ORIGINAL

Rice bran extract containing acylated steryl glucoside fraction decreases elevated blood LDL cholesterol level in obese Japanese men

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Abstract : People who frequently consume whole grains show a lower incidence of arteriosclerotic disease than people who consume primarily refined grains. We examined whether or not rice bran extract containing the acylated steryl glucosides (ASG) fraction decreases blood LDL cholesterol levels in obese Japanese men with high blood levels of LDL cholesterol. The study utilized a randomized, double-blind design. A total of 51 subjects were randomly allocated to either a rice bran extract containing ASG fraction (RB-ASG) group or a placebo group. Subjects in the RB-ASG group received 30-50 mg/day of RB-ASG, and the placebo group took 9 capsules/day for 12 weeks. Before and after intake, height, weight, body fat percentage, systolic and diastolic blood pressure were measured, blood was collected, and visceral fat area, subcutaneous fat area, and abdominal circumference were determined based on umbilical computed tomography. Percentage decreases in blood LDL cholesterol, non-HDL cholesterol, LDL/HDL ratio, abdominal circumference and subcutaneous fat area were significantly better in the RB-ASG group than in the placebo group. These findings suggest that RB-ASG fraction may reduce blood LDL cholesterol levels and the risk of arteriosclerosis in obese Japanese men with high LDL cholesterol levels. J. Med. Invest. 62 : 80-84, February, 2015

Keywords **:** *Blood LDL cholesterol, abdominal circumference, Rice bran, acylated steryl glucoside, human*

INTRODUCTION

More than 25% of deaths among Japanese are attributed to arteriosclerotic disease, such as myocardial infarction and cerebral infarction (1). Brought on by atherosclerosis, arteriosclerotic disease is a coronary artery disease which is closely related to dyslipidemia. To prevent arteriosclerotic disease, managing risk factors, such as high blood pressure, diabetes, and chronic kidney disease (CKD), not to mention dyslipidemia, has been shown to be effective (2). Modifications in eating habits and exercise habits have constituted the chief methods to improve these risk factors. For cases that cannot be controlled by these methods, treatment by drugs has been relied on. Instruction on meals to adjust eating habits has been tried, but due to the difficulty in complying with such instructions, its effectiveness has not been satisfactory. More aggressive measures that use food and its ingredients are being pursued.

It is well known that the intake of whole grains, such as brown rice (BR), improves lipid metabolism (3). Pre-germinated brown rice (PGBR) is rice which has been slightly germinated by soaking BR in water. PGBR is being widely supplied throughout Japan.

The content of protein, carbohydrate, dietary fiber, vitamins and minerals in PGBR is the same as that of BR, but the process of germination has increased components such as gamma-amino acid (GABA) and acylated steryl glucosides (ASG). The effectiveness of PGBR on lipid abnormality and glucometabolic abnormality confirmed in tests on animal models and on humans has been reported (4-11). Moreover, it has been confirmed that the ASG fraction extracted from PGBR bran promoted the activity of homocystine thiolactone hydroxylase (HTLase) in diabetic rats (12). The authors have also confirmed that the lipid metabolism of diet-induced obese mice is improved by feeding with ASG fraction extracted from rice bran (manuscript in preparation). When ASG fraction extracted from rice bran was added to AIN-93G formula with the carbohydrate source changed from corn starch to WR and this feed was fed to Senescence-accelerate mice (SAM) P8 for 18 weeks, an improvement in lipid metabolism compared to the WR diet was observed (manuscript in preparation). ASG fraction is contained in the bran of PGBR and BR, but it is not contained in the white rice that Asians prefer to eat. Therefore, ASG fraction is considered to be one of the important effective components of BR, particularly of PGBR.

We can anticipate the improvement of dyslipidemia by the intake of ASG fraction, but the effectiveness of its intake by humans has not been confirmed. We have obtained rice bran extract containing ASG fraction (RB-ASG). We examined whether or not RB-ASG decreases blood LDL cholesterol (LDL-C) level in obese Japanese men.

MATERIALS AND METHODS

Setting and study subjects.

The protocol of this study was approved by the institutional review board at FANCL Corp. before being conducted. All subjects were fully informed about the nature and methods of the studies, and informed consent was obtained in compliance with the Declaration of Helsinki. The subjects were volunteers recruited via third party institutions and unrelated to the authors' affiliated institution. The study utilized a randomized, double-blind design. Eligibility criteria were Japanese obese (BMI$\geq$ 25 kg/m^2) men aged 40 years or older with blood LDL-C level$\geq$ 120 mg/dL. Major exclusion criteria include the following : Those who were being treated by doctors for some medical problems and those who were

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regularly taking medication ; those who were suffering from serious heart disease, brain disease, kidney disease, liver disease, gastrointestinal disease and their complications ; those who were using pace-makers and those who did not feel well due to sudden changes in weight two months after the start of the test. 104 subjects participated in the screening test. Of these, 60 participated in the test.

They were divided into the two groups as follows, with care taken that there was no bias with respect to age, gender, BMI or blood LDL-C : a RB-ASG group (n=40) and a Placebo group (n=20). The subjects in the RB-ASG group received 30-50 mg/day of RB-ASG, and the Placebo (corn oil) group took 9 capsules/day for 12 weeks. All participant and capsule provider were blinded to the intervention. We used FANCL-manufactured PSG® for RB-ASG. All subjects were asked to avoid modifying their lifestyle during the study. We instructed the subjects not to intake any pharmaceuticals or food that claimed cholesterol-reduction action, inhibitory action for the rise of triacylglycerol (TG), or body-fat-reduction action during for the duration of the study.

All the tests were conducted at Kenkoin Medical Corporation Foundation. We carried out measurements, blood collection and the surveys on meals before the start of intake (baseline) and after intake (final). For the day before the test, we instructed the subjects not to smoke and to have their specified evening meal (consisting of meat and potato stew, hijiki (a kind of brown algae) and soybean stew, simmered ostrich fern and rice, totaling 614 kcal) by hour 21 and to have no food thereafter ; only water was allowed. On the day of the test, we required the subjects to fast all day, until the end of the test. Only water was allowed. All measurements were conducted in the morning. Placebo group and RB-ASG group were mesured on same day.

Anthropometrical measurements.

Visceral fat area, subcutaneous fat area and abdominal circumference were determined by abdominal computed tomography (CT). Body fat percentage was measured by dual-energy x-ray absorptiometry. We calculated BMI, using the already-reported calculation formula.

Blood collection.

Total cholesterol (TC), HDL cholesterol (HDL-C), TG, glucose and HbA1c (NGSP) levels in the blood were measured. We calculated LDL-C/HDL-C (LH) ratio using the already-reported calculation formula.

Diet survey.

We used a brief-type self-administered diet history questionnaire (BDHQ) for the diet surveys (13).

Statistical analyses.

What constituted the primary outcome measure of our evaluation was the percent change in LDL-C at baseline and final. What constituted the items of our secondary evaluation were TC, HDL-C, TG, BMI, visceral fat area, subcutaneous fat area, abdominal circumference and body fat percentage. We calculated the percent change of the final versus the baseline for each items evaluated. We calculated the percent change of the final versus the baseline for each items evaluated. The percent change in the RB-ASG group and the Placebo group were compared using the unpaired t-test. The final and the baseline data in the RB-ASG group and the Placebo group were compared using the paired t-test. Items with confirmed homoscedasticity were compared by Student's t-test and those with no confirmed homoscedasticity using Welch's t-test. P-values of less than 0.05 were considered statistically significant for all the analyses. The above statistical procedures were performed using JMP version8 (SAS Institute Inc., North Carolina).

RESULTS

Subjects.

Of the 60 subjects, 4 from the RB-ASG group and 1 from the Placebo group withdrew from the test either before or after the start of their ingestion period, due to personal reasons. Moreover, 2 from the RB-ASG group and 2 from the Placebo group were excluded from the analysis, because the results of their basal test did not meet the selection criteria. As a result, the number of subjects in the analysis was 51. All subjects compliance were > 90%. During the period of the test, neither group developed subjective symptoms related to the intake of the testing substances.

Baseline characteristics.

We show the background of the subjects in Table 1. Compared to that of the RB-ASG Group, HbA1c of the Placebo group was significantly higher, but both groups were within the reference range. No significant difference was observed in other parameters.

Table 1. Comparison of physical characteristics and blood biochemical parameters between ASG and Placebo groups at baseline.

	RB-ASG	Placebo	Total
Age (year)	52 ± 8	56 ± 8	54 ± 8
BMI (kg/m^2)	28.1 ± 3.0	27.1 ± 2.2	27.8 ± 2.7
Body fat (%)	31.7 ± 5.3	28.7 ± 4.2	30.7 ± 5.1
Systolic blood pressure (mmHg)	142.9 ± 16.4	143.6 ± 15.4	143.1 ± 15.9
Diastolic blood pressure (mmHg)	90.1 ± 11.3	91.6 ± 11.9	90.6 ± 11.4
Abdominal circumference (cm)	95.1 ± 8.1	92.4 ± 7.7	96.9 ± 7.7
Visceral fat area (cm^2)	158.1 ± 39.8	160.4 ± 62.6	158.8 ± 47.9
Subcutaneous fat area (cm^2)	195.7 ± 87.2	163.5 ± 51.7	185 ± 78.2
Total cholesterol (mg/dL)	244.7 ± 31.8	246.8 ± 24.3	245.4 ± 29.3
non HDL cholesterol (mg/dL)	194.8 ± 31.9	193.1 ± 24.3	194.2 ± 29.4
LDL cholesterol (mg/dL)	165.4 ± 29.0	163 ± 24.1	164.6 ± 27.3
HDL cholesterol (mg/dL)	49.9 ± 11.1	53.8 ± 14.3	51.2 ± 12.3
LDL-C/HDL-C ratio	3.5 ± 1.0	3.2 ± 0.9	3.4 ± 1.0
Triacylglycerol (mg/dL)	159.4 ± 82.0	174.8 ± 85.7	164.5 ± 82.8
HbA1c (%)	5.5 ± 0.3 *	5.8 ± 0.4	5.6 ± 0.4

Values are means± SD for 34 (RB-ASG) or 17 (Placebo) subjects.
*Significant difference between RB-ASG and Placebo group by unpaired t-test at $p < 0.05$.

Energy and nutrient intakes.

We show the intake amount of energy and nutritional composition in Table 2. Between the two groups, there was no significant difference in the intake amount of energy and nutritional composition at the respective times of baseline and final.

Table 2. Energy and nutrient intakes of ASG and Placebo groups at baseline and final

		Baseline	Final
Energy (kcal)	RB-ASG	2073.3 ± 963.1	2025.9 ± 809.3
	Placebo	1932.0 ± 701.3	2048.9 ± 711.0
Lipid (g)	RB-ASG	56.9 ± 31.1	60.2 ± 31.1
	Placebo	57.7 ± 22.5	60.3 ± 25.8
Protein (g)	RB-ASG	73.4 ± 33.6	70.9 ± 28.5
	Placebo	72.6 ± 26.5	76.2 ± 27.9
Carbohydrate (g)	RB-ASG	282.1 ± 118.9	269.8 ± 109.5
	Placebo	257.7 ± 109.6	271.3 ± 113.1
Fiber (g)	RB-ASG	11.6 ± 4.9	11.3 ± 5.2
	Placebo	12.1 ± 4.2	11.3 ± 3.4

Values are means± SD for 34 (RB-ASG) or 17 (Placebo) subjects.

Physical characteristics.

In Table 3, we indicate the physical characteristics of the two groups at the times of baseline and final. No significant difference was observed between the groups in BMI or body fat percentage from baseline to final. In the RB-ASG group, the abdominal circumference improved significantly from baseline to final ; the subcutaneous fat area also improved significantly. Moreover, the visceral fat area changed, showing a significant tendency to improve ($p=0.09$). As for percentage change for abdominal circumference and subcutaneous fat area of the RB-ASG group, there was significant improvement, compared to that of the Placebo group.

Table 3. Physical characteristics at final in ASG and Placebo groups.

		Final	Percent change (%)
BMI	RB-ASG	27.9 ± 27.9	-0.7 ± 2.2
(kg/m^2)	Placebo	27.1 ± 27.1	0.0 ± 1.7
Body fat	RB-ASG	31.9 ± 4.9	0.9 ± 4.7
(%)	Placebo	29.5 ± 4.5	2.6 ± 3.1
Abdominal circumference	RB-ASG	93.9 ± 7.8#	-2.6 ± 4.0*
(cm)	Placebo	92.6 ± 7.0	-0.9 ± 2.6
Visceral fat area	RB-ASG	151.0 ± 40.8	-4.1 ± 14.4
(g/cm^2)	Placebo	160.9 ± 55.7	2.1 ± 11.5
Subcutaneous fat area	RB-ASG	188.0 ± 82.9#	-3.6 ± 7.5*
(g/cm^2)	Placebo	164.1 ± 48.2	1.6 ± 8.7

Values are means± SD for 34 (RB-ASG) or 17 (placebo) subjects.
* Significant difference compared to Placebo by unpaired t-test ; $p< 0.05$
# Significant difference compared to baseline by paired t-test ; $p< 0.05$

Blood biochemical parameters.

In Table 4, we show the blood biochemical parameters of the RB-ASG group and the Placebo group at the time of baseline and final. No significant difference was observed between HDL-C and TG. In the RB-ASG group, LDL-C dropped significantly from baseline to final. TC and non HDL-C also dropped significantly. The LH ratio also improved significantly from baseline to final. In the RB-ASG group, the percentage change from baseline to final improved quite significantly, compared to that of the Placebo group LDL-C, TC, non HDL-C, LH ratio. In Figure 1, we show the individual changes and average levels of LDL-C for each subject.

Table 4. Blood biochemical parameters at final in RB-ASG and Placebo groups.

		Final	Percent change (%)
Total cholesterol	RB-ASG	226.9 ± 29.0#	-6.7 ± 10.2*
(mg/dL)	Placebo	245.6 ± 33.5	-0.6 ± 8.4
LDL cholesterol	RB-ASG	145.2 ± 24.0#	-11.2 ± 12.4*
(mg/dL)	Placebo	160.4 ± 24.1	-1.3 ± 9.2
non HDL cholesterol	RB-ASG	176.5 ± 28.3#	-8.6 ± 11.5*
(mg/dL)	Placebo	190.2 ± 28.9	-1.4 ± 8.8
HDL cholesterol	RB-ASG	50.4 ± 10.8	1.7 ± 12.3
(mg/dL)	Placebo	55.4 ± 18.1	2.4 ± 9.9
Triacylglycerol	RB-ASG	164.2 ± 71.8	12.1 ± 41.1
(mg/dL)	Placebo	170.1 ± 83.1	1.3 ± 28.0
LDL-C/HDL-C ratio	RB-ASG	3.0 ± 0.7#	-12.0 ± 13.7*
	Placebo	3.1 ± 0.9	-3.4 ± 6.2

Values are means± SD for 34 (RB-ASG) or 17 (Placebo) subjects.
* Significant difference compared to Placebo by unpaired t-test ; $p< 0.05$
# Significant difference compared to baseline by paired t-test ; $p< 0.05$

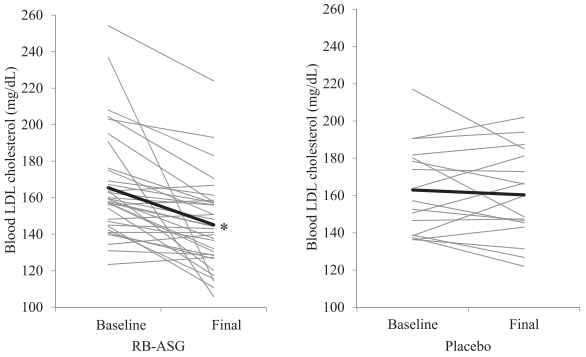

Figure 1 Serum LDL cholesterol level at baseline and final.
Bold Line : mean for 34 (RB-ASG) or 17 (Placebo) subjects. Thin line : individual data.*Significant difference compared to baseline by paired t-test ; $p< 0.05$

DISCUSSION

The results of this study suggest that the intake of RB-ASG improved the blood LDL cholesterol level of humans who were obese and who had high LDL cholesterol. Moreover, the body perimeter and the subcutaneous fat area of the RB-ASG group also improved very significantly, compared to those of the Placebo group. In this study, we made the intake amount of RB-ASG 30-50 mg/day, but this is an amount equivalent to 300 to 500 g (2-3 servings) of boiled PGBR. In a study that has been conducted on Taiwanese (10) and Vietnamese subjects (11), we observed an improvement in lipid metabolism and a reduction in body circumference by switching the staple food from WR to PGBR in their three meals per day. It may be possible to explain part of PGBR's lipid metabolism action and body-perimeter-reduction action by RB-ASG which contained PGBR.

Regarding phytosterol, which is an important component of RB-ASG, an LDL-C reduction effect has been reported (14, 15). It has been reported that in human subjects whose cholesterol level was between a normal range and a somewhat high range, having them intake margarine that contained 1.5 to 3.3 g/day of plant sterol for 3.5 weeks led to the result of their LDL-C decreasing to 13% from 8% (14). It may be possible to explain part of the RB-ASG improvement action on lipid metabolism that was confirmed in

this study as the effect of phytosterol. However, the intake amount of RB-ASG (30 to 50 mg/day) was low, compared to the intake amount of phytosterol that was reported in the margarine study. In experiments that used animal models, Lin et al have reported on the importance of ASG that had undergone acylation, by comparing it with steryl glucosides (16). The amount of cholesterol discharged in the excrement was found to increase from the intake of ASG. The current study did not clearly reveal the mechanism of ASG fraction, but it may be no different from what had been reported by Lin *et al.*

The results of the abdominal CT test revealed that the percentage change in the subcutaneous fat area and body perimeter of the RB-ASG group was significantly greater, compared with that of the Placebo group. The visceral fat area showed the tendency to decrease after intake only in the RB-ASG group. The fact that the decrease was in the fat area led us to believe that it contributed to the reduction of diabetes, dyslipidemia, high blood pressure and, by extension, arteriosclerotic disease, for which obesity constituted a risk factor. Furthermore, the reductions of the visceral fat area and the subcutaneous fat area, as well as the rate of change in body perimeter, were interrelated. On the other hand, no changes were observed in BMI and body fat percentages. It is also conceivable that the intake duration of three months was too short to clearly perceive weight reduction resulting from the composition of food being consumed, without guidance on special meals and exercise. According to the dietary survey, the final energy intake of the Placebo group rose by 5.7% compared to the baseline. In this study, one month within a three-month intervention period was targeted for the dietary survey. Therefore the results may not necessarily reflect the dietary content for the entire intervention period. Moreover, subcutaneous fat areas of the Placebo group showed lower than those of the RB-ASG group, though not significantly. To clarify the decrease in subcutaneous fat areas due to RB-ASG intake, investigation based on a strict dietary survey and a longer intervention period may be necessary.

However, this study clearly confirmed that the intake of RB-ASG improved the blood LDL cholesterol level of people who were obese and who had high LDL cholesterol. Many epidemiological studies conducted in Japan have confirmed the continuous rise in the relative risks of arteriosclerotic disease, along with the rise in LDL-C (17-21). In addition, it has been shown that arteriosclerotic disease was controlled by intervention in high LDL-C by using pravastatin (22-24). Moreover, many epidemiological studies have elucidated that non HDL-C, which is the index obtained by subtracting HDL-C from TC, is related to arteriosclerotic disease. There are also reports that have indicated that non HDL-C is superior to LDL-C as the index for forecasting the onset of arteriosclerotic disease, because it contains remnant lipoprotein that causes arteriosclerosis. In this study, non HDL-C also decreased significantly by the intake of RB-ASG. The intake of RB-ASG has the potential to reduce the risk of developing arteriosclerotic disease mainly by improving LDL-C and non HDL-C.

From this study, we can conclude that the ingestion of RB-ASG for three months suggested its potential to contribute to the improvement of blood lipids of those with dyslipidemia.

CONFLICT

I've confirmed that all authors agree to this submission.

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