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Original article

Effect of *Yokan* intake on postprandial blood glucose

Masayuki Yagi [1)], Akari Yoshimura [1)], Takuya Yokoi [2)], Yutaka Aoyama [2)], Kaoru Masuda [2)], Chieko Sakiyama [1)], Mari Ogura [1)], Yoshikazu Yonei [1)]

1) Anti-Aging Medical Research Center and Glycative Stress Research Center, Faculty of Life and Medical Sciences, Doshisha University, Kyoto, Japan
2) Toraya Confectionery Co. Ltd., Tokyo, Japan

Abstract

Persistent postprandial hyperglycemia contributes to increased glycative stress. Therefore, it is important to understand the effects of carbohydrates in food on postprandial glycative stress. In this study, we evaluated the effects of *Yokan*, a Japanese confectionery (*Wagashi*) made of sugar, azuki beans, and agar, on glycative stress by comparing blood glucose changes after intake of *Yokan*, sugar water, and rice.

The subjects were 16 healthy 20～30 year men and women who attended the briefing session in advance and gave their written consent to participate in the study. The test foods were rice (**A**) as the reference food, *Yokan* (**B**, **C**, **D**) as the test food, and sugar water (**E**) with 50 g of carbohydrate, and the subsequent blood glucose changes were verified. FreeStyle Libre Pro was used for the study, and glucose concentrations in tissue interstitial fluid were measured as blood glucose levels. Blood glucose was collected prior to 120 min after intake of the test food. Results were evaluated by blood glucose change (ΔBG), maximum blood glucose (ΔCmax) and area under the glucose curve (iAUC). Study results were analyzed using multiple testing with the Bonferroni method.

The study was free of adverse events and no subjects met the exclusion criteria for analysis. The glucose change curve for the 16 subjects was higher for test foods **E** > **A** > **B, C**, and **D**, in that order. ΔBG after intake of **A** was higher than **B**, **C**, and **D** at 90 and 120 min, respectively. ΔBG in **B** was lower than that of **E** after 45 min. ΔBG in **C** tended to be lower than that of **E** after 45 min. The iAUCs were higher in the order **A** > **E** > **B** > **C** > **D**, with significantly lower values for **B**, **C**, and **D** compared to **A**. The iAUC of **D** tended to be lower than that of **E**. The ΔCmax was higher in the order of **E** > **D** > **A** > **B** and **C**. The ΔCmax of **B** and **C** tended to be lower than that of **E**.

The factors that caused the lower ΔBG, iAUC, and ΔCmax in test foods **B**, **C**, and **D** compared to **A** and **E** were presumed to be the effects of the azuki bean component and agar in *Yokan*, and changes in structure and function during food processing. From the perspective of glycemic index (GI), the effects of sugar on *Yokan* intake were considered comparable to those of common foods. *Yokan* may be a functional food with less effect on glycative stress compared to rice or sugar intake if consumed in appropriate amounts.

KEY WORDS: glycative stress, postprandial blood glucose, *Yokan*, azuki beans

Introduction

Glycative stress is one of the negative effects on the body caused by the generation and accumulation of advanced glycation end products (AGEs)[1)]. Glycative stress is involved in aging and various age-related diseases, and is a factor in the development of skin aging, diabetic complications, osteoporosis, and dementia. There are several ways to reduce glycative stress, i.e., suppressing hyperglycemia, inhibiting glycation reactions, and promoting the breakdown and excretion of AGEs[2, 3)]. Even in healthy individuals, rapid postprandial hyperglycemia causes an increase in blood aldehydes, which in turn increases glycative stress[4, 5)]. Therefore, it is important to understand the effect of carbohydrates in foods on postprandial glycemic index (GI), and elevation as a countermeasure against glycative stress.

Contact Address: Professor Masayuki Yagi, PhD
Anti-Aging Medical Research Center, and Glycative Stress Research Center,
Faculty of Life and Medical Sciences, Doshisha University
1-3, Tataramiyakodani, Kyotanabe-shi, Kyoto, 610-0321 Japan
TEL & FAX: +81-774-65-6394 e-mail: myagi@mail.doshisha.ac.jp
Co-authors: Yoshimura A, ctuh2036@mail4.doshisha.ac.jp;
Yokoi T, t.yokoi@toraya-group.co.jp; Aoyama Y, aoyama@toraya-group.co.jp;
Masuda K, kaoru.masuda@toraya-group.co.jp; Sakiyama C, csakiyam@mail.doshisha.ac.jp;
Ogura M, m-ogura@po.kbu.ac.jp; Yonei Y, yyonei@mail.doshisha.ac.jp

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To control postprandial hyperglycemia, it is important to reduce carbohydrate intake, select low GI foods that cause a slow rise in postprandial blood glucose levels [6], eat foods rich in protein, fat, acetic acid, and dietary fiber along with carbohydrates [7], and eat vegetables first rather than carbohydrates [8]. Confectionery is consumed mainly as a snack or dessert, and often contains a lot of sugar and has a strong sweet taste. Excessive intake of sugar-rich foods is a factor in the development of dental caries, obesity, and metabolic syndrome [9]. While, the consumption of sweets as snacks improves attention and memory [10, 11]. Furthermore, it has been reported that confectioneries can enhance communication and creativity in group activities [12]. The purpose of this study was to evaluate the effect of *Yokan*, a Japanese confectionery (*Wagashi*) made of sugar, azuki beans, and agar as main ingredients, on glycative stress after intake of *Yokan*, sugar-water, and steamed rice as test foods with a unified carbohydrate content of 50 g.

Methods

Subjects

Sixteen subjects met the following selection criteria (*Table 1*). Males and females between the ages of 20 and 30 years at the time of obtaining consent to participate in the study. All subjects were healthy and free from chronic physical diseases. Subjects who have been fully informed of the purpose and content of the study, are competent to consent, understand the study well, volunteer to participate, and are able to consent to participation in the study in writing. They were able to come to the office on the designated study date and be able to complete the study. Those who have been approved by the study investigator as suitable participated in the study.

Survey items and examination details

Subjects completed a subject background survey, in which they self-reported their age, medical history, and food allergies, concurrently underwent blood tests (*Table 2*). The test was performed using FreeStyle Libre Pro (Abbott Laboratories, Chicago, IL, USA), and the glucose concentration in the tissue interstitial fluid measured during the study period was used as the blood glucose level [13].

Study protocol

As previously reported [14-18], this study was conducted in accordance with the unified protocol by the Japanese Association for the Study of GI [19]. During the study period, subjects were instructed to observe to the following. Avoid an irregular lifestyle, such as lack of sleep and binge eating and drinking, and lead a normal life. Diet,

Table 1. Subjects profile.

	Unit	Total	Male	Female
Number of subjects		16	8	8
Age	years	22.5 ± 0.9	22.6 ± 0.7	22.4 ± 1.0
Body height	cm	166.0 ± 10.1	174.4 ± 4.1	157.6 ± 6.6
Body weight	kg	58.9 ± 11.6	67.9 ± 9.2	49.8 ± 4.6
BMI		21.2 ± 2.8	22.3 ± 2.6	20.2 ± 2.5

Results are expressed as mean ± standard deviation. BMI, body mass index.

Table 2. Result of the blood chemistry test.

Test item	Unit	Measured value	Reference range
FBG	mg/dL	83.6 ± 4.9	≦ 99
HbA1c	%	5.1 ± 0.2	≦ 5.5
IRI	μU/mL	5.3 ± 1.5	–
Total cholesterol	mg/dL	181.5 ± 24.3	–
HDL-C	mg/dL	61.3 ± 13.8	≧ 40
LDL-C	mg/dL	103.6 ± 19.8	60 – 119
TG	mg/dL	75.4 ± 62.6	30 – 149
AST	U/L	17.8 ± 5.8	≦ 30
ALT	U/L	15.8 ± 18.4	≦ 30
γ-GT	U/L	17.3 ± 9.3	≦ 50

Results are expressed as mean ± standard deviation, n = 16, FBG, fasting blood glucose; IRI, immunoreactive insulin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; AST, aspartate transaminase; ALT, alanine transaminase; γ-GT, γ-glutamyltransferase.

exercise, and sleep should be maintained in the same quantity and quality as prior to participation in the study. The initiation of new health foods, supplements, *etc*. will be prohibited. Other activities that may affect the results of the study are prohibited. On the day before and the day of the examination, the following items were instructed to be observed. Excessive exercise is prohibited during the pre-test and the day before the test. Sleep at least 6 hours on the day before the examination. Alcohol consumption is prohibited from the day before until the end of the examination on the day. Avoid fatty foods for dinner and drink nothing but water after 10:00 p.m. on the day before the pre-test and the day of the exam. Exercise and any physical activity that may cause sweating is prohibited until the end of the examination on the day of the examination. For women, the examination will not be conducted during menstrual periods. During the test, the subject should remain in a sitting position and should not use the telephone, sleep, engage in excessive brain activity (*e.g*., texting, computers), or engage in physical activity. After intake of the test foods, the subjects should fast until the end of the study.

Subjects affixed the Libre Pro sensor to themselves on the lateral upper arm at least 2 days prior to the test. No restrictions were placed on bathing, swimming, or exercise during the period of wearing the Libre Pro Sensor. The test was conducted at 10:00 a.m. The test food was consumed in a 10-min period. The subjects then watched a video in a sitting position, allowing them to remain relaxed until 12:00, when the test ended.

The test food was ingested after chewing each mouthful at least 30 times before swallowing. Blood glucose readings were collected before (1st time), 15 min (2nd time), 30 min (3rd time), 45 min (4th time), 60 min (5th time), 90 min (6th time), and 120 min (7th time) after ingesting the test food.

Test foods

Nutritional components of the test foods used in this study were calculated using the values labeled on each food, and the carbohydrate intake per serving was standardized to 50 g (***Table 3***). Commercially available packaged rice, sprinkle, *Yokan* products, and sugar water were used in this study. Packaged rice was "Sato no Gohan, Niigata Koshihikari 150 g" (Sato Shokuhin Kogyo, Niigata, Japan). The sprinkle was "Noritama" (Marumiya Shokuhin Kogyo, Suginami-ku, Tokyo, Japan). Three types of *Yokan* products were used: Small *Yokan*: Yoru no Ume, Sora no Tabi, Omokage (Toraya, Minato-ku, Tokyo). Granulated sugar (Mitsui Sugar, Chuo-ku, Tokyo) was used as the sugar. Wilkinson Soda Water (Asahi Soft Drinks, Sumida-ku, Tokyo) was used as the soda water. The test foods were **A**~**E**, and the intake amounts were as follows.

A (reference food): 150 g packaged rice + 2.5 g sprinkles (total carbohydrate: 50 g)
B (test food): 71 g small *Yokan* "Yoru no Ume" (total carbohydrate: 50 g)
C (test food): 73 g small *Yokan* "Sora no Tabi" (total carbohydrate: 50 g)
D (test food): 73 g small *Yokan* "Omokage" (total carbohydrate: 50 g)
E (test food): Sugar water (50 g sugar dissolved in 150 mL water containing approximately 10 % carbonated water) (total carbohydrate content: 50 g)

All **A** ~ **E** test foods were ingested within 10 min after the start of the test.

Selection of subjects for safety analysis

The subjects for the safety analysis were those who had consumed the test food at least once.

Selection of subjects for efficacy analysis

The subjects for the efficacy analysis were those who completed the prescribed study schedule and reviewed all study details, excluding those who met the exclusion criteria for analysis as described below. Persons whose conduct was conspicuously found to undermine the reliability of the test results. Subjects who were found after the start of study to have met the exclusion criteria or were unable to comply with the restrictions.

Statistical analysis

The safety evaluation and analysis of the study were performed on the safety analysis subjects, and adverse events and side effects were evaluated by tabulating the symptoms, severity, and frequency of adverse events and side effects.

Efficacy analysis of the test results was performed on the "subjects for the efficacy analysis". The value obtained by subtracting the blood glucose level over time after consumption of the test food from the blood glucose level

Table 3. Nutrition facts of test food.

Test food	Serving unit (g)	Energy (kcal)	Protein (g)	Fat (g)	Carbohydrate (g)	Sodium chloride amount (g)
A	152.5	220	3.5	0.6	50	0.23
B	71	210	3	0	50	0
C	73	215	3	0	50	0.03
D	73	213	3	0	50	0
E	50	194	0	0	50	0

A, rice 150 g + sprinkle 2.5 g; **B**, small *Yokan* Yoru no Ume; **C**, small *Yokan* Sora no Tabi; **D**, small *Yokan* Omokage; **E**, sugar water 150 mL.

before consumption of the test food (first time; 0 min value) was the blood glucose change value (Δ blood glucose; ΔBG), and the maximum blood glucose change value up to 120 min after the test started was the maximum blood glucose change value (ΔCmax; maximum blood glucose concentration). The area under curve of the elevated blood glucose (incremental area under curve; iAUC) was calculated according to the unified protocol of the Japanese Association for the Study of GI [19]. Statistical analysis was performed using the software BellCurve for Excel (Shakai Joho Service, Shinjuku-ku, Tokyo). Blood glucose values were expressed as mean ± standard error (SE). For cross-group comparisons of study results, after multiple testing using the Bonferroni method, a two-tailed test with a risk rate of less than 5% ($p < 0.05$) indicated a significant difference, and a two-tailed test with a risk rate of $0.05 \leq p < 0.1$ indicated a significant trend.

Ethical standards

This study was conducted in compliance with the Declaration of Helsinki (as amended by the 2013 WMA Fortaleza Assembly) and the Ethical Guidelines for Medical Research Involving Human Subjects (notified by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labor and Welfare). The study was conducted after the subjects were fully informed of the study details in advance, and after they expressed their willingness to participate in the study and voluntarily submitted a consent form. This study was conducted under the deliberation and approval of the Ethics Review Committee on "Research on Human Subjects" of the Glycation and Stress Research Society (GSE #2021013). In addition, this study was conducted by registering with the public database set up by the University Medical Institutions of National Universities (UMIN #000045927).

Results

Safety assessment

No adverse events were reported in this study (data not shown).

Evaluation of efficacy

Since no subjects met the exclusion criteria for analysis, all 16 study participants were included in the efficacy analysis.

Efficacy analysis

Overall analysis

The subjects' blood glucose levels before consumption of each test food ranged from 83.8～91.9 mg/dL, reaching their highest level 45 min after the start of the study and then declining (***Table 4***). The changes in blood glucose (ΔBG) after consumption of test food **A** were all higher at 90 min ($p < 0.001$) and 120 min ($p < 0.001$) compared to **B**, **C**, and **D**, and lower at 30 min ($p = 0.032$) and 45 min ($p = 0.053$) compared to E and higher at 90 min ($p = 0.002$) and 120 min ($p < 0.001$) and higher at 90 min ($p = 0.002$) and 120 min ($p < 0.001$, ***Fig.1***). ΔBG after intake of **B** was lower than **E** after 45 min ($p = 0.032$). ΔBG after intake of **C** tended to be lower than **E** after 45 min ($p = 0.086$). No differences were observed in ΔBG at other measurement times after intake of **B**, **C**, and **D**.

The iAUCs of the test foods were higher in the order **A** > **E** > **B** > **C** > **D** and significantly lower in **B** ($p = 0.018$), **C** ($p = 0.008$) and **D** ($p = 0.004$) compared to **A** (***Fig.2-a***). There was a trend toward lower iAUCs for **D** compared to **E** ($p = 0.094$).

The ΔCmax of the test foods were higher in the order of **E** > **D** > **A** > **B** and **C** (***Fig. 2-b***). The ΔCmax of **B** ($p = 0.064$) and **C** ($p = 0.062$) tended to be lower than that of **E**.

Subclass analysis

In the subclass analysis, all 16 subjects were divided into the top 8 highest (high group) and the bottom 8 lowest (low group) based on the iAUC at the intake of test food **A**, the reference diet, to examine differences in iAUC and ΔCmax after intake of test foods (**B**, **C**, **D**, **E**) (***Fig.3***). The iAUC and ΔCmax were 1.75-fold ($p < 0.001$) and 1.47-fold ($p = 0.0046$) higher in the high group than in the low group, respectively, when test food **A** was consumed. The iAUC of the high value group was 1.74-fold ($p = 0.02$) higher in

Table 4. Blood glucose level fluctuation after test food intake.

Time (min)	A	B	C	D	E
0	85.6 ± 3.0 (5.8)	83.8 ± 1.8 (3.5)	91.9 ± 2.6 (5.0)	88.3 ± 2.1 (4.1)	83.8 ± 2.5 (4.9)
15	98.5 ± 3.2 (6.2)	102.1 ± 3.4 (6.6)	112.9 ± 3.6 (7.0)	103.4 ± 3.0 (5.9)	105.2 ± 4.2 (8.3)
30	126.4 ± 3.8 (7.5)	130.9 ± 4.7 (9.2)	142.8 ± 4.6 (9.1)	131.7 ± 4.3 (8.4)	140.7 ± 5.4 (10.6)
45	139.8 ± 5.1 (10.0)	136.9 ± 4.7 (9.1)	147.1 ± 5.4 (10.7)	143.8 ± 4.9 (9.7)	154.4 ± 5.0 (9.8)
60	133.1 ± 6.0 (11.7)	122.9 ± 5.4 (10.6)	130.4 ± 6.2 (12.2)	132.4 ± 7.3 (14.2)	137.3 ± 5.3 (10.4)
90	125.0 ± 4.9 (9.6)	99.5 ± 5.0 (9.7)	103.8 ± 4.2 (8.3)	99.7 ± 5.4 (10.5)	102.4 ± 3.9 (7.6)
120	125.0 ± 4.5 (8.9)	89.3 ± 4.9 (9.5)	91.0 ± 3.3 (6.4)	87.2 ± 4.0 (7.8)	88.1 ± 4.8 (9.4)

Results are expressed as mean ± standard error (95%CI), n = 16, **A-E**; details of the test food are shown in **Table 3**.

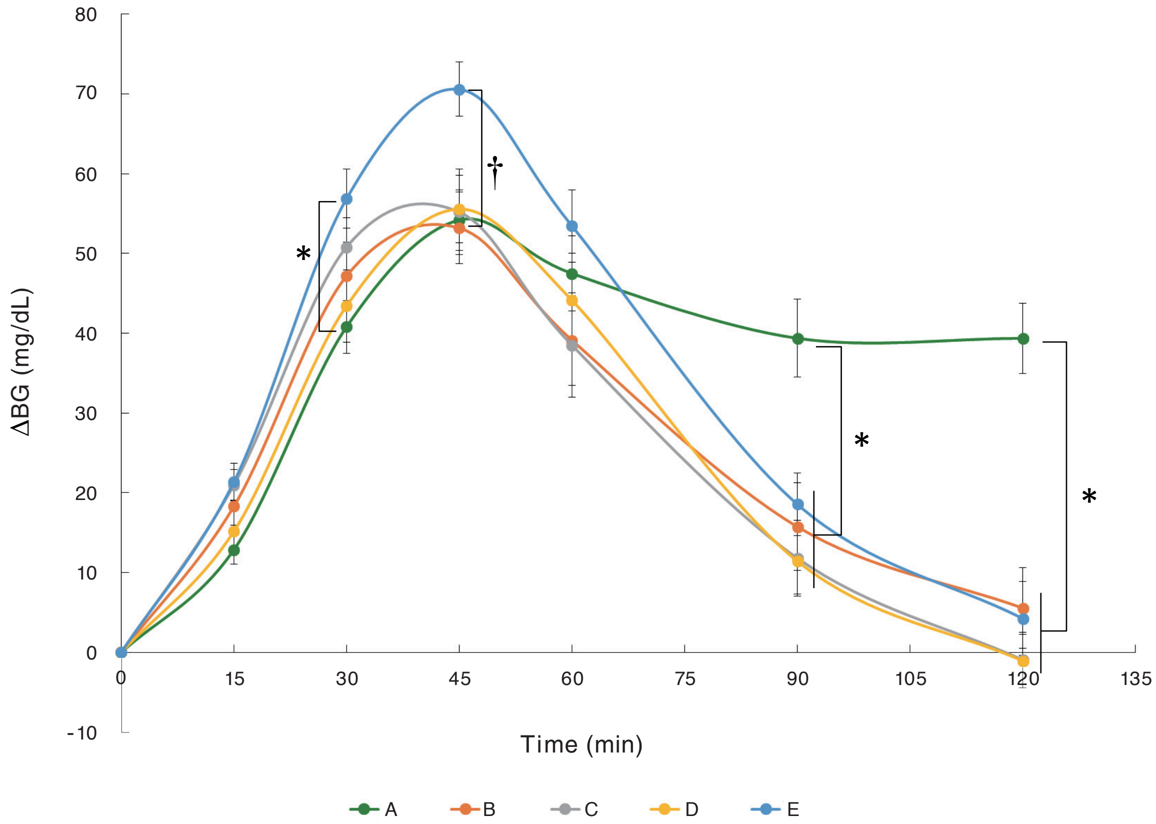

Fig. 1. **Fluctuation of the ΔBG level at the time of test food intake.**

Results are expressed as mean ± standard error, n = 16, †p < 0.1, * p < 0.05 vs standard food (**A**), Bonferroni test, **A～E**; details of the test food are shown in **Table 3**.

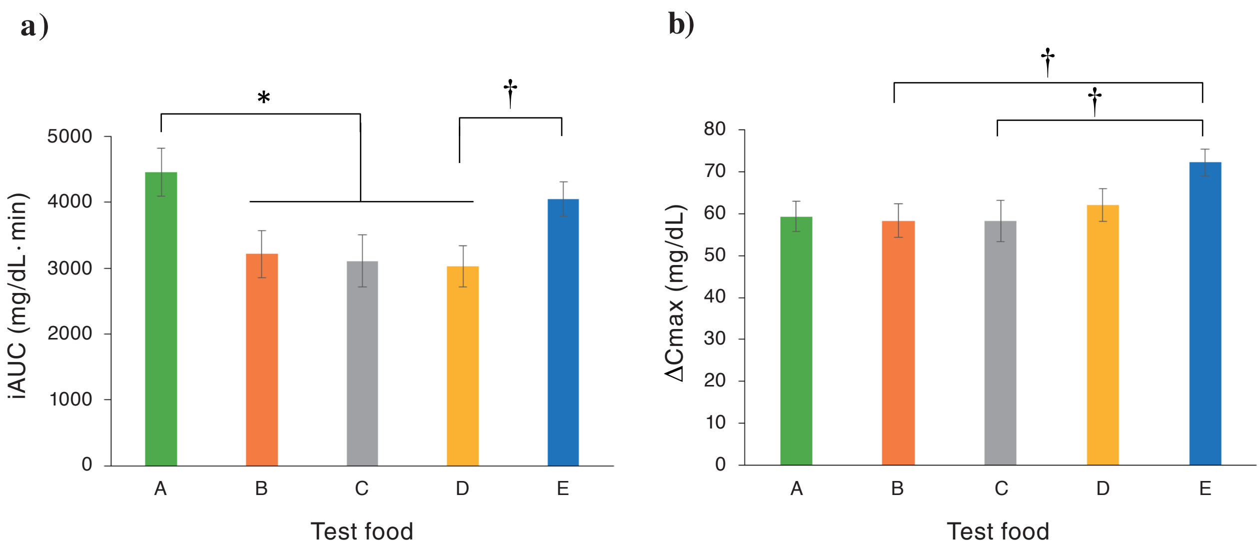

Fig. 2. **The amount of iAUC and ΔCmax after test food intake.**

a) iAUC, **b)** ΔCmax. Results are expressed as mean ± standard error, n = 16. † p < 0.1, * p < 0.05, Bonferroni test. ΔCmax, maximum blood glucose change; iAUC, incremental area under the curve of blood glucose change. **A～E**; details of the test food are shown in **Table 3**.

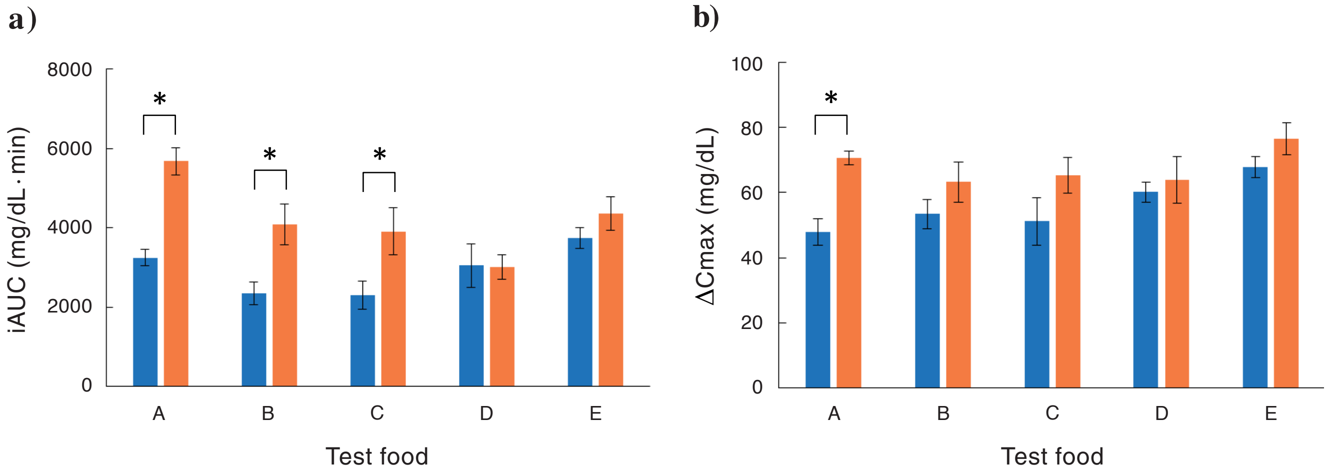

Fig. 3. **Subclass analysis of iAUC and ΔCmax after test food intake.**

a) iAUC, **b)** ΔCmax. ■, higher group (n = 8); ■, lower group (n = 8), Results are expressed as mean ± standard error, * $p < 0.05$, Bonferroni test. ΔCmax, maximum blood glucose change; iAUC, incremental area under the curve of blood glucose change. **A**～**E**; details of the test food are shown in **Table 3**.

B and 1.69-fold (p = 0.003) higher in **C** than in the low value group, but no difference was observed in **D** and **E**. The ΔCmax of **B**, **C**, **D**, and **E** did not differ between the high and low groups.

Discussion

Blood glucose changes after Yokan intake

In this study, the amount of carbohydrate in the test foods was uniformly set at 50 g. Test foods **B**, **C**, and **D** are *Yokan*, which are processed with sugar, beans such as azuki beans and agar as main ingredients. Compared to the intake of sugar water (**E**) alone, **B** showed lower ΔBG (p = 0.032) and ΔCmax (p = 0.064) after 45 min, **C** showed lower ΔBG (p = 0.086) and ΔCmax (p = 0.062) after 45 min, and **D** showed a lower iAUC (p = 0.094).

In a study in which rice was cooked with 1.7～2.5% agar added to rice, the agar inhibited thermal changes in the rice and glucose formation in the digestive tract, resulting in suppression of postprandial hyperglycemia[20]. Combined intake of rice and 50% xanthan gum solution suppressed postprandial hyperglycemia by prolonging the residence time of the rice in the stomach through food mass formation and by inhibiting digestion through sol (colloid) formation of rice and xanthan gum[21]. Furthermore, flavonoids[22] and catechin glycosides[23] contained in azuki beans extract have been reported to inhibit α-glucosidase. From these results, it was presumed that the low ΔBG of **B**, **C**, and **D** was caused by the azuki beans and agar contained in *Yokan*.

The ΔBG of **A** (rice) decreased more slowly than that of the other test foods after 60 min. The main carbohydrates in **A** are rice-derived starch, **B**, **C**, and **D** are sugar and azuki bean-derived starch, and **E** is sugar. Factors that influence the postprandial hyperglycemia include the gastric emptying time of ingested carbohydrates, the rate of digestion and absorption in the small intestine, and the promotion of insulin secretion by incretin[24]. The difference in ΔBG after intake of **A** may involve differences in digestion and absorption of starch and sugar in rice. In our previous study[5], the suppression of elevated blood glucose levels after intake of bread containing heat-moisture-treated high-amylose corn starch (HMT-HAS) was more pronounced in business workers (mean age: 36.9 ± 9.3 years, n = 19) than in university students (22.6 ± 1.3 years, n = 13). The differences in the age and insulin resistance of the subjects were presumed to be factors in the blood glucose level differences.

The results of the subclass analysis in this study showed that differences between the high and low iAUC groups in **A** (rice) were observed only in **B** and **C,** while not in **D** and **E**. Test foods **B**, **C,** and **D** are *Yokan*, and their main ingredients are the same. Azuki bean paste obtained by cooking azuki beans changes the structure and function of starch and protein during the heating process and storage[25]. Therefore, food processing and cooking methods may also play a role in blood glucose changes after food intake.

GI of test foods

The GI is the potential ability of a carbohydrate-rich food or meal to raise postprandial blood glucose elevation and is an index developed to evaluate the quality of physiological functions of carbohydrates[6]. The GI value is calculated by using rice or glucose as the reference food.

When glucose is used as the reference food, 70 or higher is defined as high GI, 69～56 as medium GI, and 55 or lower as low GI. In addition, when rice is used as the reference diet, foods that are 83 or higher, multiplied by 1.2 times the definition of the GI value category, are considered high GI foods, foods between 82 and 65 are considered medium GI foods, and foods 64 or lower are considered low GI foods[26]. The iAUCs obtained from the results of this study were calculated based on the protocol (unified method)[19] recommended by the Japanese Association of the study of GI, with the GI of test food **A** (rice) as 100. The GI were 72.1 for **B**, 69.8 for **C**, 68.0 for **D**, and 90.9 for **E**

(***Fig. 2-a***). Therefore, in terms of GI, **E** was estimated to be a high GI food, and **B**, **C**, and **D** were estimated to be medium GI foods. The average GI value of the diet consumed by Japanese women (when glucose is used as the reference diet) is 67[27]. Therefore, the effect of carbohydrates on the *Yokan* intake (**B**, **C**, and **D**) in terms of GI was considered to approximate that off common foods. In contrast, *Yokan* is not a staple food but a luxury food. Thus, it is not expected to lower GI as a composite food consisting of a staple food, main dish, and a side dish. It is common practice to consume *Yokan* and wagashi together with tea or matcha tea. Catechin-induced α-amylase and α-glucosidase inhibitory effects have been observed in tea[28, 29]. Therefore, the GI of *Yokan* in the general eating habits of Japanese is expected to be even lower.

Effects of Yokan intake on glycative stress

Glycative stress is also increased by postprandial hyperglycemia, oxidative stress, and mental stress[1]. Generally, sweetened confectionery is considered a food that increases glycative stress because of its high sugar content and its tendency to cause a postprandial glucose elevation. In this study, in which the amount of carbohydrate was standardized to 50g, the iAUC (**D**) or ΔCmax (**B**,**C**) of *Yokan* was lower than that of sugar water. The inhibitory effect of *Yokan* on glycative stress is presumed to be due not only to the inhibitory effect of agar, a raw material, on elevated blood glucose[20], but also to the effect of components contained in azuki beans. Azuki beans contain 15 flavonoids[30] and have been shown to have antioxidant effects[31] and α-amylase and α-glucosidase inhibitory effects[22, 23]. The red azuki bean paste obtained by cooking azuki beans contains 70 different aroma components[32], and maltol is presumed to be involved as a characteristic sweet aroma component[33]. The aroma component of azuki bean paste is involved in imparting a sense of deliciousness satisfaction in food intake[33]. *Yokan* has also been developed as a space food, not only for its long-term shelf life and suitability as a food with reduced dispersibility when ingested, but also for its function as a mental stress-relieving food for astronauts[34]. Based on these findings, *Yokan* intake was considered to be a functional food with a smaller influence on glycative stress than rice or sugar water when consumed in appropriate amounts.

Research limitations

The subjects of this study were healthy 20～30 year-old men and women. The effects of *Yokan* on blood glucose with age and on food intake after intake such as a snack have not been verified. These effects need to be further verified in the future.

Conclusion

The results of the examination of blood glucose changes after *yokan* intake indicate that *Yokan* may be a functional food with a smaller effect on glycative stress than rice or sugar intake, if consumed in appropriate amounts.

Conflict of interest declaration

This research received support from Toraya Confectionery Co. Ltd. (Minato-ku, Tokyo, Japan).

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