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Effect of Glutinous Barley Intake on Lipid Metabolism in Middle-Aged Rats Fed a High-Fat Diet

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Abstract : This study was designed to determine whether dietary glutinous barley (GB) affects lipid metabolism in middle-aged rats previously fed a high-fat diet. To induce obesity, 20 male 9-month-old Sprague Dawley rats were raised for 1 month on a diet containing 20%(w/w) lipid. The rats were allocated to 1 of 2 groups of 10 rats each and for the subsequent 2 months were fed an 8%(w/w) lipid diet containing well-milled rice (WMR) or GB powder. Rats fed the GB diet had significantly lower concentrations of plasma triglyceride, plasma total cholesterol, and liver cholesterol than rats fed the WMR diet. Fecal excretions of triglyceride and bile acids were significantly greater for the GB group than for the WMR group. In conclusion, dietary GB has positive effects on lipid metabolism: it decreases plasma cholesterol concentration by increasing fecal excretion of bile acids.

Keywords: middle-aged rat, high-fat diet, glutinous barley, cholesterol, bile acid

Introduction

The incidence of obesity is at epidemic levels in Korea and is increasing worldwide. Currently, more than 30.6% of the Korean adult population is overweight, as defined by a body mass index (BMI) greater than 25 kg/m^2 (1). Epidemiological studies have identified a significant positive correlation between dietary fat intake and the incidence of obesity (2). A constellation of metabolic disorders associated with obesity may contribute to increased risk of coronary heart disease (3). Predominant among these is dyslipidemia. Characteristics of dyslipidemia that positively contribute to increased risk of cardiovascular disease include increased levels of plasma very low- or low-density lipoprotein cholesterol, altered low-density lipoprotein (LDL) composition, and increased levels of plasma triglycerides with reduced levels of high-density lipoproteins (HDL) (4).

The traditional Korean diet includes a high intake of vegetables and grains that are rich in dietary fiber. This diet should be encouraged for reasons of public health. However, in Korea, the daily consumption of cereal grains decreased from 559.0 g/person in 1969 to 310.5 g/person in 2001 (5) and the daily intake of barley decreased from 7.5 g/person in 1993 to 3.1 g/person in 2003 (6). The decrease in consumption of grains that are rich in dietary fiber may be associated with the increasing prevalence of chronic diseases. Current evidence suggests that dietary fiber, abundant in whole and unrefined grains, plays important roles in preventing or delaying the onset of chronic disorders such as coronary heart disease (7).

Barley (*Hordeum vulgare* L.), which is high in soluble dietary fiber (particularly β-glucans), is hypocholesterolemic in chicks (8), rats (9), and humans (10). Some barley cultivars, notably those of the hull-less type, which contain a waxy type of starch, have high concentrations of soluble fiber (11) and are potential sources of dietary fiber.

A previous study (12) demonstrated that lipid levels in plasma were increased with aging. In addition, Silvia *et al.* (13) reported that the maximum benefit per lipid lowering treatment year was gained by starting treatment at middle-age; however, experimental animals of growth phase were used in most studies of barley. Furthermore, little systematic research has been conducted on elucidating the mechanism involved in the physiological effects of glutinous barley (GB). Therefore, we performed a study to determine whether diets containing GB have any beneficial effects on lipid metabolism in middle-aged rats. To induce obesity, the rats were raised for 1 month on a high-fat diet.

The overall goal of this study was to verify whether GB can be used to develop practical human diets for prevention of coronary artery diseases by decreasing plasma cholesterol concentrations and to elucidate the mechanisms involved in the effects of dietary GB.

Materials and Methods

Animals and diets *Preparation of grain samples*: Grain samples were purchased from an agricultural cooperative association. The variety of the well-milled rice (WMR) was 'Chuchungbyeo' (*Oryza sativa* cv. Chuchungbyeo, Icheon, Gyeonggi, Korea). The variety of the barley was 'Saechalssalbori' (*Hordeum vulgare* cv. Saechalssalbori, Nonsan, Chungnam, Korea), which is glutinous. Grains were washed twice with water, frozen, lyophilized, and ground through a 40-mesh sieve using a Fitz mill (No. DAS06; Fitz Patrick, Toronto, ONT, Canada). All grain powders contained less than 5% moisture and were stored at -80°C until they were used to constitute the experimental diets.

***Animals and dietary treatments*:** Twenty male 9-month-old Sprague Dawley rats [CD(SD)IGS, Outbred, Charles River Origin; Bio-Genomics, Inc., Seoul, Korea] were placed in individual stainless steel wire-mesh cages in a

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climate-controlled room. The room had a 12:12 hr light–dark cycle, a temperature of 22-24°C, and a relative humidity of 45±5%. The rats were fed a pelleted diet (Harlan Teklad, Madison, WI, USA) for the first 10 days (adaptation period). They weighed 758.3±19.3 g at the end of the adaptation period. To induce obesity, they were then fed the high-fat diet, which contained 20%(w/w) lipid for a month (Table 1). A 1:1:1:1 (w/w) mixture of corn oil (CJ Co., Incheon, Korea), soybean oil (CJ Co.), lard (Harlan Teklad), and beef tallow (Harlan Teklad) was used as the lipid source. Of the total energy content of the 20%(w/w) fat diet, about 45, 15, and 40% was derived from carbohydrate, protein, and fat, respectively. Cholesterol (0.05%, w/w; Harlan Teklad) was added to the 20% fat diets. The rats weighed 893.3±23.7 g after this period. They were then stratified according to body weight and randomly blocked into 2 treatment groups for the experimental period, which lasted for 2 months.

The 2 experimental diets differed in respect of the variety of grain (WMR or GB). The compositions of the experimental diets are shown in Table 1. The diets were formulated according to the nutrient content of the 93M diet of the American Institute of Nutrition (AIN) (14), with slight modifications. Of the total energy content of the 8%(w/w) fat diet, about 65, 15, and 20% was derived from carbohydrate, protein, and fat, respectively.

The rats were allowed free access to the experimental diets and to deionized water during the experimental period. This study was conducted in compliance with the guidelines of the Guide for the Care and Use of Laboratory Animals (15).

Table 1. Composition of experimental diets (g/kg diet)

Ingredient	High-fat	Group[1)]	
		WMR	GB
Well-milled rice powder	510.2	670.7	0
Glutinous barley powder	0	0	670.7
Sucrose	100.0	100.0	100.0
Casein	140.0	100.0	100.0
Corn oil	50.0	20.0	20.0
Soybean oil	50.0	20.0	20.0
Lard	50.0	20.0	20.0
Beef tallow	50.0	20.0	20.0
Mineral mixture[2)]	35.0	35.0	35.0
Vitamin mixture[3)]	10.0	10.0	10.0
L-Cystine	1.8	1.8	1.8
Choline bitartrate	2.5	2.5	2.5
tert-Butylhydroquinone	0.008	0.008	0.008
Cholesterol	0.5	0	0
Total	1,000	1,000	1,000

[1)]WMR, 8%(w/w) fat/well-milled rice powder; GB, 8%(w/w) fat/glutinous barley powder.
[2)]*AIN-93M* mineral mixture (g/kg): anhydrous calcium carbonate, 357; monobasic potassium phosphate, 250; sodium chloride, 74; potassium sulfate, 46.6; tripotassium citrate monohydrate, 28; magnesium oxide, 24; ferric citrate, 6.06; zinc carbonate, 1.65; manganous carbonate, 0.63; cupric carbonate, 0.3; potassium iodate, 0.01; anhydrous sodium selenate, 0.01025; ammonium paramolybdate 4-hydrate, 0.00795; sodium metasilicate 9-hydrate, 1.45; chromium potassium sulfate 12-hydrate, 0.275; boric acid, 0.0815; sodium fluoride, 0.0635; nickel carbonate, 0.0318; lithium chloride, 0.0174; ammonium vanadate, 0.0066; powdered sucrose 209.806.
[3)]*AIN-93* vitamin mixture (g/kg): nicotinic acid, 3; Ca-pantothenate, 1.6; pyridoxine-HCl, 0.7; thiamin-HCl, 0.6; riboflavin, 0.6; folic acid, 0.2; D-biotin, 0.02; vitamin B12 (0.1% cyanocobalamin in mannitol), 2.5; vitamin E (all-*rac*-α-tocopheryl acetate, 500 IU/g), 15; vitamin A (all-*trans*-retinyl palmitate, 500,000 IU/g), 0.8; vitamin D_3 (cholecalciferol, 400,000 IU/g), 0.25; vitamin K (phylloquinone), 0.075; powdered sucrose, 974.655.

Specimen collection During the final 8 days of the experimental period, feces voided over periods of 12 hr were collected on 4 occasions at 24-hr intervals. Food was withheld during the collection periods. Feces were weighed and stored at -80°C until analysis for lipid and bile acid content.

At the end of the experimental period, the animals were deprived of food for 12 hr and killed after anesthetization with ethyl ether. After blood samples had been collected directly from the heart using a syringe treated with heparin, liver samples were removed, snap frozen in liquid nitrogen, and stored at -80°C until analysis for biochemical indices of lipid metabolism. Heparinized plasma was frozen at -80°C until analysis for lipid content.

Measurements ***Plasma lipids*****:** Plasma total lipid concentration was determined using the method of Frings (16). Absorbance at 540 nm was measured using a spectrophotometer (Genesys 10UV; Thermo Electron Co., Waltham, MA, USA). Plasma triglyceride concentration was measured using a kit (YD Diagnostics, Yongin, Gyeonggi, Korea) based on an enzymatic colorimetric method (17). Plasma total cholesterol concentration was measured using a kit (YD Diagnostics) based on an enzymatic colorimetric method (18). Plasma HDL cholesterol concentration was measured using a kit (YD Diagnostics) based on the precipitation method (19). All procedures were done in accordance with the Manufacturers' Instructions.

Liver lipids**:** The concentration of total lipids in liver was measured using the method of Bligh and Dyer (20). The assay was done in 2 successive steps. In the first step, lipids were extracted from a liver homogenate with chloroform and methanol. In the second step, nonlipid substances present in the extract were removed from the lipid fraction by washing with water. The lipid extract was dissolved in methanol and concentrations of triglyceride and cholesterol were determined as described for plasma.

Fecal excretion of lipids and bile acids**:** Frozen feces were lyophilized, weighed, and ground. Total lipid concentrations of feces samples were analyzed using the method (20) described for liver samples. Fecal lipid extracts were dissolved in methanol and concentrations of triglyceride and cholesterol were determined as described for plasma. Using the enzymatic method of Porter *et al.* (21), bile acid was extracted from feces and bile acid concentrations were measured.

LDL receptor level in liver**:** Liver samples were prepared using the method of Croce *et al.* (22). Liver was homogenized using a Teflon homogenizer and 4 volumes of Tris-buffered saline (TBS) containing 10 mM Tris-HCl, pH 7.4, 150 mM NaCl, and 1 mM $CaCl_2$. The homogenizing buffer also contained a protease inhibitor cocktail for mammalian tissue homogenates (Sigma-Aldrich Co., St.

Louis, MO, USA). The homogenate was then centrifuged at 500×g for 10 min at 4°C. The supernatant was sonicated at 4°C and diluted in TBS (0.08 mg protein per mL) for slot-blot analysis.

Liver LDL receptor level was determined using the slot-blot method, a nonradioactive immunoblot assay (23). Liver homogenates (200 μL) were applied to nitrocellulose membranes (0.45 μm, Bio-Rad Laboratories, Inc., Hercules, CA, USA) and allowed to filter through the membranes under gentle vacuum using slot-blot microfiltration units (Bio-Rad Laboratories, Inc.). Excess binding sites on the membranes were neutralized by blocking with 5% instant nonfat dried milk.

The membranes were probed with a purified goat polyclonal antibody (Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA). The antibody solution was diluted 1:1,000. The membranes were then probed with rabbit anti-goat IgG conjugated to alkaline phosphatase (Santa Cruz Biotechnology, Inc.), which was used at a dilution of 1:5,000. Subsequently, the membranes were immersed in the color development solution, nitroblue tetrazolium/5-bromo-4-chloro-3-indolyl phosphate (NBT/BCIP) substrate (Bio-Rad Laboratories, Inc.). Membranes were washed 3 times in distilled water to remove residual color development solution and air dried. The density of the colored blots was measured using an image analyzer system (Gel-pro analyzer 3.1, Media Cybernetics, Inc., Silver Spring, MD, USA) equipped with a charge-coupled-device color camera (Toshiba Teli Co., Irvine, CA, USA).

Because rat LDL receptor standards were not commercially available, a pooled tissue homogenate was used as an internal standard and applied to each membrane to correct for membrane-to-membrane variability. The coefficient of variation (CV) for color densities of internal standards was less than 5%. Results were expressed as density per 10 μg of total protein to facilitate comparison between groups. All samples were run in triplicate to enhance the reliability of instrumentation.

Statistical analysis Data were expressed as the mean ± standard error (SE), and differences between groups were determined using Student's *t* test. A *p* value of less than 0.05 was considered significant.

Results and Discussion

Food consumption and body weight change of rats Daily food and calorie intake, weekly body weight change, and body weight change per 100 kcal consumed are shown in Table 2. Rats fed the GB diet had significantly lower food and calorie intakes than rats fed the WMR diet ($p<0.05$). The body weight change and body weight change per 100 kcal consumed of the group fed the GB diet were significantly lower than those of the group fed the WMR diet ($p<0.01$). Although the fat contents of the experimental diets were less than that of the diet fed during the phase in which obesity was induced, the mean body weight of the group fed the WMR diet increased slightly during the experimental period. On the other hand, the mean body weight of the group fed the GB diet decreased.

Body weight gain was significantly affected by cereal source: rats fed GB gained less weight than rats fed WMR. The lower weight gain of the GB group may have been caused by lower food intake and therefore a lower calorie intake compared with rats fed the WMR diet. The lower food intake of rats fed GB diet may have resulted from the higher volume per weight of GB diet compared with WMR diet. But more studies should be conducted in order to verify how GB acts on food intake.

As food efficiency was less for rats fed the GB diet than for those fed the WMR diet, the low weight gain may have been a consequence of altered nutrient availability caused by nonstarch polysaccharides (NSP). Abbey *et al.* (24) reported that dietary NSP isolates differed in their effects on body weight gain. In pigs, pearl barley, a grain rich in soluble NSP, tended to reduce body weight gain and digestible energy intake in comparison with cooked white rice (25). This resulted from a decrease in ileal starch digestibility and an increase in intestinal viscosity in animals fed the NSP-rich diet. Wang *et al.* (26) demonstrated that β-glucans, particularly those in barley diets, form viscous masses in the small intestines of chickens, causing poor digestibility of lipids and protein and reducing body weight gain. The quantity of dietary fiber in the GB (96.3 mg/g dry powder) used in this study was greater than that of the WMR (43.63 mg/g dry powder) and the GB (20.11 mg/g dry powder) contained a greater quantity of soluble fiber than the WMR (5.03 mg/g dry powder) (27). Kim and Paek (28) found that the soluble dietary fiber and β-glucan contents of barley are about 3 times higher than those of rice.

Lipid metabolism ***Plasma lipid concentrations in rats*****:** Plasma concentrations of total lipids, triglyceride, total cholesterol, and HDL cholesterol are shown in Table 3. In plasma concentrations of total lipids, there was no significant difference between groups. However, plasma triglyceride concentration was significantly influenced by grain variety. Plasma triglyceride concentrations of the group fed the WMR diet were significantly higher than those of the group fed the GB diet ($p<0.01$). Rats fed the GB diet had significantly lower concentrations of plasma total cholesterol than rats fed the WMR diet ($p<0.01$). Although there was

Table 2. Food intake and body weight change of rats

Group[1)]	Food intake (g/day)	Calorie intake (kcal/day)	Body weight change (g/week)	Weight change/calorie intake (g/100 kcal)
WMR	24.83±0.68[2)]	98.23±2.67	4.01±1.11	0.61±0.16
GB	21.87±1.00*	85.93±3.92*	−3.11±1.62**	−0.61±0.29**

[1)]WMR, 8%(w/w) fat/well-milled rice powder; GB, 8%(w/w) fat/glutinous barley powder.
[2)]Mean±SE (n=10); Student's *t* test (*$p<0.05$, **$p<0.01$).

Table 3. Plasma concentrations of total lipids, triglyceride, total cholesterol, and HDL cholesterol in rats (mg/mL)

Group[1)]	Total lipids	Triglyceride	Total cholesterol	HDL cholesterol
WMR	4.19±0.25[2)]	1.67±0.14	0.87±0.044	0.30±0.036
GB	3.76±0.17[NS]	1.17±0.10**	0.68±0.044**	0.32±0.031[NS]

[1)]WMR, 8%(w/w) fat/well-milled rice powder; GB, 8%(w/w) fat/glutinous barley powder.
[2)]Mean±SE (n=10); Student's *t* test (**$p<0.01$, [NS] not significant).

no significant difference in plasma HDL cholesterol concentrations between the experimental groups, those of rats fed the GB diet tended to be higher than those of rats fed the WMR diet.

In our study, the GB diet significantly decreased lipid levels in rats. These data are consistent with the results of Li *et al.* (29), who found that a barley diet significantly decreased plasma levels of total cholesterol and triglyceride in rats with type 2 diabetes mellitus compared with rats fed a white rice diet. And there was no significant difference in the plasma concentration of HDL cholesterol between the two groups. Another study (30) yielded similar results in that a barley diet significantly decreased plasma total cholesterol and triglyceride levels in rats with type 2 diabetes (GK rats) compared with a rice diet. Low plasma HDL cholesterol levels and elevated triglyceride levels are both positive risk factors for coronary heart disease (31, 32). It is therefore important to demonstrate that barley diets do not adversely affect the plasma levels of these metabolites in humans.

***Liver lipid concentrations in rats*:** Liver weights and liver concentrations of total lipids, triglyceride, and cholesterol are shown in Table 4. Liver weights were not affected by grain variety. There were no significant differences between the experimental groups in the liver concentrations of total lipids and triglyceride. Liver cholesterol concentration was significantly affected by grain variety. The group fed the GB diet had significantly lower liver cholesterol concentrations than the group fed the WMR diet ($p<0.05$).

Although there was no significant difference between the experimental groups, liver total lipid and triglyceride concentrations tended to decrease in rats fed the GB diet. Liver cholesterol concentration was significantly lower in rats fed the GB diet than in rats fed the WMR diet. The higher liver cholesterol level in animals fed the WMR diet is consistent with increased entry of steroids into the circulation and their uptake by the liver. The lower liver cholesterol content of rats fed the GB diet may be consistent with the concept that barley lowers plasma cholesterol.

***Fecal excretion of lipid in rats*:** Fecal weights and fecal excretion rates of lipid, triglyceride, cholesterol, and bile acids are shown in Table 5. Fecal excretion was significantly affected by grain variety. The wet and dry fecal weights of rats fed the GB diet were higher than those of rats fed the WMR diet ($p<0.001$). There was no significant difference between total lipid concentrations of feces of the experimental groups. Triglyceride concentrations of feces were significantly influenced by grain variety. Rats fed the GB diet had significantly higher fecal excretions of triglyceride than rats fed the WMR diet ($p<0.05$). In cholesterol concentrations of feces, there was no significant difference between groups. Fecal bile acid excretion was significantly influenced by grain variety. Fecal bile acid excretion was significantly higher in rats fed the GB diet than in those fed the WMR diet ($p<0.001$).

In this study, total lipids and cholesterol tended to be higher in feces of rats fed the GB diet than in feces of rats fed the WMR diet. The results of this study agree with those of Martinez *et al.* (8) who found that crude fat levels in excreta were greater for barley-fed chickens than for chickens fed wheat. The higher fat content of excreta suggests that the reduction in plasma cholesterol levels was due in part to less absorption of dietary fat. The fecal mass and the excretion of fecal bile acids increased in rats fed the GB diet. The results of this study agree with those of others (33) who found that consumption of a barley diet increased the total dry mass of rat colon contents and colon bile acid concentration compared with rats fed a wheat-starch diet.

***Liver LDL receptor level in rats*:** Liver LDL receptor

Table 4. Liver weights and liver concentrations of total lipids, triglyceride, and cholesterol in rats

Group[1)]	Weight (g)	Total lipids (mg/g wet liver)	Triglyceride (mg/g wet liver)	Cholesterol (mg/g wet liver)
WMR	23.72±1.12[2)]	39.88±5.88	4.83±0.69	0.604±0.059
GB	20.91±1.27[NS]	27.58±4.15[NS]	3.79±0.55[NS]	0.439±0.043*

[1)]WMR, 8%(w/w) fat/well-milled rice powder; GB, 8%(w/w) fat/glutinous barley powder.
[2)]Mean±SE (n=10); Student's *t* test (*$p<0.05$, [NS] not significant).

Table 5. Fecal weights and fecal excretions of total lipids, triglyceride, cholesterol, and bile acids in rats

Group[1)]	Wet weight (g/day)	Dry weight (g/day)	Total lipids (mg/day)	Triglyceride (mg/day)	Cholesterol (mg/day)	Bile acids (mg/day)
WMR	0.86±0.11[2)]	0.55±0.06	8.81±3.34	0.059±0.026	1.19±0.30	5.55±0.81
GB	2.88±0.21***	1.49±0.10***	22.44±8.58[NS]	1.031±0.295*	2.84±0.69[NS]	13.83±1.32***

[1)]WMR, 8%(w/w) fat/well-milled rice powder; GB, 8%(w/w) fat/glutinous barley powder.
[2)]Mean±SE (n=10); Student's *t* test (***$p<0.001$, *$p<0.05$, [NS] not significant).

Table 6. Level of liver LDL receptor in rats

Group[1)]	LDL receptor (density/10 μg protein)
WMR	9.340±0.527[2)]
GB	10.763±0.508[NS]

[1)]WMR, 8%(w/w) fat/well-milled rice powder; GB, 8%(w/w) fat/glutinous barley powder.
[2)]Mean±SE (n=10); Student's *t* test ([NS] not significant).

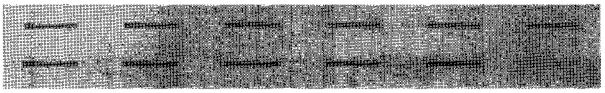

Fig. 1. A representative slot blot image of liver LDL receptor. The liver homogenate samples were loaded per well (16 g protein/slot); the pooled liver homogenate was loaded in the first column from the right and 8 g of protein is loaded in the only second well in the column form the top. The liver homogenate samples, in order of WMR and GB group, were loaded in the each rank from the top.

levels are shown in Table 6 (Fig. 1). In our study, hepatic LDL receptor level was used as an index of lipoprotein cholesterol uptake by the liver. Liver LDL receptor level was not affected by grain variety and there was no significant difference between groups.

Plasma cholesterol concentrations are controlled by several factors, including the entry of dietary cholesterol into the circulation and the clearance of lipoproteins from the circulation. One possible interpretation of the effect of GB on cholesterol metabolism is that cholesterol is withdrawn from the plasma and liver to replace bile acids removed from the digestive tract by the soluble fiber components in barley. Yang *et al.* (34) found that the addition of 2.5% refined β-glucan or 30% waxy barley to diets decreased serum levels of total cholesterol and LDL cholesterol and increased bile acid excretion compared to a control group. It is likely that changes in gut viscosity, disturbances of micelle formation and lipid digestion, and inhibition of bile acid absorption, all caused by dietary fiber components, are responsible for the high concentrations of bile acids in feces of rats fed barley diets. A relationship between the amount of bile acids excreted and a decrease in plasma cholesterol levels in hypercholesterolemic humans and animals has been discussed (35, 36). This would enhance bile acid synthesis from cholesterol in the liver (34).

However, barley contains other components that may be involved in this effect. Brewer's spent barley grain, depleted in soluble NSP, also lowers plasma cholesterol in human subjects (37). In barley, other components besides water-soluble NSP are almost certainly involved in the effects of barley on plasma cholesterol levels. These components might be tocotrienols. These compounds may have the potential to inhibit hepatic cholesterol synthesis (38). The mechanisms and relative contributions of various barley components to the effects of a barley diet on plasma lipids remain to be established.

In conclusion, the results of the present study demonstrated that dietary GB decreased the plasma triglyceride and cholesterol concentrations in middle-aged rats fed a high-fat diet. The lower plasma cholesterol concentration of the GB group may have been caused by increased fecal excretion of bile acids. It is expected that diets containing GB could play important roles in preventing or delaying the onset of chronic disorders such as coronary artery disease.

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