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Original article

Effect of the postprandial blood glucose on lemon juice and rice intake.

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Abstract

***Objective*:** Persistence of postprandial hyperglycemia causes elevation of glycative stress. The purpose of this study was to examine the suppressing effect of lemon juice on postprandial hyperglycemia when ingesting cooked rice, thereby, the changes in blood glucose (BG) levels were compared and verified, based on an intake of cooked rice alone as a standard, when lemon juice was ingested before cooked rice.
***Methods*:** Subjects were 12 healthy males and females aged 20 to 30 years old who participated in a briefing session held in advance and provided written consent. The changes in BG level were verified between three test foods as follows: when the cooked rice was ingested alone (**A**), 15 g of lemon juice was ingested before the rice (**B**), and 30 g of lemon juice was ingested before the rice (**C**). Lemon juice was ingested after diluting it with 150 mL of water. FreeStyle Libre Pro was used for the test, and the measured glucose concentration in the interstitial fluid was taken as the BG level. The BG levels evaluated were collected before ingesting the test food (0 min), 15, 30, 45, 60, 90, and 120 min after the start of the test. The results were evaluated by the BG level, the maximum BG change (ΔCmax) and the incremental area under the curve of BG (iAUC). Bonferroni multiple test was performed for statistical analysis.
***Results*:** here were no adverse events and no subject met the exclusion criteria for analysis, therefore, all 12 subjects were included in the efficacy analysis. The blood glucose change (ΔBG) increased until 45 min after the start of the **A** to **C** intake test, and decreased until 120 min thereafter. After 30 min, ΔBG of test food **C** tended to be lower than that of **A** and **B** ($p < 0.1$). The highest value was shown 45 min after ingestion of the test foods **A** to **C**, when ΔBG was significantly lower in **C** than in **A** ($p < 0.05$). ΔCmax was 20.3% lower in **C** than in **A** ($p < 0.05$). iAUC in **C** tended to be 24.8% lower than that of **A** ($p < 0.1$).
***Conclusion*:** This study showed that a diet that ingest lemon juice prior to rice suppressed postprandial hyperglycemia that was observed when 30 g of lemon juice was taken. A dietary habit of ingesting a beverage containing lemon juice before meals may reduce glycative stress by suppressing postprandial hyperglycemia, and may contribute to the prevention of aging and disease progression.

***KEY WORDS*:** glycative stress, postprandial hyperglycemia, lemon, citric acid

Introduction

Due to the acceleration of glycative stress, advanced glycation end products (AGEs) are produced and accumulated in our body. AGE-modification of tissue proteins involves cross-linking, inflammation, and browning. Therefore, glycative stress causes physical, physiological, and visual damage to tissues and cells *in vivo* [1)]. Glycative stress is one of the risk factors for aging, and may be a cause of progression of skin aging, diabetic complications, osteoporosis, and dementia. One of the factors that elevates glycative stress is the persistent hyperglycemic state.

Even in healthy subjects, extreme postprandial hyperglycemic conditions cause glycative stress. The methods

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to reduce glycative stress include suppression of postprandial hyperglycemia, suppression of AGE production/accumulation, and reduced intake of diet-derived AGEs[2, 3]. Postprandial hyperglycemia can be suppressed by selecting low glycemic index (GI) foods and dietary modification. It has been reported that postprandial hyperglycemia can be suppressed by ingesting carbohydrates (*i.e.* rice, bread), a vegetable salad[4, 5], vinegar[6], vinegar beverage[7], grapefruit[8], or plain yogurt[9] before meals. Furthermore, the suppression of postprandial hyperglycemia is reported to be more effective than eating udon or cooked rice alone by eating them with side dishes such as eggs, vegetable salad, Mabo eggplant[10], or beef bowl[11]. The food information and ingestion methods that suppress postprandial hyperglycemia may widen the variety of diets that reduce glycative stress and provide health information that can be reasonably and comfortably continued. In this study, for the purpose of verifying the effect of lemon juice on postprandial blood glucose (BG) when ingesting cooked rice, the BG changes were compared under two conditions, when the rice was ingested alone as a standard and when the lemon juice was ingested before rice.

Methods

Subject

Subject were 12 individuals who met the following selection criteria (***Table 1***): Men and women between the ages of 20 and 30 at the time of obtaining consent to participate in the study; A healthy person without chronic illness; A person who has a sufficient explanation about the purpose and contents of this study, is capable of consenting, who voluntarily participate after understanding well, and who can participate with a written consent; A person who can visit and take the examinations on the designated day.

Survey items and examination contents

As a background survey, the subjects filled out a questionnaire on their age, medical history and food allergy, and underwent a blood examination (***Table 2***). The test used FreeStyle Libre Pro (Abbott Laboratories, Chicago, USA) and the glucose concentration in the tissue interstitial fluid measured during the test period was used as the BG level[12].

Testing protocol

In this study, as in the previous report[4-11], the test was conducted according to a uniform protocol by the Japanese Association for the Study of Glycemic Index (GI)[13].

Subjects were instructed to observe the following items during the test period: Avoid irregular life such as lack of sleep or overeating, and live a normal life; Diet, exercise, and sleep should be maintained in the same quantity and quality as before participation in this study; It is prohibited to start taking health foods and supplements; Other than that, it is prohibited to affect the test results.

Instructions were given on the day before and on the day of the test so that the following items were observed: Excessive exercise is prohibited the day before the pre-examination and test; Sleep 6 hours or more the day before

Table 1. Subject's profile.

	Unit	Total	Male	Female
Number of subjects		12	4	8
Age	years	23.1 ± 1.2	23.8 ± 0.5	22.8 ± 1.4
Body heigt	cm	161 ± 9.8	172.1 ± 5.5	155.5 ± 5.6
Body weight	kg	54.9 ± 10.7	65.1 ± 13.4	49.8 ± 3.8
BMI		21 ± 2.2	21.8 ± 3.4	20.6 ± 1.6

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

Table 2. Results of the blood chemistry test.

Test item	Unit	Measured value	Reference range
FBG	mg/dL	80.3 ± 6.3	70 - 109
HbA1c	%	5.3 ± 0.2	4.6 - 6.2
IRI	μU/mL	5.8 ± 2.2	1.7 - 10.4
Total cholesterol	mg/dL	186.3 ± 19.7	120 - 219
TG	mg/dL	74.3 ± 31.4	30 - 149
HDL-C	mg/dL	67.4 ± 13.5	40 - 85
LDL-C	mg/dL	104.7 ± 17.9	65 - 139

Results are expressed as mean ± standard deviation. FBG, fasting blood glucose; IRI, immunoreactive insulin; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

the test; Intake of alcoholic beverages is prohibited from the day before the test until the end of the test; For dinner on the day before the pretest and the test, avoid high fat foods and do not ingest anything other than water after 22:00; On the day of the test, physical activity that may result in exercise and sweating is prohibited until the end of the test; For women, the test is not conducted during the menstrual period.

During the test, participants were kept in a sitting and rest position; Prohibited phone calls, sleep, excessive brain activity (*i.e.* e-mail, computer) and physical activity; Fasted after eating the test food until the end of the test.

Subjects self-attached the Libre Pro sensor to the outside of the upper arm two days or more before the test. During the wearing period of the sensor, no restrictions were placed on bathing, swimming, or exercise. In the test, the test food was ingested for 10 min at 10:00. Subjects then watched the DVD in a sitting position, allowing them to remain relaxed until 12:00, when the test ended.

The test food was swallowed 30 times or more after chewing. The BG level was expressed as the measurement value collected 15 min after starting the test food (first time), 15 min after starting the intake (second time), 30 min (third time), 45 min (forth time), 60 min (fifth time), 90 min (sixth time), and 120 min (seventh time).

Test foods

In this study, the nutritional components of the test foods used were calculated using the values displayed on each food (***Table 3***). Commercial packed rice and lemon juice products were used as test foods. The test foods used were as follows: a packaged cooked rice, "Sato no Gohan, 200 g of Koshihikari from Niigata" (Sato Foods Co., Ltd., Niigata, Japan), and a lemon juice product, "Pokka Lemon 100" (Pokka Sapporo Food & Beverage Co., Ltd., Nagoya, Aichi, Japan). The test foods were classified from **A** to **C**, and each intake were as follows:

Test food **A** : Cooked rice 200 g
(total carbohydrate: 67.8 g)
Test food **B** : Lemon juice 15 g + Cooked rice 200 g
(total carbohydrate: 69.2 g)
Test food **C** : Lemon juice 30 g + Cooked rice 200 g
(total carbohydrate: 70.6 g)

As for the intake method of the test food, both **A** to **C** were ingested within 10 min after the start of the test. In particular, when the test foods **B** and **C** were ingested, lemon juice was ingested for the first 5 min, followed by the ingestion of 200 g of rice. Lemon juice was ingested after diluting it with 150 mL of water.

Selection of safety analysis objects

The objects for safety analysis selected the subjects who took the test food only once.

Selection of efficacy analysis objects

The objects for efficacy analysis selected the subjects who completed all the prescribed test schedules and test contents, however, those who met the following exclusion criteria were excluded: A person who was found to be prominent in acts that impair the reliability of test results; A person who was found to have met the exclusion criteria or was unable to comply with the restrictions after the start of ingestion.

Statistical analysis

Evaluation and analysis of the study were conducted by the safety analysis objects. The adverse events and side effects were evaluated by tabulating the symptoms, degree, frequency, and relevance to the test food.

The efficacy analysis was conducted by the efficacy analysis objects. The change in BG level (ΔBG) was obtained by subtracting the value before ingesting the test food (first time; 0 min value) from the BG level after the test food was ingested. The maximum change in BG level up to 120 min after the start of the test was defined as the maximum BG change value (ΔCmax; maximum BG concentration). Incremental area under curve (iAUC) was calculated according to the uniform protocol of the Japan GI Study Group[13]. IMB SPSS Statics 26 (IMB Japan, Tokyo, Japan) was used for the statistical analysis. The BG level was expressed as the average value ± standard error (SE). For comparison of test results between groups, Bonferroni multiple test was performed, and it was judged as a significant difference when the risk rate was less than 5% ($p < 0.05$) in a two-sided test.

Ethical standards

This study was conducted in compliance with the Declaration of Helsinki (revised at the 2013 WMA Fortaleza General Assembly) and the ethical guidelines for human-based medical research (notification by Ministry of Education, Culture, Sports, Science and Technology [MEXT]

Table 3. Nutrition facts of test foods.

Test foods	Serving unit (g)	Energy (kcal)	Protein (g)	Fat (g)	Carbohydrate (g)	Fiber (g)	Citric acid (g)
A	200	294	4.2	0	67.8	0.6	0.0
B	215	299	4.2	0	69.2	0.6	0.95
C	230	304	4.2	0	70.6	0.6	1.9

Test foods **A**, cooked rice; **B**, lemon juice (15 g) before cooked rice; **C**, lemon juice (30 g) before cooked rice.

and Ministry of Health, Labour and Welfare [MHLW]). The test content was fully explained to the subjects in advance. The test was implemented after the applicant requested participation in the test and received a voluntary consent form. This study was conducted under the deliberation and approval of the Ethics Review Committee of Doshisha University (application No. 18039) and Sapporo Holdings Group Research Ethics Committee (reception No. 19-005). Concurrently, this test was registered in the public database established by the National University Hospital Meeting (UMIN Test ID: 000034009).

Results

Safety evaluation

There were no reports of adverse events in this study (data not shown).

Efficacy evaluation

In this study, none of the subjects met the exclusion criteria. Therefore, all 12 participants were included for the efficacy analysis.

Effect of ingestion of lemon juice and cooked rice on postprandial BG level

Table 4 shows the changes in BG levels after the start of the test. There was no significant difference in fasting BG levels (0 min) before ingesting the test foods **A** to **C**. The BG level of the subjects increased after ingestion of each test food, reached the maximum value after 45 min, and then reduced until after 120 min. The BG level at each measurement time was slightly different between the test foods, but it was not significant.

The transition of ΔBG is shown in ***Fig. 1***. ΔBG increased in all test foods **A** to **C** until 45 min after the start of the test.

Table 4. Blood glucose level transition after a test food intake.

Time	A (mg/dL)	B (mg/dL)	C (mg/dL)
0 min	73.8 ± 4.0 (8.8)	77.3 ± 3.0 (6.5)	73.7 ± 4.7 (10.2)
15 min	95.8 ± 5.2 (11.4)	101.5 ± 7.4 (16.4)	89.8 ± 5.1 (11.3)
30 min	129.8 ± 5.7 (12.5)	133.0 ± 6.2 (13.7)	115.3 ± 4.9 (10.8)
45 min	143.5 ± 6.3 (13.8)	141.3 ± 5.9 (12.9)	126.8 ± 5.3 (11.7)
60 min	133.4 ± 8.2 (18.0)	127.8 ± 7.4 (16.4)	118.3 ± 6.2 (13.6)
90 min	110.3 ± 7.4 (16.2)	106.0 ± 5.2 (11.3)	101.2 ± 5.1 (11.3)
120 min	99.5 ± 3.8 (8.4)	91.8 ± 3.9 (8.6)	93.3 ± 4.2 (9.2)

Results are expressed as mean ± standard error and parentheses show 95% confidence interval, n = 12. Test foods **A**, cooked rice; **B**, lemon juice (15 g) before cooked rice; **C**, lemon juice (30 g) before cooked rice.

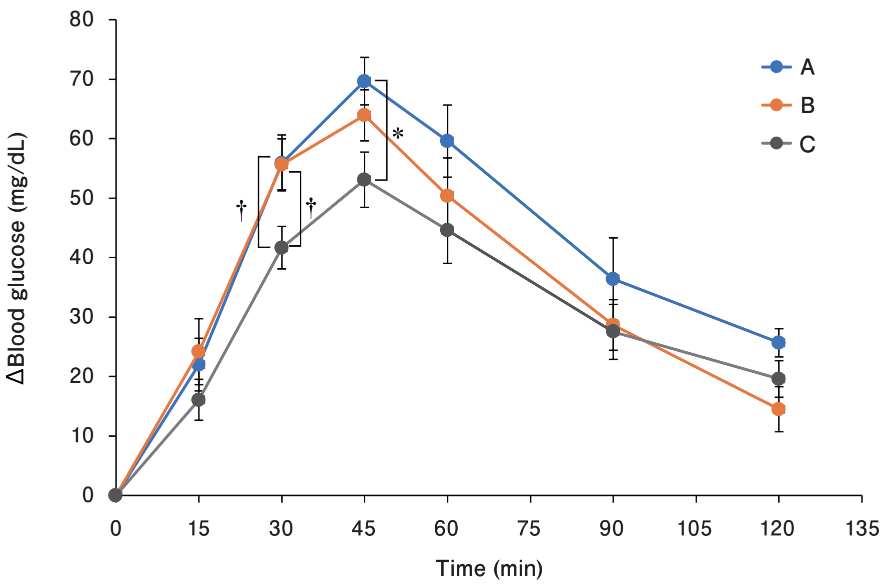

Fig. 1. **Fluctuation of the blood glucose level at the time of intaking lemon juice ahead of rice.**

Results are expressed as mean ± standard error, n = 12, * p < 0.05, † p < 0.1 by Bonferroni test. Test foods **A**, cooked rice; **B**, lemon juice (15 g) before cooked rice; **C**, lemon juice (30 g) before cooked rice.

After 30 minutes, ΔBG of test food **C** tended to be lower than that of test foods **A** and **B** ($p < 0.1$). ΔBG showed the highest value 45 min after ingesting the test foods **A** to **C**, and ΔBG of **C** was lower than that of **A** ($p < 0.05$). ΔBG of **A** to **C** decreased from 45 min to 120 min. The average value of ΔBG at each time was lower in **B** and **C** than in **A**, however, the difference was not significant.

ΔCmax was **A**: 71.3 ± 4.2 mg/dL, **B**: 67.4 ± 4.2 mg/dL, **C**: 56.8 ± 3.6 mg/dL (*Fig. 2*). ΔCmax of **C** was 20.3 % (−14.5 mg/dL) lower than in **A** ($p < 0.05$).

The iAUC was **A**: 5,032 ± 433 mg/dL・min, **B**: 4,368 ± 354 mg/dL・min, **C**: 3,784 ± 323 mg/dL・min (*Fig. 3*). The iAUC of **C** tended to be 24.8 % (−1,248 mg/dL・min) lower than that of **A** ($p < 0.1$).

Discussion

Postprandial hyperglycemia suppression effect of lemon juice

For the purpose to examine the effect of lemon juice on postprandial BG levels when ingesting cooked rice, the effects on postprandial BG changes were compared and verified under the following three test foods: A single ingestion of cooked rice (**A**) as a standard, and 15 g (**B**) or 30 g (**C**) of lemon juice before ingested rice.

The intake of test food **C** was lower than that of **A** in ΔBG ($p < 0.1$) after 30 min and in ΔBG ($p < 0.05$), ΔCmax ($p < 0.05$), and iAUC ($p < 0.1$) after 45 min. The test food **B** was lower than that of **A** in ΔBG (15.4 %), ΔCmax (5.5 %) and iAUC (13.2 %) after 60 min, but that was not significant.

When the effects of test foods **B** and **C** were compared with those of **A**, reduction in ΔBG, ΔCmax and iAUC was observed depending on the intake of lemon juice. Therefore, the inhibitory effect on postprandial hyperglycemia was considered to be the effect of the components contained in lemon juice.

The lemon juice used in the test contained 6.3% citric acid. The amount of citric acid in the test food calculated from the intake was **B**: 0.95 g and **C**: 1.9 g (*Table 3*). Thus, it was estimated that the effective amount of citric acid for suppressing postprandial hyperglycemia when ingesting 200 g of cooked rice was 1.9 g.

It has been already reported that the intake of one grapefruit prior to bread can suppress postprandial hyperglycemia [8]. The amount of citric acid contained in one grapefruit (about 200 g) is estimated to be about 2 g [14], that was comparable to 30 g of lemon juice (test food **C**) in this study. As well as citric acid, lemon contains various organic acids such as ascorbic acid, malic acid, oxalic acid, and acetic acid [15]. Vinegar [6] and plain yogurt [9] have been reported to suppress postprandial hyperglycemia when food containing acid is ingested before carbohydrate intake. It has been reported that the postprandial hyperglycemia suppressing action of acetic acid contained in vinegar involves delayed gastric emptying [16], α-glucosidase inhibition [17], and improvement of glucose metabolism [18]. The inhibitory effect of plain yogurt on postprandial hyperglycemia has been reported to relate to the gelation of digests by lactate contained in whey [19], the energy production by mitochondria in muscle tissue via monocarboxylate transporter [21], the elongated gastric emptying by suppressing the gastrin secretion due to stimulated cholecystokinin (CCK) and secretin release [20], the elevated incretin secretion by whey peptide [22]. The organic acids other than citric acid may be involved in the suppressing action of lemon juice on postprandial hyperglycemia. Concurrently, it has been reported that polyphenols contained in fruits have an α-glucosidase inhibitory effect [23], that has shown also in lemon peel extract [24]. Taken together, these findings suggest that the postprandial hyperglycemia-suppressing action of lemon juice may have been due to the organic acids, mainly citric acid, and polyphenols contained in lemon.

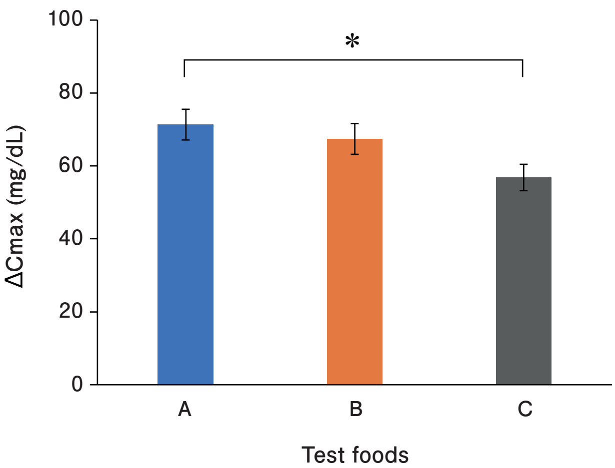

Fig. 2. **The amount of maximum blood glucose level change (ΔCmax) after intaking test food.**

Results are expressed as mean ± standard error, n = 12, * $p < 0.05$ by Bonferroni test. Test foods **A**, cooked rice; **B**, lemon juice (15 g) before cooked rice; **C**, lemon juice (30 g) before cooked rice.

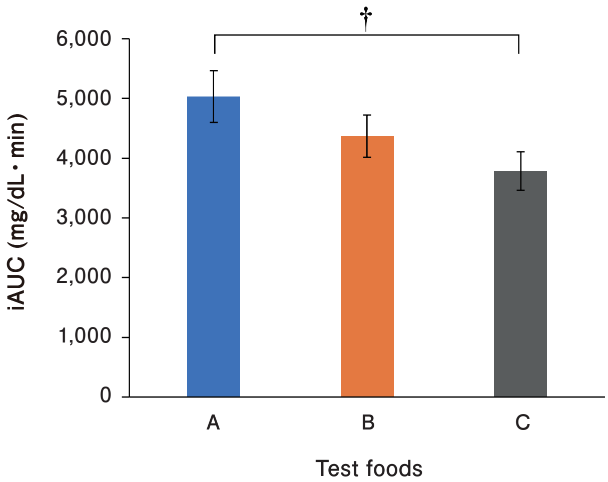

Fig. 3. **The area under curve blood glucose level change (iAUC) after intaking test food.**

Results are expressed as mean ± standard error, n = 12, † $p < 0.1$ by Bonferroni test. Test foods **A**, cooked rice; **B**, lemon juice (15 g) before cooked rice; **C**, lemon juice (30 g) before cooked rice.

Reduction of glycative stress by suppressing postprandial hyperglycemia

Measures for reducing glycative stress include suppressing postprandial hyperglycemia, inhibition of the production and accumulation of AGEs, and reducing the intake of dietary AGEs[2,3]. Since postprandial hyperglycemia leads to excessive secretion of insulin, repeated extreme hyperglycemia is involved in the induction of insulin resistance[25]. It has also been reported that blood levels of glycation intermediates, *i.e.* 3-deoxyglucosone, glyoxal, and methylglyoxal, increase in response to an elevation in postprandial BG[26]. Methylglyoxal in blood damages vascular endothelial cells[27]. Therefore, suppression of postprandial hyperglycemia may prevent tissue or organ damage secondary to microangiopathy. On the other hand, the dietary guidance to eat vegetables first prior to staple food may continue to suppress postprandial hyperglycemia, thus is linked to HbA1c reduction and prevention of complications in diabetic patients[28]. There is also a meta-analysis that the habit of eating fruits reduces the risk of type 2 diabetes[29]. Taken together with these findings, the dietary habit of ingesting a beverage or food containing lemon juice before meal may reduce glycative stress by suppressing postprandial hyperglycemia, thus contributing to the prevention of aging and age-related diseases.

Conclusion

This study showed that a diet that ingest lemon juice prior to rice suppressed postprandial hyperglycemia that was observed when 30 g of lemon juice was taken. A dietary habit of ingesting a beverage containing lemon juice before meals may reduce glycative stress by suppressing postprandial hyperglycemia, and may contribute to the prevention of aging and disease progression.

Conflict of Interest Statement

This research received support from Pokka Sapporo Food & Beverage Ltd.

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