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Effect of exercise timing on elevated postprandial glucose levels

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Running title: Exercise timing for decreasing postprandial glucose

Abstract

There is no consensus regarding optimal exercise timing for reducing post prandial glucose (PPG). The purpose of the present study was to determine the most effective exercise timing. Eleven participants completed four different exercise patterns 1) no exercise; 2) preprandial exercise (jogging); 3) postprandial exercise; and 4) brief periodic exercise intervention (3 sets of 1 min jogging + 30 s rest, every 30 min, 20 times total)] in a random order separated by a minimum of five days. Pre- and postprandial exercise consisted of 20 sets of intermittent exercise (1 min jogging + 30 s rest per set) repeated 3 times per day. Total daily exercise volume was identical for all three exercise patterns. Exercise intensities were 62.4 ± 12.9% $\dot{V}O_2$ peak. Blood glucose concentrations were measured continuously throughout each trial for 24 h. After breakfast, peak blood glucose concentrations were lower with brief periodic exercise (99±6 mg/dl) than those with pre- and postprandial exercise (109±10 and 115±14 mg/dl, respectively, $p < 0.05$, effect size = 0.517). After lunch, peak glucose concentrations were lower with brief periodic exercise than those with postprandial exercise (97±5 and 108±8 mg/dl, $p < 0.05$, effect size = 0.484). After dinner, peak glucose concentrations did not significantly differ among exercise patterns. Areas under the curve over 24 h and 2 h postprandially did not differ among exercise patterns. These findings suggest that brief periodic exercise may be more effective than pre- and postprandial exercise at attenuating PPG in young active individuals.

NEW & NOTEWORTHY

This was the first study to investigate the effect of different exercise timings (brief periodic vs. preprandial vs. postprandial exercise) on PPG（post prandial glucose） attenuation in active healthy men. We demonstrated that brief periodic exercise attenuated peak PPG levels more than pre- and postprandial exercise, particularly in the morning. Additionally, PPG rebounded soon after discontinuing postprandial exercise. Thus, brief periodic exercise may be better than pre- and postprandial exercise at attenuating PPG levels.

Introduction

Higher postprandial glucose (PPG) concentration is a risk factor for cardiovascular disease (CVD) (27), mortality (34), and cognitive performance impairment (30) in patients with type 2 diabetes. In addition, in non-diabetic populations, elevated PPG is a risk factor for coronary heart disease, ischemic stroke (24), and CVD (21). Endothelial dysfunction is predictive of a future cardiovascular event and caused by hyperglycemia through oxidative stress (4). Furthermore, oscillating glucose levels increase oxidative stress more than constant high glucose levels and have a more deleterious effect on endothelial dysfunction (3). For these reasons, controlling PPG levels may lead to cardiovascular event prevention.

A single bout of aerobic exercise has been demonstrated to reduce PPG levels (26, 31, 32). In particular, the issue of exercise timing around meals to attenuate PPG concentrations has been

64 widely discussed (5, 15). Many previous studies have reported that postprandial aerobic exercise
65 effectively lowers PPG concentrations (15, 17, 19, 20, 26, 29, 35, 38). Larsen et al. reported that
66 postprandial cycling exercise (53±2% $\dot{V}O_2$ max) for 45 min reduced the incremental area under the
67 curve (AUC) of glucose for 240 min after breakfast (19).
68 A review of exercise timing also reported that postprandial exercise is more effective at lowering
69 PPG levels than preprandial exercise in healthy individuals and patients with diabetes (15). However,
70 recent studies have reported that preprandial aerobic exercise can effectively lower PPG
71 concentrations (10, 32). To date, there is little research directly comparing the effects of pre- versus
72 postprandial aerobic exercise on PPG concentrations at one meal (dinner) (7), and there are no
73 studies comparing all three meals throughout the same day. Moreover, it has been recently
74 demonstrated that sitting interspersed with brief bouts of light to moderate intensity exercise
75 attenuates PPG levels, indicating that frequent physical activity potentially increases glucose uptake
76 (1, 2, 9, 28).
77 Thus, although postprandial exercise is considered to be ideal timing for attenuating PPG
78 concentrations, the question has been raised as to whether preprandial and frequent aerobic exercise
79 attenuate PPG to the same extent as postprandial exercise. To the best of our knowledge, there has
80 been no research comparing the effects of preprandial, postprandial, and frequent aerobic exercise on
81 PPG levels for every meal of the day (breakfast, lunch, and dinner). We hypothesized that all

exercise approaches would improve PPG equally based on previous evidence. The purpose of the present study was to determine the most effective exercise timing (preprandial versus postprandial versus brief periodic moderate exercise intensity) on PPG concentrations throughout the day in healthy men using a continuous glucose monitoring system.

Methods

Study participants

Eleven comparatively active (not necessarily trained in any sport in particular) healthy men participated in the present study. Participants were recruited through a poster on the laboratory information board at the Faculty of Sports and Health Science at Fukuoka University. Participant characteristics are displayed in Table 1. All subjects gave informed consent after reviewing the purpose, methods, and significance of the study. The study was approved by the Ethics Committee of Fukuoka University (No.140601).

Baseline testing

Aerobic capacity exercise test

The participants fasted for 12 h before baseline testing. Participants completed the multistage aerobic capacity test using a treadmill. This test had two purposes: 1) to determine peak oxygen

consumption ($\dot{V}O_2$ peak); and 2) to determine the lactate threshold (LT) of running speed (this value was used in trials). After a 1 min rest, the multistage exercise tolerance test was initiated at each subject's running speed according to individual fitness levels. The speed was increased in increments of 10 m/min with each load (4 min/load), with 1 min rest sessions between each load. Blood lactate concentrations (LA, Lactate Pro 2LT-1730 ARKRAY, Japan) were measured immediately from the earlobe after each load (1 min rest) until levels of 4 mmol/L were reached. Heart rate (HR, Polar RS800CX) was measured during the final 30 s of each stage. Participants were asked for their rating of perceived exertion (RPE) during the rest period of each stage. Once LA levels exceeded 4 mmol/L, the treadmill incline was increased 2% per minute until the participant was completely exhausted. During the exercise test, the concentration of expired gas was measured continuously every 12 s by a mixing chamber method using a mass spectrometer for respiratory analysis (ARCO-2000, ARCO SYSTEM, Chiba, Japan).

Determination of LT

The LT is the initial breakpoint in the elevation of blood lactate concentrations. The LT was determined by measuring blood lactate concentrations during each stage of the aerobic capacity test until 4 mmol/L was reached. The LT was based on visual inspection by five trained staff members, and the mean LT was calculated from three of the five results (40). The multistage exercise test was

118 completed more than four days before the first trial. In the present study, the LT intensity was used
119 for the following reasons: 1) if exercise intensity is based on % $\dot{V}O_2$ peak, some subjects will
120 perform below the LT, but others will perform above the LT; 2) exercise above the LT intensity
121 acutely increases catecholamine release (36), which influences glucose metabolism during and after
122 exercise (39); 3) the LT intensity improves insulin sensitivity (25); and 4) the LT intensity would be
123 expected to activate glucose uptake, because the it may activate 5′ AMP-activated protein kinase
124 (AMPK) by decreasing phosphocreatine and ATP and increasing AMP. This increase in AMPK
125 levels increases glucose transport by stimulating GLUT4 translocation to the cell surface in the
126 muscle (11, 18) and thereby lowering blood glucose concentrations (33). Thus, LT intensity exercise
127 should be effective at attenuating PPG concentrations and is a practical exercise method.
128
129 **Body composition**
130 Body composition was estimated using the underwater weighing method, and body density was
131 calculated after correction for residual air by the O_2 re-breathing method. Body fat percentage was
132 calculated using a standard formula (14). Body weight (BW) was measured using a calibrated
133 balance beam scale (Shinko Denshi Vibra Co., Ltd., Tokyo, Japan) to the nearest 0.01 kg, with the
134 subjects wearing only light undergarments. Fat mass and fat-free mass were calculated using the
135 formula: BW × body fat percentage / 100 and BW – fat mass. Height was measured to the nearest

136 0.1 cm with a stadiometer.

137

138 **HbA1c**

139 Blood samples for HbA1c measurements were obtained by finger-stick with assay kits at baseline
140 (Cobas b 101, Roche Diagnostics K.K., Tokyo, Japan). Before analyzing the blood samples, the
141 device was checked with standard samples for accuracy.

142

143 **Experimental design**

144 The present study was a crossover design with four different trials separated by more than 5 days.
145 Trials were undertaken in random order. All participants were asked to avoid exercise, which may
146 enhance insulin sensitivity for up to 72 h (22), and alcohol before the trial day. Additionally,
147 participants were asked to refrain from consumption of caffeine starting the day before the trial. All
148 participants were directed to consume the same meals on the day before the trial and come to the
149 laboratory after fasting for more than 10 h.

150 The study protocol is displayed in Figure 1. All participants completed four trials: 1) control
151 (sedentary throughout the day); 2) preprandial exercise (20 sets of 1 min exercise [jogging] and 30 s
152 rest) 30 min before every meal; 3) postprandial exercise (20 sets of 1 min exercise [jogging] and 30 s
153 rest) 30 min after every meal; and 4) brief periodic exercise (three sets of 1 min exercise [jogging] +

30 s rest, resulting in total duration of 4 min for each bout of exercise, every 30 min throughout the day, 20 times in total). Participants jogged at LT intensity using a treadmill, and total exercise time was 60 min for all exercise trials. When not exercising, participants were asked to remain sedentary except for daily living activities, such as using the bathroom and brushing teeth. HR and RPE were measured immediately after the first bout of exercise in each exercise trial.

Determination of standardized meal volume on the experiment day

Basal metabolic rate (BMR) × 1.5 (physical activity level [PAL]) was used to standardize meal composition and volume. BMR was estimated in the participants by the formula for Japanese individuals (12). We used BMR × 1.5 to calculate energy intake to roughly adjust for energy balance in exercise interventions. We calculated total energy expenditure as PAL × 1.2 (total energy expenditure with sedentary activity in a day (37)) + estimated energy expenditure during exercise. The energy intake and estimated energy expenditure profiles are displayed in Tables 1 and 3. The timing of meals was identical among all trials, and participants were asked to consume the meal within 15 min and in the same order. The only beverage allowed on the experiment day was water.

Glucose monitoring

Glucose was measured using a continuous glucose monitoring (CGM; iPro2, Medtronic,

172 Northridge, CA, U.S.A.) device. The CGM was placed on each participant's abdomen one day
173 before the experiment. Participants were asked to record their blood glucose concentrations more
174 than four times by finger-stick on the day before the experiment for calibration purposes. The
175 coefficient of variance for 14.5-h blood glucose AUCs was 2.8% by CGM when compared with
176 paired self-monitoring of blood glucose at 18 time points.
177
178 **Evaluation of PPG elevation**
179 Glucose AUCs were calculated from the start of every meal to 120 min after using the trapezoidal
180 method. The post-meal 120-min AUC was calculated using absolute values. Peak PPG values were
181 obtained from the highest value recorded within 120 min of meal onset. We think that exercise
182 timing is particularly important for preventing elevated postprandial glucose values. Thus, we
183 focused on the 120-min postprandial period for each meal.
184
185 **Statistical analysis**
186 Data are reported as mean ± SD. Glucose AUCs and average glucose values over 24 hours were
187 compared. Postprandial glucose levels over 6 h were calculated as the sum of the three postprandial
188 2-h AUCs for each trial. Additionally, peak PPG values and absolute 120-min AUCs after every meal
189 were compared. All analyses were conducted using one-way repeated measures ANOVA with

Bonferroni post hoc test (SPSS version 23, IBM Corporation, USA). A p value <0.05 was considered to be statistically significant.

Results

All participants successfully completed the experiment. The mean HbA1c of participants was 5.3±0.3, and all participants were healthy. The mean HRs and RPEs after the first preprandial, postprandial, and brief periodic exercises are displayed in Table 2. Mean HRs and RPEs after the first preprandial and postprandial exercises were not significantly different, but HRs and RPEs after brief periodic exercise were significantly lower ($p < 0.05$). The mean CGM results for all four exercise patterns throughout the day and after the morning meal are displayed in Figures 2 and 3, respectively. The mean glucose values and AUCs recorded over 24 h were not significantly different among the four exercise patterns (data not shown, continuous 24-h glucose values are displayed in Figure 2). The PPG AUCs for 120 min after onset of each meal (i.e., breakfast, lunch, and dinner) were not significantly different among the four trials (Figure 4). Similarly, 6-h AUCs, which were calculated as the sum of the three postprandial AUCs, were not significantly different.

Peak PPG values were significantly lower at breakfast for brief periodic exercise compared with the other exercise patterns ($p<0.05$, effect size = 0.517) and significantly lower at lunch for brief periodic exercise compared with postprandial exercise ($p<0.05$, effect size = 0.484, Figure 5). There

were no significant differences among the peak PPG values for preprandial exercise, postprandial exercise, and controls at any meal.

Discussion

Elevated PPG is a risk factor, especially for CVD, in both patients with diabetes and non-diabetic individuals. One reason for this is that high blood glucose levels, and particularly oscillating glucose levels, increase oxidative stress, leading to endothelial dysfunction. The present study examined whether preprandial and brief periodic exercise are as effective as postprandial exercise at improving blood glucose control throughout the day using CGM. To our knowledge, there have been no studies comparing the effect of pre- and postprandial and brief periodic exercise on blood glucose control. This study demonstrated that brief periodic exercise may be more effective at blunting PPG compared with pre- and postprandial exercise, particularly at breakfast.

Recent studies have examined the effect of sitting interrupted by walking on PPG levels for 5 h in the morning after an overnight fast in obese and healthy individuals (1, 9). They reported that sitting interrupted with 2 min of walking every 20 min for 5 h (total exercise bouts and duration were 14 times and 28 min, respectively) reduced the 5-h PPG AUC compared with no exercise. Peddie et al. reported that a regular-activity-break intervention, which included walking for 1 min 40 s every 30 min, reduced 9-h blood glucose AUCs (28). The present study compared the effect of brief periodic

226 exercise with postprandial exercise on PPG levels. Although postprandial continuous exercise is
227 generally thought to be effective at lowering PPG concentrations, the present result demonstrated
228 that brief bouts of exercise of only 3 min every 30 minutes are better than postprandial exercise at
229 attenuating PPG levels especially at breakfast and lunch. As fluctuating blood glucose levels increase
230 oxidative stress (3, 23), attenuating peak PPG may protect endothelial function. However, as our
231 participants were young, healthy and active, it is likely that statistical significance might not always
232 equal clinical significance.

233 An effect of brief periodic exercise in the evening was not observed. A possible reason is that the
234 brief periodic exercise volume was less around dinner compared with that at breakfast and lunch.
235 Thus, there may have been an insufficient exercise volume to lower peak PPG. The present study did
236 not elucidate the mechanism by which brief periodic exercise was effective at lowering PPG levels.
237 One potential reason could be that frequent brief exercise (frequent muscle contraction) may
238 maintain stimulation of blood glucose uptake into skeletal muscle, which would increase GLUT4
239 translocation to the cell surface, resulting in continuous increased glucose uptake from the blood (16,
240 31).

241 Interestingly, in the present study, postprandial exercise reduced PPG levels during exercise, but
242 PPG levels rebounded soon after discontinuing exercise, attaining peak PPG and PPG AUC levels
243 comparable to those of the control pattern. Our participants were comparatively active men with

244 good glucose metabolism, as indicated by HbA1c values of 5.3±0.3. Thus, as blood glucose levels
245 did not elevate abnormally without exercise, peak PPG levels and AUCs would not be expected to
246 differ between the control and postprandial exercise trials. However, it is unclear whether blood
247 glucose values would rebound similarly after short continuous aerobic exercise in obese individuals
248 or those with diabetes. In a few studies, blood glucose levels appeared to rebound after discontinuing
249 postprandial continuous aerobic exercise (17, 19, 38). The glucose kinetics associated with
250 postprandial exercise may be due to a relationship between glucose uptake in muscles and hepatic
251 glucose output.

252 For this phenomenon, exercise duration may be important in sustaining the effect of PPG lowering
253 associated with postprandial continuous exercise. Nygaard et al. compared the effects of 15 min and
254 40 min of walking immediately after breakfast on PPG levels (26). Both exercise durations reduced
255 the 2-h AUCs compared with those with no exercise, although 40 min of exercise was superior to 15
256 min. Walking for only 15 min did not blunt peak PPG levels. A review analyzing exercise timing
257 reported that 60 min of cycling at 60% $\dot{V}O_2$ max is most effective at lowering blood glucose when
258 performed postprandially. Although light to moderate exercise for 45–60 min would lower PPG
259 levels, it is difficult to exercise for this duration around every meal, particularly for those who work
260 throughout the day. The present results indicated that for individuals who do not have time to
261 exercise after every meal, brief physical activity durations surrounding the meal may be effective at

262 blunting PPG elevation. As previous studies have suggested (8, 10), more feasible exercise timing
263 and duration are needed for effective integration into daily life.

264 The present results revealed no significant differences in peak PPG levels and PPG AUCs between
265 pre- and postprandial exercise. Preprandial exercise stimulates glucose uptake and, therefore, would
266 be expected to lower PPG concentrations (13). Colberg et al. (7) compared the effects of pre- and
267 postprandial self-paced walking (40.3±2.7% heart rate reserve) for 20 min on glycemic responses.
268 They reported that postprandial walking blunted peak PPG levels compared with those following
269 rest and preprandial exercise. However, recent studies have reported that preprandial exercise
270 lowered PPG levels using exercise intensities above the LT (10, 32). The exercise intensity
271 performed by Colberg's study could not attain the LT. Although preprandial exercise may stimulate
272 glucose uptake, the intensity of preprandial exercise may result in prolonged lower PPG levels
273 because of activation of AMPK, which increases glucose transport by stimulating GLUT4
274 translocation in the muscle (6, 11). There are few studies directly comparing the glycemic responses
275 between pre- and postprandial exercise, and further research is needed in the future.

276 There are some limitations to the present study. First, there were no significant differences
277 particularly in PPG AUC values between exercise trials and control conditions. The participants in
278 the present study were comparatively healthy active young men without insulin resistance, as
279 indicated by HbA1c values, which would explain why PPG levels were similar among all four trials.

Brief periodic exercise lowered peak PPG levels compared with pre-postprandial exercise at breakfast. However, we do not know whether this phenomenon leads to positive effects on health outcomes, particularly cardiovascular disease. Based on evidence indicating that within-day glucose fluctuations are an independent risk factor for cardiovascular disease (23) and increase oxidative stress, we believe that lowering peak glucose levels should positively impact endothelial dysfunction. In addition, it is unclear whether brief periodic exercise is the ideal exercise pattern for the general population, obese individuals, or those with diabetes, because the participants were comparatively young active men. Future experiments should include individuals with insulin resistance or diabetes. Furthermore, the present study did not measure hormones related to glucose metabolism, which may further clarify the mechanisms underlying the effects of exercise timing on PPG control.

In conclusion, we examined the effect of exercise timing on PPG control and found that brief periodic exercise attenuated peak PPG levels compared with longer bouts of preprandial or postprandial exercise in young comparatively active healthy men. In addition, our results revealed that brief bouts (within 20 minutes) of postprandial continuous exercise were not likely to mitigate acute blood glucose elevation. This information may be helpful for people who do not have much time to exercise around a meal, such as young to middle aged workers.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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423

424

425 **Figure legends.**

426 Figure 1. Experiment protocol.

427 Gray boxes indicate 15-min meals. White boxes indicate exercise performed. Pre- and postprandial
428 exercises were performed at each meal, and exercise included 20 sets of 1 min exercise (jogging)
429 and 30 s rest. Brief periodic exercise included three sets of 1 min exercise (jogging) and 30 s rest.
430 The total exercise duration was equivalent for all groups. Exercise intensity in this study was based
431 on the lactate threshold intensity.

432

433 Figure 2. Mean variation of glucose associated with different exercise timings until immediately
434 before sleep (n = 11). CON, black line; preprandial exercise, gray line; postprandial exercise, gray
435 dashed line; and brief periodic exercise, black dotted line.

436

437 Figure 3. Mean variation of glucose associated with different exercise timings before and after
438 breakfast. Preprandial exercise started 45 min before breakfast. Postprandial exercise started 30 min
439 after breakfast. The small black box on the graph depicts the timing of brief periodic exercise.

440

441 Figure 4. Glucose area under the curve for 120 min following a standardized morning meal under
442 control and preprandial, postprandial, and brief periodic exercise conditions. There were no
443 significant differences (mean ± SD).
444
445 Figure 5. Peak glucose levels associated with different exercise timings within 120 min after meals
446 under control (white bar) and preprandial (light gray bar), postprandial (dark gray bar), and brief
447 periodic exercise conditions (black bar). *$p<0.05$ vs. control and preprandial exercise, $^{\dagger}p<0.01$ vs.
448 postprandial exercise at breakfast, and $^{\#}p<0.05$ vs. postprandial exercise at lunch.

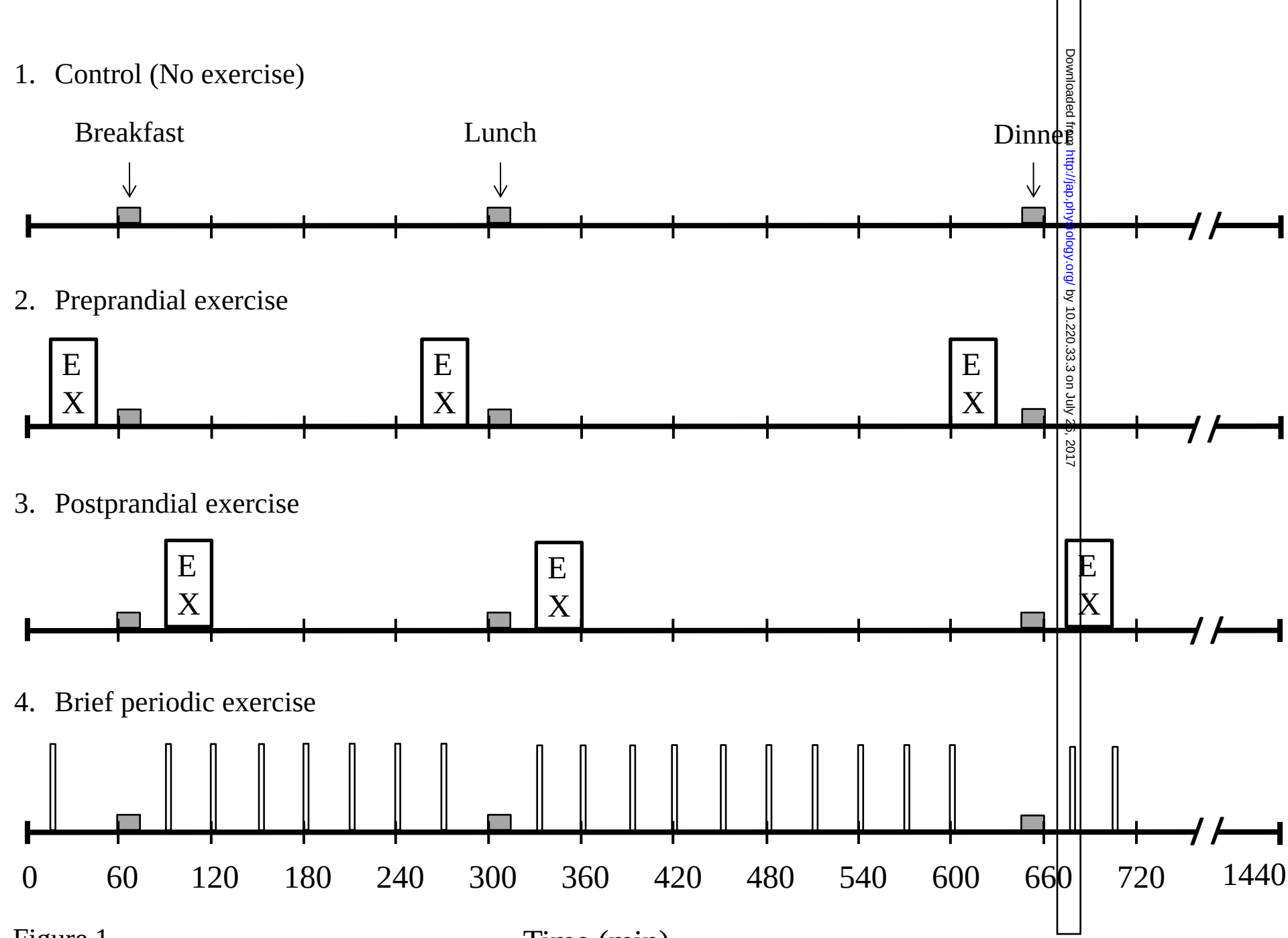

Figure 1.

Figure 2.

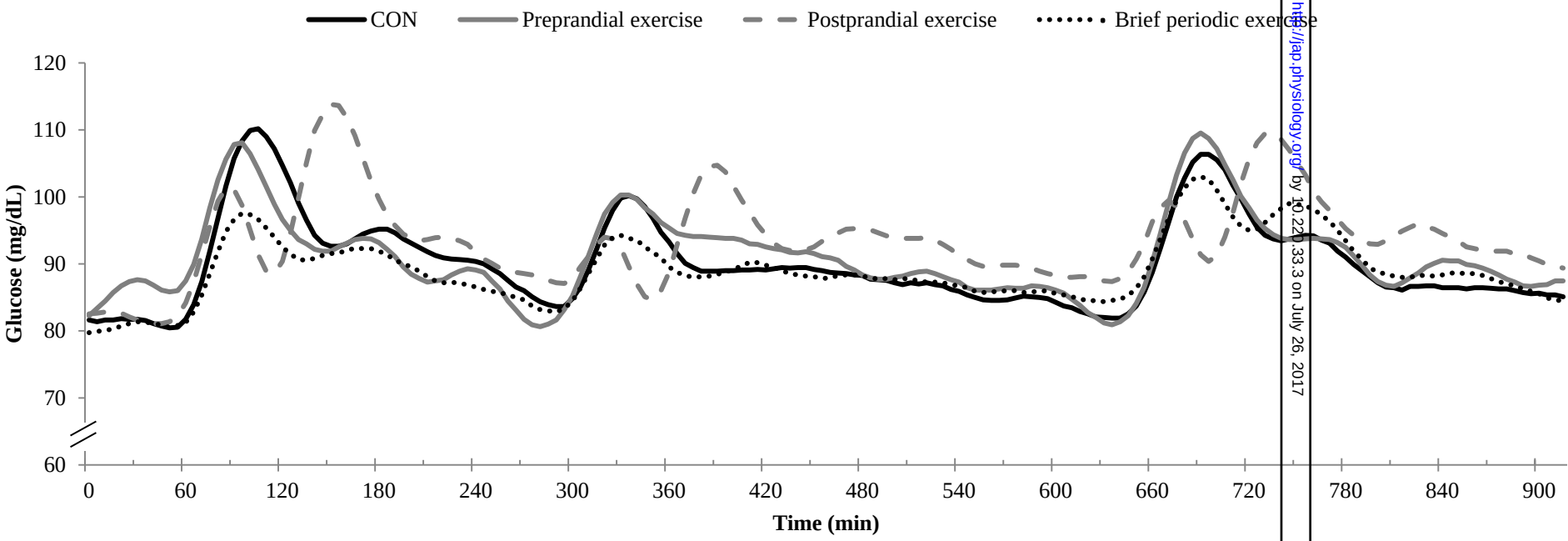

Figure 3

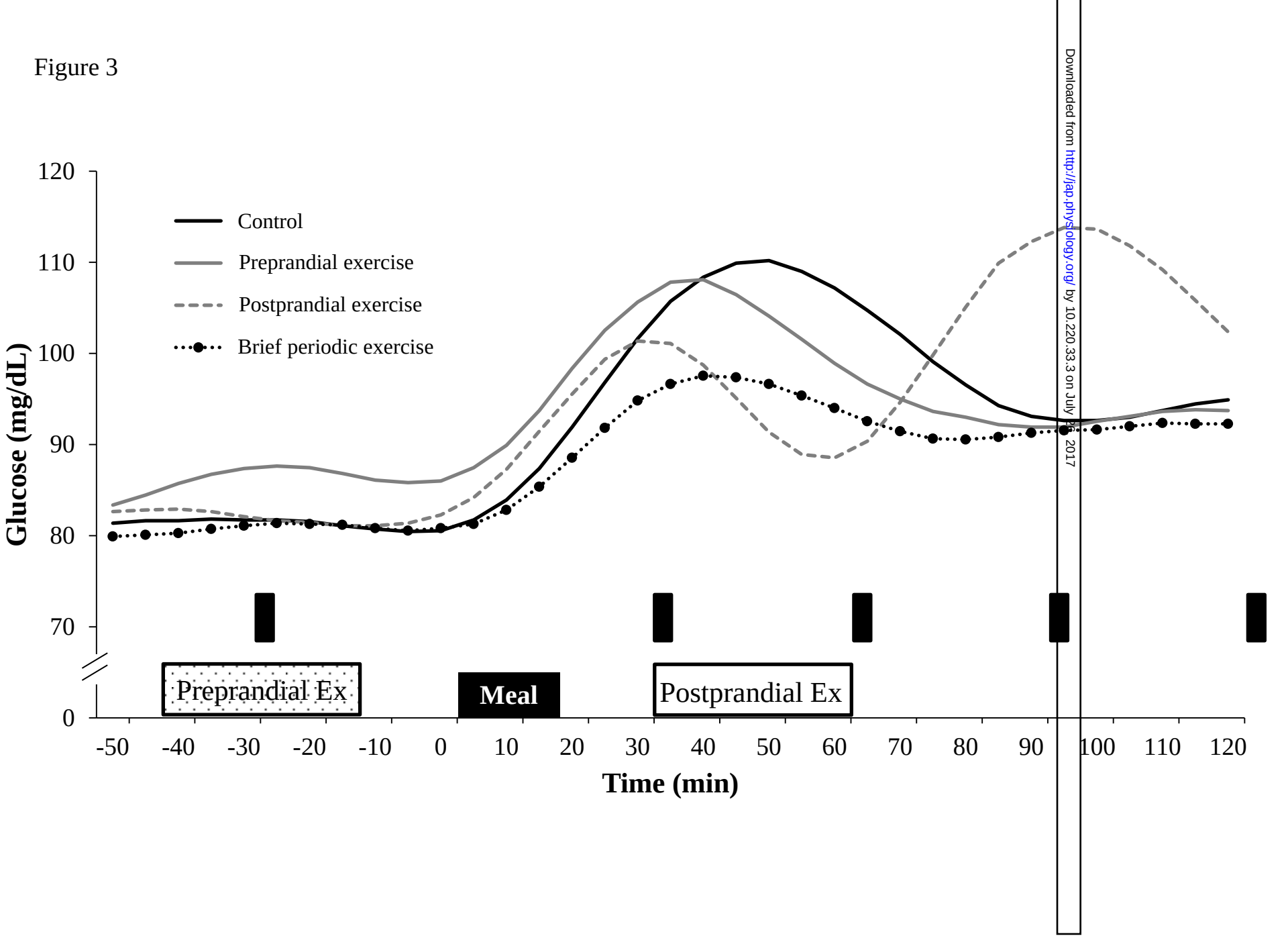

Figure 4.

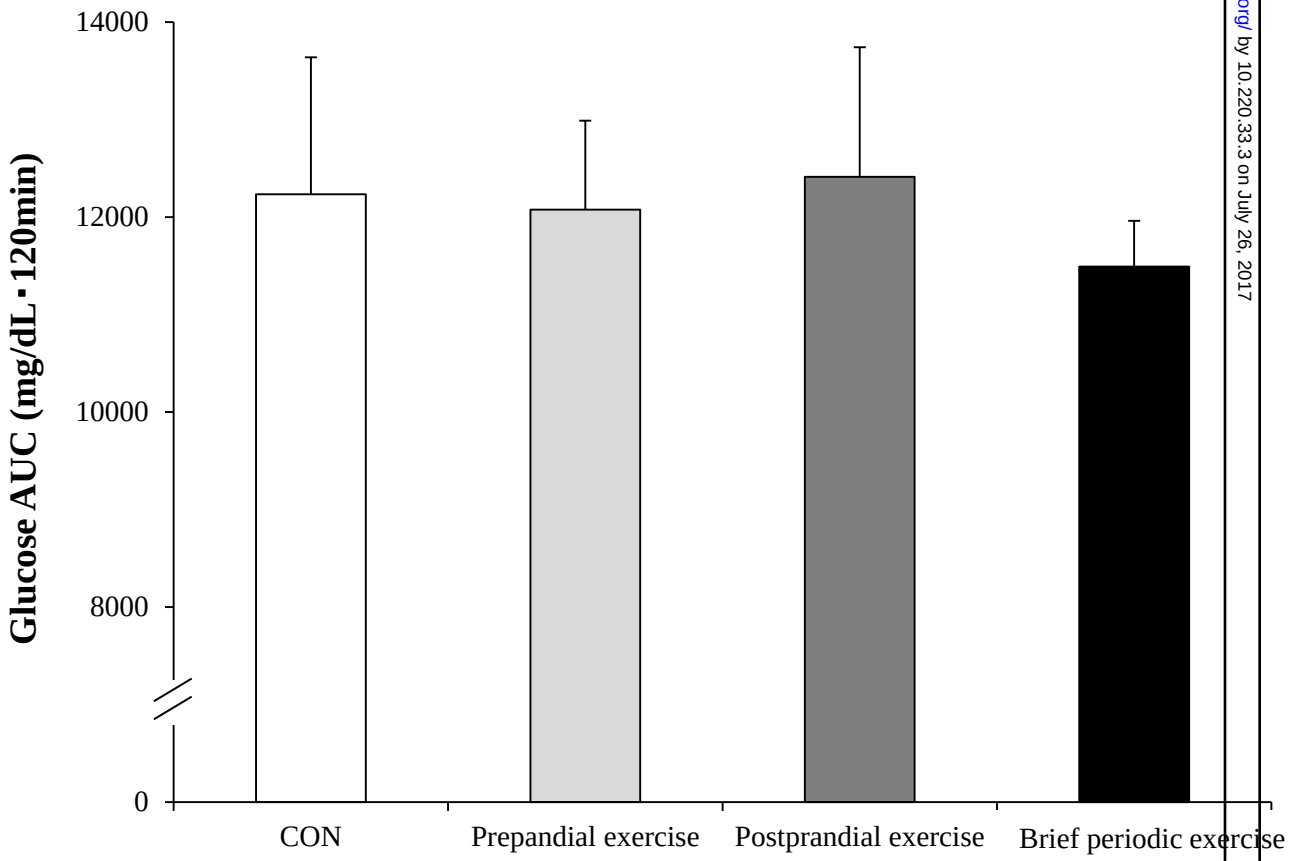

Figure 5.

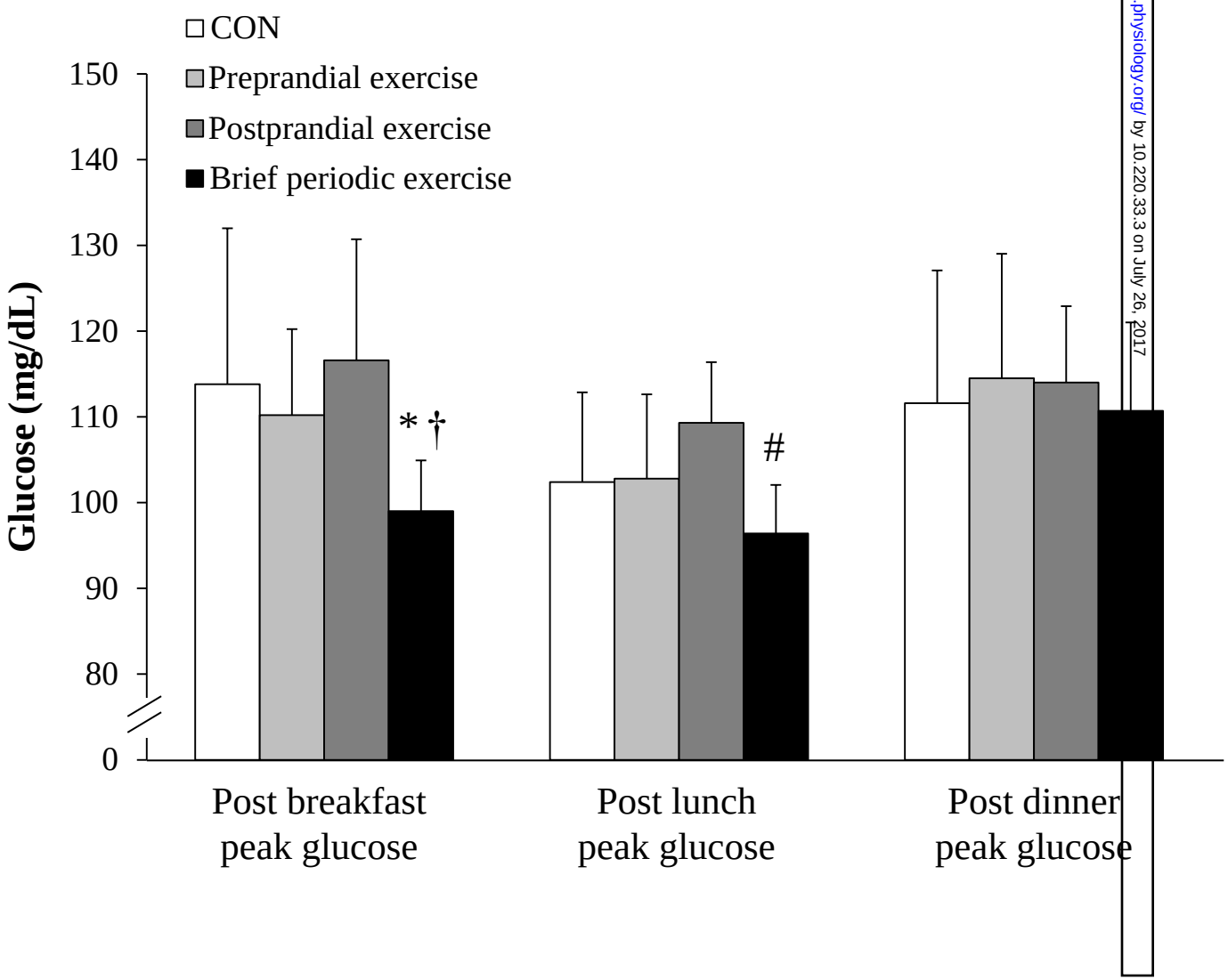

Table 1. Participant characteristics and energy balance of the experiments.

	Mean	SD
Age (yr)	23	2
Height (cm)	172	7
Weight (kg)	63.6	4.8
Body mass index (kg/m^2)	21.5	1.0
Body fat (%)	16.0	4.2
HbA1c (%)	5.3	0.3
VO_2 peak (ml/kg/min)	51.0	5.9
%VO_2 peak (%)	66	13
Running speed at LT (m/min)	161	34
Energy intake in each trial (kcal/day)	2299	153
Estimated energy expenditure in control trial (no exercise) day (kcal/day)	1741	107
Estimated energy expenditure in exercise trial day (kcal/day)	2389	218

Table 2. HR and RPE after first exercise (mean ± SD).

	Preprandial exercise	Postprandial exercise	Brief periodic exercise
Heart rate (beats/min)	134±17	136±15	117±20
RPE	11.9±1.2	12.7±0.8	10.5±1.3

Table 3. Energy intake, nutrients, and meal components for three standardized meals on the experiment day.

	Break fast	Lunch	Dinner
Energy Intake (kcal/day)	658 ± 97	737 ± 24	904 ± 80
Macronucrient（g）			
CHO	113.8 ± 16.6	104.5 ± 0.1	121.6 ± 11.7
Fat	14.6 ± 2.7	22.8 ± 0.8	28.0 ± 3.5
Protein	17.9 ± 4.2	28.5 ± 4.0	31.7 ± 2.9
Macronucrient（%）			
CHO	69 ± 3	57 ± 2	58 ± 2
Fat	20 ± 2	28 ± 0	28 ± 2
Protein	11 ± 1	15 ± 2	14 ± 1
Meal content (Frozen meals are marked FM.)	Chicken with rice (FM) Egg soup	Meat spaghetti (FM) Pizza (FM)	Stir-fried noodles (FM) Steamed meat dumplings (FM) Vegetable juice Banana Yogurt