Original Article

Tomato juice preload has a significant impact on postprandial glucose concentration in healthy women: A randomized cross-over trial

Yuuki Saito RD[1], Ayasa Nitta RD[1], Saeko Imai PhD[1], Shizuo Kajiyama MD[2,3], Takashi Miyawaki MD[1], Neiko Ozasa MD[4], Shintaro Kajiyama MD[5], Yoshitaka Hashimoto MD[3], Michiaki Fukui MD[3]

[1]*Department of Food and Nutrition, Kyoto Women's University, Kyoto, Japan*
[2]*Kajiyama Clinic, Kyoto, Japan,*
[3]*Department of Endocrinology and Metabolism, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kyoto, Japan,*
[4]*Department of Cardiovascular Medicine, Kyoto University, Graduate School of Medicine, Kyoto, Japan,*
[5]*Japanese Red Cross Kyoto Second Hospital, Kyoto, Japan*

Background and Objectives: Our aim was to evaluate the effect of consuming tomato juice before carbohydrate on postprandial glucose concentrations in healthy women. **Methods and Study Design:** In this randomized controlled cross-over study, 25 healthy women (age 21.6±3.8 years, HbA1c 5.3±0.2 %, mean±SD) consumed either 200 g of tomato juice, tomato, or water (control) at 30 min before consuming 200 g of boiled white rice at 9:00 and consumed identical lunch at 13:00 for 3 days. The blood glucose concentrations were measured by self-monitoring blood glucose at 0, 30, 45, 60, 90, 150, and 210 min pre- and post-breakfast, and at 0, 30, 60, 120, 150, and 180 min pre- and post-lunch. The concentration of postprandial glucose, incremental glucose peak (IGP), and incremental area under the curve for glucose after the test meals were compared among 3 days. **Results:** Incremental blood glucose concentrations at 60 min (2.32±0.16 vs 2.97±0.19 mmol/L, $p<0.05$, mean±SEM), 90 min (2.36±0.23 vs 3.23±0.24 mmol/L, $p<0.01$), and IGP (2.77±0.19 vs 3.68±0.22 mmol/L, $p<0.001$) in consuming tomato juice 30 min before carbohydrate were all significantly lower than those of water, while IGP of consuming tomato was tended to be lower than that of water (2.82±0.19 mmolL, $p=0.023$). No significant difference was observed in glycaemic parameters after consuming lunch among 3 days. **Conclusions:** Consuming tomato juice half hour before carbohydrate ameliorates the postprandial blood glucose concentrations, although total amounts of energy and carbohydrate of tomato juice are higher than those of water.

Key Words: diet, tomato juice, vegetable, postprandial glucose, carbohydrate, diabetes

INTRODUCTION

Postprandial hyperglycemia promotes arteriosclerosis in people with and without diabetes. Hyperglycemia causes vascular endothelial disorders and inflammation, as a results to develop arteriosclerosis, cerebral infarction, and myocardial infarction.[1] Thus, reducing the blood glucose excursion is effective to decrease the risk of the macrovascular complications. Even for healthy individuals as well as people with diabetes, suppressing postprandial glucose concentration is one of the keys for extension of healthy life expectancy.

We have reported that a simple and easy meal plan of consuming vegetables first and carbohydrates last was effective to suppress the postprandial glucose concentrations and insulin secretion in people with and without diabetes[2-6] and this method is widely used for dietary education for patients with diabetes and healthy individuals in Japan.[7,8] A follow-up study of meal sequence was conducted and significant effects were confirmed on obese type 2 diabetes patients in the United States.[9]

However, according to the National Health and Nutrition Survey in Japan, the average vegetable intake was 276.5 g, which was below the target of 350 g that was recommended by Japanese Ministry of Health, Labor and Welfare.[10] The Dietary Guidelines for Americans by the United States Department of Agriculture (USDA) recommended 2 and half cups of vegetable intake per day for a reference 2,000 kcal intake.[11] Despite intensive public educational campaigns, surveys showed that 70% of U.S. people do not reach vegetable intake of the USDA rec-

Corresponding Author: Prof. Saeko Imai, Department of Food and Nutrition, Kyoto Women's University, 35 Kitahiyoshi-cho, Imakumano, Higashiyama-ku, Kyoto, 605-8501, Japan.
Tel: +81-75-531-7128; Fax: +81-75-531-7170
Email: imais@kyoto-wu.ac.jp; poooch@hotmail.co.jp
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ommendation, and surprisingly 25% of people do not eat vegetable at all.[12] There are several reasons for low vegetable intake, such as economic burden, lack of knowledge of the benefits of vegetable intake, low availability of fresh products, taste preference, and limited cooking time and skills. Therefore eating vegetables every day is not easy for many people.

A Mediterranean diet has been associated with broad healthy benefits on human health[13] and one of its signature food is tomato. Epidemiologic and intervention trials of tomato juice have focused on serum lipids concentrations[14,15] whereas the effect on postprandial blood glucose has rarely been investigated. Tomato juice is easy to consume and lower cost than fresh vegetable, therefore it is important to approve if consuming tomato juice suppress the postprandial blood glucose concentrations as well as consuming vegetables. In this randomized controlled cross-over study, we explored the effect of tomato juice on postprandial glucose response after consuming breakfast. In addition, we explored the glycaemic response to lunch to clarify how long the effect of consuming tomato juice continued in healthy individuals.

METHODS

Subject of study

We recruited volunteers as research participants in Kyoto Women's University (Supplemental Figure). Exclusion criteria are as follows. (1) People with type 1 and type 2 diabetes (2) taking drugs that affect blood glucose concentrations (3) pregnant or willing to become pregnant (4) smoking more than 40 cigarettes per day or drinking 50 ml alcohol per day (5) people with mental illness (6) people who were considered inappropriate for the study by the doctor. This study was conducted after complying with the ethical guidelines for medical research involving human subjects in accordance to the Helsinki Declaration. The study was approval by the Clinical Research Review Committee in Kyoto Women's University (30-5) and registered UMIN-CTR (000034944). The study purpose, design, and risks of the study were explained to each participant and the written informed consent was obtained prior to the study. The study was conducted between Nov. 2018 and Oct. 2019.

Test meal

The composition and macronutrient content of the test meals as breakfast were shown in Table 1. The nutritional contents of the test meals were analyzed by computer software (Microsoft Excel Eiyokun for Windows ver.7.0 Kenpakusya, Tokyo, Japan). Participants consumed either 200 g of tomato juice (Kagome Co., Ltd., Tokyo), 200 g of tomato, or 200 g of water (control) at 30 min before consuming 200 g of boiled white rice with herb salt (0.7 g of salt, Mishima Foods Co., Ltd., Hiroshima, Japan) for 3 separate mornings (Figure 1). The amounts of nutrients in tomato and tomato juice were adjusted to be equal, but the amount of energy, carbohydrate content, and dietary fiber in water (control) were less than tomato and tomato juice (Table 1). All participants consumed identical lunch at 13:00 consisting of 100 g of tomato, 80 g of spinach, 200 g of boiled white rice, and the frozen lunch box of fried fish and vegetable (Tokatsu Foods, Yokohama, Japan) with energy 624 kcal, protein 25.1 g, lipid 11.5 g, carbohydrate 104.0 g, and dietary fiber 8.1 g for 3 days.

Study method

Three weeks prior to the study, the anthropometric measurements and blood samples of participants were examined in Rakuwakai Toji Minami Hospital. Fasting blood glucose (FBG) was measured using amperometic method and Haemoglobin A1c (HbA1c) were determined by high-performance liquid chromatography (HPLC) method. This study is a randomized controlled three-treatment cross-over within-participant clinical trial (Figure 1 and Supplemental Figure). The participants consumed 200 g of tomato juice, tomato, or water at 8:30 and 30 min later consumed 200 g of boiled white rice and consumed lunch at 13:00 (Figure 1). All meals were prepared and served by the research group on 3 days at Kyoto Women's University. Each participant performed the capillary finger pricks (Gentlet, Sanwa Chemical Institute, Nagoya, Japan) and blood glucose analyses with self-monitoring blood glucose (SMBG) device (Glutest neo alpha, Sanwa Chemical Institute, Nagoya, Japan). The blood glucose concentrations were measured at 0, 30, 45, 60, 90, 150, and 210 min pre- and post-breakfast and at 0, 30, 60, 120, 150, and 180 min pre- and post-lunch (Figure 1). The

Table 1. Test meals of breakfast with tomato juice, tomato, and water (control) and macronutrient content of each meal[†]

	Tomato juice	Tomato	Water (control)
Boiled white rice (g)	200	200	200
Tomato (g)	—	200	—
Tomato juice (g)	200	—	—
Energy (kcal)	379	377	339
Carbohydrate (g)	81.9	81.5	74.1
Boiled white rice (g)	73.6	73.6	73.6
Shiso seasoning (g)	0.5	0.5	0.5
Tomato(g)	—	7.4	—
Tomato juice (g)	7.8	—	—
Dietary fiber (g)	2.2	2.8	0.8
Fat (g)	0.6	0.8	0.6
Protein (g)	7.0	6.6	5.2
Salt (g)	1.2	0.7	0.7

[†]The nutritional contents of the test meals were analyzed by computer software (Microsoft Excel Eiyokun for Windows ver.7.0 Kenpakusya, Tokyo, Japan).

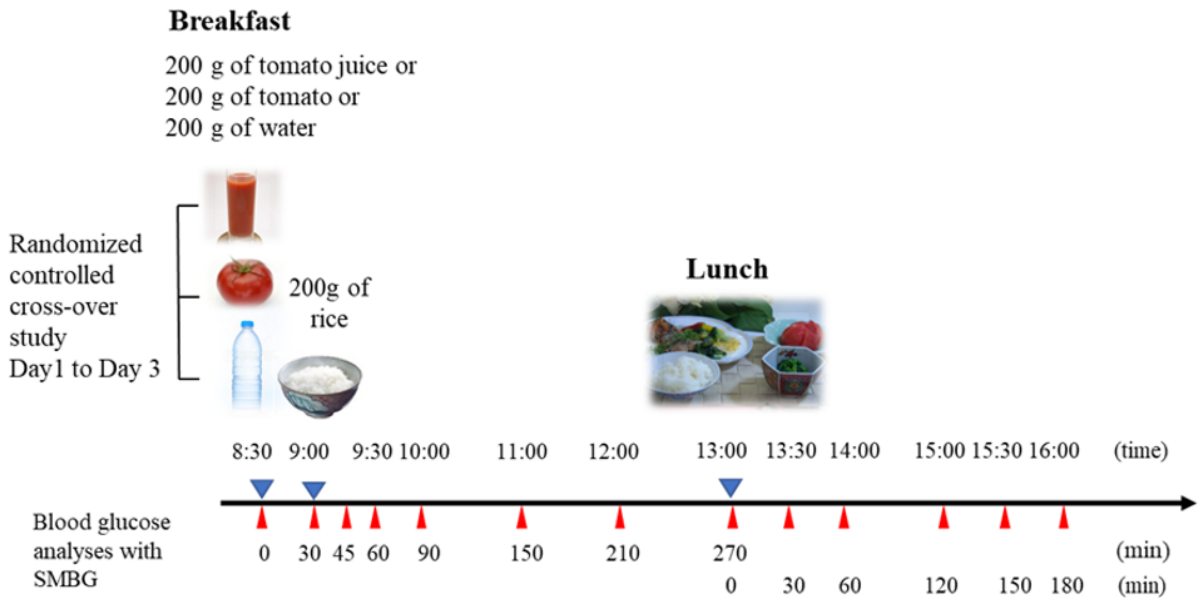

Figure 1. The study protocol: all participants consumed 200 g of tomato juice, tomato, or water at 8:30 and 30 min later consumed 200 g of boiled white rice and consumed identical lunch with main dish, vegetable, and boiled white rice at 13:00. Each participant performed the capillary finger pricks and blood analyses with self-monitoring blood glucose (SMBG) device. The blood glucose concentrations were measured at 0, 30, 45, 60, 90, 150 and 210 min pre- and post-breakfast and at 0, 30, 60, 120, 150, and 180 min pre- and post-lunch.

incremental glucose concentrations, incremental glucose peak (IGP), and incremental area under the curve for glucose (IAUC) after the test meals were compared among 3 days.

Data analysis

Sample size of 19 participants conferred a 90% power to detect a 5% difference (G*Power 3.1, Heinrich-Heine-Universität Düsseldorf, Germany) in incremental glucose peak (IGP) based on our previous study of eating vegetable before carbohydrate in healthy individuals.[3] Twenty five participants were enrolled and completed the study. Incremental blood glucose concentrations and IGP were calculated by subtracting the blood glucose concentration of baseline at 8:30 for breakfast and at 13:00 for lunch. IAUC were calculated by trapezoidal method. As a normal distribution and homogeneity of all glycaemic parameters could not be confirmed by Shapiro-Wilk and Levene test, we performed a paired comparison by Wilcoxon matched-pairs signed-rank test followed by post hoc Bonferroni's inequality (p<0.017) when Friedman's test revealed significant effects for glycaemic parameters (p<0.05). All analyses were performed with SPSS Statistics version 22 software (IBM Corp., Armonk, NY, USA). The data are reported as means ± standard error of the mean (SEM) unless otherwise stated.

RESULTS

Twenty five healthy women (age 21.6±3.8 years, body weight 52.2±6.7 kg, BMI 21.0±1.8 kg/m^2, FBG 4.9±0.29 mmol/L, HbA1c 5.3±0.2%: mean±SD) enrolled and completed the study. The incremental blood glucose concentrations were shown in Table. 2. When participants consumed tomato and tomato juice, the incremental blood

Table 2. Incremental blood glucose concentrations after consuming test meals with tomato juice, tomato, and water in healthy women (n=25)

	Tomato juice (mmol/L)	Tomato (mmol/L)	Water (control) (mmol/L)
30 min after test meals (9:00)	0.54±0.11†	0.84±0.09	0.09±0.07$^{**\#\#}$
45 min (9:15)	0.81±0.10	1.12±0.15	0.66±0.12
60 min (9:30)	2.32±0.16	2.22±0.18	2.97±0.19*
90 min (10:00)	2.36±0.23	2.43±0.21	3.23±0.24**
150 min (11:00)	1.41±0.15	1.29±0.17	1.60±0.14
210 min (12:00)	0.74±0.17†	1.17±0.21	1.05±0.15
270 min (13:00)	0.37±0.17	0.39±0.19	0.36±0.12
30 min after lunch (13:30)	1.30±0.20	1.43±0.13	1.62±0.20
60 min (14:00)	1.28±0.26	1.11±0.22	1.23±0.19
120 min (15:00)	0.85±0.21	0.79±0.17	0.94±0.14
150 min (15:30)	0.84±0.22	1.08±0.20	0.81±0.17
180 min (16:00)	0.76±0.21	1.08±0.16	0.93±0.17

The incremental blood glucose concentrations were calculated each blood glucose concentration from the fasting value at 8:30.
Data are mean±SEM.
Tomato juice vs Water (control) $^{*}p$<0.05, $^{**}p$<0.01. Tomato vs Water (control) $^{\#\#}p$<0.01. Tomato juice vs Tomato $^{\dagger}p$<0.05.

glucose concentration at 9:00 were higher than that of water (control), however, after consuming boiled white rice at 60 min (9:30) and 90 min (10:00), the incremental blood glucose concentrations of tomato juice were significantly lower than those of water (Table 2). There was no significant difference in incremental blood glucose concentrations between tomato juice and tomato, except incremental blood glucose concentration of tomato juice at 210 min (12:00) was significantly lower than that of tomato (p=0.015, Table 2). Moreover, IGP of tomato juice was significantly lower than that of water (2.77±0.19 vs 3.68±0.22 mmol/L, p<0.001, mean±SEM), and IGP of tomato was tended to be lower than that of water (2.82±0.19 mmol/L, p=0.023, Figure 2A). However, IAUC 8:30-11:00 of water showed no significant difference compared to those of tomato juice or tomato (water 270±15 vs tomato juice 228±18, vs tomato 236±16 mmol/L×min, Figure 2B). No difference was observed in incremental blood glucose concentrations after consuming identical lunch at 13:00 among 3 days (Table 2).

DISCUSSION

In this acute cross-over trial, we showed that consuming tomato juice 30 minutes prior to a carbohydrate meal was effective to suppress the postprandial blood glucose concentrations compared to those of water in healthy women, despite the energy and carbohydrate contents of water were smaller than those of tomato or tomato juice. However, this acute effect of consuming tomato juice before carbohydrate on amelioration of postprandial blood glucose concentration did not last more than 4 hours, since there was no significant difference in glycaemic parameters after consuming lunch among 3 days. Interestingly, IGP of lunch was lower than that of breakfast despite the amount of energy and carbohydrate of lunch were greater than those of breakfast. This phenomenon can be explained by the second meal effect that the insulin response is enhanced at the second meal as induced by the first meal. In the present study the insulin release at lunch might be enhanced by previous glucose exposure of breakfast. Additionally, Kameyama N et al reported that the combination of main dish and vegetable with boiled rice was beneficial for lowering postprandial glucose concentrations compared to boiled rice alone because with increased incretin response without excessive increased in insulin and GIP responses.[16] Thus, this was another reason that the postprandial glucose concentrations after lunch with the combination of the main dish, vegetable, and boiled rice, showed the lower postprandial glucose concentrations compared to those of breakfast in the present study.

Our previous study of consuming vegetable before carbohydrate demonstrated 20-30% reduction of postprandial blood glucose concentration and insulin secretion compared to those of the reverse regimen of rice first in people with and without type 2 diabetes.[2-4] Thus, in this study, dietary fibers contain in tomato or tomato juice might play a role to suppress the postprandial blood glucose concentrations. Because water-soluble dietary fiber has stickiness to slow the absorption of carbohydrates and delay the transition from the stomach to the small intestine, as a result, suppress the increase of postprandial glucose concentrations.[17]

Other beneficial acute effects of tomato juice have been demonstrated such as reducing of serum cholesterol concentrations, triglyceride concentrations,[14,18] inflammatory adipokine,[19] and increasing the resting energy consumption.[20] Chronic effects of tomato, lycopene, and carotenoid intake on lower prevalence of metabolic syndrome and cardiovascular risk factors have been reported,[15,21] since high serum triglyceride concentration increases insulin resistance, reducing serum triglyceride concentrations may lead to improve glycaemic control in epidemiological research.[22] Lycopene and 13-oxo-9, 11-octadecadienoic acid (13-OXO-ODA) in tomato juice have effect of antioxidant, modulating adipokine secretion, lowering plasma glucose and serum lipids concentrations in animal or cell culture.[23,24] Therefore, tomato

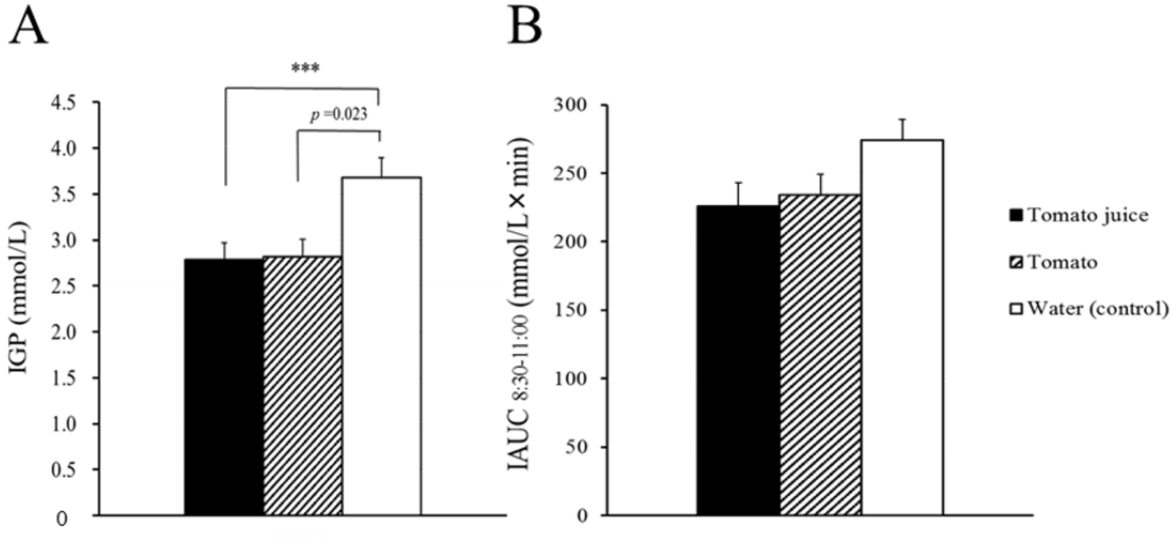

Figure 2. IGP of breakfast (A) and IAUC 8:30-11:00 (B) in each test meal (n=25). Data are mean ± SEM. IGP; incremental glucose peak, IAUC; incremental area under the curve for glucose. The IGP was calculated as the maximal blood glucose concentration from the fasting value at 8:30 over the 4-h postprandial period. The IAUC 8:30-11:00 for glucose was calculated by the trapezoidal method above the baseline value for glucose at 8:30. Tomato juice vs Water; $^{***}p$<0.001.

juice supplementation may be effective to shift circulating adipokine concentrations for antiinflammtory profile and ameliorate the postprandial glucose concentrations in human.

Similar report concluded the acute effect of vegetable juice on suppression of the postprandial blood glucose concentrations after consuming rice in healthy adults.[25] However, the results of their study have problem to apply for dietary education. Because they compared glycaemic parameters between 150 g of boiled rice with water and 110 g of boiled rice with vegetable juice in order to unify the amount of carbohydrate of test meals. Postprandial glucose concentrations positively correlate the amount of carbohydrate, so postprandial blood glucose concentrations were lower in consuming 110g of boiled rice with vegetable juice than those in consuming 150 g of boiled rice with water. Therefore, their conclusion of the acute effect of vegetable juice preload on amelioration of postprandial blood glucose concentrations is uncertain whether the effect is caused by vegetable juice preload or by the smaller amount of boiled rice.

This study has two limitations that must be considered. The first limitation of this study was that we measured blood glucose concentration by SMBG, not by laboratory analysis with venous sampling blood and did not measure hormone secretion. In our previous study, insulin secretion was suppressed 30% by consuming vegetable salad before rice compared to the reverse regimen.[2] Additionally Nishino K *et al* reported that the insulin secretion was suppressed when the participants consumed the meal sequence of vegetables → meat→ rice.[26] Consequently, in this study, consuming tomato and tomato juice prior to carbohydrate insulin secretion was presumed to be suppressed compared to that of consuming water. The second limitation was that the study was conducted in Japanese healthy women, the effect of different gender, people with diabetes or impaired glucose tolerance has not been confirmed. Care should be taken in extrapolating the present finding to other populations. However, in our series of studies on meal sequence and meal timing, the same effects on postprandial glucose concentrations were obtained in patients with type 2 diabetes as well as healthy people.[2-6,27-30] Furthermore, it is not realistic to drink tomato juice a half hour prior to a carbohydrate meal in daily life, so it is necessary to verify the effect of suppress the postprandial glucose concentrations by consuming tomato juice less than 30 time before carbohydrate. Further studies are required for detailed mechanisms of tomato juice preload of carbohydrate on glycaemic responses in other population.

Conclusion

Consuming tomato juice 30 min before carbohydrate meal significantly reduce the postprandial glucose concentrations as well as tomato preload in healthy women, although total amounts of energy and carbohydrate of tomato juice and tomato were higher than those of water. Tomato juice preload may be one of the convenient and cost effective methods to lower the postprandial glucose concentrations.

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AUTHOR DISCLOSURES

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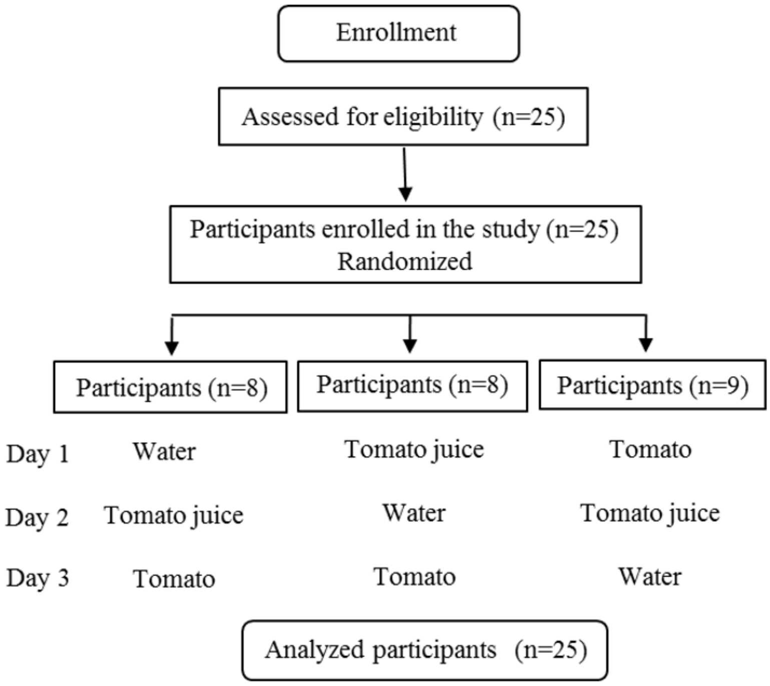

Supplemental figure 1. Flow diagram of the participants.