Research Article

High β-Glucan Barley Improves Postprandial Hyperglycemia after Meal Loading in Patients with Type 2 Diabetes

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Abstract

Objective: We investigated whether barley with a high β-glucan content (7.2 g per 100 g) improves postprandial plasma glucose levels and fluctuations using a meal tolerance test and Continuous Glucose Monitoring (CGM) in patients with type 2 diabetes.

Methods: A meal tolerance test (500 kcal) was conducted using two types of test meals: one with white rice (WR diet) and one with white rice mixed 1:1 with high β-glucan-containing barley (BR diet). Both meals included the same side dish. Plasma glucose changes over 180 minutes were compared after ingestion of the test meals. In addition, participants wore a CGM device for the 2 study days, to measure the daily variations in glucose levels when the WR or BR diet as staple food was provided 3 times a day with the same side dish in both meals.

Results: Twenty-nine patients with type 2 diabetes (age 52.5 ± 15.1 years, BMI 27.5 ± 4.7 kg/m², HbA1c 8.1 ±1.8 %) were included in this study. The incremental area under the curve of plasma glucose levels after BR diet ingestion was significantly lower than that after WR diet ingestion (7934.0 ± 4151.2 *vs* 9434.0 ± 4701.2 mg·min/dL). CGM showed a 24-hour standard deviation of blood glucose after the BR diet was significantly lower than that after the WR diet.

Conclusion: These results suggest that postprandial plasma glucose elevation and fluctuation in patients with type 2 diabetes are suppressed by adding high-β-glucan barley to white rice in meals.

Keywords: Diet therapy; Beta glucan; Barley; Postprandial hyperglycemia; Type 2 diabetes

Introduction

The association between diabetes and a marked increase in the risk of coronary heart disease is well-established [1,2]. Although many factors are involved in the development of atherosclerosis and coronary heart disease, the two most important are hyperglycemia and insulin resistance [2,3]. There is growing evidence that the generation of oxidative stress and inflammation that occurs during postprandial hyperglycemia is an important mechanism for the initiation and progression of endothelial dysfunction in type 2 diabetes [3,4]. The postprandial increase in plasma glucose level is primarily governed by the amount of carbohydrate in the meal [5-7] and may vary depending on the quality of the carbohydrate [8]. Carbohydrate quality is assessed by the Glycemic Index (GI), which ranks carbohydrates based on the rate of glycemic response [8]. A recent study revealed that dietary fiber intake was inversely associated with all-cause mortality [9]. Brown rice and barley have a lower GI value and suppress postprandial elevation of plasma glucose level because they contain a higher amount of dietary fiber than White Rice (WR) [10-12]. Barley, in particular, contains a high amount of insoluble and soluble dietary fiber, and most of the soluble dietary fiber is β-glucan [13,14], which may reduce the risk of cardiovascular diseases in part through its blood cholesterol-lowering action [15].

High intake of carbohydrate, including WR, causes an increase in postprandial plasma glucose level and is associated with an increased risk of cardiovascular disease, metabolic syndrome and diabetes [16,17]. Intake of high β-glucan barley leads to a reduction in visceral fat [18], and we previously showed that it suppressed postprandial plasma glucose elevation and oxidative stress, as well as reducing the mean blood glucose level over 24 hours, and blood glucose fluctuations, in volunteers with normal glucose tolerance [19].

Here, we conducted meal tolerance tests in patients with type 2 diabetes, using a test meal of WR mixed with two-rowed hull-less barley, which contains more β-glucan (7.2 g per 100 g) than common barley [20], to examine whether high β-glucan barley improves postprandial plasma glucose levels. In addition, Continuous Glucose Monitoring (CGM) system was used to assess blood glucose fluctuations of the day.

Materials and Methods

Study participants

Participants were recruited among patients admitted to Saiseikai

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Yokohamashi Tobu Hospital for diabetic control between January 2015 and August 2015. Twenty-nine patients with type 2 diabetes (15 men and 14 women) were included. The inclusion criteria were as follows: 1) age <75 years; 2) fasting plasma glucose levels ≤140 mg/dL; 3) daily plasma glucose fluctuations <100 mg/dL as shown in Table 1. Patients diagnosed with severe renal dysfunction (estimated glomerular filtration rate <50 mL/min/1.73 m²) and/or serious cardiovascular diseases were excluded. Patients were also required to not have eaten food containing barley for 1 week prior to the study. This was confirmed using a dietary survey. Study participants had a mean age of 57.2 ± 15.1 years. Mean body mass index, fasting plasma glucose and HbA1c levels were 27.5 ± 4.7 kg/m², 119.3 ± 16.1 mg/dL, and 8.1 ± 1.8%, respectively. Three patients were treating their diabetes with diet alone, 15 patients were receiving insulin with oral hypoglycemic agents, and 11 patients were receiving oral hypoglycemic agents alone. Of the 29 patients treated with insulin or oral hypoglycemic agents, 14 were receiving a Dipeptidyl Peptidase-4 (DPP-4) inhibitor. All treatments, including oral antidiabetic agents and doses of insulin, remained unchanged throughout the study period.

The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. All procedures were approved by the Saiseikai Yokohamashi Tobu Hospital ethics committee (Ethics committee file number 2013030), and written informed consent was obtained from all patients.

Meal tolerance test

The meal tolerance test was performed in the morning after overnight fast, with no food or drink after 21:00 the evening before the test. Early in the morning, on an empty stomach, the patients consumed two types of diet adjusted to 500 kcal in about 15 minutes, and oral hypoglycemic drugs and insulin injections were administered in normal doses, remained unchanged throughout the study period. The meal tolerance test was performed on 2 consecutive days in randomized crossover design. Two different diets were prepared: one consisted of WR with a side dish (WR diet), and the other was WR mixed 1:1 with β-glucan rich barley (BR) with the same side dish as in the WR diet (BR diet). The patients were randomized into two groups. One had the WR diet on the first day and the BR diet the next day, and the other had the BR diet on the first day and the WR diet the next day. For lunch and dinner after the breakfast tolerance test, the main dish was WR for the WR diet and BR for the BR diet.

The specific barley used in this study was "Kirarimochi". Kirarimochi was registered as a new breed of two-rowed hull-less barley in 2009 and has a high β-glucan content (7.2 g per 100 g) [20], about 1.5 times higher than that of normal covered barley (4.7 g per 100 g). This barley type was developed by the National Agriculture and Food Research Organization in Japan, and is not a genetically modified crop. The high β-glucan barley was pearled to remove the bran (pearled to 60% yield) and the remaining 60% was rice-shaped barley, which was used in the meal [20]. The BR diet consisted of 50% Kirarimochi and 50% WR.

The WR diet comprised 504 kcal, 80 g carbohydrate (glucose 76.9 g, dietary fiber 3.5 g), 18.7 g protein, and 11.4 g lipid. In comparison, the BR diet was 479 kcal, comprising 75 g carbohydrate (glucose 68.8 g, dietary fiber 6.3 g), 18.9 g protein and 11.6 g lipid. The amount of staple food was adjusted to 150 g for both WR and BR diets.

Plasma glucose was measured before the test meal and 30, 60, 120, and 180 minutes after. The Incremental Area Under the Curve (IAUC) of plasma glucose levels was calculated using the trapezoidal method [21] from values up to 180 minutes after ingestion, with the value at fasting state as baseline. Plasma triglyceride and free fatty acid (FFA) levels were measured before the meal and 60 and 180 minutes after. Plasma triglyceride and FFA levels were measured using enzymatic methods (BML, Tokyo, Japan). Serum high-sensitivity CRP (h-CRP) and urinary 8-hydroxydeoxyguanosine (8-OHdG) levels were also measured. Urinary 8-OHdG was corrected with urinary creatinine. Enzyme-linked immunosorbent assay methods (SRL, Tokyo, Japan) were used for the measurements of h-CRP and urinary 8-OHdG.

Continuous Glucose Monitoring (CGM) system

The 29 subjects who underwent the meal tolerance test continued to participate in the CGM study. A CGM system was fitted to examine the daily fluctuation in blood glucose after meals with WR or BR as the main dish. The test was conducted in a randomized crossover design and the patients were divided into two groups: one had the WR diet as the main dish for breakfast, lunch, and dinner on the first day and the BR diet at equivalent times the next day, and the other had the BR diet as the main dish for breakfast, lunch, and dinner on the first day and the WR diet at equivalent times the next day. The side dishes were the same in both groups. Oral hypoglycemic drugs and insulin injections were administered in usual doses, remained unchanged throughout the study period, and activity was adjusted to remain the same as far as possible over the 2 days.

The daily calorie intake was adjusted to 1800 kcal for men and 1600 kcal for women. The diets were prepared with identical-looking content and number of side dishes. For 1600 kcal per day, the WR diet contained 1677 kcal and 64.5 g protein, 47.1 g lipid and 241 g carbohydrate (glucose 232.5 g, dietary fiber 7.2 g), and the BR diet contained 1602 kcal, 65.1 g protein, 47.7 g lipid and 226 g carbohydrate (glucose 209 g, dietary fiber 16.9 g). For 1800 kcal per day, protein and lipid content were identical to the 1600 kcal diet, but the WR diet contained 291 g carbohydrate (glucose 280 g, dietary fiber 8.6 g), and the BR diet contained 276 g carbohydrate (glucose 250 g, dietary fiber 20.3 g).

CGM was carried out using the iPro®2 (Medtronic, MiniMed Northridge, CA, USA), which was placed on each participant's abdomen before lunch on the day before the test. The following CGM variables were calculated: daily mean blood glucose levels (24-hour MBG), 24-hour standard deviation of blood glucose (24-hour SDBG), and Mean Amplitude of Glucose Excursion (MAGE) [22]. MAGE is an index of glycemic variability calculated from the value larger than one standard deviation (SD) from the mean glycemic values ± SD. The other indexes of glycemic variability were calculated as follows; coefficient of variance (%CV) = SD/MBG×100, and J-index =0.001 ×(MBG+SD)² [22].

Statistical analysis

Results are expressed as the mean ± SD. Temporal changes in plasma glucose, triglyceride, FFA, h-CRP and urinary 8-OHdG levels from the fasting state up to 180 minutes after ingestion were evaluated by paired Student's *t*-tests. When the variables did not

Table 1: Clinical characteristics of subjects.

Type 2 diabetic patients n=29		
Age (years)	57.2±15.1	
Gender (male/female)	15/14	
Body mass index (kg/m²)	27.5±4.7	
HbA1c (%)	8.1±1.8	
Fasting plasma glucose (mg/dL)	119.3±16.1	
Duration of diabetes (years)	6.3±5.9	
Diabetic treatment	Diet alone	n=3
	OH agents	n=11
	Insulin treatment	n=15
	DPP-4 inhibitor (+/-)	14/15

OH agents: Oral Hypoglycemic agents; DPP-4 inhibitor: Dipeptidyl Peptidase-4 inhibitor.
Values are mean ± standard deviations.

exhibit a normal distribution, the Wilcoxon rank-sum test was used to compare the two groups. Differences between WR and BR diet were evaluated using unpaired Student's *t*-tests, and Welch's *t*-test was used for analysis if equal variances were not assumed. The Mann-Whitney U test was used to compare the IAUC of plasma glucose levels between the WR and BR diets. $p < 0.05$ in a two-sided test was considered significant. SAS JMP version 11 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses.

Results

Meal tolerance test

Plasma glucose level before ingestion of the WR diet was 114.7 ± 16.8 mg/dL, and this increased significantly to a peak of 173.3 ± 38.9 mg/dL at 60 minutes after ingestion ($p < 0.0001$), and returned to 150.7 ± 33.1 mg/dL at 180 minutes after ingestion. Basal plasma glucose level in the BR diet was 114.6 ± 16.6 mg/dL, the peak value was 165.2 ± 27.2 mg/dL at 60 minutes after ingestion, which was significantly higher than the basal value ($p < 0.0001$), and it returned to 140.4 ± 26.5 mg/dL at 180 minutes. Plasma glucose levels at 180 minutes in the BR diet were significantly lower than those in the WR diet ($p < 0.05$), but there was no significant difference between the WR and BR diets in plasma glucose levels at 60 minutes. As indicated in Table 2, the IAUC of plasma glucose levels over 180 minutes after ingestion of the BR diet was significantly lower ($p < 0.01$) than that after ingestion of the WR diet. Plasma triglyceride levels were significantly higher 180 minutes after ingestion of the WR or BR diets than at baseline ($p < 0.001$), and its level after ingestion of the BR diet showed significant high compared to those after the WR diet ($p < 0.001$). FFA levels 180 minutes after ingestion of the test meals were significantly lower than those before ingestion levels, with no significant difference between the two groups as shown Table 3. No significant changes were seen in urinary 8-OHdG and h-CRP before and after ingestion of WR diet or BR diet.

Continuous Glucose Monitoring (CGM) system

Table 4 depicts the results of the parameters of glycemic variability.

Table 2: The Incremental Area Under the Curve (IAUC) of blood glucose levels over 180 minutes after the consumption of test meals with White Rice alone (WR diet) or white rice mixed 1:1 with β-glucan rich barley (BR diet).

	WR diet	BR diet	P value
IAUC mg/min/dL	9434.0±4701.2	7934.0±4151.2	<0.01

Values are mean ± standard deviations.

There was no significant difference in 24-hour MBG level between the WR and BR diets. The 24-hour SDBG and %CV were significantly lower for the BR diet than the WR diet ($p < 0.05$); however, no significant difference in MAGE and J-index between the WR and BR diets was observed. In addition, the daily fluctuation in blood glucose levels were compared across diabetes treatment modalities. In the 14 patients who were taking a DPP-4 inhibitor, MAGE for WR diet was significantly lower than in the 15 patients who were not (43.7 ± 17.9 mg/dl *vs* 60.5 ± 26.4 mg/dl; $p < 0.05$), and also MAGE for BR diet in the 14 patients taking a DPP-4 inhibitor was significantly lower than in the 15 patients who were not (40.7 ± 20.9 mg/dl *vs* 61.0 ± 24.8 mg/dl; $p < 0.05$). However, the differences between WR diet and BR diet in two groups were not significant. No significant differences in parameters of glycemic variability were seen between patients with and without insulin treatment.

Discussion

We previously reported that postprandial glucose elevation and glucose fluctuations were suppressed by ingestion of a mix of high β-glucan barley and WR in volunteers with normal glucose tolerance [19]. Similarly, the present study showed that high β-glucan barley also ameliorated postprandial hyperglycemia and glucose level fluctuations in patients with type 2 diabetes. Therefore, high β-glucan barley might decrease postprandial hyperglycemia not only in healthy people but also in people with type 2 diabetes. At least 4 g of β-glucan and 30–80 g available carbohydrate can significantly reduce postprandial blood glucose [23]. Conventionally, β-glucan content in barley is reported to be 4.7 g per 100 g. In contrast, the Kirarimochi barley used in this study has a content of β-glucan as high as 7.2 g per 100 g [20]. In this study, the composition of the BR diet was almost 4 g of β-glucan and 54 g available carbohydrate, fulfilling Tosh's recommendation [23]. In healthy people, preloading with β-glucan mixed in water before a meal reduced the glucose AUC

Table 3: Changes in plasma lipid levels after consumption of test meals with white rice alone (WR diet) or white rice mixed 1:1 with β-glucan rich barley (BR diet).

		0 min	60 min	180 min
Triglyceride (mg/dL)	WR diet	118.4±47.3	121.1±46.6	138.3±52.8*
	BR diet	125.8±50.5	128.4±47.4	155.9±58.4
Free fatty acids (mEq/L)	WR diet	0.52±0.19	0.41±0.16	0.27±0.14
	BR diet	0.51±0.17	0.41±0.19	0.28±0.14

*: $p < 0.001$ were obtained WR diet *vs* BR diet using unpaired student's *t* test.
Values are mean ± standard deviations.

Table 4: The daily mean blood glucose and daily variation of blood glucose levels in Continuous Glucose Monitoring (CGM) system after consumption of White Rice alone (WR diet) or white rice mixed 1:1 with β-glucan rich barley (BR diet).

	WR diet	BR diet	P value
24-hMBG mg/dl	133.6±18.1	134.0±16.7	NS
MAGE mg/dl	52.4±23.9	51.2±24.8	NS
24-hSDBG mg/dl	25.2±10.2	22.2±10.7	<0.05
%CV	18.9±7.5	16.5±7.9	<0.05
J-index	25.8±7.5	24.9±7.1	NS

24-hMBG: 24-hour daily mean blood glucose, MAGE: mean amplitude of glucose excursion, 24-hSDBG: 24-hour standard deviation of blood glucose, %CV: coefficient of variance.
Values are mean ± standard deviations.

and energy intake [24,25], whereas in people with type 1 diabetes, β-glucan tablets did not improve glycemic control or glucose variability [26]. Insoluble dietary fiber improves bowel movement by increasing stool volume [27], whereas soluble dietary fiber, which is mixed with food inside the intestine, suppresses the acute elevation of glucose and serum cholesterol levels due to its slow movement within the intestine [28,29]. In addition, the high viscosity of soluble dietary fibers, especially β-glucan, results in them strongly delaying the digestion and absorption of nutrients [28]. Beta glucan is likely to be involved in complex processes and interactions with the food matrix [30]. The present findings show that a mix of high β-glucan barley and WR is effective in managing postprandial hyperglycemia. The American Diabetes Association recommends eating a moderate amounts of fiber (total, 24 g; 8 g soluble fiber and 16 g insoluble fiber) [31]. In this study, 1800 kcal of BR diet contained 20.3 g fiber for a day, approaching this recommendation, in contrast to the WR diet, which contained 8.6 g.

Consumption of glutinous brown rice improved postprandial glucose excursion and insulin hypersecretion [12]. Glutinous brown rice contains gamma-oryzanol, which may improve metabolic parameters [12,32]. We previously reported that high β-glucan barley suppressed an increase in postprandial insulin levels, possibly by delaying digestion, absorption, and gastric emptying [33]. Meals that include vegetables and dietary fiber increase glucagon-like peptide 1 (GLP-1) more than meals of WR alone, and suppress hyperglycemia and excessive secretion of endogenous insulin after meals [34]. A previous study reported significant differences in the effects of glutinous brown rice between patients treated with and without DPP-4 inhibitors [12]. This may be explained by glutinous brown rice stimulating GLP-1 secretion as a result of increased production of short-chain fatty acids from dietary fiber by gut microbial flora [34,35]. In the present study, patients receiving a DPP-4 inhibitor showed smaller postprandial glucose fluctuations than those not receiving a DPP-4 inhibitor, regardless of whether they ate the WR or BR diet, which might association with a augmentation of plasma GLP-1 concentrations and slowing of gastric emptying, as suggested previously [12,36]. Consequently, it is difficult to say whether high β-glucan barley is effective for patients taking a DPP-4 inhibitor.

Soluble dietary fiber lowers serum cholesterol and triglycerides and improves intrahepatic lipid accumulation [37]. We observed no differences in serum triglyceride or FFA levels between the BR and WR diets. Longer-term observation studies are needed to clarify the effect of β-glucan barley on lipid metabolism. Mixing Kirarimochi barley with WR improves postprandial blood glucose levels and may prevent diabetes and metabolic syndrome [18,38], as well as preventing cardiovascular disease by decreasing postprandial glucose fluctuations, insulin hypersecretion, and antioxidant status [39]. However, in this study the marker of oxidative stress and inflammation showed no changes during postprandial hyperglycemia. A long-term study is necessary to clarify whether β-glucan barley improves oxidative stress or inflammation after ingestion of the meal. Normal covered barley generally has a β-glucan content of about 4.7%, whereas that of Kirarimochi is about 1.5-times higher. Further investigation is needed to clarify whether common barleys also reduce postprandial hyperglycemia and glucose fluctuation. Our study has limitation. First, the sample size was small and study duration was short. Second,

there was no wash out period between WR diet and BR diet.

In conclusion, in the meal tolerance test and CGM study, IAUC for glucose over 180 minutes and glucose level fluctuation after ingestion were significantly decreased by the consumption of WR mixed 1:1 with high β-glucan barley in patients with type 2 diabetes. Lowering the GI of WR by adding β-glucan appears to suppress postprandial hyperglycemia. This might contribute to preventing obesity and suppressing the onset of vascular disease in Asian patients with diabetes who use WR as a staple food. Nonetheless, long-term research is still needed to clarify whether high β-glucan barley improves postprandial blood glucose levels.

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Author Contributions

Study concept and design: SA, AF and MH; acquisition of data: YF, and MF; analysis and interpretation of data: TI, YF and MH; drafting of the manuscript: YF, MH and TH; critical revision of the manuscript: MH and TH; statistical analysis: TI; obtained funding: SA; administrative, technical, or material support: SA and AF; and study supervision: all authors.

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