

Original Article

Effects of cooked rice containing high resistant starch on postprandial plasma glucose, insulin, and incretin in patients with type 2 diabetes

Yuta Nakamura MD, PhD¹, Ayaka Takemoto MD¹, Takeshi Oyanagi MD¹, Shingo Tsunemi MD¹, Yui Kubo MD¹, Tomoko Nakagawa MD, PhD¹, Yoshio Nagai MD, PhD^{1,2}, Yasushi Tanaka MD, PhD^{1,3}, Masakatsu Sone MD, PhD¹

¹Division of Metabolism and Endocrinology, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Kanagawa, Japan

²Division of Diabetes and Endocrinology, Kanto Rosai Hospital, Kawasaki, Kanagawa, Japan

³Department of Internal Medicine, Yokohama General Hospital, Yokohama, Kanagawa, Japan

Background and Objectives: Few studies exist on resistant starch in rice grains. The Okinawa Institute of Science and Technology Graduate University (OIST) has developed a new rice (OIST rice, OR) rich in resistant starch. This study aimed to clarify the effect of OR on postprandial glucose concentrations. **Methods and Study Design:** This single-center, open, randomized, crossover comparative study included 17 patients with type 2 diabetes. All participants completed two meal tolerance tests using OR and white rice (WR). **Results:** The median age of the participants was 70.0 [59.0–73.0] years, and the mean body mass index was 25.9±3.1 kg/m². The difference in total area under the curve (AUC) of plasma glucose was -8223 (95% confidence interval [CI]: -10100 to -6346, $p < 0.001$) mg·min/dL. The postprandial plasma glucose was significantly lower with OR than with WR. The difference in the AUC of insulin was -1139 (95% CI: -1839 to -438, $p = 0.004$) μU·min/mL. The difference in the AUC of total gastric inhibitory peptide (GIP) and total glucagon-like peptide-1 (GLP-1) was -4886 (95% CI: -8456 to -1317, $p = 0.011$) and -171 (95% CI: -1034 to 691, $p = 0.673$) pmol·min/L, respectively. **Conclusions:** OR can be ingested as rice grains and significantly reduced postprandial plasma glucose compared to WR independent of insulin secretion in patients with type 2 diabetes. OR could have escaped absorption not only from the upper small intestine but also from the lower small intestine.

Key Words: resistant starch, type 2 diabetes, diet therapy, postprandial plasma glucose, incretin

INTRODUCTION

Diet therapy is one of the basic treatments for diabetes. Carbohydrates/sugars are important targets for diet therapy since these nutrients directly affect plasma glucose. However, insufficient evidence exists on the carbohydrate quality and means for its consumption.

“Rice” is considered a staple food and an indispensable ingredient in the Asian population. Recently, similar to non-glutinous and glutinous rice, the effect of the different starch constituents on postprandial plasma glucose rise has been investigated.¹ Resistant starch is characterized by evading digestion and absorption in the small intestine. Foods rich in resistant starch possess a reportedly low glycemic index (GI). In the European Union (EU), foods containing 14% or more of resistant starch can be labeled as “reduction of postprandial glycemic responses.”²

In recent years, the development of resistant starch rice has been progressing for the improvement of postprandial hyperglycemia. A wx/ae rice was developed by crossing the amylose-free waxy (wx) mutant and amylose-extender (ae) mutant.³ The wx/ae rice lacks amylose and

is composed of long unit chains of amylopectin that are difficult to digest.^{4,5} Thus, the wx/ae rice possesses the characteristics of resistant starch. The Okinawa Institute of Science and Technology Graduate University (OIST) has further improved wx/ae rice and developed a new variety rich in resistant starch. We decided to call this new variety OIST rice (OR). Thus, it is reported that 38.5% of OR is composed of resistant starch (Supplementary Table 1). On the contrary, less than 1% of white rice (WR), and approximately 15% of wx/ae rice are composed of resistant starch. According to a meta-analysis,⁶ resistant starch has a triglyceride-lowering effect in

Corresponding Author: Dr Yuta Nakamura, Division of Metabolism and Endocrinology, Department of Internal Medicine, St. Marianna University School of Medicine, 2-16-1, Sugao, Miyamae-ku, Kawasaki, Kanagawa 216-8511, Japan.

Tel: +81-44-977-8111; Fax: +81 44 976 8516

Email: y3nakamura@marianna-u.ac.jp;
y.nakamura19850926@gmail.com

Manuscript received 07 September 2022. Initial review completed 01 December 2022. Revision accepted 10 February 2023. doi: 10.6133/apjcn.202303_32(1).0008

healthy participants (-0.10 [-0.19, -0.01] mmol/L, Mean Difference [95% confidence interval, CI]) and a weight loss effect in patients with type 2 diabetes (-1.29 [-2.40, -0.17] kg). However, the efficacy for fasting plasma glucose (-0.30 [-0.69, 0.10] mmol/L) or HbA1c (-0.27 [-0.57, 0.03] %) has not been demonstrated in patients with type 2 diabetes. On the other hand, most of the studies adopted in this meta-analysis used milled and processed high amylose starch, such as resistant starch. The use of rice grains for glycemic control is considered crucial since rice is consumed as a staple food; however, few studies exist on resistant starch in rice grains.⁷ Moreover, past studies may have demonstrated that the amount of resistant starch (10 to 30 g daily) was insufficient for the improvement of glycemic control. On the contrary, OR can be used as cooked grains in the form of granules. Thus, plasma glucose improvement can be expected owing to its high resistant starch content. Therefore, in the present study, we aimed to prove the efficacy of OR in improving the plasma glucose concentrations in patients with diabetes.

The purpose of this study was to compare the plasma glucose improving effect of OR with WR in patients with type 2 diabetes. Furthermore, to clarify the mechanism of the plasma glucose improving effect of OR, the component analysis of OR and dynamics of insulin and incretin following the ingestion of OR were evaluated.

METHODS

Study population

The study included 20 patients with type 2 diabetes admitted to the Diabetes Center at St. Marianna Medical University Hospital, Kawasaki, Japan, from April 2020 to March 2021. The inclusion criteria were as follows: 1) patients with insulin-independent type 2 diabetes mellitus, fasting serum C-peptide ≥ 0.6 ng/mL and glutamic acid decarboxylase (GAD) antibody negative; 2) patients with a fasting plasma glucose concentration of 54–300 mg/dL during the last 3 days; 3) male or female over the age of 20 at the time of obtaining informed consent; 4) patients who permitted the use of their urine and plasma test data; and 5) patients with written informed consent after receiving a full explanation. The exclusion criteria were as follows: 1) patients using any of the following diabetes treatments, such as dipeptidyl peptidase-4 (DPP4) inhibitor, glucagon-like peptide-1 (GLP-1) receptor agonist,

and α -glucosidase inhibitor; 2) patients who require more than 15 units of rapid-acting insulin in the morning; 3) patients with unstable oral intake, 4) females who were pregnant, possibly pregnant, or were breastfeeding; 5) those having their menstrual period during testing; 6) rice allergy or brown rice allergy; and 7) those considered unsuitable for inclusion in the study by the study investigators.

The study was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki and was approved by the ethics committee at St. Marianna University School of Medicine (Approval ID: 4632). All the patients provided written informed consent. This study was registered with the Japan Registry of Clinical Trials (jRCT) (registration number: jRCTs031200008).

Protocol

This was a single-center, open, randomized, crossover comparative study. Figure 1 illustrates the study protocol. After confirming each participant's eligibility, the participants were assigned to two groups, the OR-preceding group, and the WR-preceding group, by simple randomization. Breakfast on the first test day was considered test meal 1. The second test day was set 1–3 days following the first test day. The breakfast on the second test day was considered test meal 2. In the OR-preceding group, test meals 1 and 2 were OR and WR, respectively. In the WR-preceding group, test meals 1 and 2 were WR and OR, respectively.

Meal tolerance test

The test day started at 8:30 in the morning, and the test meal was consumed in 10 minutes. The test meal comprised only 150 g of cooked OR or 150 g of cooked WR. The OR was cooked by a person with the educational qualifications of a dietician and was not the research coordinator. The cooked OR weighed 150 g each and was stored frozen until the test day. Immediately before eating the test meal, it was thawed and warmed in a microwave oven and provided to the participants. WR was provided with 150 g of commercially available packed rice (SATO NO GOHAN®, Sato Foods Co., Niigata, Japan). Immediately before eating the test meal, it was warmed in a microwave oven and provided to the participants. The nutrition facts of the cooked test meal are shown in Table 1. The nutritional facts of OR and WR were analyzed by

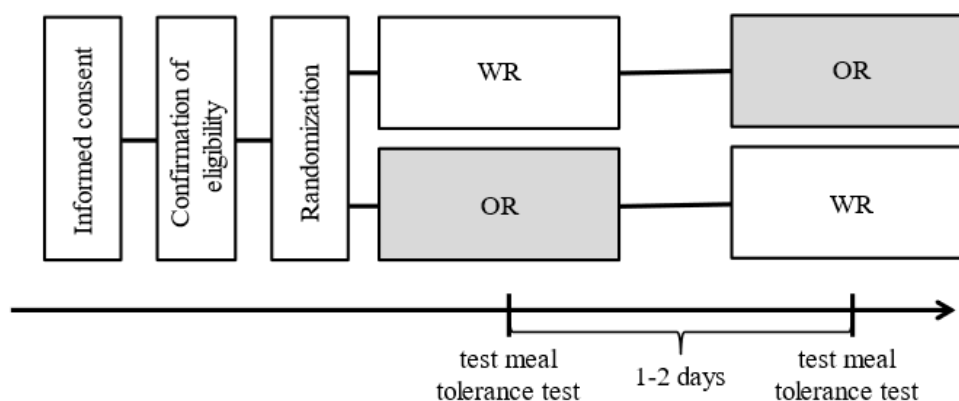


Figure 1. Study protocol. WR: white rice; OR: OIST rice.

the Japan Food Research Laboratory (Tokyo, Japan). Resistant starch was measured with a Resistant Starch Assay Kit (Megazyme, Wicklow, Ireland). Although the amount of energy and carbohydrates was nearly the same between the two types of rice, OR contained approximately 5 times more resistant starch than WR (4.7 g/100 g vs. 0.9 g/100 g).

All hypoglycemic agents on the morning of the test day were discontinued except for basal insulin. Blood was collected after 0, 30, 60, 120, and 240 minutes from the time of eating the test meal. Blood tests evaluated the plasma glucose, insulin, plasma C-peptide, total gastric inhibitory peptide (GIP), and total GLP-1. The sample was collected, centrifuged at 1400 g for 10 minutes, and the supernatant was used. Total GIP was measured by

enzyme-linked immunosorbent assay (ELISA) kits (# 27203, IBL Co. Ltd, Gunma, Japan), and total GLP-1 was measured by ELISA kits (YK 161, Yanaihara Institute Inc., Shizuoka, Japan) according to the manufacturer's instructions.

Food palatability questionnaire

We followed the previously reported method.⁸ A self-administered questionnaire was completed after the test to assess the palatability of OR and WR. The questionnaire comprised the following five items: taste (delicious or not), texture (rice cake-like or dry), consumability (can be eaten every day or not), habitual intake (possible to consume for one meal every day or not), and satiety (feeling of fullness or not). Each item was assigned a score, which

Table 1. Nutrition facts of test meal (per 100 g)

	OR	WR	Ratio OR/WR
Energy (kcal)	148	140	1.06
Water (g)	64.2	65.4	0.98
Carbohydrates (g)	30.0	32.3	0.93
Protein (g)	3.9	2.0	1.95
Fat (g)	1.4	0.3	4.67
Starch (g)	23.2	30.4	0.76
Resistant starch (g)	4.7	0.9	5.22
Dietary fiber			
Soluble dietary fiber (g)	<0.5	<0.5	—
Insoluble dietary fiber (g)	1.7	<0.5	—
Sodium (mg)	4.6	1.2	3.83
Phosphorus (mg)	102	20.6	4.95
Iron (mg)	0.38	not detected	—
Calcium (mg)	7.5	2.9	2.59
Potassium (mg)	109	9.2	11.85
Magnesium (mg)	40.1	2.4	16.71
Copper (mg)	0.15	0.06	2.50
Zinc (mg)	1.40	0.38	3.68
Manganese (mg)	1.13	0.18	6.28
Selenium (mg)	not detected	not detected	—
Thiamine (mg)	0.10	not detected	—
Riboflavin (mg)	0.02	not detected	—
Vitamin B6 (mg)	0.118	0.007	16.86
Vitamin E (mg)	0.3	not detected	—
Folic acid (µg)	3	2	1.50
Amino acid			
Arginine	321	180	1.78
Lysine	173	75	2.31
Histidine	100	53	1.89
Phenylalanine	197	112	1.76
Tyrosine	156	96	1.63
Leucine	309	172	1.80
Isoleucine	156	83	1.88
Methionine	92	51	1.80
Valine	232	123	1.89
Alanine	236	117	2.02
Glycine	194	97	2.00
Proline	182	99	1.84
Glutamic acid	595	363	1.64
Serine	196	108	1.81
Threonine	147	74	1.99
Aspartic acid	366	192	1.91
Tryptophan	57	29	1.97
Cystine	84	46	1.83
Free γ-aminobutyric acid	7	not detected	—
Oryzanol	8.4	not detected	—
Total ferulic acid	20	4.9	4.08
Polyphenol	0.04	not detected	—

WR: white rice; OR: OIST rice.

could range from the most positive response (+3 points) to the most negative response (-3 points).

Outcome

The primary outcome of this study was the difference in the area under the curve (AUC) of plasma glucose (0–240 min) during the meal tolerance test. Secondary outcomes included the difference in the AUC of insulin, plasma C-peptide, total GIP, and total GLP-1. In addition, the differences in the incremental AUC (iAUC) of plasma glucose, insulin, plasma C-peptide, total GIP, and total GLP-1 were considered the secondary outcomes. Moreover, the food palatability questionnaire was evaluated as the secondary outcome.

Statistical analysis

The results are expressed as mean \pm standard deviation (SD) or median (interquartile range [IQR]). Treatment effects were analyzed with an analysis of variance model adjusted for the timing effects and baseline values. Analyses were performed with R version 3.4 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $p < 0.05$.

RESULTS

Table 2 shows the baseline characteristics of the participants. Three of the 20 participants were unable to complete the test meal; thus, 17 participants were included in the main analysis (Figure 2). The median age of the participants was 70.0 [59.0–73.0] years, 10 participants were males (58.8%), and the median disease duration was 1.0 [0.1–5.0] years. The mean body mass index (BMI) was 25.9 ± 3.1 kg/m². The mean plasma glucose was 193.0 ± 66.5 mg/dL, and the mean HbA1c was 11.5 ± 3.0 %.

Figure 3 shows the time course and AUC of plasma glucose, insulin, plasma C-peptide, total GIP, and total GLP-1. Considering the plasma glucose, no difference was observed between the OR and WR for up to 60 minutes. However, after eating OR, the plasma glucose concentration peaked at 60 minutes, while WR peaked at 120 minutes. The plasma glucose concentration after eating OR was significantly lower at 120 minutes than after eating WR. Considering the insulin and plasma C-peptide, there was no difference between the OR and WR for up to 60 minutes. The insulin concentration after eating OR was significantly lower at 120 minutes than after eating WR. The plasma C-peptide concentration was significantly lower at 240 minutes than after eating WR.

Table 3 shows the difference in the AUC and iAUC for each evaluation item. The difference in the total AUC of plasma glucose, which is the primary endpoint of this study, was -8223 (95% CI: -10100 to -6346 , $p < 0.001$) mg·min/dL. The difference in iAUC of plasma glucose was -8162 (95% CI: -9985 to -6340 , $p < 0.001$) mg·min/dL. Therefore, the postprandial plasma glucose was significantly lower when OR was ingested than when WR was ingested. The difference in the total AUC of insulin and

Table 2. Characteristics of the participants (mean \pm SD, median [IQR])

	Participants
Number	17
Gender	
Male	10
Female	7
Type of diabetes	
Type 1	0
Type 2	17
Other	0
Age (years)	70.0 [59.0-73.0]
Weight (kg)	69.7 \pm 12.6
BMI (kg/m ²)	25.9 \pm 3.1
Disease duration (years)	1.0 [0.1-5.0]
Neuropathy (+/-)	4 / 13
Retinopathy (+/-)	0 / 17
Nephropathy	
Stage 1	14
Stage 2	3
Stage 3	0
Stage 4	0
Stage 5	0
HbA1c (%)	11.5 \pm 3.0
GA (%)	29.1 \pm 9.1
PG (mg/dL)	193.0 \pm 66.5
Cre (mg/dL)	0.78 \pm 0.15
F-CPR (ng/mL)	1.9 \pm 0.6
Urine albumin (mg/day)	9.4 [5.6-19.4]
Other antidiabetic drugs	
insulin	16
metformin	11
SGLT2-I	1

BMI: body mass index; HbA1c: hemoglobin A1c; PG: plasma glucose; Cre: serum creatinine; F-CPR: fasting serum C-peptide immunoreactivity; SGLT2-I: sodium glucose co-transport inhibitor.

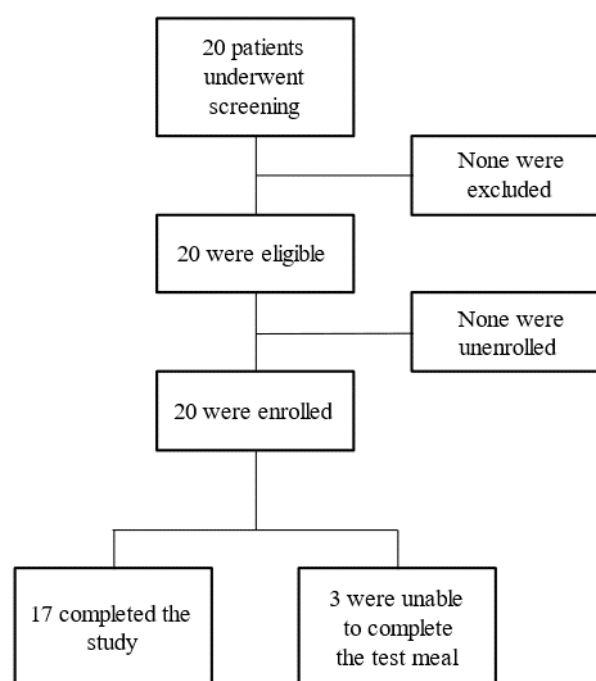


Figure 2. Flow chart of participants.

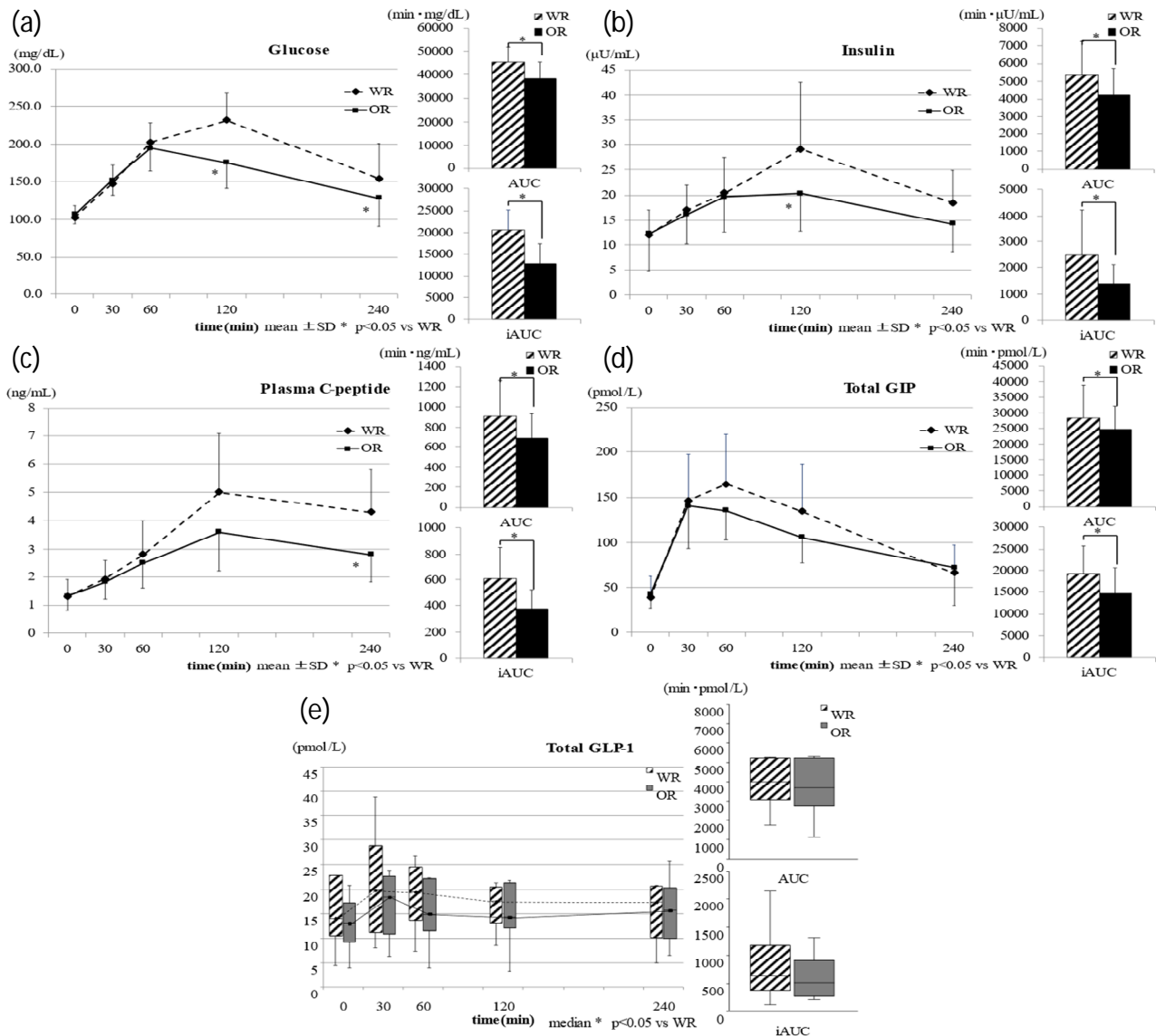


Figure 3. Result of the meal tolerance test. (a) glucose, (b) insulin, (c) plasma C-peptide, (d) total GIP, (e) total GLP-1. The line graph shows the time course of each parameter. The bar graph shows the area under the curve (AUC) for each parameter. The dashed and solid lines show white rice (WR) and OIST rice (OR), respectively. The diagonal stripes and the black bar show WR and OR, respectively. Since total GLP-1 was not normally distributed, it shows median (IQR) (e). iAUC; incremental AUC.

plasma C-peptide was -1139 (95% CI: -1839 to -438 , $p=0.004$) $\mu\text{U}\cdot\text{min}/\text{mL}$, and -225 (95% CI: -316 to -133 , $p<0.001$) $\text{ng}\cdot\text{min}/\text{mL}$, respectively; the difference in the iAUC of insulin and plasma C-peptide was -1068 (95% CI: -1770 to -365 , $p=0.006$) $\mu\text{U}\cdot\text{min}/\text{mL}$ and -225 (95% CI: -316 to -134 , $p<0.001$) $\text{ng}\cdot\text{min}/\text{mL}$, respectively. Therefore, insulin secretion was significantly lower when OR was ingested than when WR was ingested. The difference in the total AUC of total GIP was -4886 (95% CI: -8456 to -1317 , $p=0.011$) $\text{pmol}\cdot\text{min}/\text{L}$, and the difference in iAUC was -4877 (95% CI: -8438 to -1316 , $p=0.011$) $\text{pmol}\cdot\text{min}/\text{L}$. The difference in the total AUC of the total GLP-1 was -171 (95% CI: -1034 to 691 , $p=0.673$) $\text{pmol}\cdot\text{min}/\text{L}$, and the difference in iAUC was 143 (95% CI: -265 to 550 , $p=0.461$) $\text{pmol}\cdot\text{min}/\text{L}$. The total GIP was significantly lower when OR was ingested; however, the difference in total GLP-1 did not reach statistical significance.

Figure 4 shows the results of the food palatability questionnaire. Compared to WR, OR was rated lower in taste,

texture, consumability, and habitual intake. No adverse events were observed during the study period. In particular, no gastrointestinal side effects such as nausea, vomiting, abdominal bloating, or diarrhea were observed after ingesting OR.

DISCUSSION

In patients with type 2 diabetes, the rise of plasma glucose following single ingestion of OR was significantly lower than that following ingestion of WR. In addition, the rise of insulin, plasma C-peptide, and total GIP were also significantly lower with OR. These indicate that OR results in postprandial plasma glucose improvement independent of insulin.

A meta-analysis published in 2019 revealed that resistant starch improved fasting plasma glucose (-0.26 [-0.5 , -0.02] mmol/L) and HbA1c (-0.43 [-0.74 , -0.13] %) in patients with type 2 diabetes.⁹ On the other hand, a similar meta-analysis published in the same year showed no effect on the fasting plasma glucose (-0.03 [-0.11 ,

Table 3. Results of group differences (OR vs WR)

	OR	WR	Group differences	95% Confidence interval		p value
				Lower limit	Upper limit	
Plasma glucose						
AUC (min·mg/dL)	38329±6944	45147±6803	-8223	-10100	-6346	<0.001
iAUC (min·mg/dL)	12910±4592	20654±4423	-8162	-9985	-6340	<0.001
Insulin						
AUC (min·μU/mL)	4230±1511	5328±1913	-1139	-1839	-438	0.004
iAUC (min·μU/mL)	1376±741	2472±1749	-1068	-1770	-365	0.006
Plasma C-peptide						
AUC (min·ng/mL)	686±247	913±352	-225	-316	-133	<0.001
iAUC (min·ng/mL)	380±140	607±242	-225	-316	-134	<0.001
Total GIP						
AUC (min·pmol/L)	24779±7497	28374±10361	-4886	-8456	-1317	0.011
iAUC (min·pmol/L)	14725±5841	19205±6529	-4877	-8437	-1316	0.011
Total GLP-1 [†]						
AUC (min·pmol/L)	3694 [2890-4890]	3970 [3258-5192]	-171	-1034	691	0.673
iAUC (min·pmol/L)	505 [301-845]	608 [376-1020]	142	-265	550	0.461

OR: OIST rice; WR: white rice; AUC: area under the curve; iAUC: incremental AUC; GIP: gastric inhibitory peptide; GLP-1: glucagon-like peptide-1.

[†]Median (IQR).

0.05] mmol/L) or HbA1c (-0.27 [-0.57, 0.03] %) levels in patients with type 2 diabetes.⁶ These results indicate that the effect of resistant starch on plasma glucose is controversial. We propose the following reasons for their inconsistency. First, the use of processed foods contain milled grains with resistant starch instead of cooked grain. Second, the included participants were often obese. Finally, the amount of resistant starch was probably inadequate. In this study, OR containing resistant starch (4.7 g/100 g) was employed to improve the postprandial plasma glucose concentrations in patients with type 2 diabetes, who had an average BMI of 25 kg/m². In addition, this study demonstrated that OR suppressed the increase in insulin and incretin following meals. α -glucosidase inhibitors (α GI) are one of the oral hypoglycemic agents. α GI inhibits the action of α -glucosidase, an enzyme that hydrolyzes α -glycosidic bonds, and suppresses postprandial hyperglycemia by delaying glucose absorption. The effect of α GI is considered to be similar to that of resistant starch. It has been demonstrated that α GI suppresses GIP and increases GLP-1.¹⁰ GIP-secreting cells (K cells) are present in the upper small intestine, and GLP-1-secreting cells (L cells) are present in the lower small intestine.¹¹ Upon delaying the absorption of carbohydrates using α GI, the stimulation of incretin secretion from the upper small intestine was reportedly suppressed, and the stimulation of incretin secretion from the lower small intestine was enhanced.¹⁰ This was not consistent with the effect of α GI and the obtained result that GIP was suppressed, but GLP-1 was not elevated in this study. OR could have escaped absorption not only from the upper small intestine but also from the lower small intestine. In addition, it has been reported that GIP secretion response to 15 g oral glucose tolerance test (OGTT) was comparatively lower than 75 g OGTT, however, no significant difference was observed in GLP-1 secretion.¹² Based on the findings of this study, it can be considered that the amount of GIP secreted depends on the amount of absorbed nutrients. However, the relationship between GLP-1 secretion and absorbed nutrients is unclear. On the other hand, in the medium to long term, resistant starch has been shown to

act as prebiotics. Ingested resistant starch is fermented by gastrointestinal microbiota. Since gastrointestinal microbiota produces short-chain fatty acids (SCFAs), there is an increase in SCFAs.^{13,14} SCFAs are also associated with elevated GLP-1.¹⁵ GLP-1 could increase in long-term OR consumption. Therefore, a long-term study should be conducted in the future.

In this study, we analyzed the nutritional components of OR and WR after cooking rice. The proportion of resistant starch in OR before cooking the rice was reportedly 38.5% (Supplementary table 1); however, after cooking rice it was 4.7 g/100 g. In cooked WR, the resistant starch was 0.9 g/100 g. The resistant starch of OR was approximately 5 times that of WR. Even after considering water to occupy nearly 65 g/100 g, the resistant starch of OR was only 13% of the components with the exception of water. In the EU, a health claim can be presented if resistant starch is 14% or more. In this study, OR did not meet the criteria of the health claim; however, it demonstrated a statistically significant plasma glucose improvement effect. A study investigating the resistant starch content and glycemic index of various rice *in vitro* reported that the resistant starch content was 0.35–2.57% and the glycemic index was 60–70.¹ Thus, resistant starch of approximately 2% may lower the glycemic index by nearly 10. On the other hand, it is generally reported that the higher the amylose content, the higher the proportion of resistant starch.¹ OR possesses the characteristics of resistant starch by extending the side chain of amylopectin. Such a difference in the starch structure could possibly improve plasma glucose control. On the other hand, several studies claimed that resistant starch increased due to low-temperature storage¹⁶ or microwave.¹⁷ In order to increase the feasibility of the study, the OR after cooking was frozen and reheated with microwave before the test. In this study, the effects of freezing and microwave have not been investigated. In the future, it is necessary to investigate how OR improves plasma glucose.

Since the rice grains of OR are easily broken, 30% of the rice is polished. Thus, the OR contains some bran.

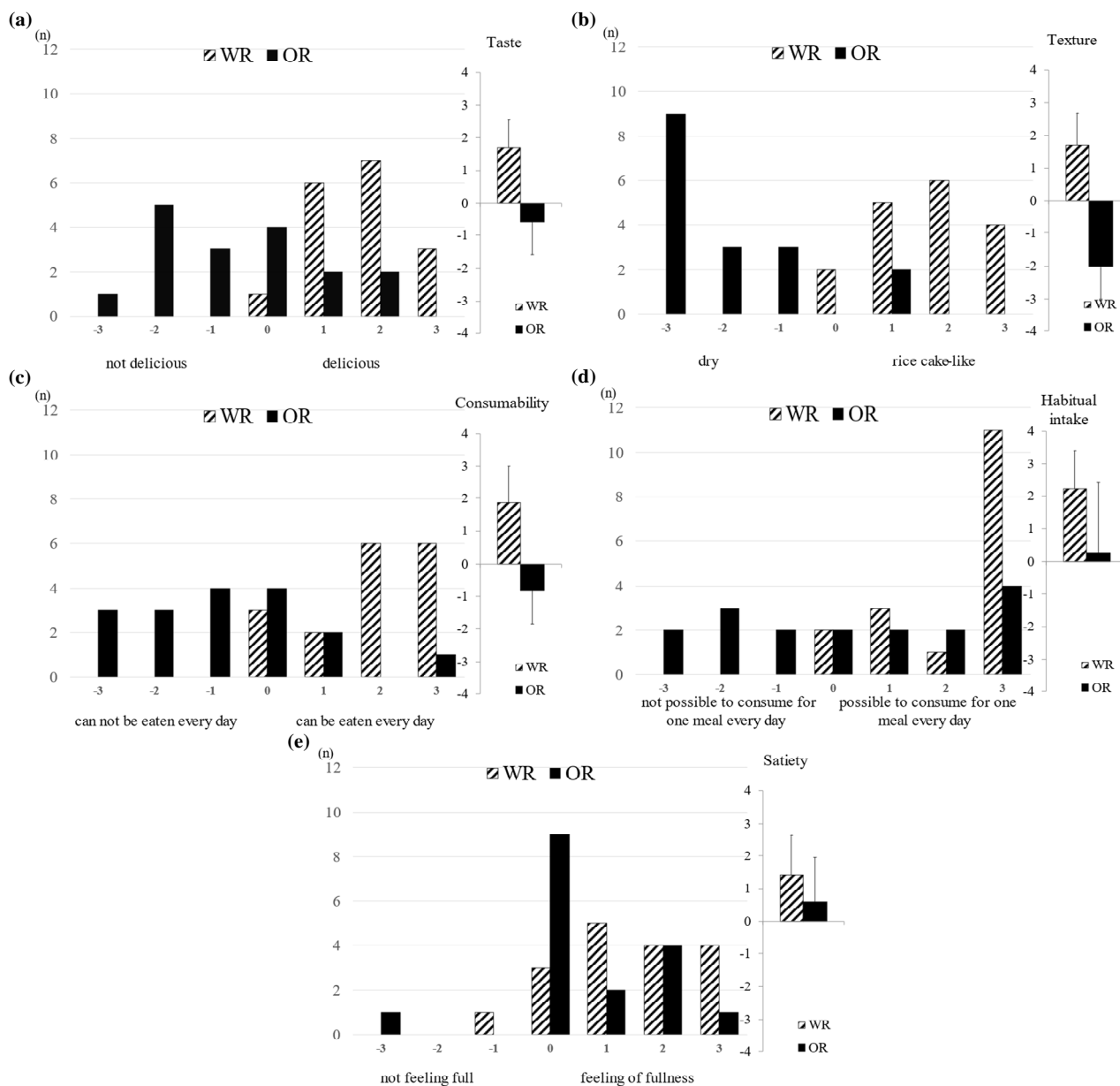


Figure 4. Result of the food palatability questionnaire. (a) taste, (b) texture, (c) consumability, (d) habitual intake, (e) satiety. The diagonal stripes and the black bar show white rice (WR) and OIST rice (OR), respectively. The figure on the left shows the histogram. The figure on the right shows the total score as mean \pm SD

Therefore, OR contains γ -oryzanol, various amino acids, and trace elements. In particular, potassium and magnesium reportedly possess insulin secretion promotion and insulin resistance improvement effects.¹⁸ Since potassium and magnesium are in greater quantity in OR than in WR, it is necessary to consider their possible role in plasma glucose control. However, considering the results of our previous study on the glycemic levels between WR, brown rice, and glutinous brown rice for one day, no significant difference was found in the glycemic levels between WR and brown rice.⁸ Therefore, nutrients contained in the bran possibly do not directly improve glycemic control. Thus, it is necessary to further investigate the cause for the plasma glucose improvement observed in this study.

In the past studies, high amylose starch was milled and processed (bread, muffins, cookies, and so forth) as resistant starch.¹⁹ On the other hand, few studies exist on

resistant starch using rice.⁷ Flour, such as wheat flour, can be processed into various dishes. If rice can be consumed as grains and not milled, the variety of meal menus would increase. In the Asian population, rice grain is consumed as a staple food, which is an indispensable ingredient. Since eating habits differ based on one's tastes, attention should be paid to one's preferences during diet therapy supervision.²⁰ Grain consumption could open up the possibility of considering the tastes of people who eat rice as their staple food.

On the other hand, according to the food preference questionnaire of this study, OR was inferior to WR in taste and consumability. In the future, it is necessary to establish a cooking method to compensate for these weaknesses. Specifically, we should investigate whether consumption of OR can be made easier by combining OR and WR without compromising on the effectiveness of glycemic control of OR. In addition, we should consider

developing a menu and including dishes such as soups, which would make consumption of OR easier.

This study has several limitations. First, the test meal was only rice. When eating meals, it is common to eat not only rice but also side dishes and soup at the same time. Second, the test meal was consumed only once. Finally, the number of participants was small, and all the participants were hospitalized at a single center. In the future, it is necessary to examine the effect of OR in improving long-term glycemic control in the real world.

In conclusion, OR, which is a type of rice rich in resistant starch, significantly reduced postprandial plasma glucose concentrations compared to WR in patients with type 2 diabetes. In addition, insulin, plasma C-peptide, and total GIP were significantly reduced during OR ingestion compared to WR ingestion. Therefore, for patients with type 2 diabetes, OR ingestion improved the plasma glucose independent of insulin secretion compared to the effects of WR.

ACKNOWLEDGEMENTS

The authors would like to thank Chisa Fujikura for her cooking support, Yuko Yasuda and Ritsuko Oikawa for their expert assistance, and the Clinical Research Data Center at St. Marianna University School of Medicine for their data management.

AUTHOR DISCLOSURES

None of the authors have any conflicts of interest associated with this study.

This work was funded by the Nichirei corporation, Okinawa Institute of Science and Technology Graduate University, JSPS KAKENHI (grant number JP20K19722), and Rice Stable Supply Support Organization (Public Interest Incorporated Association), Tokyo, Japan. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript.

REFERENCES

- Pereira C, Lourenço VM, Menezes R, Brites C. Rice compounds with impact on diabetes control. *Foods*. 2021; 10:1992. doi: 10.3390/foods10091992.
- EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). Scientific opinion on the substantiation of health claims related to resistant starch and reduction of postprandial glycaemic responses (ID681), “digestive health benefits” (ID 682) and “favours a normal colon metabolism” (ID 783) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. *EFSA J*. 2011;9:2024. doi: 10.2903/j.efsa.2011.2024.
- Kubo A, Yuguchi Y, Takemasa M, Suzuki S, Satoh H, Kitamura S. The use of micro-beam x-ray diffraction for the characterization of starch crystal structure in rice mutant kernels of waxy, amylose extender, and sugary1. *J Cereal Sci*. 2008;48:92-7. doi: 10.1016/j.jcs.2007.08.005.
- Kubo A, Akdogan G, Nakaya M, Shojo A, Suzuki S, Satoh H, Kitamura S. Structure, physical, and digestive properties of starch from wx ae double-mutant rice. *J Agric Food Chem*. 2010;58:4463-9. doi: 10.1021/jf904074k.
- Matsumoto K, Maekawa M, Nakaya M, Takemitsu H, Satoh H, Kitamura S. Wx/ae double-mutant brown rice prevents the rise in plasma lipid and glucose levels in mice. *Biosci Biotechnol Biochem*. 2012;76:2112-7. doi: 10.1271/bbb.120501.
- Snelson M, Jong J, Manolas D, Kok S, Louise A, Stern R, Kellow NJ. Metabolic effects of resistant starch type 2: A systematic literature review and meta-analysis of randomized controlled trials. *Nutrients*. 2019;11:1833. doi: 10.3390/nu11081833.
- Kwak JH, Paik JK, Kim HI, Kim OY, Shin DY, Kim HJ, Lee JH, Lee JH. Dietary treatment with rice containing resistant starch improves markers of endothelial function with reduction of postprandial blood glucose and oxidative stress in patients with prediabetes or newly diagnosed type 2 diabetes. *Atherosclerosis*. 2012;224:457-64. doi: 10.1016/j.atherosclerosis.2012.08.003.
- Terashima Y, Nagai Y, Kato H, Ohta A, Tanaka Y. Eating glutinous brown rice for one day improves glycemic control in Japanese patients with type 2 diabetes assessed by continuous glucose monitoring. *Asia Pac J Clin Nutr*. 2017; 26:421-6. doi: 10.6133/apjcn.042016.07.
- Wang Y, Chen J, Song YH, Zhao R, Xia L, Chen Y et al. Effects of the resistant starch on glucose, insulin, insulin resistance, and lipid parameters in overweight or obese adults: A systematic review and meta-analysis. *Nutr Diabetes*. 2019;9:19. doi: 10.1038/s41387-019-0086-9.
- Enç FY, Imeryüz N, Akin L, Turoğlu T, Dede F, Haklar G et al. Inhibition of gastric emptying by acarbose is correlated with GLP-1 response and accompanied by CCK release. *Am J Physiol Gastrointest Liver Physiol*. 2001;281:G752-63. doi: 10.1152/ajpgi.2001.281.3.G752.
- Seino Y, Yamazaki Y. Roles of glucose-dependent insulinotropic polypeptide in diet-induced obesity. *J Diabetes Investig*. 2022;13:1122-8. doi: 10.1111/jdi.13816.
- Yamane S, Harada N, Hamasaki A, Muraoka A, Joo E, Suzuki K et al. Effects of glucose and meal ingestion on incretin secretion in Japanese subjects with normal glucose tolerance. *J Diabetes Investig*. 2012;3:80-5. doi: 10.1111/j.2040-1124.2011.00143.x.
- Nilsson AC, Ostman EM, Granfeldt Y, Björck IME. Effect of cereal test breakfasts differing in glycemic index and content of indigestible carbohydrates on daylong glucose tolerance in healthy subjects. *Am J Clin Nutr*. 2008;87:645-54. doi: 10.1093/ajcn/87.3.645.
- Włodarczyk M, Śliżewska K. Efficiency of resistant starch and dextrins as prebiotics: a review of the existing evidence and clinical trials. *Nutrients*. 2021;13:3808. doi: 10.3390/nu13113808.
- Byrne CS, Chambers ES, Morrison DJ, Frost G. The role of short chain fatty acids in appetite regulation and energy homeostasis. *Int J Obes (Lond)*. 2015;39:1331-8. doi: 10.1038/ijo.2015.84.
- Li H, Liu B, Bess K, Wang Z, Liang M, Zhang Y, Wu Q, Yang L. Impact of low-temperature storage on the microstructure, digestibility, and absorption capacity of cooked rice. *Foods*. 2022;11:1642. doi: 10.3390/foods11111642.
- Cheng Z, Li J, Qiao D, Wang L, Zhao S, Zhang B. Microwave reheating enriches resistant starch in cold-chain cooked rice: A view of structural alterations during digestion. *Int J Biol Macromol*. 2022;208:80-7. doi: 10.1016/j.ijbiomac.2022.03.034.
- Fardet A. New hypotheses for the health-protective mechanisms of whole-grain cereals: what is Beyond fibre? *Nutr Res Rev*. 2010;23:65-134. doi: 10.1017/S0954422410000041.
- Bergeron N, Williams PT, Lamendella R, Faghiniha N, Grube A, Li X et al. Diets high in resistant starch increase plasma levels of trimethylamine-N-oxide, a gut microbiome metabolite associated with CVD risk. *Br J Nutr*. 2016;116:2020-9. doi: 10.1017/S0007114516004165.
- Powers MA, Bardsley JK, Cypress M, Funnell MM, Harms D, Hess-Fischl A et al. Diabetes self-management education

and support in adults with type 2 diabetes: A consensus report of the American Diabetes Association, the Association of Diabetes Care & Education Specialists, the Academy of Nutrition and Dietetics, the American Academy

of Family Physicians, the American Academy of PAs, the American Association of Nurse Practitioners, and the American Pharmacists Association. *Diabetes Care.* 2020;43:1636-49. doi: 10.2337/dci20-0023.

Supplementary table 1. Nutrition facts of test meal (uncooked)

	OIST rice	Brown rice
Energy (kcal/100g)	352	389
Water (%)	4.8	5.0
Carbohydrates (%)	76.4	77.4
Protein (%)	11.0	7.3
Fat (%)	5.9	4.7
Digestible starch (%)	-	77.4
Resistant starch (%)	38.5	<1.0
Dietary fiber (%)	25.5	3.7

It is reported that 38.5% of OR is composed of resistant starch. On the contrary, less than 1% of white rice (WR) is composed of resistant starch.