Glycative Stress Research

Online edition : ISSN 2188-3610
Print edition : ISSN 2188-3602
Received : March 19, 2017
Accepted : May 30, 2017
Published online : June 30, 2017

Original article

A study for evaluating the effect of the intake of meal containing Salacia extract on postprandial hyperglycemia.

Nobuko Kajiwara [1], Ken-ichi Onodera [1], Tomoko Tsuji [1], Yoshikazu Yonei [2]

1) Yoshinoya Holdings Co., LTD, Merchandising Division, Tokyo, Japan
2) Anti-Aging Medical Research Center / Glycative Stress Research Center, Faculty of Life and Medical Sciences, Doshisha University, Kyoto, Japan

Abstract

Purpose: *Salacia* extract is reported to show an inhibitory effect on postprandial blood glucose (PBG) level. In this study, the effects of a single intake of *gyudon** topping containing *salacia* extract on PBG and serum insulin level in borderline diabetics and those with normal-high fasting blood glucose level were evaluated by a double-blinded crossover comparison test between two groups.
Gyudon*: a bowl of steamed rice topped with beef and onion cooked in soy sauce based *tare*-sauce
Method: The subjects were 32 (25 males and 7 females and aged 45.4 ± 10.1). They were divided randomly into two groups, a group who took the control food in the first time and the test food in the second time and the other group who took the test food in the first time and the control food in the second time. A double-blinded crossover comparison test was conducted following the food intake. The test food was the *gyudon* toppings supplemented with *salacia* extract (0.5 mg as salacinol), and the control food was the *gyudon* toppings without *salacia* extract. Steamed white rice was taken as glucose-load food with the *gyudon* topping in both groups.
Results: The maximum blood glucose level (Cmax) after the intake of the test meal and the control meal was 149.7 ± 25.2 mg/dL in the test group and 155.4 ± 27.5 mg/dL in the control group; the Cmax of the test group was significantly lower ($p < 0.01$). The blood glucose area under the curve (AUC) of the test group was 248.6 ± 48.9 mg*h/dL compared to the control group which was 257.9 ± 53.9 mg*h/dL; the AUC of the test group was significantly smaller ($p = 0.035$). The serum insulin AUC of the test group was 81.3 ± 50.6 µIU*h /mL and that of the control group was 93.4 ± 62.2 µIU*h /mL; the insulin AUC of the test group was significantly smaller ($p < 0.01$).
Conclusion: The results of this study proved the inhibitory effects of the test food, *gyudon* toppings supplemented with *salacia* extract (0.5 mg as salacinol), on the PBG level and serum insulin level. It was suggested that the test food is possibly useful for borderline diabetics and those with normal-high fasting blood glucose level.

KEY WORDS: postprandial blood glucose level, postprandial insulin level, insulin resistance, salacia and salacinol

Introduction

The number of patients with diabetes is rapidly increasing in association with the changes in lifestyle habits and social environments. According to the 2015 Japanese National Health and Nutrition Survey, the number of people, males in particular, who were strongly suspicious of having diabetes was increasing (19.5%), the highest since 2006. After the onset of diabetes, the cure is often difficult. Furthermore, as it progresses, it leads to complications including retinopathy, nephropathy and nerve disorder, as well as potentially causing blindness. Blood dialysis may often become necessary in the late stages of the disease. The cost of medical care for these patients is ever increasing in Japan and is putting pressure on the government budgets. In light of these circumstances, early stage prevention of diabetes is strongly desired.

In many cases, pre-diabetes occurs through the stage where metabolic syndrome was diagnosed. Metabolic syndrome is called “visceral fat syndrome.” Fat accumulates around intestines or in the abdominal cavity, and mild degrees of hypertension, high blood glucose and dyslipidemia are observed. The accumulated visceral fat tissue secretes various adipocytokines and they cause and contribute to metabolic abnormalities. For example, the tumor necrosis factor-α (TNF-α) secreted from enlarged adipocytes induces insulin resistance and the clearance of blood glucose by insulin becomes insufficient, and therefore postprandial high

Contact Address: Nobuko Kajiwara
Yoshinoya Holdings Co.,LTD, Merchandising Division
Daiwa Rivergate 18F, 36-2 Nihonbashi Hakozaki-cho, Chuo-ku, Tokyo 103-0015, Japan
TEL: +81-3-5651-8779 FAX: +81-3-5651-8778 Email: n.kajiwara@ysn.yoshinoya.com
Co-authors: Onodera K, k.onodera@ysn.yoshinoya.com ;
Tsuji T, t.tsuji@ysn.yoshinoya.com ; Yonei Y, yyonei@mail.doshisha.ac.jp

blood glucose levels continue. Compared to Westerners, insulin secretion levels in Japanese are lower [1]. In addition, recently, the number of people with "visceral fat syndrome" has been increasing due to westernized dietary and lifestyle habits, thus, the number of people with type 2 diabetes accompanied by insulin resistance has increased and the increase of patients is becoming a serious problem.

As a countermeasure against type 2 diabetes accounting for a large portion of Japanese patients with diabetes, the control of PBG is important, in addition to obesity prevention and moderate exercise. Beside the use of medicines, functional food having an inhibitory effect on the PBG rise may be useful for the PBG control.

Yonei *et al*. reported that the PBG rise was significantly inhibited when steamed white rice was taken together with the *gyudon* toppings, compared to the intake of steamed white rice only [2]. In this study, a new functional food was developed, in which the effect of inhibiting PBG rise was enhanced by addition of the extract from *salacia* plants (hereafter referred as to "*salacia* extract") as a functional ingredient, which is said to have an effect of inhibiting PBG rise. The effects of a single intake of the above new functional food on PBG level and serum insulin level were evaluated.

Subjects and Method

Subjects

The test plan was designed based upon the Declaration of Helsinki and approved by Ageo Kousei Hospital Ethics Review Committee (UMIN Registration No. UMIN000022283). The subjects were 32 individuals between 20 and 65 years of age, (25 males and 7 females aged 45.4 ± 10.1), whose fasting blood glucose levels were 100 mg/dL – 125 mg/dL, whose normal alcohol intake was less than 20 g a day, who were not attending a hospital or being treated with medication for the purpose of medical treatment, who were not undergoing dietary restriction and who were not suffering from a serious hepatic disorder, kidney disorder, cardiac disorder, cerebrovascular disease, organ damage or allergy disease, and those who were pregnant or possibly pregnant, those who were breastfeeding and whom the doctor supervising the test judged inappropriate, were excluded.

The subjects were fully informed of the contents and methods of this test, and the informed consents in writing were exchanged between researchers and subjects.

Foods for experiment

The hot-water extract from the stems of *salacia reticulata* was used as *salacia* extract. The test food was the *gyudon* toppings, which were prepared by the following process: *Salacia* extract was dissolved in 1.7% potassium chloride solution, mixed with *tare*- sauce, and onion and beef were added to it and heated. The amount of the *salacia* extract is adjusted so that 0.5 mg of salacinol is contained in each meal. The *gyudon* toppings for the control food were prepared in the same way, excluding the addition of *salacia* extract. Both the test food and the control food can be stored stably at a temperature lower than -18 °C. At the time of the test, they were heated in a prescribed way and prepared. Packed aseptic steamed rice (Maruchan Attakagohan, 250 g, Toyo Suisan Kaisha, Ltd., Tokyo, Japan) was used as the glucose-load food. The subjects ingested a meal, a bowl of steamed rice with the toppings of the test food or the control food.

Table 1 and ***2*** show the material compositions and nutrient components of each food for the experiment (test food, control food and glucose-load food).

Study Design

Subjects were randomly assigned to one of two groups, the first group which took the control food in the first time and the test food in the second time and the second group which took the test food first and the control food second, and a double-blinded crossover test was conducted. The interval between the first intake and second intake was a week. The subjects visited the hospital by 21:00 the day before the test and took a prescribed diet, and after that, abstained from any food or beverage except water. After the blood samples were collected the next morning, the subjects ingested the meal for the experiment with mineral water (280 mL). In order to fix the speed of the ingestion of the meal, they were instructed to chew each bite of food 20 times. All subjects consumed all of their meal in about 8 min. Blood samples were collected from the participants at 30, 45, 60, 90 and 120 min after the start of the ingestion of the meal, and the levels of blood glucose and serum insulin were measured. The area under the curve (AUC) from at 0 to 2 hours was

Table 1. Food consumption in test meal.

Food items		Placebo	Salacia
Beef rib	g	65	65
Onion	g	30	30
Sauce	g	40	20
Salacia extract	g	–	20

Table 2. Food nutrients in test meal.

		Placebo	Salacia	Rice
Energy	kcal	320	254	358
Protein	g	12.4	13.8	5.3
Lipid	g	26.7	18.8	1.0
Carbohydrate	g	7.4	7.3	81.9
Sodium	mg	936	763	0-20

calculated using the trapezoidal rule. A physical examination, blood test, urine test and medical interview were conducted before and at 120 min after the ingestion of the meal and the safety of the test was confirmed.

Statistical analysis

All data of all participants in the study were analyzed and the data were shown as an average ± standard deviation. The actual value of blood glucose and serum insulin at each sampling time was comparatively tested by a paired t-test. The increments in blood glucose and serum insulin levels from 0 to each sampling time were also calculated and analyzed. Besides those analyses of all subjects' data, differential analysis was performed, based on the value of HOMA-R (homeostasis model assessment insulin resistances). The effects of *salacia* extract were analyzed in two groups, a high HOMA-R group (≧ 1.73) and a low HOMA-R group (< 1.73), respectively. SPSS StatisticsVer 22.0 (IBM Japan Ltd., Tokyo, Japan) was used. The risk rate of less than 5% by a two-sided test was regarded as a significant difference.

Results

All subjects accomplished the test, and all of them were subjected to statistical analysis. The classification of the subjects is shown in ***Table 3.***

Influence on blood glucose level

The changes in blood glucose levels over time when the test or the control food was ingested with the glucose-load food are shown in ***Fig. 1***, and AUC and the maximum blood glucose level (Cmax) are shown in ***Table 4***.

As the analysis targeted all subjects, Cmax was 155.4 ± 27.5 mg/dL in the control group and was 149.7 ± 25.2 mg/dL in the test group, which shows that Cmax of the test group was significantly suppressed ($p < 0.01$). The blood glucose levels of the test group (106.3 ± 23.3 mg/dL) at 120 min after the intake was significantly lower than that of the control group (114.1 ± 30.3 mg/dL, $p < 0.05$). As for the increments at each sampling point from the start of intake, the blood glucose level at 60 min after the intake was 33.8 ± 37.0 mg/dL in the control group and 24.8 ± 37.5 mg/dL in the test group, respectively. Those of the control group and the test group at 120 min were 11.0 ± 27.1 mg/dL and 2.3 ± 23.8 mg/dL, respectively. As the results, the increments of the blood glucose level in the test group were significantly lower than in the control group at both 60 and 120 min after the intake ($p = 0.03$, $p = 0.01$).

The AUC obtained from these over-time-curves was 248.6 ± 48.9 mg*h/dL in the test group and 257.9 ± 53.9 mg*h/dL in the control group, which shows that the AUC of the test group was significantly smaller ($p = 0.035$).

Then, a similar analysis was conducted for the subjects (n = 25) whose HOMA-R, one of the index of insulin resistance, was ≧ 1.73. As for the blood glucose levels change over time, the blood glucose levels of the test group at 60 and 120 min after intake were 126.7 ± 42.4 mg/dL and 103.0 ± 18.9 mg/dL, respectively and both were significantly lower than those of the control group (138.7 ± 41.5 mg/dL and 113.2 ± 30.6 mg/dL, respectively, $p < 0.01$, $p < 0.01$). AUC of the test group (245.9 ± 52.5 mg*h/dL) was significantly smaller than that of the control group (257.7 ± 57.8 mg*h/dL), and Cmax of the test group was also significantly lower ($p < 0.01$).

In the case of the subjects whose HOMA-R was < 1.73, any significant difference was detected in neither the blood glucose level over time nor AUC, nor Cmax .

Influence on serum insulin concentration

The serum insulin levels changes over time when the test or the control was taken with glucose-load food, are shown in ***Fig. 2***. AUC and maximum serum insulin concentration are shown in ***Table 5***.

In the analysis targeting all subjects (n = 32), the serum insulin levels at 60, 90 and 120 min after the intake of the test food (48.2 ± 33.5 μIU/mL, 42.0 ± 36.2 μIU/mL and 37.3 ± 35.4 μIU/mL, respectively) were significantly lower than those after the intake of the control food (55.2 ± 40.2 μIU/mL, 50.6 ± 41.0 μIU/mL and 52.3 ± 53.1 μIU/mL, respectively, each $p < 0.05$). The AUC of the serum insulin levels of the test group (81.3 ± 50.6 μIU*h/mL) was significantly smaller than those of the control group (93.4 ± 62.2 μIU*h/mL, $p < 0.01$). These results show that the insulin secretion was reduced in the test group. There was no significant difference in Cmax of serum insulin between the groups.

Table 3. Subjects information.

Subjects	All subjects (n = 32)	HOMA-R≧1.73 (n = 25)	HOMA-R < 1.73 (n = 7)
Age (years)	45.4 ± 10.1	44.1 ± 10.8	50.0 ± 4.6
Hight (cm)	170.0 ± 9.1	168.7 ± 8.2	174.7 ± 11.0
Weight (kg)	75.1 ± 12.8	75.9 ± 14.2	727 ± 8.6

Date are expressed as mean ± SD. HOMA-R, homeostasis model assessment insulin resistances; SD, standard deviation.

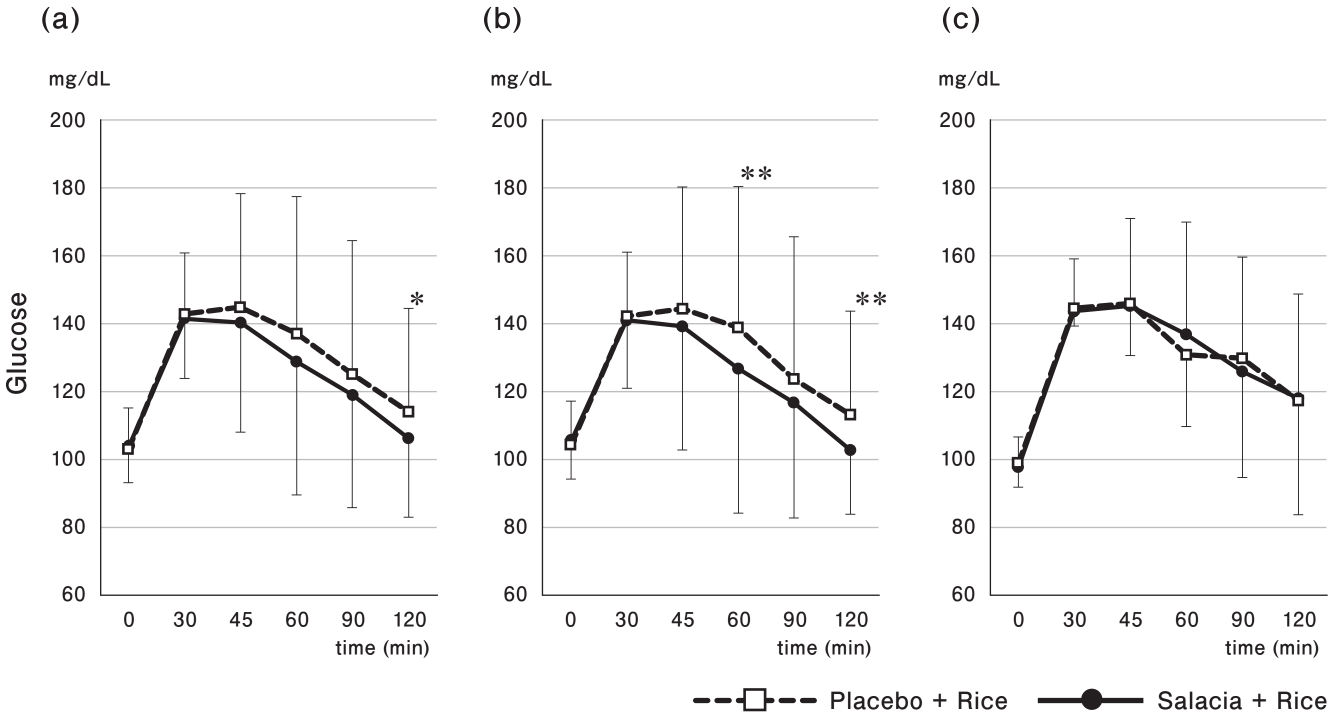

Fig. 1. Postprandial blood glucose changes.
a) All subjects (n = 32), b) HOMA-R ≧ 1.73 (n = 25), c) HOMA-R < 1.73 (n = 7). Date are expressed as mean ± SD. * $p < 0.05$, ** $p < 0.01$ vs. Salacia + Rice by a paired t-test. HOMA-R, homeostasis model assessment insulin resistances; SD, standard deviation.

Table 4. AUC, Cmax of the blood glucose curve.

Subjects		All subjects (n = 32)	HOMA-R ≧ 1.73 (n = 25)	HOMA-R < 1.73 (n = 7)
Blood glucose AUC (mg*h/dL)	Placebo + Rice	257.9 ± 53.9	257.7 ± 57.8	258.5 ± 41.1
	Salacia + Rice	248.6 ± 48.9*	245.9 ± 52.5*	258.3 ± 34.0
Blood glucose Cmax (mg/dL)	Placebo + Rice	155.4 ± 27.5	155.2 ± 29.4	156.0 ± 21.2
	Salacia + Rice	149.7 ± 25.2**	148.5 ± 27.5**	153.7 ± 14.9

Date are expressed as mean ± SD. * $p < 0.05$, ** $p < 0.01$ vs. Placebo + Rice by a paired t-test. AUC, area under curve; Cmax, maximum concentration; HOMA-R, homeostasis model assessment insulin resistances; SD, standard deviation.

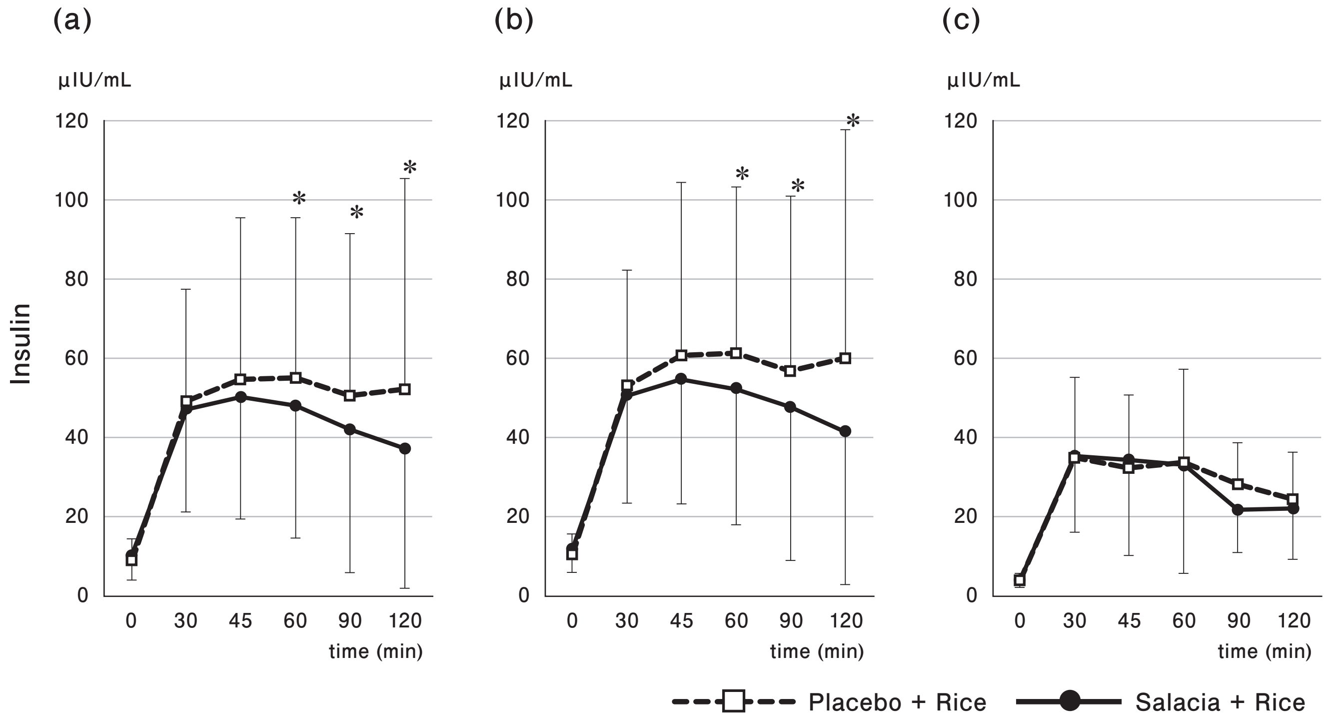

Fig. 2. Postprandial insulin changes.

a) All subjects (n = 32), b) HOMA-R ≧ 1.73 (n = 25), c) HOMA-R < 1.73 (n = 7). Date are expressed as mean ± SD. * $p < 0.05$, vs. Salacia + Rice by a paired t-test. HOMA-R, homeostasis model assessment insulin resistances; SD, standard deviation.

Table 5. AUC, Cmax of the insulin curve.

Subjects		All subjects (n = 32)	HOMA-R ≧ 1.73 (n = 25)	HOMA-R < 1.73 (n = 7)
Insulin AUC	Placebo + Rice	93.4 ± 62.2	104.2 ± 65.2	54.8 ± 27.4
(μIU*h/ml)	Salacia + Rice	81.3 ± 50.6**	89.6 ± 52.3*	51.4 ± 31.1
Insulin Cmax	Placebo + Rice	73.5 ± 53.7	82.4 ± 57.0	41.6 ± 19.7
(μIU/ml)	Salacia + Rice	63.7 ± 40.3	70.3 ± 41.7	39.9 ± 25.0

Date are expressed as mean ± SD. * $p < 0.05$, ** $p < 0.01$ vs. Placebo + Rice by a paired t-test. AUC, area under curve; Cmax, maximum concentration; HOMA-R, homeostasis model assessment insulin resistances; SD, standard deviation.

As a result of the similar analysis with the subjects whose HOMA-R were ≧ 1.73 (n = 25), the serum insulin levels of the test group at 60, 90, and 120 min after the intake were 52.4 ± 34.3 μIU/mL, 47.7 ± 38.8 μIU/mL and 41.5 ± 38.6 μIU/mL, respectively. They were significantly lower than those of the control group at each corresponding time (61.3 ± 42.2 μIU/mL, 56.8 ± 44.3 μIU/mL and 60.2 ± 57.6 μIU/mL, respectively). AUC of the test group was also smaller than that of the control group ($p < 0.05$). No significant difference in Cmax was observed between the groups.

On the other hand, in the case of the subjects whose HOMA-R was < 1.73, any significant difference was detected in neither the serum insulin level over time nor AUC, nor Cmax .

Hematology and biochemistry

The hematological and biochemical parameters were measured to assess the safety of the test and the control food.

There was no biochemical parameters in which significant difference was observed except for triglyceride (TG) level ($p = 0.023$) and creatinine level ($p < 0.001$) at 120 min after the intake. However, both of them were judged to be within the range of physiological variation. No significant difference was observed in the urinalysis results.

No adverse event that was recognized to have a causal relationship with the test food was observed. There was no drastic variation or abnormal values in the measurements for blood pressure or body temperature, and there were no problems in safety.

Discussion

For the purpose of halting the ever increasing number of diabetics, it would be a very effective to improve dietary habits at the stage of pre-diabetes. However, the trend of eating-out and home-meal replacement continues to increase, and few people can take the food that can suppress PBG rise in home cooking.

Although supplements and drinks which claim to inhibit the rise of blood glucose by consuming them just before taking a meal are known, most of their inhibiting effects were confirmed by a glucose tolerance test using sugar water or cooked rice [3, 4]. There are only few products that showed their efficacy under the conditions where various foods are mixed in the digestive system. Numao *et al*. reported that even if the products showed efficacy of inhibiting the PBG rise in some conditions, it is difficult to reproduce the effect in daily meals [5].

As seen in the case example of *gyudon* that Yonei *et al*. reported, they confirmed that the PBG level which was elevated by the intake of steamed rice was inhibited by the intake of the *gyudon* toppings at the same time, and furthermore, they found that the main effective component of the ingredients constituting the toppings of *gyudon* was beef [6]. It is considered that the insulin secretion through incretin secretion stimulated by peptides derived from the beef protein is involved in this function.

The function of the test food in this study was enhanced by adding the *salacia* extract solution to the control food (equivalent to the test food used in Reference 2). *Salacia* extract is known to have an effect of inhibiting the rise of blood glucose. All nutrient components of the control food are conformable to the Dietary Reference Intakes for Japanese (2015). To adjust the liquid volume of the test food to that of the control food, the added *salacia* extract solution's volume was subtracted from the original *tare*-sauce volume of the control food. As a result, the salt of the test food was reduced by 18% and the fat by 30%. The solid components were not different in both foods.

The authors confirmed that the differences in the content of salt and fat did not affect the blood glucose within 2 hours after a single intake, so that it is considered that the effect of inhibiting the rise of PBG was caused by the *salacia* extract, a functional determinant.

Meanwhile, it is known that if fat is excessively ingested for a long period, it accumulates in fatty tissue, muscles and liver and develops insulin resistance as a secondary effect. Though depending on the kinds of fatty acids, it is considered that reducing fat ingestion and preventing obesity lead to the improvement of insulin resistance in the long term. Furthermore high blood glucose is likely to develop high-blood pressure, cutting salt down is effective for the prevention of high-blood pressure. There was almost no difference in the amount, taste, or appearance in each food and in the taste of the *tare*-sauce caused by added *salacia* extract and no subject noticed the difference between the test food and the control food.

Salacia genus plant is a woody plant of the family *Hippocrateaceae* that grows in subtropical regions such as India and Sri Lanka, and it has been known that it is effective for the prevention of diabetes since 3,000 years ago. The hot-water extract from the stems of *salacia* has been sold on the market as a component of health food also in Japan. Yoshikawa *et al*. reported that its active ingredient has the inhibitory effect on PBG. One of the active compounds from *salacia* extract is salacinol, of which chemical structure is classified as thiosugar, and it blocks α-glucosidase activity that breaks down disaccharide into monosaccharide [7].

In the present experiments, the rise of blood glucose at 60 and 120 min after steamed rice loading was significantly inhibited by the intake of the test food, and its effect of inhibiting the rise of insulin at 60, 90 and 120 min after steamed rice loading was recognized and insulin AUC also significantly decreased. From the above, it is considered that the digestion and decomposition of steamed rice was inhibited by the intake of *gyudon* toppings supplemented with *salacia* extract, and the rise of blood glucose levels was alleviated, and as a result, insulin secretion was controlled.

It is known that the insulin secretion levels of Japanese are intrinsically lower than that of Westerners [1]. Insulin secretion of Japanese is lower even in those whose glucose tolerance is within the normal range, and if insulin resistance is added to this condition, diabetes is likely to develop. Oimatsu *et al*. investigated the index that most sharply reflects the insulin resistance in case of essential hypertension often accompanied by insulin resistance and that can be easily measured in clinical sites routinely. They found that HOMA index (fasting blood glucose level × fasting plasma insulin level/403) of 1.73 is the cut-off value of the positive insulin resistance [8].

The subjects who showed the level of 1.73 or more in HOMA-R, a rough indication of insulin resistance, in both or either one of the two intake opportunities (the control food and the test food) were 25 among 32 subjects, and it means the majority of the subjects already had positive insulin resistance even if their fasting blood glucose value was normal or in the cutoff zone. Insulin resistance easily leads to high PBG levels and increases the progression rate of diabetes. Furthermore, high PBG levels, even in the non-diabetic range, is an independent risk factor of large vessel disease [9, 10].

In this study, the subjects were divided into the group of HOMA-R ≧ 1.73 and < 1.73 and a differential analysis was conducted. As a result, in the group with HOMA-R ≧ 1.73, which is believed to have insulin resistance, a rise of PBG level was inhibited in the test group more than in the control group and there were significant differences in the PBG level at 60 and 120 min after the intake ($p = 0.009$, $p = 0.008$, respectively) and the inhibiting effect of test food was more remarkable compared to the case where all subjects were analyzed.

On the other hand, there was no difference between the test food group and the control group with HOMA-R less than 1.73. In this case, the test food did not excessively lower PBG levels, and the test food is considered to be safe as a health food product.

Conclusion

The effect of the *gyudon* toppings containing *salacia* extract on PBG rise caused by the intake of steamed rice was evaluated. As a result, the *gyudon* toppings supplemented with *salacia* extract (0.5 mg as salacinol) showed the inhibitory effect on the PBG rise, and as a result, lowered the secretion of insulin. Since the *gyudon* toppings supplemented with *salacia* extract showed effectiveness under the condition that it is taken together with steamed rice as seen in the way of eating *gyudon* in daily life, it would be effective as a meal for those in pre-diabetes.

Declaration of Conflict of Interest

This research received support from Yoshinoya Holdings.

References

1) Fukushima M, Suzuki H, Seino Y. Insulin secretion capacity in the development from normal glucose tolerance to type 2 diabetes. Diabetes Res Clin Pract. 2004; 66: S37-43.
2) Kawabata A, Yagi M, Ogura M, et al. Glucose level after intake of a bowl of topped with beef. Glycative Stress Res. 2015; 2: 67-71.
3) Hori T, Hori T, Komori M, et al. Influence of indigestible dextrin-containing powdered tea on postprandial blood glucose and the safety evaluation of long-term intake. Journal of Nutritional Food. 2005; 8: 27-35. (in Japanese)
4) Beppu H, Matsumoto M, Watanabe H, et al. Inhibitory effect of indigestible dextrin-containing food "Kento Raku-cha" on blood glucose elevation by sucrose tolerance test. Journal of Urban Living and Health Association (Seikatsu Eisei). 2009; 53: 153-159. (in Japanese)
5) Numao N, Suzuki M. Problems in the food for specified health uses: Comparison of inhibitory effects on blood glucose elevation between tea beverage and dumbbell exercise under the daily living condition. Journal of Japanese Society of Clinical Nutrition. 2010; 31: 136-143. (in Japanese)
6) Ogura M, Kubo R, Kobayashi T, et al. Influence of beef bowl (gyudon) materials on postprandial blood glucose. Glycative Stress Res. 2016; 3: 210-221.
7) Yoshikawa M, Morikawa T, Matsuda H, et al. Absolute stereostructure of potent α-glucosidase inhibitor, Salacinol, with unique thiosugar sulfonium sulfate inner salt structure from Salacia reticulate. Bioorganic Medicinal Chem. 2002; 10: 1547-1554.
8) Oimatsu H, Saitoh S, Ura N, et al. A practical index for evaluation of insulin resistance. Journal of the Japan Diabetes Society. 2000; 43: 205-213. (in Japanese)
9) Hanefeld M, Koehler C, Schaper F, et al. Postplandial plasma glucose is an independent risk factor for increased carotid intima-media thickness in non-diabetic individuals. Atherosclerosis. 1999; 144: 229-235.
10) Coutinho M, Gerstein H, Wang Y, et al. The relationship between glucose and incident cardiovascular events. Diabetes Care. 1999; 22: 233-240.