Original Article

Adverse effect of switching only once low-carbohydrate diet to high-carbohydrate diet on postprandial glucose concentration in healthy women

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Background and Objectives: Our aim was to evaluate the acute effect of switching low-carbohydrate diet (LCD) to high-carbohydrate diet (HCD) on glycemic parameters in healthy women. **Methods and Study Design:** Twenty-two women (age 21.7±4.0 years; HbA1c 5.3±0.3 %, mean±SD) wore flash glucose monitoring system and consumed test meals for 3 days from Day 4 to 6. Participants consumed identical HCD meals except LCD dinner on Day 5. The energy ratio of carbohydrate, fat, and protein were 64%, 21%, and 15% for HCD and 47%, 35%, and 18% for Day 5 with LCD dinner (19%, 59%, and 22%). **Results:** The incremental glucose peak (IGP, both $p<0.001$) and incremental area under the curve for glucose (IAUC, both $p<0.001$) 3h of LCD dinner were all significantly lower than those of HCD dinner on Day 4 and 6. However, after consuming LCD dinner on Day 5, IGP breakfast (2.33±0.15 vs 1.71±0.15 mmo/L, $p<0.01$), IGP lunch (3.31±0.25 vs 2.54±0.18 mol/L, $p<0.01$), IAUC 3h of breakfast (210±18 vs 136±14 mmol/L×min, $p<0.001$), mean blood glucose (5.72±0.11 vs 5.40±0.11 mmol/L, $p<0.01$), and standard deviation (1.11±0.06 vs 0.88±0.04 mmol/L, $p<0.01$) on Day 6 were all significantly higher than those of corresponding meals before LCD dinner on Day 4, in spite of consuming all identical HCD meals. The glycemic parameters returned to the levels before consuming LCD on Day 7. **Conclusions:** Consuming LCD only once is enough to cause 24-h higher postprandial blood glucose concentration in subsequent consumption of HCD in healthy women.

Key Words: low-carbohydrate, high-carbohydrate, postprandial glucose, type 2 diabetes, healthy women

INTRODUCTION

Postprandial glycemic responses to diet are highly dependent on the macronutrient composition of the meals in individuals with and without type 2 diabetes (T2DM).[1-3] Various studies have attempted to identify the ideal mix of macronutrients ratio for eating plans for people with diabetes.[1-3] However, there is no evidence of an ideal calorie ratio of carbohydrate, protein, and fat for people with and without diabetes.[1,2] The American Diabetes Association (ADA) mentioned that a "one-size-fits-all" eating plan is not evident for the prevention or management of diabetes. The nutritional counseling includes macronutrients proportion that work toward improving glycemic targets, blood pressure and serum lipids profiles, and decreasing the cardiovascular risk factors should be based on an individualized assessment of current eating patterns, preferences, and metabolic goals.[4-6]

Low-carbohydrate diet (LCD) has been shown to reduce haemoglobin A1c (HbA1c) and the need for antihyperglycemic medications in people with T2DM[3,7-9] and to decrease the body weight in people with obesity.[10,11] The ADA has confirmed the effectiveness of LCD in reducing body weight, improving glycemic control and blood lipid profiles in people with T2DM.[5]

On the other hand, the calorie restriction diet is mainly recommended to help improve glycemic control in people with T2DM in Japan.[12] The range of 50 to 65% is considered appropriate for energy ratio of carbohydrate in Japan

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The basis for this high figure is high content of carbohydrate, mainly due to traditional preference to boiled rice among Japanese people.[13] Because of that, behavior change of eating pattern from high carbohydrate diet (HCD) to LCD is not easy for Japanese people. Only a few reports relating to the effects of LCD on glycemic parameters in people with T2DM has been reported in Japan, and many of the researches were epidemiological and observational studies.[14-16]

Therefore, this clinical interventional study was elaborately designed to replace only dinner to LCD making it relatively easy to adapt to eating pattern of Japanese real-life. One characteristic of Japanese dietary habit is that Japanese consume relatively large amount of carbohydrate in breakfast and lunch, making dinner the only meal that can be used to reduce the overall consumption of carbohydrate.

The aim of the present study was to evaluate the acute effect of switching LCD to HCD with iso-caloric test meals on glycemic parameters using flash glucose monitoring systems (FGMs, FreeStyle LibrePro, Abbott Japan, Tokyo, Japan)[17] in young healthy women.

METHODS

Subjects

Volunteers were recruited from students of Kyoto Women's University. The participants had no history of any metabolic diseases. None of the participants were neither pregnant, smoker, had eating disorder, weight loss and any other special diet. Volunteers taking supplement or medications known to affect their metabolism were excluded. The purpose, the protocol, and the risks of the study were explained to each participant and all enrolled participants signed a consent form prior to the study. The study was recruited and conducted from August 2018 to September 2019. This study followed the Declaration of Helsinki and Guidelines for Good Clinical Practice. The study protocol was approved by the Ethics Committee of the Kyoto Women's University (30-4) and registered UMIN Clinical Trial Registry (UMIN 000034873).

Study design

The participants wore FGMs on the back of their left upper arm under the physician's instruction at Kyoto Women's University for 8 days. In order to obtain accurate glycemic measurements, the interventional study was started on Day 4. All participants consumed identical test meals of HCD for breakfast, lunch, and dinner from dinner on Day 3 to lunch on Day 7, except LCD was replaced with HCD for dinner on Day 5 (Figure 1). In LCD dinner carbohydrate was reduced by replacing boiled rice to tune, cheese, and mayonnaise resulting the increment of protein and fat content, but the amount of calorie was maintained equal to HCD dinner. The composition and macronutrient content of the test meals were shown in Table 1. The energy ratio of carbohydrate, fat, and protein were 64%, 21%, and 15% respectively for HCD on Day 4 (before consumption of LCD dinner) and Day 6 (after consumption of LCD dinner) whereas 47%, 35%, and 18% on Day 5 with LCD dinner of 19%, 59%, and 22%, respectively. The test meals of frozen set menu (Tokatsu Foods, Yokohama, Japan), packed tuna (Seachikin L flake, Hagoromo Foods Corporation, Shizuoka, Japan), mayonnaise (Kewpie Corporation, Tokyo, Japan), and cheese (Snow brand 6P cheese, Megmilk Snow Brand Co., Ltd., Tokyo, Japan) were provided by the study group, but rice, bread, spinach, broccoli, and tomato were prepared by the participants themselves according to the protocol prepared by the dietitians of the study group. Particularly, the participants were instructed to measure strictly the amount of boiled white rice (200 g) and white bread (90 g). The test meals were heated by microwave prior to the consumption. The test meals were consumed in the following order and time: vegetable dish for 7 min, main dish for 7 min and rice or bread for 6 min for HCD, whereas for LCD dinner vegetable dish for 7 min, the main dish for 7 min, and tune, mayonnaise, and cheese for 6 min. The participants were allowed to drink water, green tea, black tea, and coffee without sugar and milk, but neither alcohol nor sweet drinks were allowed to take. Excessive physical exercise for 2 days prior to the study and during the study period were prohibited. On Day 8,

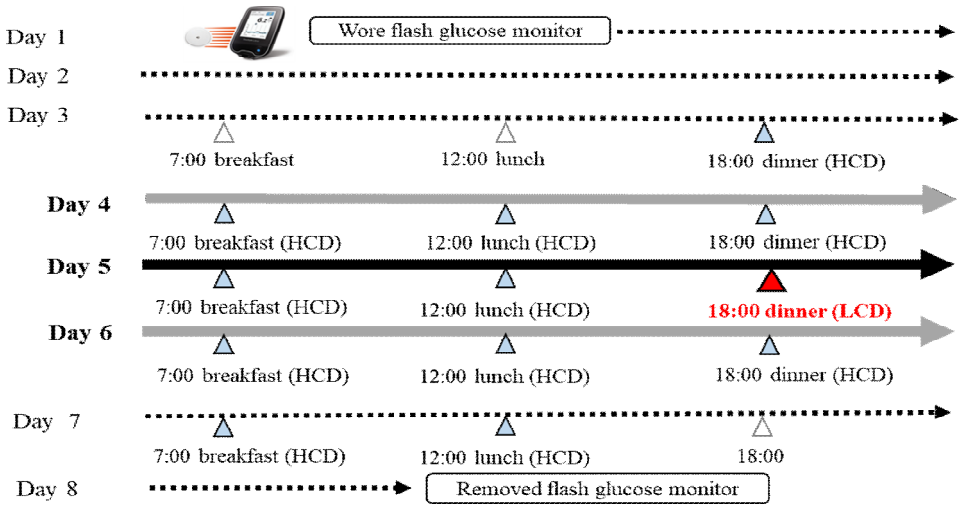

Figure 1. Study protocol. All participants consumed identical HCD meals from dinner on Day 3 to lunch on Day 7 except LCD was consumed in dinner on Day 5. Participants consumed test meals of breakfast at 07:00, lunch at 12:00, and dinner at 18:00. HCD: high-carbohydrate diet (grey triangle); LCD: low-carbohydrate diet (black triangle).

FGMs were removed by the participants themselves under the physician's management at Kyoto Women's University. The study design was explained to each participant prior and during the study period, and the participants were reminded to follow the protocol by phone call or e-mail. Each participant was instructed to record the amount of food and meal time, and these records were assessed for compliance of the study protocol by the dietitians of the study group. The participants were excluded if they did not follow the study protocol. Daily glycemic parameters during 3 days, from Day 4 to Day 6, were compared within-participant consuming identical meals with HCD and iso-caloric LCD dinner.

Measurements

The anthropometric measurements and blood sample of participants were collected in the morning after an overnight fast in two weeks before the study. Fasting plasma glucose concentration was measured by amperometric methods, and HbA1c were determined by high-performance liquid chromatography (HPLC) in Rakuwakai Toji Minami Hospital. The incremental area under the curves (IAUC) for glucose of breakfast, lunch and dinner were calculated from the baseline by the trapezoidal method. The mean amplitude of glycemic excursion (MAGE) was calculated described elsewhere.[18] The glycemic parameters were compared within-participants for 3 days from the following meals; all three HCD meals on Day 4, two HCD (breakfast and lunch) and LCD (dinner) on Day 5, all three HCD meals on Day 6 (Figure 1).

Sample size calculation and statistical analysis

A sample size of 17 participants in the current study to provide 95% power to detect 5% difference in postprandial glucose concentrations (G*Power 3.1, Heinrich-Heine-Universität Düsseldorf, Germany) were referred to our previous study of consuming identical meals by eating different speed in healthy women.[19] The primary outcome was the postprandial glucose concentrations and the secondary outcomes were IAUC for glucose. The mean blood glucose concentration, standard deviation (SD), and MAGE were calculated from 7:00 to 6:45 of the following day. We could not confirm normal distribution and homogeneity for all glycemic parameters by Shapiro–Wilk and Levene tests, so 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 parameters ($p<0.05$). The results are reported as mean ± SEM unless otherwise stated. All statistical analyses were performed using SPSS 22.0 software (IBM Corp., Armonk, NY, USA). A p value of <0.05 was considered statistically significant.

RESULTS

Twenty-two healthy women (age 21.7±4.0 years; BMI 21.1±1.7 kg/m^2, FPG 87.5±5.4 mg/dl, HbA1c 5.3±0.3%, mean±SD) were assigned and all participants were assessed for compliance of the study protocol in this clinical study. The profiles of the mean blood glucose concentration were shown in Figure 2. The postprandial blood glucose concentration of LCD dinner (Day 5) demonstrated lower than those in dinners of HCD before (Day 4) and after consuming LCD dinner (Day 6). However, on Day 6 that was day after consuming LCD dinner, the postprandial blood glucose concentrations of breakfast, lunch and dinner were all higher than those of corresponding meals consumed before LCD dinner, despite identical HCD were provided in all these meals. This may indicate that consuming LCD affects glucose metabolism not only immediately after the meal, but also continuously for the following 24 hours.

The glycemic parameters were shown in Table 2. Obviously, IGP of dinner and the IAUC 3h for glucose of

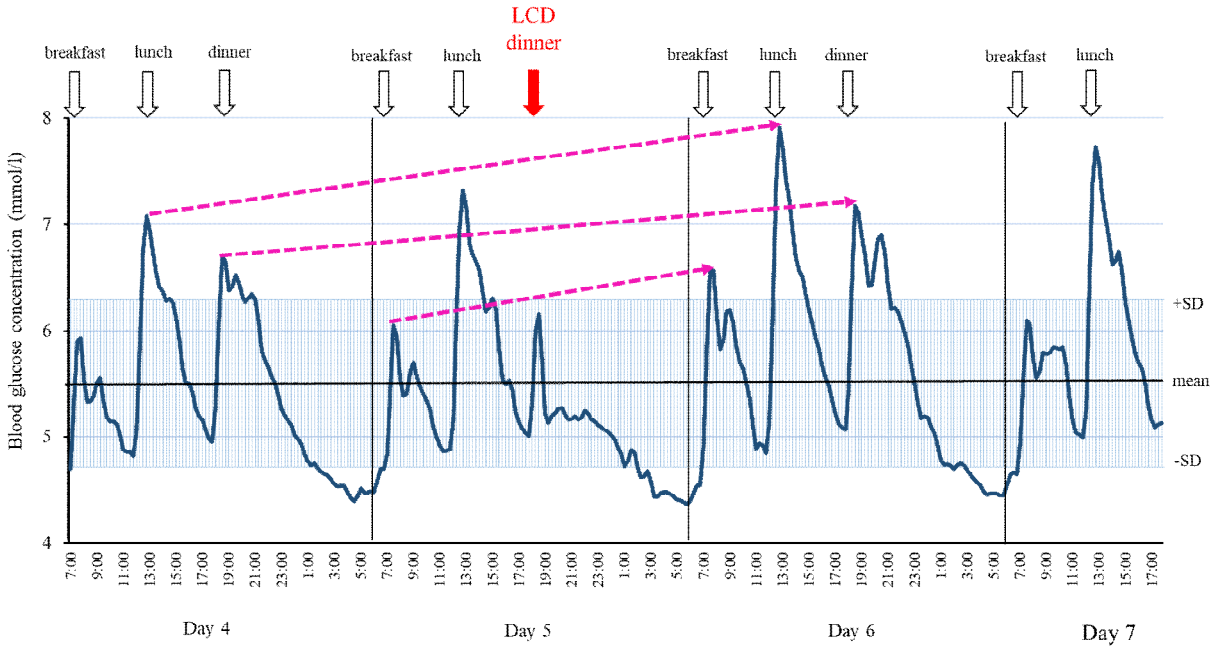

Figure 2. The mean blood glucose profiles of HCD and LCD in healthy women (n=22). The participants consumed identical HCD meals from dinner on Day 4 to lunch on Day 7 except LCD was consumed dinner on Day 5. Day 4 with all HCD before consumption of LCD dinner. The glycemic parameters were compared within-participants. HCD: high-carbohydrate diet; LCD: low-carbohydrate diet.

Table 1. The composition and macronutrient content of the test meals

	Meal	Energy (kcal)	Protein (g)	Fat (g)	Carbohydrate (g)	Fiber (g)	Detail content
HCD	Breakfast	437	18.2	12.0	70.1	5.8	white bread 90 g, tomato 100 g, broccoli 60 g, milk 200 g, strawberry jam (sugar free) 13 g
	Lunch	624	25.1	11.5	104.0	8.1	boiled white rice 200 g, frozen lunch box of fried fish with vegetable, tomato 100 g, spinach 80 g
	Dinner	689	23.6	17.4	107.6	7.8	boiled white rice 200 g, tomato 100 g, frozen lunch box of gluten-meat steak with vegetable, spinach 80 g with fried tofu 15 g
LCD	Dinner	677	37.1	44.2	34.2	7.2	tune 60 g, mayonnaise 12 g, and cheese 36 g, tomato 100 g, frozen lunch box of gluten-meat steak with vegetable, spinach 80 g with fried tofu 15 g
Day 4, 6 (HCD)	Total	1750	66.9	40.9	281.7	21.7	
Day 5 (LCD)	Total	1738	80.4	67.7	208.3	21.1	

HCD: high-carbohydrate diet; LCD: low-carbohydrate diet.
The macronutrient content of the test meals was calculated by computer software (Microsoft Excel Eiyokun for Windows Ver.7.0, Kenpakusya, Tokyo, Japan).

Table 2. Characteristics of glycemic parameters of pre-LCD on Day 4, Day 5 with LCD dinner, and post-LCD on Day 6 and Day 7 in healthy women (n=22)

Glycemic parameters	Day 4	Day 5	Day 6	Day 7
MBG (mmol/L)	5.40±0.11	5.34±0.10†††	5.72±0.11¶	-
SD (mmol/L)	0.88±0.04	0.85±0.04†††	1.11±0.06¶	-
MAGE (mmol/L)	2.67±0.14	2.52±0.12†††	3.20±0.17	-
IGP after breakfast (mmol/L)	1.71±0.15	1.70±0.12†	2.33±0.15¶	1.67±0.10 ‡‡‡
IGP after lunch (mmol/L)	2.54±0.18	2.77±0.22†	3.31±0.25¶	2.91±0.18
IGP after dinner (mmol/L)	2.06±0.20	1.12±0.12 ***†††	2.54±0.23	-
IAUC of breakfast 3h (mmol/L × min)	136±14	137±11†††	210±18¶¶¶	151±13
IAUC of lunch 3h (mmol/L × min)	251±26	271±23††	327±27	291±17
IAUC of dinner 3h (mmol/L × min)	202±26	53±9***†††	246±32	-

MBG: mean blood glucose concentration; SD: standard deviation of blood glucose concentration; MAGE: mean amplitude of glycemic excursion; IGP: incremental glucose peak; IAUC: incremental area under the curve for glucose.
Data are mean±SEM. The glycemic parameters were compared within-participants for 3 days from the following meals; all three HCD meals on Day 4; two HCD (breakfast and lunch) and LCD (dinner) on Day 5; all three HCD meals on Day 6. The mean plasma glucose, SD, and MAGE were calculated from 7:00 to 6:45 in the following day. The IAUCs for glucose of each meal were calculated by the trapezoidal method. Day 4 with all HCD before consumption of LCD dinner. Day 5 with HCD breakfast and lunch, LCD dinner. Day 6 with all HCD after consumption of LCD dinner. Day 4 vs Day 5 *** $p<0.001$, Day 5 vs Day 6 $^{\dagger}p<0.05$, $^{\dagger\dagger}p<0.01$, $^{\dagger\dagger\dagger}p<0.001$, Day 4 vs Day 6 ¶ $p<0.01$, ¶¶¶ $p<0.001$, Day 6 vs Day 7 ‡‡‡ $p<0.001$.

dinner on Day 5 showed significantly lower in LCD dinner than those of dinners of Day 4 (before consuming LCD) and Day 6 (after consuming LCD). The mean blood glucose concentration, SD, and MAGE were significantly lower on Day 5 with LCD dinner than those of after consuming LCD dinner on Day 6. However, after consuming LCD dinner on Day 6, IGP and IAUC 3h for glucose of breakfast and lunch all showed significantly higher than those of corresponding meals before consuming LCD dinner on Day 5, although all HCD meals were identical. Furthermore, IGP after breakfast and lunch, IAUC 3h for glucose of breakfast, mean blood glucose, and SD were all significantly higher on Day 6 than those on Day 4. IAUC 3h for glucose of dinner and MAGE also tended to be higher on Day 6 than those of Day 4 (both, p=0.052). IGP breakfast on Day 7 was significantly lower than that of Day 6, but there was no significant difference among IAUC 3h for glucose of breakfast, IGP lunch, and IAUC 3h for glucose of lunch on Day 7 and those of corresponding HCD meals during the study days (Table 2 and Figure 2).

DISCUSSION

We investigated the acute effect of replacing only one meal to iso-caloric LCD on glycemic parameters in young healthy women. This is the first clinical interventional study to investigate the acute effect of switching low-carbohydrate diet to high-carbohydrate diet on glycemic parameters by FGMs with fixed identical test meals for all participants. Our findings demonstrated that after consumption of one low-carbohydrate dinner, high-carbohydrate diet in the following day caused higher mean blood glucose concentration, SD, and postprandial glucose concentrations than consuming the same high-carbohydrate meals before consumption of LCD dinner. Notably, replacing with low-carbohydrate meal only once increased postprandial glucose concentration of the subsequent high-carbohydrate diet for 24 hours, since IGP breakfast on Day 7 returned to the level before consuming LCD. The adverse effect shown in the present study might explain the undesired effect previously reported in the long-term study that regaining of body weight can often be observed after quitting low-carbohydrate diet.[20] Most of all, the larger amplitude of glycemic excursions observed during consuming low-carbohydrate diet to high-carbohydrate diet in the study might increase the risk of metabolic syndrome and cardiovascular diseases for long term in healthy individuals,[21,22] and this adverse effect might remain more than 24 hours in individuals with type 2 diabetes and it increases the risk of micro and macro-vascular complications.

Numerous meta-analysis have reported the effect of LCD in reduction of body weight and HbA1c. Sainsbury E et al. reported that the meta-analysis of randomized controlled trials (RCTs) comparing a low-carbohydrate eating pattern (defined as ≤45% of calorie from carbohydrate) to high-carbohydrate eating patterns (defined as >45% of calorie from carbohydrate) found that HbA1c benefits were more pronounced in the very low carbohydrate interventions (where <26% of calorie came from carbohydrate) at 3 and 6 months, but not at 12 and 24 months.[3] In another meta-analysis comparing a low-carbohydrate eating pattern (defined as <40% of calorie from carbohydrate) to a low-fat eating pattern (defined as <40% of calorie from fat), the low-carbohydrate eating pattern improved HbA1c more, and raised HDL-cholesterol, lowered blood pressure, and resulted in greater reductions in diabetes medication for 6 months.[7] Also, in systematic review and meta-analysis comparing low-carbohydrate and high-carbohydrate eating patterns, it has been suggested that the lower the carbohydrate content, greater reduction in HbA1c was observed at durations of 1 year.[8] The Dietary Intervention Randomized Controlled Trial (DIRECT) study was conducted in obese participants among 3 dietary plans; low-carbohydrate diet, low-fat diet, and Mediterranean. Mediterranean and low-carbohydrate diet were more effective than low-fat diet on serum lipid levels and weight loss after 2 years. However, in the follow-up of 6-year period, 11% of the participants had switched to another diet, and 22% were no longer dieting. Overall, the participants in the low-carbohydrate group regained 4.1 kg of body weight after 6-year period and the changes from baseline in body weight and the lipids profiles were similar among the 3 groups after the entire 6-year-period.[20] These meta-analyses proved that low-carbohydrate eating patterns improves body weight, HbA1c, serum lipid profiles, and blood pressure, but only for the limited duration of period, which was about 1 to 2 years. After all, these researches revealed that it is difficult for any individuals to continue any dietary plan, including lower-carbohydrate diet, for long-term.[3,7,8,20] Therefore, long-term studies should focus the importance of adherence in evaluations of the effects and adverse effects of carbohydrate reduction to prevent obesity and diabetes.

One of the reasons for the adverse effect of glycemic response observed in the present study might have caused by high fat contained in low-carbohydrate dinner. Several reports mentioned that consuming low-carbohydrate/high-fat diet decreased early insulin secretion and increased postprandial glucose concentration in the following meal.[23] High fat in LCD used in the present study (59% energy ratio) might deteriorate glucose tolerance on the next day. Since consuming high fat diet elevates plasma free fatty acid (FFA) and serum triglyceride concentration, increased plasma FFA and triglyceride have possibly reduced insulin sensitivity and the first-phase insulin release, resulting deterioration in postprandial glucose concentrations after consuming LCD meal as shown in the present study.[24]

Increased postprandial blood glucose concentrations after consuming LCD meal observed in the present study might increase the risk of cardiovascular diseases,[25-28] and increased inflammatory cytokine.[29] Meanwhile, there are concerns in the safety of LCD which derived from high protein and high fat diet in LCD on renal function.[30,31] Also, the risk of the reduction in bone mineral density in non-obese adults due to the long-term calorie and carbohydrate restriction was pointed out.[32] Moreover, low carbohydrate and high protein intake was indicated to be associated with increased total mortality, particularly cardiovascular mortality in cohort studies.[33,34]

Several limitations of the present study should be mentioned. First, the present study is an acute interventional

open-labeled study of LCD on glycemic responses, therefore, it is unable to apply these effects to long-term benefits. Second, the participants of this study consisted of Japanese young healthy women, therefore, we should be cautious to translate our results to individuals with other gender, race, genetic backgrounds, lifestyle, and individuals with type 2 diabetes. Third, interstitial fluid glucose levels measured by FGM was reported to be accurate,[17,35,36] although blood glucose concentration should also be measured with other method to make our data solid. Fourth, the mechanisms under the adverse effect of glycemic spikes caused by switching LCD to HCD is not fully understood in this study, because we did not examine serum insulin, serum incretin hormones, lipid profiles, and the possibility of gluconeogenesis. Therefore, the role of insulin, incretin hormones, cytokines, FFA, and endogenous glucose production on glycemic spikes is still unclear. Additionally, the participants were prohibited the excessive physical exercise for 2 days prior to the study and during the study period, although we should have checked the physical activity. Therefore, in future studies, additional investigations are required to clarify the mechanisms under these effects of LCD and the shift from LCD to HCD in individuals with and without diabetes. Particularly, long-term studies are needed to evaluate whether the effects are sustained and amplified over long-term, because the dietary plans should be participant-centered and adherence is important in real-life eating pattern.

Conclusions

Consuming one low-carbohydrate meal caused higher postprandial glucose concentrations in subsequent consumption of high-carbohydrate meal, and the adverse effect lasted 24 hours in young healthy women.

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AUTHOR DISCLOSURES

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