Brief Report

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Modulatory effects of ingesting dietary fiber and protein before carbohydrates on postprandial interstitial glucose responses

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SUMMARY: Rapid postprandial elevations in interstitial glucose contribute to the progression of type 2 diabetes and associated vascular complications. Nutritional sequencing strategies, such as consuming dietary fiber or protein before carbohydrate intake, have been proposed to attenuate glucose excursions by delaying gastric emptying, stimulating incretin secretion, and enhancing insulin responsiveness. However, observational evidence under real-world conditions remains scarce in both healthy individuals and those with diabetes. We performed an observational study including healthy participants and individuals with type 2 diabetes. All participants were equipped with a continuous glucose monitoring system (FreeStyle Libre™) for 14 days to capture interstitial glucose profiles under daily living conditions. Participants simultaneously recorded dietary intake and meal timing. Postprandial glucose excursions were evaluated by comparing carbohydrate ingestion alone with ingestion preceded by fiber and/or protein. Preceding carbohydrate intake with dietary fiber or protein was associated with significant attenuation of postprandial glucose excursions compared with carbohydrate alone. This effect was particularly evident within the first 120 minutes after eating and was most pronounced when fiber and protein were consumed in combination. Attenuation occurred in both healthy individuals and participants with type 2 diabetes, though the magnitude of suppression varied across groups. Our findings indicate that consuming fiber and protein prior to carbohydrate intake can substantially mitigate rapid postprandial glucose rises. These results support the physiological rationale for macronutrient sequencing and underscore the potential of simple, practical dietary strategies to improve glycemic control in daily life among both healthy individuals and those with diabetes.

Keywords: Continuous glucose monitoring (FreeStyle Libre™), postprandial glucose excursions, macronutrient sequencing, type 2 diabetes mellitus and healthy individuals

1. Introduction

The global prevalence of diabetes has markedly increased in recent decades, mainly driven by the continuous rise in type 2 diabetes mellitus (T2DM). According to the International Diabetes Federation (*1*), more than 537 million adults aged 20–79 years were living with diabetes in 2021, corresponding to a prevalence of 10.5%, and the numbers are projected to continue rising. In 2021, marking the centenary of the discovery of insulin, the World Health Organization launched the Global Diabetes Compact to accelerate efforts to prevent diabetes and ensure universal access to care, underscoring the urgent need for global action (*2*).

Shared risk factors underlying the rise in T2DM include urbanization, population aging, reduced physical activity, and increasing rates of overweight and obesity. These observations indicate that T2DM is, to a significant extent, preventable through lifestyle modification, particularly dietary management.

Postprandial hyperglycemia plays a key role in the development of diabetic vascular complications and thus represents a central target of dietary therapy (*3,4*). The amount and type of dietary carbohydrate are primary determinants of postprandial glycemic responses, with the total carbohydrate intake being the strongest predictor (*5*). Dietary research in diabetes has traditionally focused on nutrient quantity and composition, but recent attention has shifted toward the influence of food order on glycemic excursions. Several studies have demonstrated that consuming vegetables (*6*), fish or meat (*7*), whey protein (*8*), or olive oil (*9*) before carbohydrate intake can attenuate postprandial glycemic excursions in patients with T2DM. However, few studies have examined the combined effects of vegetables and protein, and comparative investigations involving both healthy individuals and patients with T2DM remain limited.

Therefore, this study aimed to evaluate the effects of pre-meal vegetable consumption, alone or in combination with protein, on postprandial glucose responses in both healthy individuals and patients with T2DM.

2. Methods

2.1. Participants

This study was conducted between 2020 and 2023 at Kraft Co., Ltd. and Meiji Pharmaceutical University. Healthy adults and patients diagnosed with T2DM were recruited. Written informed consent was obtained from all participants prior to enrollment. Exclusion criteria for healthy participants included (I) myocardial infarction or stroke within 6 months; (II) angina, heart failure, or severe arrhythmia; (III) diagnosis of diabetes; (IV) chronic obstructive pulmonary disease; (V) acute joint pain, arthritis, lumbago, or neuralgia; (VI) acute pneumonia or hepatitis; (VII) use of implantable medical devices (contraindicated with FreeStyle Libre™); and (VIII) physician-directed dietary restrictions or difficulty in food intake due to dysphagia or anorexia. A total of 34 healthy participants and 4 patients with T2DM were deemed eligible.

The study protocol was approved by the Ethics Committee of Meiji Pharmaceutical University (Approval No. 202020) and conducted in accordance with the Declaration of Helsinki.

2.2. Glucose Monitoring

The blood glucose level was evaluated by measuring the glucose level in the interstitial fluid using a minimally invasive continuous glucose monitoring system, FreeStyle Libre™ (Abbott Japan, Tokyo Minato-ku) (Figure 1), which does not require blood sampling and has a high correlation with the blood glucose level (*10*).

Attached to the upper arm, the sensor automatically recorded glucose levels every 15 min for up to 14 days without requiring participant or clinician intervention. Considering that glucose readings are less stable during the first 2 days after sensor placement, all experimental sessions were initiated from day 3 onward.

2.3. Experimental procedures

Participants wore the glucose sensor for 14 consecutive days and recorded dietary intake and meal times in a diary. After a fasting period of at least 3 h (water only), participants consumed two rice balls (salmon onigiri, Seven-Eleven Japan, Tokyo Chiyoda-ku). Three test conditions were applied: (I) rice balls alone, (II) rice balls preceded by salad (lettuce mix with Japanese-style dressing), and (III) rice balls preceded by salad with chicken breast (plain "salad chicken"). In condition (III), participants consumed the salad/chicken salad first, followed immediately by the rice ball. The order of interventions was randomized across days. For 3 h postprandially, participants refrained from vigorous exercise and from consuming anything other than water.

All test meals were commercially available products from Seven-Eleven convenience stores, chosen for their wide availability, ensuring standardized access and feasibility for all participants (Table 1).

2.4. Statistical analysis

Data were analyzed using Microsoft® Excel® version 2108 and BellCurve for Excel version 4.09. Friedman test was used to compare mean values, expressed as the mean ± standard error (SE). A *P*-value < 0.05 was considered significant.

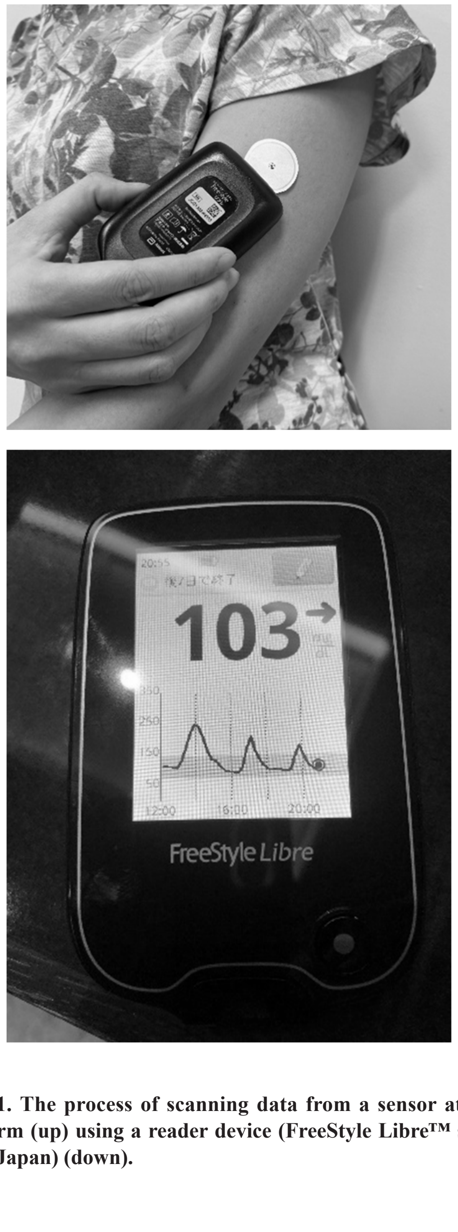

Figure 1. The process of scanning data from a sensor attached to the arm (up) using a reader device (FreeStyle Libre™ system, Abbott Japan) (down).

3. Results and Discussion

3.1. Effects of vegetable- and protein-first intake

A total of 9 healthy men, 25 healthy women, and 4 male patients with T2DM participated in the study. All participants completed all experimental sessions. The effects of consuming salad alone ("vegetable-first") or salad with protein ("vegetable & protein-first") prior to carbohydrate intake on postprandial glucose excursions were evaluated.

At baseline (0 min), interstitial glucose concentrations were significantly higher in the T2DM group (103 ± 26 mg/dL) than in the healthy group (67 ± 8.9 mg/dL) (Figure 2). In both groups, an increase in interstitial glucose was observed following rice ball consumption; however, the peak occurred at 68 ± 38 min in healthy subjects (Figure 2A) and was markedly delayed to 86 ± 38 min in patients with T2DM (Figure 2B). Baseline interstitial glucose concentrations did not significantly differ among the experimental conditions (rice ball-alone, vegetable-first, and vegetable & protein-first) in either group (healthy: 67, 67, and 66 mg/dL; T2DM: 103, 92, and 92 mg/dL).

In healthy subjects, postprandial glucose increases were evident 15 min after ingestion for both the rice

Table 1. Meal composition and nutrient content in the experimental schedule

Days	Experimental diet	Nutrition facts
1-2	Preparation period until the sensor becomes stable	
3-8	Two rice balls	Calories: 173 kcal Protein: 4.6 g Total fats: 1.7 g Total carbohydrate: 33.8 g Dietary fiber: 1.9 g
9-10	Salad → two rice balls	Calories: 234 kcal Protein: 5.8 g Total fats: 5.3 g Total carbohydrate: 38.5 g Dietary fiber: 4.5 g
11-12	Salad with steamed chicken → two rice balls	Calories: 348 kcal Protein: 29.9 g Total fats: 7.3 g Total carbohydrate: 38.5 g Dietary fiber: 4.5 g
13-14	Spare days for retests	

Day 3-14 can be in a different order.

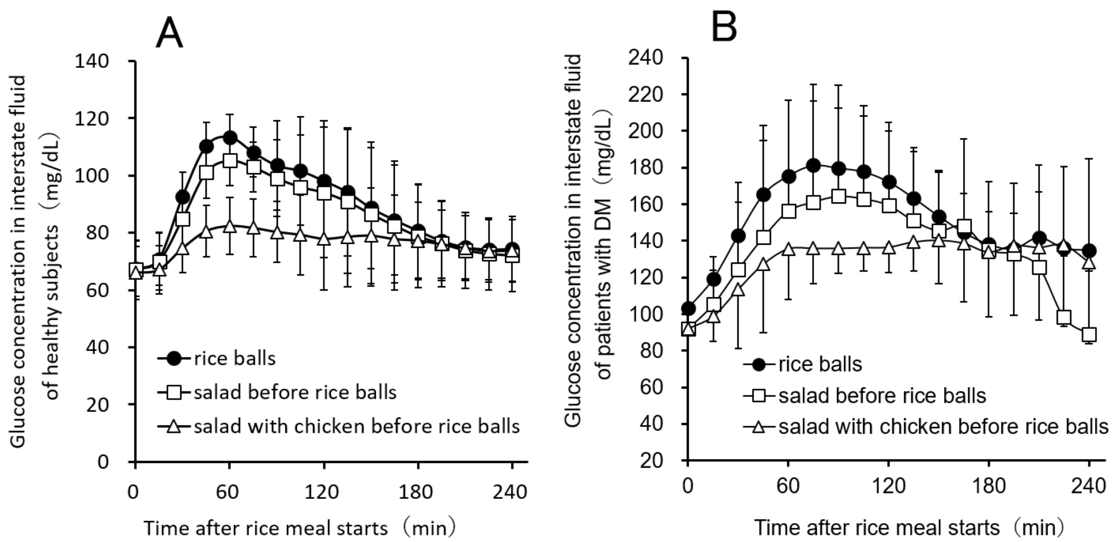

Figure 2. Glucose concentration in the interstitial fluid of healthy subjects (*n* = 34) (A) and patients with T2DM (*n* = 4) (B). A: healthy subjects, B: patients with T2DM. Closed cercle: rise balls, Open square: salad before rise balls, Open triangle: salad with chicken before rice balls.

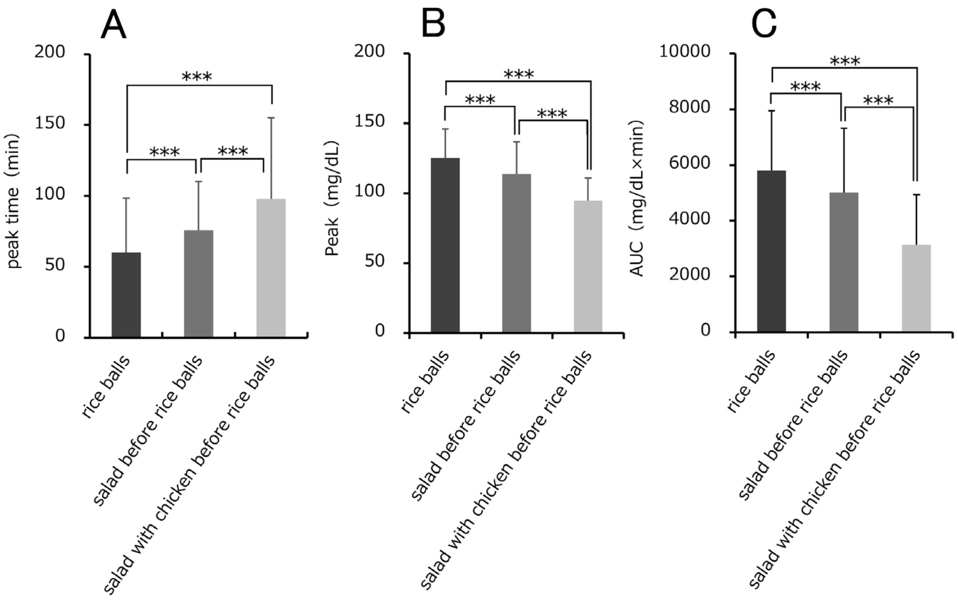

Figure 3. The time of peak (A), the peak glucose concentration in interstate fluid (B) and the AUC (C) of healthy subjects (*n* = 34). A: Peak time, B: Peak, C: AUC. ****P* < 0.001, Friedman-test.

ball-alone and vegetable-first conditions, whereas the increase was delayed to 30 min for the vegetable & protein-first condition (Figure 2A). From 30 to 120 min, glucose concentrations were lower for the vegetable-first condition than for the rice ball-alone condition ($P < 0.05$), and from 30 to 150 min, they were significantly lower for the vegetable & protein-first condition than for the rice ball-alone condition ($P < 0.05$) (Figure 2A).

3.2. Effects on peak glucose and Area Under the Curve (AUC)

When vegetables were consumed first (72 ± 34 min), the time to reach the peak glucose level was significantly delayed compared with consuming rice balls alone (68 ± 38 min) ($P < 0.001$). The delay was even greater when vegetables and protein were consumed first (110 ± 57 min) ($P < 0.001$) (Figure 3A). Peak glucose concentrations were significantly lower for the vegetable-first condition (114 ± 23 mg/dL) compared with the rice ball-alone condition (125 ± 21 mg/dL) and were further reduced for the vegetable & protein-first condition (95 ± 16 mg/dL) ($P < 0.001$) (Figure 3B). The area under the glucose concentration–time curve (AUC) was significantly lower for the vegetable-first (5,013 ± 2,302 mg/dL·min) and vegetable & protein-first (3,144 ± 1,791 mg/dL·min) conditions compared with the rice ball-alone condition (5,804 ± 2,136 mg/dL·min) ($P < 0.001$) (Figure 3C).

In the T2DM group, although no significant differences were observed, glucose concentrations from 15 to 150 min were lower for both the vegetable-first and vegetable & protein-first conditions than for the rice ball-alone condition (Figure 2B). The time to peak glucose concentration was 86 ± 38 min for the rice ball-alone condition, 120 ± 64 min for the vegetable-first condition, and 176 ± 89 min for the vegetable & protein-first condition; the peak was slightly delayed for the vegetable & protein-first condition compared with the rice ball-alone condition, but the difference was not significant (Figure 4A). The peak glucose level tended to be lower in the condition where vegetables were consumed first (174 ± 40 mg/dL) compared with the rice-ball–only condition (193 ± 39 mg/dL), and was even lower when vegetables and protein were consumed first (169 ± 43 mg/dL) (Figure 4B). Similarly, the AUC also tended to be lower in both the vegetable-first condition (8,995 ± 8,306 mg/dL·min) and the vegetable-plus-protein-first condition (7,599 ± 4,732 mg/dL·min) compared with the rice-ball–only condition (11,956 ± 6,176 mg/dL·min) (Figure 4C).

This study demonstrated that pre-ingesting vegetables and protein, using readily available commercial food products, effectively modulated postprandial glucose responses. By employing standardized and easily accessible foods, the intervention was feasible across all participants, including those unable to prepare meals themselves. This practical design highlights the potential for translating dietary strategies into daily life as supportive measures for glycemic management. The underlying mechanisms likely involve the complementary actions of dietary fiber and protein. Fiber slows gastric emptying and delays carbohydrate absorption (*11*), while protein stimulates insulin and incretin secretion and further contributes to delayed gastric emptying. When combined, these actions produced additive effects, resulting in greater suppression of postprandial glycemia compared with fiber alone.

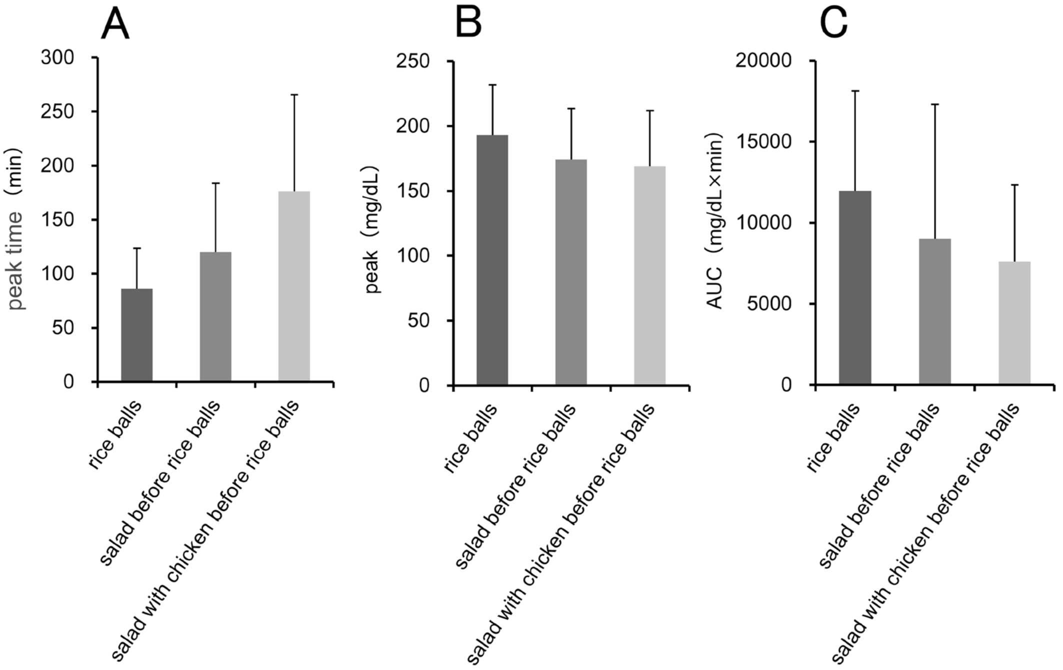

Figure 4. The time of peak (A), the peak glucose concentration in interstate fluid (B) and the AUC (C) of patients with T2DM (*n* = 4). A: Peak time, B: Peak, C: AUC.

Considerable inter-individual variability was also noted. Participants with higher insulin sensitivity exhibited smaller glycemic excursions and correspondingly modest intervention effects, whereas those with greater baseline responses experienced more pronounced benefits. Due to the limited sample size, only a trend toward reduced glucose levels was observed in the T2DM group, and further validation with a larger sample size is warranted. Such heterogeneity has been reported in previous studies (*12*) and underscores the importance of personalized approaches when applying dietary strategies in clinical practice.

Beyond mechanistic insights, this study also highlights the utility of noninvasive interstitial glucose monitoring. The method not only facilitates continuous data collection but also offers practical advantages for patients, including the avoidance of finger-prick sampling, lower cost, and real-time visualization of transient glucose levels using a smartphone. These features suggest its potential role as an educational and self-management tool for guiding dietary behavior.

Several limitations should be considered. Anthropometric and metabolic baseline data were not collected, insulin and incretin levels were not measured, and interventions were conducted at participants' homes, limiting full standardization. Furthermore, interstitial rather than blood glucose was used as the primary endpoint, and the COVID-19 pandemic restricted opportunities for more comprehensive metabolic assessments.

Future studies should involve larger and more diverse cohorts, with integrated assessments of blood glucose, insulin, incretin hormones, and indices of insulin resistance under researcher-supervised conditions. Such investigations are expected to help clarify both the physiological basis and clinical relevance of vegetable- and protein-first strategies, and further define their role as practical adjuncts to pharmacological therapy for optimizing glycemic control.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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