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Effect of skipping breakfast for 6 days on energy metabolism and diurnal rhythm of blood glucose in young healthy Japanese males

Hitomi Ogata,[1,2,3] Momoko Kayaba,[4] Yoshiaki Tanaka,[3] Katsuhiko Yajima,[3,5] Kaito Iwayama,[3] Akira Ando,[3] Insung Park,[4] Ken Kiyono,[6] Naomi Omi,[3] Makoto Satoh,[4] and Kumpei Tokuyama[3]

[1]Graduate School of Integrated Arts and Sciences, Hiroshima University, Hiroshima, Japan; [2]Japan Society for the Promotion of Science, Tokyo, Japan; [3]Faculty of Health and Sport Science and [4]International Institute for Integrative Sleep Medicine, University of Tsukuba, Tsukuba, Japan; [5]Faculty of Health and Nutrition, Tokyo Seiei College, Tokyo, Japan; and [6]Graduate School of Engineering Science, Osaka University, Osaka, Japan

ABSTRACT

Background: Skipping breakfast has become a common trend that may lead to obesity and type 2 diabetes. Previous studies, which imposed a single incidence of breakfast skipping, did not observe any decrease in 24-h energy expenditure. Furthermore, the effects of breakfast skipping on diurnal blood glucose profiles over 24 h are contradictory.

Objective: The aim of this study was to clarify the influence of 6 consecutive days of breakfast skipping and sedentary behavior on energy metabolism and glycemic control.

Methods: Ten young men participated in 2 trials (with or without breakfast) that lasted for 6 consecutive days, and the 2 trials were conducted 1 wk apart with a repeated-measures design. During the meal intervention, each subject's blood glucose was measured using the continuous glucose monitoring system. If breakfast was skipped, subjects ate large meals at lunch and dinner such that the 24-h energy intake was identical to that of the 3-meal condition. At 2200 on the fifth day, the subjects entered a room-sized respiratory chamber, where they remained for 33 h, and were instructed to carry out sedentary behavior.

Results: The glucose levels were similar between the 2 meal conditions during the first 5 d of meal intervention, but the blood glucose at 2300 was higher in the breakfast-skipping condition than in the 3-meal condition. Breakfast skipping elevated postprandial glycemic response after lunch on the first day of meal intervention. On the sixth day, there were no significant differences in 24-h energy expenditure and substrate oxidation. When subjects remained in a metabolic chamber, the level of physical activity significantly decreased, glycemic stability slightly deteriorated, and mean blood glucose over 24 h was higher in the breakfast-skipping trial than in the 3-meal trial.

Conclusions: Sedentary lifestyle and repeated breakfast skipping caused abnormal glucose fluctuations, whereas 24-h energy metabolism remained unaffected. Clinical Trial Registry: This trial was registered at http://www.umin.ac.jp/english/ as UMIN000032346. *Am J Clin Nutr* 2019;110:41–52.

Keywords: skipping breakfast, energy metabolism, continuous glucose monitoring system, glucose fluctuation, sedentary lifestyle

Introduction

The current therapeutic strategies for obesity have mostly focused on the imbalance between energy expenditure and energy intake (1), but meal timing has also been studied as a factor that controls body weight (2). The meal consumed after an overnight fasting, i.e., breakfast, is often described as "the most important meal of the day" (3), and it is believed to contribute to good health and nutrition by providing essential nutrients early in the day (4). Systematic reviews, including a meta-analysis,

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Supplemental Figure 1 is available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

Address correspondence to HO (e-mail: hogata@hiroshima-u.ac.jp).

Abbreviations used: BN, breakfast followed by no breakfast; CGMS, continuous glucose monitoring system; CONGA*n*, continuous overall net glycemic action; DFA, detrended fluctuation analysis; MIME, mean indices of meal excursions; NB, no breakfast followed by breakfast; RQ, respiratory quotient; $\dot{V}CO_2$, CO_2 production; $\dot{V}O_2$, O_2 consumption; α_1, short-range scaling exponent; α_2, long-range scaling exponent; ΔG, glucose rise to peak; ΔT, time to peak; % baseline, timeliness of recovery to baseline glycemia.

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suggest that a positive association between skipping breakfast and being overweight or obese is globally observed, regardless of cultural differences among countries (5–7). The thermic effect of food after breakfast is greater than that after lunch and dinner (8), and this suggests a possibility that accumulated energy expenditure over 24 h (24-h energy expenditure) is affected by differences in daily eating habits: eating breakfast or skipping breakfast. However, our previous study observed no effect of breakfast skipping on 24-h energy expenditure (9), and another study reported a slight increase in 24-h energy expenditure upon breakfast skipping compared with a 3-meal pattern (10). Taken together, results of the tightly controlled room calorimetry studies did not underscore the epidemiological link between breakfast skipping and increased body weight (4, 11–13).

Misalignment of meals with the biological clock is associated with an increased risk of obesity and type 2 diabetes (14–17). The effects of skipping breakfast on 24-h glucose profile have been assessed using a continuous glucose monitoring system (CGMS), but the results are inconsistent; the 24-h mean glucose was increased by skipping breakfast in our previous study (9), whereas the 24-h area under the glycemic curve in another study was no different between breakfast skipping and 3-meal conditions (10). In an attempt to obtain a better insight into glycemic dynamics, advanced time-series analysis methods have been developed. Detrended fluctuation analysis (DFA) of glycemic dynamics revealed that reducing and breaking up sitting time with intermittent light-intensity activity may play a role in maintaining glycemic control (18, 19). It is possible therefore that the effects of breakfast skipping on glycemic dynamics in a free-living condition may be different from those observed when a subject remains in a metabolic chamber.

One plausible way to clarify the effects of breakfast skipping on energy metabolism and glycemic control is to evaluate the effects of repeated breakfast skipping rather than the effects of a single incident of breakfast skipping. We hypothesized that repeated breakfast skipping and sedentary behavior affect energy metabolism and glycemic fluctuation. Note that the meal intervention period was 6 d as the upper limit period of the CGMS. The purpose of this study was to clarify the influence of 6 consecutive days of breakfast skipping on energy metabolism and glycemic control in healthy young males, and change in body composition as secondary outcomes.

Materials and Methods

Subjects

Eleven students voluntarily participated in this study, but 1 subject dropped out, because he could not wear a wrist motion sensor all day. All subjects were healthy males, aged 20–30 y. Exclusion criteria were food allergies, occasional or habitual breakfast skippers, smoking, chronic diseases, or regular use of medications. The Consolidated Standards of Reporting Trials flowchart shows the passage of subjects through the different stages of the present trial, including enrollment, allocation to the interventions, and analysis (**Supplemental Figure 1**). We informed the subjects about the experiments and their associated risks. This study was approved by the Local Ethics Committee of the University of Tsukuba, and all subjects provided written informed consent to participate. The trial is registered at www.umin.ac.jp/english/ (UMIN000032346). Note that the trial was registered post study completion.

Study protocol

A crossover meal intervention was conducted in alternating assignment, and an outline of the study protocol is given in **Figure 1**. The subjects participated in 2 trials (i.e., with breakfast followed by no breakfast [BN] condition – BN group; and no breakfast followed by with breakfast [NB] condition – NB group) that lasted for 6 consecutive days: with breakfast (i.e., 3-meal condition) or without breakfast (i.e., breakfast-skipping condition), and these conditions were assigned alternately. The 2 meal interventions were conducted 1 week apart (i.e., wash-out) with a repeated-measures design to remove the effects of 6-d breakfast omission. From 1 week before the meal intervention, i.e., baseline or wash-out period, subjects were asked to keep a regular sleep (2300)/wake (0600) schedule and meal schedule (0700, 1230, and 1800). Each meal intervention trial was proceeded following a baseline/wash-out period of 7 d, and the subjects ate breakfast (33.3% of daily energy intake) or no breakfast (0 kcal), lunch (33.3% or 50.0% of daily energy intake, for the 3- and 2-meal conditions, respectively), and dinner (33.3% or 50.0% of daily energy intake), such that the 24-h energy intake was equal for both dietary conditions. The subjects were also instructed to refrain from consuming beverages containing energy, caffeine, alcohol, or extreme exercise during the meal intervention. During the first 5 d of meal intervention, the meals provided were individually adjusted (3042 ± 598 kcal/d, 14% protein, 25% fat, and 61% carbohydrates) based on the estimated energy requirement and normal macronutrient balance for Japanese adults (20) assuming a physical activity factor of 1.75.

At 2200 on the fifth day, the subjects entered a room-sized respiratory chamber and remained there for 33 h (until 0700 of the seventh day). In the metabolic chamber, the subjects slept for 7 h from 2300 to 0600 the next morning, and the 24-h energy metabolism was evaluated from 0600 on the sixth day to 0600 on the seventh day of the intervention period. During the indirect calorimetry, the subjects were asked to remain seated and received breakfast at 0700 (33.3% of daily energy intake) or no breakfast (0 kcal), lunch at 1230 (33.3% or 50.0% of daily energy intake) and dinner at 1800 (33.3% or 50.0% of daily energy intake). The size of the standardized meal during the 24-h indirect calorimetry in the metabolic chamber was individually adjusted (2197 ± 405 kcal/d, 15% protein, 25% fat, and 60% carbohydrates), based on the estimated energy requirement assuming a physical activity factor at 1.30 (20).

Measurements

Physical activity.

Spontaneous physical activity and sleep/wake schedule were estimated using a wrist motion sensor, ActiGraph (Ambulatory Monitoring Inc.), in zero crossing mode (21). During the study, the subjects wore the ActiGraph on their nondominant hand, and the gross motor activity of the accelerometer was estimated at

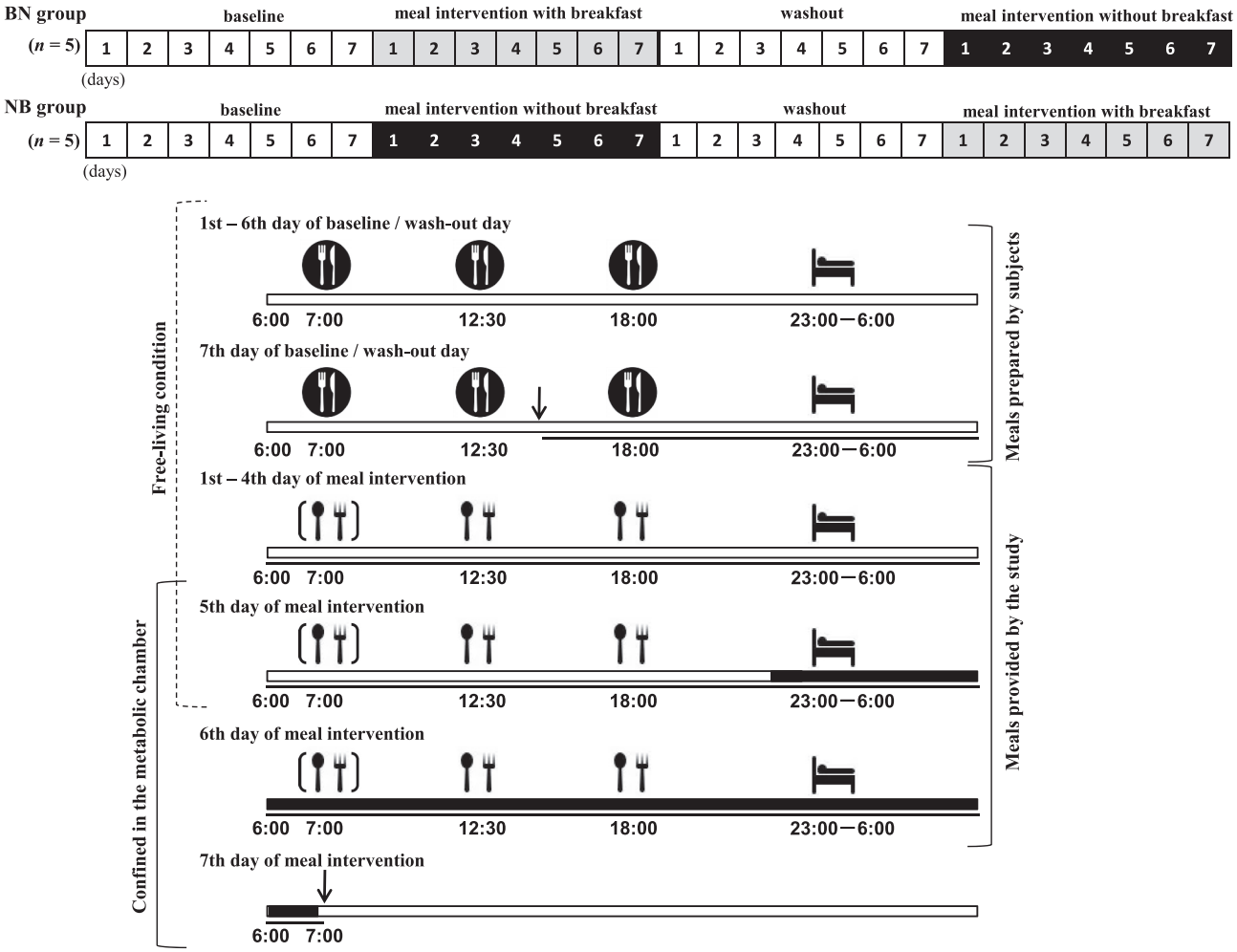

FIGURE 1 Schematic overview of the study protocol (upper panel) and time schedule of meal intervention following the baseline and/or wash-out period (lower panel). All subjects ate meals prepared by themselves during the baseline and/or wash-out (fork+knife symbol), and they ate 3 meals/d. During the meal intervention days, the subjects ate meals provided by the study (spoon+fork symbol). Before (at seventh day of baseline/wash-out) and after the meal intervention (at seventh day of meal intervention), body composition was measured (↓). Before the meal intervention, a continuous glucose monitor was attached to subjects under the skin on the abdomen (thin black bar). At the fifth day of meal intervention, subjects arrived at the laboratory, entered the metabolic chamber at 2200, and stayed until the morning of the seventh day (thick black bar). Note that the timings of meals and sleep were predetermined by the experimental protocol. BN, breakfast followed by no breakfast; NB, no breakfast followed by breakfast.

1-min intervals and subsequently analyzed by a Cole–Kripke algorithm (22) to estimate the sleeping period.

CGMS.

A CGMS provides information on direction, magnitude, duration, and frequency of glycemic oscillations (9, 23). The glucose levels were continuously measured with a glucose monitor (iPro2, Medtronic MiniMed) connected to a glucose sensor (Enlite Glucose Sensor, Medtronic MiniMed). The mean absolute relative difference value of this device is 11% (24). The sensor was inserted under the skin on the abdomen where it measured interstitial glucose every 5 min for 7 d. The readings were converted to blood glucose level by calibration against finger-stick blood glucose measurements 4 times a day. This CGMS was attached to the subjects 1 day before the meal intervention (on the seventh day of baseline/wash-out).

Postprandial blood glucose response was calculated as the area under the curve of the blood glucose curve above premeal levels during 4 h using the trapezoidal method. The glycemic variability was evaluated by the following approaches:

a) Mean indices of meal excursions (MIME) define glucose rise to peak (ΔG), time to peak (ΔT), and timeliness of recovery to baseline glycemia (% baseline) (25).
b) DFA, which accurately quantifies the temporal correlation property of time series data (26), has been described in detail previously (19, 27, 28). In DFA, long-range correlation is characterized by the exponent α in the scaling (power-law) relation $F(n) \sim n^{\alpha}$, where $F(n)$ is the square root of mean-square deviations around a polynomial trend averaged over segments with length n of integrated time series. In DFA, n represents the analyzed window size in minutes, and $F(n)$ is referred to as the fluctuation function. In this study, we used glucose data measured

every 5 min, calculated $F(n)$ over the range $40 \leq n \leq 350$ min (in the logarithmic scale, $1.602 \leq \log_{10} n \leq 2.544$), and estimated the crossover of its scaling behavior using linear least-squares fitting. Finally, the short-range scaling exponent (α_1) was shorter than the crossover point, and the long-range scaling exponent (α_2) was longer than the crossover point. In addition, we calculated the mean values of $\log_{10} F(n)$ at each scale in a single subject, which was denoted by $\log_{10} Fm(n)$. White noise (uncorrelated time series) is characterized by $\alpha = 0.5$, and Brownian motion (integrated white noise) is characterized by $\alpha = 1.5$. Similar to the relation between white noise and Brownian motion, the value of α after the integration is increased by 1. Therefore, a negatively correlated long-range fluctuation of increments is represented by $1 < \alpha < 1.5$ for the measured glucose time series, whereas a positively correlated increment is represented by $1.5 < \alpha < 2.0$ (furthermore, $\alpha > 2.0$ can be explained by the repeated integration).

c) The J-index is a measure of both the mean level and variability of glycemia (29) calculated from mean and SD of measured glucose (mg/dL) as $0.001(\text{mean} + \text{SD})^2$.

d) Continuous overall net glycemic action (CONGA*n*) is defined as the SD of all the differences between the current observation and the observation at n h (1, 2, and 4 h before the observation) (30). For instance, for $n = 1$, the calculations would begin as follows: blood glucose at 0700 minus blood glucose at 0600, blood glucose at 0705 minus blood glucose at 0605, blood glucose at 0710 minus blood glucose at 0610, and so on, until blood glucose 0600 (the next day) minus blood glucose at 0500. Then, the SD of the summed differences of these data were calculated. CONGA*n* is similar to SD but assesses glucose variability within a predetermined time window.

Whole-body indirect calorimetry.

Whole-body indirect calorimetry with an improved transient response was performed as described in our previous studies (31, 32). Briefly, the dimensions of the airtight chamber for the whole-body indirect calorimeter were 3.45 m width × 2.00 m depth × 2.10 m height, with an internal volume of 14.49 m^3 (FHC-15S, Fuji Medical Science Co., Ltd). We precisely measured the concentrations of O_2 and CO_2 in the outgoing air using online process mass spectrometry (VG Prima δB, Thermo Electron Co.). Every minute, O_2 consumption ($\dot{V}O_2$) and CO_2 production ($\dot{V}CO_2$) rates were calculated using an algorithm for the improved transient response. Energy expenditure, carbohydrate oxidation, fat oxidation, protein oxidation, and respiratory quotient (RQ) were calculated from $\dot{V}O_2$, $\dot{V}CO_2$, and 24-h urinary nitrogen excretion as previously described (9, 23, 33).

The thermic effect of food was calculated as an accumulated increase in energy expenditure above the preprandial energy expenditure for 4 h after each meal. Sleeping energy expenditure was calculated by summing the values of the sleeping period (from 2300 to 0600).

Secondary outcome.

Body weight and composition were measured using the bioimpedance method (BC-118E, TANITA Co.) at 1 day before the meal intervention (at 1430 on the seventh day of baseline/wash-out) and after exiting the chamber (at 0730 on the seventh day of meal intervention). Changes in body compositions were analyzed as secondary outcomes.

Statistical analysis

According to our previous study (9), a power analysis revealed that a sample size of 8 subjects is required to provide 80% power to detect a 5% difference between 2 dietary conditions in the 24-h mean blood glucose. To allow discontinuation or measurement errors during the meal intervention, 10 subjects were recruited. A power analysis was conducted using G-Power 3.1.7 software (written by Faul F., University of Kiel, Germany). Data are presented as means ± SDs. Differences in the 24-h mean of physical activity level, blood glucose, glycemic variability (MIME, J-index, and CONGA*n*) and DFA indices (α_1, α_2, and Fm), 24 h total of sleep-wake times, and energy metabolism between the 3-meal and breakfast-skipping conditions were analyzed by paired t-test. Differences in body composition between treatments orders (BN and NB groups) and between before and after meal interventions were analyzed by paired t-test. To investigate the effect of treatment order for physical activity, blood glucose, energy metabolism, and body compositions, a multiple variable analysis that added "treatment order" as explanatory variable was carried out. The differences between the DFA scaling exponents (α_1 and α_2) and the uncorrelated "reference" value of $\alpha = 1.5$ were also evaluated by paired t-test. To evaluate the differences in blood glucose and energy metabolism between the 2 meal conditions, mean values in the morning (0600–1230), afternoon (1230–1800), evening (1800–2300), and sleep (2300–0600) were calculated for each subject, and repeated-measures two-way analysis of variance (ANOVA), followed by a post hoc Bonferroni test, were used. All statistical analyses were performed using SPSS version 22.0 (SPSS Japan Inc.). The level of significance was set at $\alpha = 0.05$.

Results

Characteristics of the study population are listed in **Table 1**. Ten men aged 22–29 y participated in this study. BMI and percentage of body fat ranged between 20.2 kg/m^2 and 29.7 kg/m^2 and 9.5% and between 25.4%, respectively. According to WHO criteria, 2 subjects were overweight. There was no difference in baseline characteristics between treatment orders, i.e., BN and NB groups.

Physical activity

During the meal interventions from day 1 to day 5, physical activity was similar between the 2 dietary conditions (115.5 ± 26.4 counts/min for the 3-meal condition compared with 117.6 ± 32.1 counts/min for the breakfast-skipping condition, $P = 0.358$). On the sixth day of the meal intervention in

TABLE 1 Characteristics of the study population at eachmeal intervention[1]

	Breakfast → no breakfast ($n = 5$)		No breakfast → breakfast ($n = 5$)		P value[2]	
Condition	Baseline	Wash-out	Baseline	Wash-out	Baseline	Wash-out
Age, y	24.8 ± 2.9		25.6 ± 3.0		0.740	
Height, cm	174.0 ± 12.0		172.4 ± 3.6		0.773	
Body weight, kg	71.0 ± 19.2	71.5 ± 19.6	70.7 ± 5.6	71.1 ± 6.4	0.967	0.966
BMI, kg/m^2	23.1 ± 3.7	23.3 ± 3.9	23.8 ± 1.5	23.9 ± 1.7	0.712	0.724
Body fat, %	16.2 ± 5.6	16.3 ± 5.8	16.9 ± 3.9	17.2 ± 4.4	0.836	0.819

[1] Values are means ± SDs.
[2] P values for treatment order differences tested by paired t-test.

the metabolic chamber, spontaneous physical activity was also similar between the 2 dietary conditions (93.6 ± 25.4 compared with 97.5 ± 28.9 counts/min, $P = 0.887$). Physical activity confined in the metabolic chamber (day 6) was lower than that in the free-living condition (days 1–5 of the meal intervention period) for 3-meal ($P < 0.001$) and breakfast-skipping conditions ($P < 0.01$). Note that according to the result of a multiple variable analysis that added "treatment order" as an explanatory variable, the order effect was not confirmed on physical activity. Based on the Cole–Kripke algorithm, there were no significant differences in sleep–wake times between the 2 dietary conditions (sleep time: 494.2 ± 95.1 compared with 501.8 ± 177.9 min, $P = 0.609$ for the entire meal intervention period of 6 d and 466.9 ± 147.2 compared with 455.4 ± 127.9 min, $P = 0.675$ for the last day of the meal intervention period in the chamber).

Blood glucose

All subjects exhibited normal glucose tolerance based on fasting glucose (66–87 mg/dL) and 2 h postprandial breakfast glucose (85–115 mg/dL) for the 3-meal condition. The blood glucose of 1 subject could not be measured from the middle of the meal intervention because the subject did not measure the finger-stick blood glucose measurements 4 times a day, so all the glycemic data from this subject were excluded from statistical analysis. Using the ΔG of MIME, the postprandial glycemic response after lunch in the breakfast-skipping condition at the first meal intervention day was significantly higher than the 3-meal condition (23.9 ± 7.9 compared with 39.9 ± 17.3 mg/dL, $P < 0.05$). There was, however, no difference in postprandial glycemic response after lunch from the second to the sixth meal intervention day between the 2 meal conditions ($P = 0.890$, 0.706, 0.978, 0.253, 0.984, respectively; **Table 2**, **Figure 2**).

The other indices, ΔT and % baseline, were not significantly different between the 2 conditions during the 6 d of intervention period (ΔT: $P = 0.159$, 0.881, 0.711, 0.085, 0.780, 0.418; % baseline: $P = 0.132$, 0.854, 0.277, 0.344, 0.072, respectively), except for % baseline on the fifth day (93.1 ± 11.4 compared with 79.9 ± 7.7%, $P = 0.027$). From days 1 to 5 of meal intervention, when subjects were in a free-living condition, there were no significant differences in the blood glucose variability indices between the 2 meal conditions, except for the blood glucose at 2300 (84.9 ± 5.4 compared with 92.7 ± 10.9 mg/dL, $P < 0.05$) (**Table 3**).

When subjects stayed in the metabolic chamber on the sixth day of the meal intervention, the mean blood glucose over 24 h was increased by breakfast skipping (90.5 ± 6.5 compared with 94.0 ± 7.5 mg/dL, $P < 0.01$; Table 3, **Figure 3**). Immediately before bedtime at 2300, blood glucose was higher in the breakfast-skipping condition than that in the 3-meal condition (83.3 ± 10.1 compared with 96.2 ± 11.7 mg/dL, $P < 0.05$). However, there was no significant difference in fasting blood glucose at 0600 between the trials ($P = 0.122$). Differences in blood glucose between the 2 meal conditions in the morning ($P = 0.280$), afternoon ($P = 0.321$), and evening ($P = 0.124$), and during sleep ($P = 0.171$) were not statistically significant. There was no significant difference for other indices of blood glucose variability (Table 3). Note that according to the result of a multiple variable analysis that added "treatment order" as an explanatory variable, the order effect was detected on blood glucose only at 0600. In the BN group, blood glucose at 0600 was significantly higher in the breakfast-skipping condition (87.63 ± 7.59 mg/dL) than in the 3-meal condition (76.83 ± 12.89 mg/dL), whereas there was no significant difference in the NB group.

When confined in the metabolic chamber, several glycemic fluctuation indices were different from those observed in the free-living conditions (Table 3). The means of $F(n)$ for the 3-meal condition (**Figure 4**A) and for the breakfast-skipping condition (Figure 4B) are shown in Figure 4. In the short-range regime

TABLE 2 Changes in ΔG for meal indices of meal excursions after lunch during the meal intervention[1]

Condition	Three-meal	Breakfast skipping	P value[2]
Day 1	23.9 ± 7.9	39.9 ± 17.3	0.030
Day 2	35.3 ± 38.7	37.2 ± 16.7	0.890
Day 3	31.7 ± 9.0	34.0 ± 16.5	0.706
Day 4	40.0 ± 9.9	40.2 ± 15.2	0.978
Day 5	31.0 ± 14.1	41.0 ± 17.4	0.253
Day 6 (stayed in chamber)	50.9 ± 15.8	51.0 ± 13.4	0.984

[1] Values are means ± SDs; $n = 9$; all units are mg/dL. ΔG, glucose rise to peak.
[2] P values for 2 conditions (3-meal and breakfast skipping) differences tested by paired t-test.

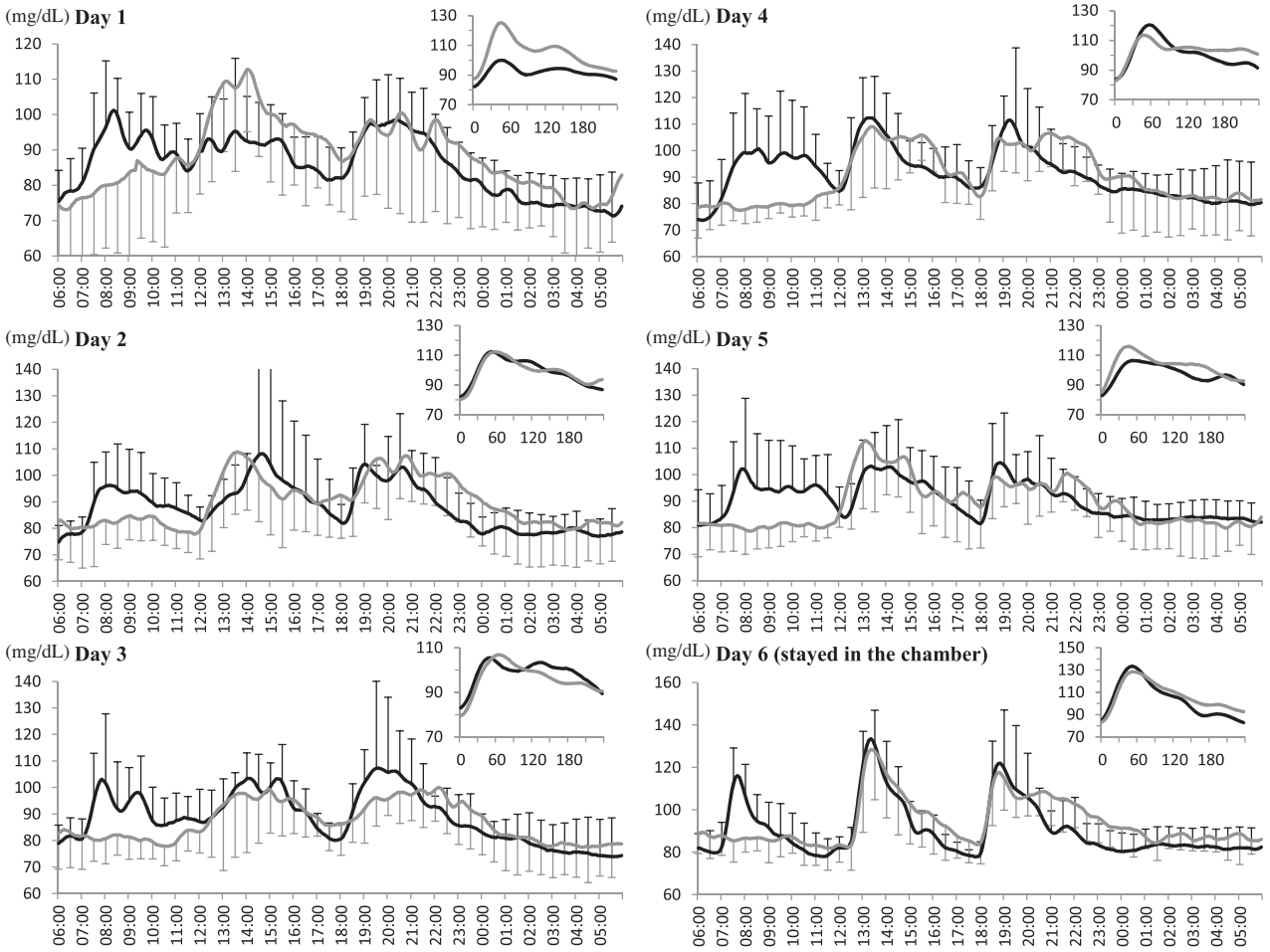

FIGURE 2 Mean glucose dynamics during the 6 d of meal intervention. Mean values of blood glucose for 9 subjects were plotted every 5 min; +SD for 3 meals and –SD for breakfast-skipping conditions were plotted every 30 min. The inserts show the changes in mean glucose from the beginning of lunch. The black lines show data for the 3-meal condition, and the gray lines show data for the breakfast-skipping condition.

(<140 min for free-living condition and <130 min for a condition confined in the metabolic chamber), the scaling exponent (α_1) for the 3-meal condition was 2.92 ± 0.11 for the free-living condition and 3.07 ± 0.10 when confined in the metabolic chamber, respectively. In the breakfast-skipping condition, α_1 (<130 min) was 2.89 ± 0.14 for the free-living condition and 2.98 ± 0.14 when confined in the metabolic chamber, respectively. These α_1 scaling exponents were significantly larger than the "uncorrelated reference value" of $\alpha = 1.5$ ($P < 0.01$), meaning that the glucose fluctuation short-range regime was positively correlated, i.e., the net effects of glucose flux/reflux persisted within these shorter timescales. In the long-range regime, the scaling exponent (α_2) for the 3-meal condition was 1.34 ± 0.17 and 1.70 ± 0.32 for the free-living condition and when confined in the metabolic chamber, respectively, and the former ($P < 0.05$) but not the latter ($P = 0.098$) was significantly different from 1.50. The scaling exponents in the long-range regime for breakfast sipping condition were 1.47 ± 0.15 and 1.69 ± 0.29 for the free-living condition and when confined in the metabolic chamber, respectively. The values were not significantly different from the "uncorrelated reference value" of $\alpha = 1.5$ ($P = 0.317$ and $P = 0.112$). Between the 2 meal conditions, there was no significant difference in *Fm*. *Fm* was significantly different between the free-living condition and when confined in the metabolic chamber when 3 meals were consumed. When breakfast was skipped, *Fm* were similar between the free-living condition and when confined in the metabolic chamber.

Breakfast skipping did not significantly affect other glycemic indices of 24-h SD, J-index, and CONGA*n* (Table 3). Comparing these glycemic indices between the free-living condition and condition confined in the metabolic chamber revealed significant differences in the 3-meal condition: 24-h SD (12.3 ± 6.1 compared with 15.6 ± 6.3 mg/dL, $P < 0.01$), J-index (10.4 ± 2.1 compared with 11.4 ± 2.3, $P < 0.05$), CONGA1 (0.748 ± 0.314 compared with 1.007 ± 0.389, $P < 0.01$), CONGA2 (0.940 ± 0.485 compared with 1.383 ± 0.651, $P < 0.01$), and CONGA4 (1.106 ± 0.598 compared with 1.553 ± 0.709, $P < 0.01$). Similarly, in the breakfast-skipping condition, J-index was significantly different between the free-living condition and when confined in the metabolic chamber (10.6 ± 1.7 compared with 11.8 ± 2.2, $P < 0.05$).

TABLE 3 Comparison of blood glucose and energy metabolism[1]

Condition	Free-living condition (from day 1 to 5 of meal intervention)			Condition confined in the metabolic chamber (on day 6 of meal intervention)			Free-living vs. condition confined in the chamber *P* value[2]	
	Three-meal	Breakfast skipping	*P* value[3]	Three-meal	Breakfast skipping	*P* value[4]	Three-meal	Breakfast skipping
Blood glucose, mg/dL[5]								
0600 (wake up time)	76.8 ± 7.2	80.1 ± 13.0	0.516	81.9 ± 6.9	88.3 ± 9.1	0.122	0.071	0.005
2300 (go to bed time)	84.9 ± 5.4	92.7 ± 10.9	0.032*	83.3 ± 10.1	96.2 ± 11.7	0.024	0.557	0.228
24-h mean glucose	88.9 ± 4.8	89.0 ± 8.3	0.975	90.5 ± 6.5	94.0 ± 7.5	0.003	0.358	0.066
Area under the curve during 4 h after meals[6]				2432 ± 890	2205 ± 734	0.528		
24-h SD	12.3 ± 6.1	13.4 ± 3.3	0.683	15.6 ± 6.3	14.2 ± 4.1	0.603	0.001	0.621
Detrended fluctuation analysis								
α_1 (short-range)	2.92 ± 0.11	2.89 ± 0.14	0.362	3.07 ± 0.10	2.98 ± 0.14	0.274	0.060	0.011
α_2 (long-range)	1.34 ± 0.17	1.47 ± 0.15	0.191	1.70 ± 0.32	1.69 ± 0.29	0.843	0.002	0.013
Fm	0.586 ± 0.12	0.595 ± 0.10	0.861	0.660 ± 0.13	0.609 ± 0.14	0.373	0.028	0.777
J-index[7]	10.4 ± 2.1	10.6 ± 1.7	0.800	11.4 ± 2.3	11.8 ± 2.2	0.559	0.042	0.029
CONGA*n*[8]								
CONGA1	0.748 ± 0.314	0.698 ± 0.155	0.692	1.007 ± 0.389	0.807 ± 0.236	0.180	0.001	0.185
CONGA2	0.940 ± 0.485	0.919 ± 0.197	0.911	1.383 ± 0.651	1.099 ± 0.322	0.238	0.001	0.137
CONGA4	1.106 ± 0.598	1.251 ± 0.307	0.568	1.553 ± 0.709	1.366 ± 0.428	0.502	0.001	0.410
Energy metabolism, kcal[9]								
24-h total energy expenditure				2175 ± 311	2178 ± 348	0.897		
7-h total sleeping energy expenditure				486.1 ± 64.8	491.1 ± 68.2	0.415		
Thermic effect of food[10]				199.2 ± 42.3	146.2 ± 66.1	0.013		
24-h mean respiratory quotient				0.892 ± 0.02	0.882 ± 0.01	0.153		
Macronutrient oxidation, kcal/24 h[9]								
Protein oxidation				246 ± 95	252 ± 47	0.815		
Fat oxidation				598 ± 170	666 ± 159	0.173		
Carbohydrate oxidation				1341 ± 219	1271 ± 216	0.166		

[1] Values are means ± SDs. CONGA*n*, continuous overall net glycemic action; α_1, short-range scaling exponent; α_2, long-range scaling exponent.
[2] *P* values for 2 conditions (free-living and condition confined in the chamber) differences tested by paired *t*-test.
[3] *P* values for 2 conditions (3-meal and breakfast skipping) differences in free-living condition tested by paired *t*-test.
[4] *P* values for 2 conditions (3-meal and breakfast skipping) differences in condition confined in the metabolic chamber tested by paired *t*-test.
[5] $n = 9$.
[6] The area under the curve of blood glucose was summed for 12 h in 3-meal condition, and 8 h in breakfast-skipping condition.
[7] J-index: defined as the square of the mean plus SD of glucose measurements.
[8] CONGA*n*, continuous overall net glycemic action—the SD of all the differences, after the first *n* h, between the current observation and the observation *n* h (1, 2, and 4 h before the observation).
[9] $n = 10$.
[10] The thermic effect of food was calculated as an accumulated increase in energy expenditure above the preprandial energy expenditure for 4 h after each meal.

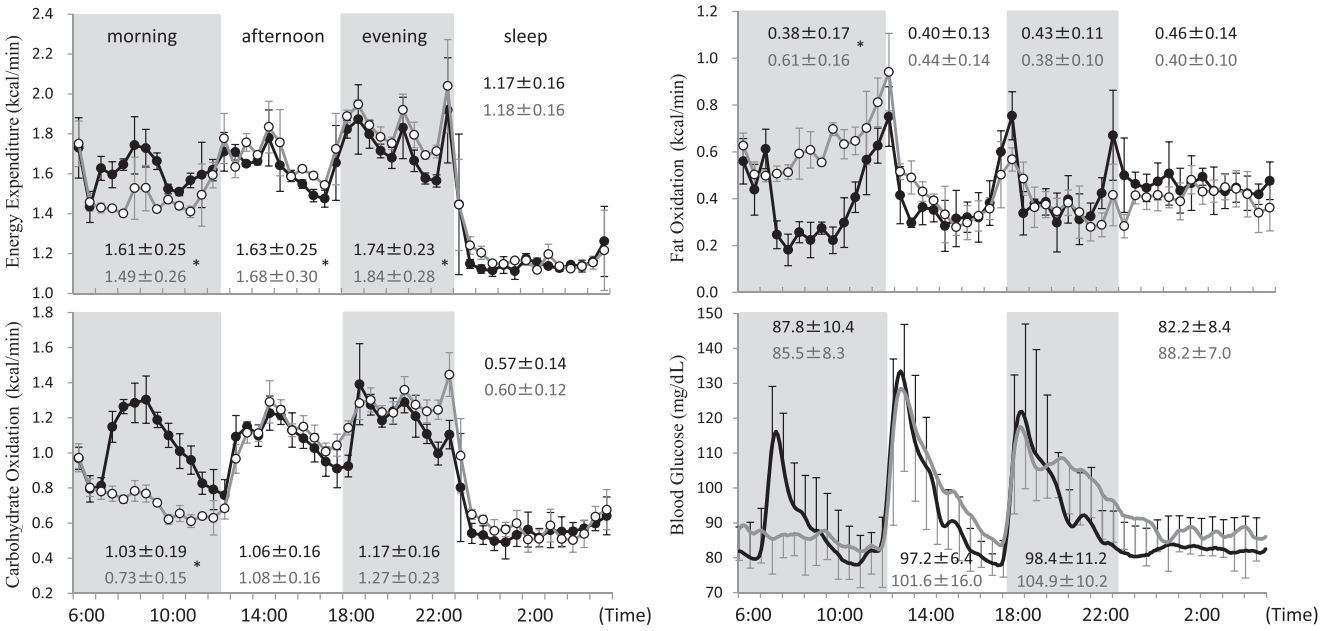

FIGURE 3 Diurnal variations ofenergy metabolism and blood glucose. Mean values ± SDs of energy metabolism for all subjects ($n = 10$) were plotted every 30 min. Mean values of blood glucose for 9 subjects were plotted every 5 min; +SD for 3 meals and –SD for breakfast-skipping conditions were plotted every 30 min. Black circles with black lines represent the 3-meal condition, and white circles with gray lines represent the breakfast-skipping condition. Mean values ± SDs of mean blood glucose in the morning (0600–1230), afternoon (1230–1800), evening (1800–2300), and during sleep (2300–0600) are also shown, and repeated-measures two-way ANOVA was used to evaluate the effect of breakfast skipping on energy metabolism and blood glucose. $^*P < 0.05$.

Area under the curve of blood glucose above premeal level increased progressively from breakfast (478 ± 265 mg/dL · min) to lunch (892 ± 249 mg/dL · min) and dinner (1062 ± 520 mg/dL · min), and the difference between that after breakfast and lunch or dinner was statistically significant in the 3-meal condition ($P < 0.01$ and $P < 0.05$). When breakfast was skipped, and 2 large meals were consumed at lunch and dinner, there was no significant difference between postprandial glucose response after lunch (1146 ± 423 mg/dL · min) and dinner (1060 ± 368 mg/dL · min, $P = 0.416$).

Energy metabolism

There were no significant differences in energy balance over 24 h (26.1 ± 135.4 compared with 14.5 ± 86.6 kcal/d, $P = 0.551$), 24-h energy expenditure, and sleeping metabolic rate between the 2 dietary conditions (Table 3). When breakfast skipping was followed by 2 large meals at lunch and dinner, the energy expenditure in the morning was lower (1.61 ± 0.25 compared with 1.49 ± 0.26 kcal/min, $P < 0.001$), but that in the afternoon (1.63 ± 0.25 compared with 1.68 ± 0.30 kcal/min, $P < 0.05$) and evening (1.74 ± 0.23 compared with

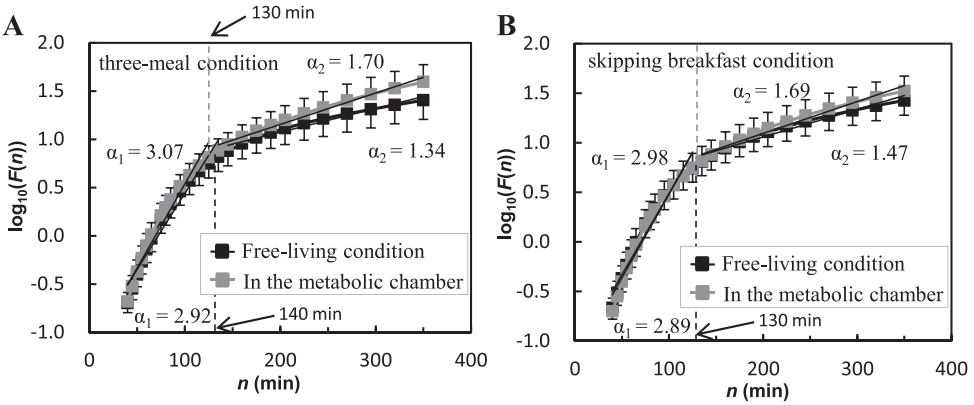

FIGURE 4 Trial mean fluctuation functions $F(n)$ for (A) 3-meal and (B) breakfast-skipping conditions with error bars representing the SDs ($n = 9$). The black lines show data for the free-living conditions, and the gray lines show data for when subjects were confined in the metabolic chamber. $F(n)$, fluctuation function; α_1, short-range scaling exponent; α_2, long-range scaling exponent.

1.84 ± 0.28 kcal/min, $P < 0.01$) was higher than those in the 3-meal condition (Figure 3). The total thermic effect of food for the 3-meal condition was significantly higher than that of the breakfast-skipping condition (199.2 ± 42.3 compared with 146.2 ± 66.1 kcal, $P < 0.05$). The accumulated oxidation of protein, fat, and carbohydrate during 24 h were also similar between the 2 dietary conditions ($P = 0.815$, 0.173, 0.166, respectively). The mean RQ over 24 h was similar between the 2 dietary conditions ($P = 0.153$). Breakfast skipping suppressed carbohydrate oxidation in the morning (1.03 ± 0.19 compared with 0.73 ± 0.15 kcal/min, $P < 0.01$); in contrast, fat oxidation in the morning was enhanced by breakfast skipping (0.38 ± 0.17 compared with 0.61 ± 0.16 kcal/min, $P < 0.01$). Reflecting these results, RQ in the morning was lower than those in the 3-meal condition. Note that according to the results from a multiple variable analysis that added "treatment order" as an explanatory variable, the order effect was not confirmed on energy metabolism (24-h energy expenditure, 7-h total sleeping energy expenditure, thermic effect of food, 24-h mean RQ, protein oxidation, fat oxidation, and carbohydrate oxidation).

When comparing the thermic effect of food among meals, the thermic effect of food after lunch (35.7 ± 23.9 kcal/4 h) was smaller than that after breakfast (75.7 ± 19.1 kcal/4 h) and dinner (87.8 ± 16.9 kcal/4 h) in the 3-meal condition ($P < 0.01$ and $P < 0.001$). Similarly, the thermic effect of food after lunch (55.6 ± 44.7 kcal/4 h) was smaller than that after dinner (90.6 ± 31.0 kcal/4 h) in the breakfast-skipping condition ($P < 0.05$).

Body composition

The change in body weight during the meal intervention period was opposite and significantly different ($P < 0.001$) between the 2 meal conditions: a slight decrease (−0.51 ± 0.83 kg) and increase (0.42 ± 0.71 kg) after the 3-meal and breakfast-skipping condition, respectively. However, changes in other indices, body fat (0.11 ± 0.89% for the 3-meal condition compared with 0.23 ± 1.44% for the breakfast-skipping condition, $P = 0.802$), fat mass (−0.07 ± 0.67 compared with 0.24 ± 0.96 kg, $P = 0.368$), fat-free mass (−0.42 ± 0.91 compared with 0.12 ± 1.17 kg, $P = 0.122$), muscle mass (−0.41 ± 0.87 compared with 0.09 ± 1.09 kg, $P = 0.119$), and total body water (−1.42 ± 3.73 compared with 0.06 ± 1.45 kg, $P = 0.274$), were not significantly different between the trials (**Table 4**). Note that according to the results from a multiple variable analysis that added "treatment order" as explanatory variable, the order effect was not confirmed on body compositions (body weight, body fat, fat mass, fat-free mass, muscle mass, and total body water).

Discussion

Epidemiological studies show that breakfast skipping is associated with a poorer diet quality (34); lower intake of total energy, vitamins, and minerals (35–37); and increased risk of central adiposity (11, 38), insulin resistance (38), and type 2 diabetes (17), and body weight gain (4, 11–13). On the other hand, controlled intervention trials have shown little or no beneficial effect of eating breakfast on body weight and energy metabolism under isocaloric conditions (9, 10, 23, 39–42).

Energy metabolism

Previous intervention studies that imposed breakfast skipping for more than 1 wk (43, 44) did not measure 24-h energy metabolism. The thermic effect of food in the morning is greater than that observed at other times of the day (8), and skipping breakfast might reduce the 24-h energy expenditure. Even though a reduction in the total thermic effect of food was observed in the present study, the 24-h total energy expenditure was not affected by 6 consecutive days of breakfast skipping. Breakfast skipping changed the time course of diurnal substrate oxidation, but the accumulated oxidation of carbohydrates and fats over 24 h was not significantly affected. Previously, we observed that a single incidence of breakfast skipping decreased carbohydrate oxidation in the morning; carbohydrate oxidation was then increased in the evening and during sleep (9). Our previous and present findings do not support the hypothesis that breakfast skipping followed by a large meal at lunch and dinner decreases accumulated energy expenditure or fat oxidation over 24 h. Our studies are slightly different from those of a recent German study (10), which found an increase in 24-h energy expenditure by breakfast skipping (+41 kcal/d). This discrepancy between studies may be due to the different characteristics of subjects' gender, subjects' BMI, number of occasional breakfast skippers included in the study, and normal macronutrient balance of habitual diet. Taken together, the available evidence from 24-h indirect calorimetry is inconsistent with the hypothesis that breakfast skipping decreases 24-h energy expenditure and/or fat oxidation.

Glycemic control

Contrary to our initial hypothesis, the mean 24-h blood glucose and glucose fluctuations in a normal-activity day did not change by skipping breakfast for 5 d. However, on the sixth day of breakfast skipping, when subjects stayed in the metabolic chamber, the mean 24-h blood glucose was significantly higher than that observed in the 3-meal condition. A previous study (38) suggested that reducing the meal frequency from 3 to 2 meals/d elevates 24-h mean blood glucose, whereas increasing the meal frequency to more than 3 meals/d has little effect. In our previous studies, a single incident of breakfast skipping (9) and a late evening meal (23) increased 24-h blood glucose, when subjects stayed in the chamber. This may suggest a possibility that a sedentary lifestyle might unmask the effect of the differences in daily eating habits on glycemic control. Breakfast skipping elevated postprandial glycemic response after lunch on the first day of meal intervention and is consistent with the previous study (9). However, despite the difference in meal size, postprandial increases in blood glucose after lunch were similar between the 2 meal conditions from the second to sixth days of meal intervention, suggesting an adapting mechanism against breakfast skipping and/or a large meal at lunch. The blood glucose at 2300 was higher in the breakfast-skipping condition than that in the 3-meal condition, probably reflecting the larger meal size for dinner in the breakfast-skipping condition. Postprandial hyperglycemia is a more

TABLE 4 Changes in of body composition during the meal intervention[1]

	Three-meal		Breakfast skipping		
Condition	Baseline	Change from baseline	Baseline	Change from baseline	*P* value[2]
Body weight, kg	71.08 ± 13.65	−0.51 ± 0.83	70.57 ± 13.53	0.42 ± 0.71	0.001
Body fat, %	16.81 ± 5.21	0.11 ± 0.89	16.78 ± 5.10	0.23 ± 1.44	0.802
Fat mass, kg	12.39 ± 5.59	−0.07 ± 0.67	12.27 ± 5.60	0.24 ± 0.96	0.368
Fat-free mass, kg	58.69 ± 9.10	−0.42 ± 0.91	58.38 ± 9.05	0.12 ± 1.17	0.122
Muscle mass, kg	55.66 ± 8.66	−0.41 ± 0.87	55.36 ± 8.59	0.09 ± 1.09	0.119
Total body water, %	40.46 ± 6.69	−1.42 ± 3.73	40.16 ± 6.67	0.06 ± 1.45	0.274

[1] Values are means ± SDs; $n = 10$. These data were calculated by subtracting the value measured before meal intervention (on the seventh day of baseline/wash-out) from that after the intervention (on the seventh day of meal intervention).

[2] *P* values for 2 conditions (3-meal and breakfast skipping) differences tested by paired *t*-test.

sensitive early symptom of diabetes than fasting blood glucose (45). Furthermore, epidemiological studies and preliminary intervention studies have shown that postprandial hyperglycemia is a direct and independent risk factor for cardiovascular disease (46).

Recently, reducing and breaking up sitting time has been highlighted for its ability to prevent weight gain and obesity (47, 48). Normal glucose homeostasis is achieved through negative-feedback regulation (49). Our previous studies suggested that the long-range negative feedback of glucose dynamics assessed by DFA which reflects clinical indicators including glycated hemoglobin and glycated albumin was attenuated in diabetes patients (26, 27). The negative autocorrelation of glucose dynamics also dissociates from normal dynamics when subjects were confined in a room-sized chamber (19). Together with the previous study (19), current results suggest an interaction between the meal condition and the level of physical activity on glycemic control; when a subject became sedentary, the effects of breakfast skipping on glycemic control became observable.

Body composition

Skipping breakfast may cause a body-weight gain. In a previous study adopting 1-wk intervention (50), weight loss was greater when a single meal was ingested at breakfast than when an equivalent meal was consumed in the evening. A number of randomized controlled trials have investigated the effect of breakfast eating/skipping on weight and body composition (51, 52); these studies suggested that skipping breakfast for 6 wk in obese and lean adults had no effect on body composition, but the results of meal intervention studies are not consistent (50–52). In the present study, breakfast skipping led to a small but statistically significant increase in body weight compared with that in the 3-meal condition, although differences in body composition explaining the small changes in body weight were not identified. During the meal interventions, the subjects ate an isoenergetic diet, there was no significant difference in physical activity and sleep/wake times between 2 dietary conditions, and the accumulated energy expenditure over 24-h of the sixth day of the intervention was similar. It is possible that changes in meal schedule affected the timing of defecation and resulted in small differences in body weight between subjects in the 2 meal conditions.

Limitations

This study has several limitations. First, subjects followed instructions to refrain from consuming beverages containing energy, caffeine, alcohol, or extreme exercise during the meal intervention. The effects of breakfast skipping under free-living conditions remain to be evaluated. Second, the incidence of breakfast skipping in men is higher than that of women in Japan (20), and young healthy men were recruited as subjects. However, the sample size was small, and the age of the subjects was limited. To generalize the present findings, experiments with young healthy women, middle-aged, and elderly are warranted. Third, a crossover meal intervention was conducted in alternating assignment in the present study, and therefore, one cannot classify the present study as strictly being a randomized design (53). Fourth, habitual breakfast eaters were recruited in the present study, but there was ambiguity in including criteria for breakfast eaters as subjects. The effects of consuming breakfast on energy metabolism of breakfast skippers remain to be studied. Experiments were carried out with an interval of at least one week following other energy metabolism studies, but it might be too short to evaluate other indices, i.e., the fasting blood glucose at 0600. It may be possible that the influence of meal interventions was underestimated in the BN group. Lastly, differences in body weight changes during the meal intervention were statistically significant, and the difference might be due to defecation status when body weight was measured. We did not match the time of the day when body weight was measured, and no information was collected concerning defecation status at weigh-in, because the body composition changes during the meal intervention were secondary outcomes of the study, and it remained to be clarified.

Implications

The present results suggest that a sedentary lifestyle and repeated breakfast skipping might cause abnormal glucose fluctuations. Accumulated energy expenditure and substrate oxidation over 24 h were not affected by 6 d of breakfast skipping. Chronic effects of breakfast skipping on glucose homeostasis and energy metabolism remain to be studied.

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the final manuscript. None of the authors report a conflict of interest related to research presented in this article.

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