the previous day or over the 24-hour period.[14] The 24-hour dietary recall data were analyzed by CAN-Pro version 3.0 (Computer Aided Nutritional Analysis Program version 3.0, The Korean Nutrition Society, Seoul, Republic of Korea).

Statistical analysis

The parameter values were all expressed as mean ± SE values. Statistical differences between before and after the study were determined by paired-samples Student's *t* test analysis, and significant differences among the groups were determined by a one-way analysis of variance using the SPSS program (SPSS Inc., Chicago, IL, USA). The differences between the means were assessed using Duncan's multiple-range test, and statistical significance was considered at $P < .05$.

RESULTS

Nutrient intake

Table 1 shows the mean nutrient intake of subjects during the experimental period. The energy intake of subjects

Table 1. Nutrient Intakes of Subjects by 24-Hour Dietary Recall During the Study

	Control (placebo)	*CH*	*RGCH*
Energy (kcal/day)	1,839.0 ± 131.4	1,871.0 ± 131.0	1,755.7 ± 193.1
Total protein (g/day)	63.4 ± 7.0	73.4 ± 5.7	66.6 ± 5.3
Total carbohydrate (g/day)	251.7 ± 27.7	265.5 ± 19.9	234.0 ± 25.7
Total dietary fiber (g/day)	14.3 ± 1.2	15.9 ± 1.7	15.6 ± 1.6
Total fat (g/day)	53.6 ± 5.3	50.4 ± 4.3	53.2 ± 6.1
Cholesterol (mg/day)	184.2 ± 14.7	208.3 ± 15.2	168.0 ± 16.0

Data are mean ± SE values ($n = 15$).
CH, *cheonggukjang*; RGCH, red ginseng CH.

tended to be higher in the CH group. There were no significant differences in nutrient intake among groups. However, dietary cholesterol intake tended to be higher in the CH group than the control and RGCH groups.

Baseline characteristics

The control, CH, and RGCH groups were similar on the basis of age, body mass index, body fat percentage, waist–hip ratio, blood pressure, and fasting glucose (Table 2).

Effects of CH and RGCH on plasma lipids concentrations

The plasma total-C concentration was significantly decreased in the CH ($P < .05$) and RGCH ($P < .001$) groups after the 8-week intervention trial. The initial mean concentrations of plasma total-C were 179.0 mg/dL, 176.8 mg/dL, and 176.4 mg/dL, respectively, for the control, CH, and RGCH groups. After 8 weeks of CH and RGCH supplementation, the mean concentrations of total-C were 161.7 mg/dL, 146.8 mg/dL, and 137.7 mg/dL, respectively, for the control, CH, and RGCH groups. The LDL-C concentration was also significantly decreased by 29.66% and 23.42% in the CH ($P < .05$) and RGCH ($P < .05$) groups, respectively, compared to the initial values. The initial mean concentrations of plasma LDL-C were 118.0 mg/dL and 115.0 mg/dL, respectively, for the CH and RGCH groups. After 8 weeks of CH and RGCH supplementation, the mean LDL-C concentrations were 83.0 mg/dL and 88.5 mg/dL, respectively, for the CH and RGCH groups. However, the HDL-C level tended to be increased by CH or RGCH supplementation compared to its initial value. The non–HDL-C concentration (107.9 mg/dL) was significantly lowered ($P < .01$) by 22.44% by RGCH supplementation compared to the initial value (139.1 mg/dL). No significant changes were observed in total-C, LDL-C, and non–HDL-C concentrations of the control group compared to the initial value. The plasma Lp(a) concentration was not significantly different in any of the groups. However, the erythrocyte TBARS levels were significantly reduced by 17.99% and 18.06% in the CH (6.5 nmol/mL) and RGCH (6.6 nmol/mL) groups after 8 weeks of supplementation, respectively, compared to the initial value (7.9 nmol/mL and 8.0 nmol/mL, respectively). No significant differences were observed among the groups in the plasma lipid profile after an 8-week intervention trial (Table 3).

Effects of CH and RGCH on changes of FBG concentration

The mean initial concentrations of FBG were 114.5 mg/dL, 110.8 mg/dL, and 120.5 mg/dL, respectively, for the control, CH, and RGCH groups. The concentration of FBG was significantly lowered ($P < .001$) by 27% in the CH group (80.9 mg/dL) and 17% in the RGCH group (99.9 mg/dL) after 8 weeks compared to the initial value. FBG levels in the CH and RGCH groups were significantly lower ($P < .05$) than in the control group after 8 weeks. No significant changes were observed in FBG concentration in the control group before or after the trial (Fig. 1).

DISCUSSION

Soybeans exhibit various activities, such as antidiabetic, antilipidemic, and antioxidant properties.[15] The American Diabetes Association's guidelines for treatment of diabetes mellitus emphasize the importance of controlling all risk factors for cardiovascular disease.[16] Fasting and postprandial levels of plasma total-C, LDL-C, and non–HDL-C represent independent risk factors for the development of cardiovascular disease.[17] The American Heart Association in 2001[18] proposed that low total blood cholesterol puts one at a relatively low risk of coronary heart disease. The mean concentrations of plasma total-C were 176.8 mg/dL and 192.3 mg/dL, respectively, for the CH and RGCH groups at

Table 2. Baseline Characteristics of Subjects with Impaired Fasting Glucose

	Control (placebo)	*CH*	*RGCH*
Number (M:F)	15 (9:6)	15 (10:5)	15 (8:7)
Age (years)	41.7 ± 3.9	45.9 ± 2.7	47.1 ± 2.8
BMI (kg/m^2)	25.4 ± 0.6	22.6 ± 2.4	24.9 ± 1.9
BFP (%)	24.3 ± 1.2	25.1 ± 0.7	25.8 ± 0.9
WHR	0.9 ± 0.02	0.81 ± 0.03	0.87 ± 0.02
Blood pressure (mm Hg)			
Systolic	119.4 ± 4.7	121.6 ± 4.2	123.3 ± 4.5
Diastolic	77.5 ± 3.8	82.3 ± 4.4	76.8 ± 2.7
FBG (mg/dL)	114.5 ± 3.4	110.8 ± 4.2	120.5 ± 4.2

Data are mean ± SE values.
BFP, body fat percentage; BMI, body mass index; F, female; FBG, fasting blood glucose; M, male; WHR, waist–hip ratio.

TABLE 3. EFFECTS OF *CHEONGGUKJANG* AND RED GINSENG *CHEONGGUKJANG* ON CHANGES IN PLASMA LIPID PROFILE IN SUBJECTS WITH MILD HYPERGLYCEMIA BEFORE AND AFTER AN 8-WEEK INTERVENTION TRIAL

	Control (placebo)	*CH*	*RGCH*
Total cholesterol (mg/dL)			
Before	179.0 ± 8.5	176.8 ± 8.6	176.4 ± 7.1
After	161.7 ± 7.3	146.8 ± 9.5*	138.7 ± 3.9***
LDL-cholesterol (mg/dL)			
Before	112.4 ± 8.1	118.0 ± 7.5	115.5 ± 8.3
After	107.8 ± 8.8	83.0 ± 8.7*	88. 5 ± 5.5*
HDL-cholesterol (mg/dL)			
Before	38.1 ± 3.0	39.3 ± 5.6	36.8 ± 4.2
After	38.9 ± 3.0	43.1 ± 3.5	43.1 ± 4.5
Non–HDL-cholesterol (mg/dL)			
Before	138.8 ± 8.6	138.3 ± 15.4	139.1 ± 8.1
After	128.7 ± 9.4	105.0 ± 10.4	107.9 ± 5.8**
Lipoprotein (a) (mg/dL)			
Before	34.3 ± 1.3	33.8 ± 1.0	35.4 ± 1.2
After	33.4 ± 3.0	32.4 ± 3.3	33.9 ± 1.7
Apo B:Apo A-1			
Before	3.1 ± 0.2	3.0 ± 0.1	2.9 ± 0.2
After	3.1 ± 0.2	2.5 ± 0.1*	2.8 ± 0.2
TBARS (nmol/mL)			
Before	7.3 ± 0.3	7.9 ± 0.4	8.0 ± 0.5
After	8.4 ± 0.6	6.5 ± 0.3*	6.6 ± 0.4*

Data are mean ± SE values ($n = 15$).

*$P < .05$, **$P < .01$, ***$P < .001$, significantly different compared to values before treatment by Student's t test.

Apo, apolipoprotein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TBARS, thiobarbituric acid-reactive substances.

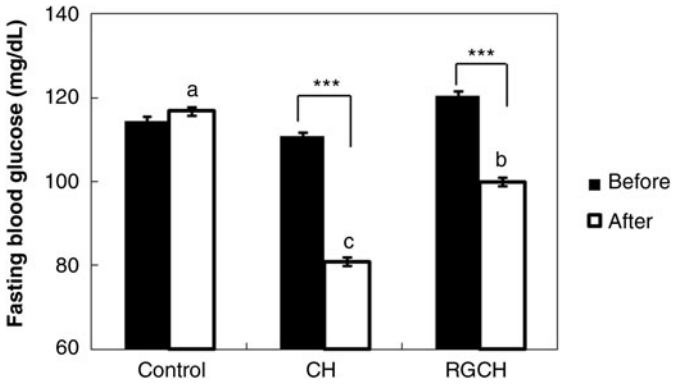

FIG. 1. Effects of CH and RGCH on changes in fasting blood glucose concentration in subjects with mild hyperglycemia before and after an 8-week trial. Data are mean ± SE values ($n = 15$). [abc]Means are significantly different among groups at $P < .05$. ***$P < .001$, significantly different compared to values before treatment by Student's t test.

baseline; however, after 8 weeks they were significantly lowered to 146.8 mg/dL and 138.7 mg/dL, respectively. In speculating about possible bioactive compounds in soybean fermented foods, Yamamoto *et al.*[19] reported that levan among viscous substances lowered the plasma total-C level. Administration of natto also induced a decrease in total-C concentration in cholesterol-fed rabbits.[20]

LDL-C is a better gauge of cardiovascular disease risk than total blood cholesterol. A high level of LDL-C is generally considered as a strong risk factor for atherosclerotic vascular disease.[21] *Monascus*-fermented soybean extracts significantly decreased the serum LDL-C level.[22] In the present study, the concentration of plasma LDL-C was significantly reduced by CH and RGCH supplementation compared to the initial values. Raising the plasma HDL-C concentration should be considered as important as lowering the LDL-C concentration.[23] Epidemiological observations have consistently indicated that high levels of plasma HDL-C concentration protect against the development and progression of atherosclerosis.[24] However, there was no significant difference produced in plasma HDL-C by CH or RGCH supplementation. Non–HDL-C is the sum of all the cholesterol in atherogenic lipoprotein particles [low-density lipoprotein, Lp(a), very-low-density lipoprotein, and intermediate-density lipoprotein] and thus reflects the cholesterol content of all apo B-containing lipoproteins. Non–HDL-C in a large study of more than 4,000 subjects was shown to be a better predictor of cardiovascular disease and mortality than the calculated LDL-C.[25] Because it is readily derived from the routine lipoprotein profile, non–HDL-C may be a highly useful lipid measurement for assessing risk and evaluation response to lipid-lowering therapy. In diabetic patients the goal for non–HDL-C level should be lower than 130 mg/dL.[26] Nakamura *et al.*[27] reported that fermented bean paste supplementation induced a significant decrease in non–HDL-C concentration in diabetic rats fed a cholesterol-free diet. Our results showed a similar pattern in which the non–HDL-C concentration was significantly lowered by 16.01% by RGCH supplementation compared to the initial value.

Hypercholesterolemia is associated with abnormalities of lipoprotein levels in the blood. Lp(a) is a genetic variation of LDL-C. A high level of Lp(a) is a significant risk factor for the premature development of fatty deposits in arteries.[28] Because Lp(a) has been thought to function as a thrombogenic factor principally via interference with the fibrinolytic system,[28] Lp(a) could enhance the expression of adhesion molecules.[29] However, the CH or RGCH did not influence the plasma Lp(a) concentration. Recent studies have reported that the serum apo B:apo A-1 ratio is a better predictor of atherosclerotic vascular disease compared to LDL-C.[30] Patients with type 2 diabetes are considered to be at increased risk of atherosclerotic vascular disease. An elevated apo B:apo A-1 ratio is a risk factor for future coronary artery disease. In the present study, the apo B:apo A-1 ratio was significantly lowered by 0.47 in the CH group compared to the initial value. A human study showed similar results in which isoflavonoid aglycones lowered the serum LDL-C level and apo B:apo A-1 ratio in adults with type 2 diabetes.[31]

Elevated glucose levels induce oxidative stress that is ultimately reflected by the increased malondialdehyde levels in the erythrocytes. Malondialdehyde, a lipid peroxide derived from polyunsaturated fatty acids, is widely used as an indicator of oxidative stress as well as lipid peroxidation because it is more abundant than other reactive carbonyl

compounds.[32] Oxygen-derived radicals and reactive oxygen species are known to attack cell membranes, resulting in the propagation of peroxidation of lipids.[33] Oxidative damage due to free radicals can be elevated in diabetic patients with macroangiopathy.[34] Thus, lipid peroxidation is associated with diabetes or diabetic complications. In the current study, CH and RGCH supplementation significantly lowered TBARS levels in the erythrocyte compared to the initial values, thus indicating a decreased rate of lipid peroxidation.

Several animal studies have evaluated the effects of fermented soybeans on blood glucose lowering. Fujita *et al*.[35] demonstrated that 0.3 g of water extract of touchi (fermented soybean) decreased fasting and postprandial blood glucose levels in KKAy diabetic mice. Kim *et al*.[36] also showed that *chungkookjang* supplementation induced a significant decrease in blood glucose concentration in *db/db* mice. CH and RGCH supplements in the current study significantly lowered the concentration of FBG (110.75 mg/dL to 80.88 mg/dL and 120.50 mg/dL to 99.92 mg/dL, respectively). Furthermore, the concentration of FBG in the CH and RGCH groups was significantly lower than in the control group after the 8-week trial.

In conclusion, the present data suggest that supplementation with CH and RGCH exerts a beneficial effect in subjects with IFG, at least in part, by reducing FBG concentration. CH seemed to be more effective than RGCH for improving blood glucose concentration. CH and RGCH supplementation improved the concentration of plasma total-C and LDL-C as well as erythrocyte TBARS concentration. The concentration of non–HDL- C was significantly decreased in the RGCH group, while the apo B:apo A-1 ratio was significantly decreased in the CH group. Overall, CH and RGCH can be applied for the prevention of diabetes or diabetic complications in human subjects with IFG.

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AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

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