Glucoregulation is more precise in women than in men during postexercise recovery[1–3]

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ABSTRACT

Background: The regulation of glycemia is challenged in healthy men and women after exercise bouts of substantial energy expenditure.

Objective: We determined rates of glucose appearance (Ra), disappearance (Rd), and metabolic clearance (MCR) before, during, and after isoenergetic moderate and hard-intensity exercise.

Design: Ten men and 8 women received primed-continuous infusion of [6,6-$^2H_2$]glucose tracer to measure glucose kinetics. Participants were studied under 3 different conditions with diet unchanged between trials: *1*) before, during, and 3 h after 90 min of exercise at 45% of peak oxygen consumption ($\dot{V}O_2$peak; E45); *2*) before, during, and 3 h after 60 min of exercise at 65% $\dot{V}O_2$peak (E65), and 3) in a time-matched sedentary control trial.

Results: In men and women, Ra, Rd, and MCR increased above the control trial during exercise and were higher in E65 than in E45 ($P < 0.05$). Average Ra, Rd, and MCR remained elevated above the control over 3 h of postexercise recovery in men after exercise in E45 and E65 ($P < 0.05$), and blood glucose concentrations were depressed below the control during recovery ($P < 0.05$). Glucose concentrations were not depressed in women during 3 h of postexercise recovery, and in contrast with that in men, average Ra and Rd did not remain significantly elevated during postexercise recovery in women, although MCR did remain elevated in E65 ($P < 0.05$).

Conclusions: After exercise bouts, women are better able to maintain glucose concentrations at sedentary control levels, thus not requiring the counter-regulation of glucose production that is seen in men and requiring less accentuation of lipid metabolism. *Am J Clin Nutr* 2008;87:1686–94.

INTRODUCTION

Because glucose and total carbohydrate oxidation increase greatly during exercise bouts of moderate and hard intensities (1, 2), physical activity can rapidly lead to a negative carbohydrate nutrient balance and places a large burden on gluconeogenic organs in maintenance of blood glucose homeostasis. When food intake is not raised to compensate for an increase in energy expenditure associated with physical activity, for example, as may be done in weight-loss programs containing an exercise component, a state of relatively negative energy balance would be achieved that would persist through the postexercise recovery period. Defense of euglycemia is a high physiologic priority and can be achieved by utilization of alternative fuels (primarily lipid) as well as by augmenting hepatic and renal glucose production. We showed previously that whereas carbohydrate oxidation is depressed for hours during postexercise recovery, the rate of lipolysis is elevated in men but not in women, and free fatty acid (FFA) mobilization and lipid oxidation are elevated to a greater extent in men than in women (3). We considered this finding to resolve the paradox that women oxidize lipid more than men do during exercise (4–12), but that women lose less body fat than do men when engaged in exercise programs (13, 14). Because the biological importance of lipid mobilization and oxidation may be to spare blood glucose in times at which carbohydrate sparing is a physiologic priority, it would seem plausible that differences in glucose kinetics and blood glucose homeostasis in postexercise recovery would underlie the sex-related differences in postexercise lipid metabolism that we reported previously (3).

Because the impact of exercise on energy metabolism can extend for many hours after exercise (9, 15–19), studying postexercise energy substrate kinetics is of interest. However, special care must be taken in interpreting the results of such studies because changes in metabolism occur throughout the day, even in a sedentary condition, and the exercise-induced changes are superimposed on the diurnal change in metabolism. In the resting postabsorptive state, glucose flux (20–23) and clearance (23) decrease throughout the day as a progression occurs toward a fasted condition. Despite what is known about normal drift in postabsorptive glucose flux, few reports exist in which glucose kinetics in the postexercise recovery period are compared with those in a time-matched sedentary control trial. Comparing postexercise glucose fluxes to pre-exercise rates, Weber et al (24) found no difference from pre-exercise glucose rate of appearance (Ra) in men during 2 h of postexercise recovery. Later, Horton et al (25) reported that glucose Ra and rate of disappearance (Rd) declined gradually to pre-exercise levels over the course of 3 h of recovery in men and more rapidly in women. In contrast with the

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previous findings of Weber (24) and of Horton (25), Boon et al (26) recently reported that glucose flux was significantly below pre-exercise rates during 2 h of recovery in healthy men. We reasoned that the discrepancies between the results of the aforementioned studies (24–26) may be attributable to the absence of a time-matched resting control trial, and that the time course of the declining glucose flux in the sedentary condition and in the postexercise conditions in both sexes would need to be measured to convincingly demonstrate the effects of a prior exercise bout on resting glucose production and disposal rates during the postexercise recovery period.

To better understand the integration of carbohydrate and lipid metabolism during the postexercise recovery period, in this report, we compare changes in glucose kinetics with our previously reported FFA and glycerol fluxes (3). As well, cognizant of findings regarding diurnal changes in glucose flux that may occur even in the absence of an exercise bout, we used a resting control trial to which metabolite kinetics during and after exercise would be compared. We hypothesized that glucose flux would be elevated over sedentary control levels after exercise.

SUBJECTS AND METHODS

Study participants

Twenty healthy, moderately active, nonsmoking, weight-stable volunteers (10 men and 10 women) were recruited from the University of California, Berkeley campus and surrounding community by posted notice and e-mail. Potential study participants underwent subsequent screening tests if they were disease-free as determined by physical examination and health history questionnaire, were not taking medications known to affect energy metabolism, had a body mass index (in kg/m^2) < 28, were neither sedentary individuals nor elite athletes, and had normal lung function as determined by a 1-s forced expiratory volume of ≥70% of vital capacity. Female study participants reported regular menstrual cycles (24–32 d) and were not taking oral contraceptives or other forms of exogenous ovarian hormones. We sought to study women in the early follicular phase of the menstrual cycle to standardize conditions between trials. Therefore, subjects were studied between days 3 and 8 of their cycles, and the cycle phase was later considered to be confirmed if estradiol was <50 pg/mL and progesterone was <1 ng/mL (27) in serum collected the morning of the tracer infusion trials. Because in 2 women, serum estrogen concentrations were >50 pg/mL, the data from those participants were removed from the analysis. Therefore, the number of female study participants included in the final analysis was reduced from 10 to 8. Procedures and risks were thoroughly explained to the study participants, and their written informed consent was obtained. The University of California, Berkeley Committee for the Protection of Human Subjects approved the study protocol (CPHS no. 2004-6-103).

Screening tests

Before beginning the study, the participants underwent 2 progressive exercise tests to assess $\dot{V}O_2$peak, and body composition was assessed by skinfold-thickness measurement (28, 29). In previous investigations, we (6, 7) found the skinfold and hydrostatic weighing methods to provide similar results on the study population of interest. $\dot{V}O_2$peak and body composition assessments were again carried out after completion of the study. Exercise was performed on a leg-cycle ergometer (Monark Ergometric 839E, Vansbro, Sweden). Dietary energy and macronutrient intakes were monitored at the beginning, middle, and end of the study by separate 3-d diet records; analysis was performed with DIET ANALYSIS PLUS, version 6.1 (ESHA Research, Salem, OR).

Experimental design

With ≥1 wk between trials for men and 1 mo between trials for women, the participants were studied under each of 3 conditions, each on separate occasions, assigned in a random order. Men and women were studied with tracer infusion and blood and breath sampling *1*) before, during, and 3 h after ≈90 min of exercise at 45% $\dot{V}O_2$peak (E45); *2*) before, during, and 3 h after ≈60 min of exercise at 65% $\dot{V}O_2$peak (E65); and *3*) during a time-matched resting condition (C). After catheterization, the study participants lay semisupine quietly reading or watching movies. After exercise, the study participants dismounted the ergometer and sat in a chair where they remained for 30 min and were then transferred to an examination table, where they remained semisupine for the remaining 2.5 h of postexercise recovery. Water was consumed ad libitum during recovery, but study participants consumed no other beverages and no food. Study participants were transported in a wheelchair for trips to the restroom. Duration of the first randomly assigned exercise trial, either E45 or E65, was set at 90 or 60 min, respectively. The appropriate duration for the subsequent exercise trial at the remaining exercise condition was predicted with the goal of matching exercise energy expenditure (EEE) between exercise bouts by using oxygen consumption ($\dot{V}O_2$) and respiratory exchange ratio data from the $\dot{V}O_2$peak assessments.

Experimental protocol

For the day before the tracer infusion trials, the study participants were instructed to consume solely a standardized diet and water ad libitum and to abstain from structured physical exercise sessions but to continue typical activities of daily living and were fed for a physical activity level of 1.5 according to the current dietary reference intake guidelines of the Institute of Medicine for estimated energy requirement (30). Dietary energy intake on the day before the tracer trials was individualized for each study participant (men, 2788 ± 44 kcal; women, 2129 ± 49 kcal) and macronutrient composition was made similar between individuals for carbohydrate (men, 49.8 ± 0.3%; women, 50.1 ± 0.2%), lipid (men, 32.0 ± 0.3%; women, 32.3 ± 0.4%), and protein (men, 18.2 ± 0.3%; women, 17.6 ± 0.2%). On the day of the tracer infusion trials, the study participants arrived at the laboratory at 0700 after fasting overnight and ate a standardized breakfast (men: 450 kcal, 67% carbohydrate, 22% fat, 11% protein; women: 345 kcal, 65% carbohydrate, 26% fat, 9% protein). We chose to feed our study participants standardized breakfasts 3 h before exercise to mimic typical nonlaboratory conditions.

On the morning of the tracer infusion trials, a catheter was placed in a hand vein to collect arterialized blood using the heated hand vein technique. After collection of background blood and breath samples, a catheter was placed in the contralateral arm for continuous infusion of stable isotope tracers. Tracers were purchased from Cambridge Isotope Laboratories (Andover, MA) and subsequently prepared in 0.9% sterile saline and tested for sterility and pyrogenicity at the University of California, San Francisco, School of Pharmacy. A continuous infusion of

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[1-^{13}C]palmitate (bound to 5% human albumin) and primed-continuous infusion of [1,1,2,3,3-$^{2}H_5$]glycerol and [6,6-$^{2}H_2$]glucose was started at 0830. Free fatty acid (palmitate) and glycerol kinetics were reported elsewhere (3). A [6,6-$^{2}H_2$]glucose-priming dose of 250 mg in men and 200 mg in women was given immediately before continuous infusion of [6,6-$^{2}H_2$]glucose at a rate of 2.0 mg/min in men and 1.6 mg/min in women. Glucose tracer infusion rate was increased 2-fold above rest at 45% $\dot{V}O_2$peak and 3-fold above rest at 65% $\dot{V}O_2$peak. For all tracers, infusion rates were immediately set back to initial resting rates at completion of exercise bouts for assessment of substrate kinetics during 3 h of postexercise recovery. On the morning of tracer infusion trials, before beginning infusion, aliquots of infusates were collected for analysis of concentration and isotopic enrichment (IE) to input more accurate infusion rates into the calculation of Ra. At each blood sampling time point pulmonary gas exchange was determined for assessment of metabolic rate. At each sampling time point, heart rate was recorded from an electrocardiograph (Quinton Q750, Seattle, WA) and blood pressure was measured by auscultation.

Blood sampling

Blood samples were drawn from the heated hand vein catheter before exercise (75 and 90 min after the start of tracer infusion), during exercise (45 and 60 min at 65% VO_2peak and 75 and 90 min at 45% VO_2peak), and after exercise (5, 15, 30, 60, 90, 120, 150, and 180 min) for a total of 12 sampling time points. During the nonexercise trials, blood samples were drawn during 6 h of rest (75, 90, 135, 150, 165, 180, 210, 240, 270, 300, 330, 360 min after the start of tracer infusion) for a total of 12 sampling time points. Additionally, blood was drawn before tracer infusion to obtain background IEs as well as estradiol and progesterone concentrations in women. Blood for glucose concentration and IE was collected as a 1:2 ratio with 8% perchloric acid for whole blood extraction, centrifuged at 3000g for 20 min, and the supernatant was stored at −20 °C. Blood for analysis of glucagon was collected in tubes with EDTA and aprotinin, for insulin with aprotinin, and for estrogen and progesterone without any additive. Hormone samples were each centrifuged at 3000 × g for 20 min with subsequent storage of supernatants at −80 °C.

Sample analyses

Insulin, glucagon, estradiol, and progesterone concentrations were determined by radioimmunoassay (Diagnostic Products Corporation, Los Angeles, CA). Lactate concentrations were measured enzymatically (31). Glucose concentrations and IEs were determined by gas chromatography–mass spectrometry (GC-MS; GC model 6890 Series and MS model 5973N, Agilent Technologies) of the pentaacetate derivative using an Agilent DB-17 GC column and [U-^{13}C]glucose as internal standard. Glucose sample preparation was carried out as described for glycerol previously (3). Methane was used for chemical ionization and selective ion monitoring was performed for mass-to-charge ratios (m/z) of 331, 333, and 337 for endogenous glucose, [6,6-$^{2}H_2$]glucose tracer, and [U-$^{13}C_6$]glucose internal standard, respectively. Selected ion abundances were compared against external standard curves for calculation of both concentration and IE, with normalization to internal standard signal for determination of concentration.

Calculations

Using a single pool non–steady state model, glucose Ra, Rd, and metabolic clearance rate (MCR) were calculated with the equations of Steele (32) as modified for use with stable isotopes (33). These equations are reported below for convenience of the reader:

$$\mathrm{Ra}(\mu\mathrm{mol}\cdot\mathrm{kg}^{-1}\cdot\mathrm{min}^{-1}) = \{F - V[(C_1 + C_2)/2] \times [\mathrm{IE}_2 - \mathrm{IE}_1)/(t_2 - t_1)]\}/[(\mathrm{IE}_2 + \mathrm{IE}_1)/2] \quad (1)$$

$$\mathrm{Rd}(\mu\mathrm{mol}\cdot\mathrm{kg}^{-1}\cdot\mathrm{min}^{-1}) = \mathrm{Ra} - V[(C_2 - C_1)/(t_2 - t_1)] \quad (2)$$

$$\mathrm{MCR} = \mathrm{Rd}/[(C_1 + C_2)/2] \quad (3)$$

where F represents the tracer infusion rate, V is the estimated volume of distribution (100 mL/kg), C_1 and C_2 are concentrations at sampling times t_1 and t_2, respectively, and IE_1 and IE_2 are isotopic enrichments at sampling times t_1 and t_2, respectively. Isotopic enrichments were corrected for background enrichments in blood samples collected before tracer infusion and in these equations are in units of moles percent excess (MPE) divided by 100 to express as a decimal.

Statistical analyses

Data are presented as means ± SEs. Within sexes, comparisons between trials and across time points were made by 2-way (time × trial) analysis of variance (ANOVA) with repeated measures with post hoc comparisons using Fisher's protected least significant difference test. The 75 and 90 min time points were collected under similar resting conditions in each of the 3 trials, and as results were not significantly different between trials for these time points, data for these time points are presented with the 3 trials pooled. Average postexercise values for variables were calculated using time points from 30 min after exercise to 180 min after exercise, and the average corresponding values in C were the average of 180 to 360 min after the start of tracer infusion which corresponded with the postexercise time-of-day. Selected planned comparisons between men and women were made by unpaired t tests, including comparison of the average values from the final 180 min of C, comparisons of average values from during the exercise bouts, and comparison of the average percent elevation of postexercise recovery above C if both sexes showed elevation above C after exercise. Statistical analyses were performed using SPSS GRADUATE PACK 11.0 software (SPSS Inc, Chicago). Statistical significance was set at $\alpha = 0.05$.

In planning the statistical analysis, we sought to minimize the number of comparisons and maximize statistical power by investigating potential sex differences by specific planned comparisons rather than adding sex as a third factor in the ANOVA. An alternative approach would have been to perform a 3-way mixed model ANOVA with sex, time, and trial as factors. However, our sex comparison was designed to evaluate significance of differences between 2 distinct groups rather than a search for subtle differences across 12 separate time points. Another alternative approach to ours would have been to use a more conservative post hoc test, such as Tukey's honestly significant difference (HSD) test. After applying our statistical approach (from which we interpret the data in this report), we additionally performed the alternative approach of a 3-way mixed model ANOVA with Tukey's HSD for the sake of comparison and

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confirmation that vastly different conclusions would not have been drawn by other investigators who may have applied a 3-way ANOVA. Significant sex × trial interactions were attained for glucose concentrations, Ra, Rd, and MCR, which as a whole agreed with our findings of sex differences by selected planned comparisons. However, the statistical methods applied in this report reflect a more targeted approach, investigating different conditions as a whole (men versus women for rest, exercise, and relative change in recovery), which we believe ultimately allowed us to describe physiologically meaningful differences between conditions and sexes.

RESULTS

Characteristics of the study participants

The data in **Table 1** were reported previously (3) but are repeated for the convenience of the reader. There were no significant differences between men and women regarding age, body mass index, exercise habits, or $\dot{V}O_2$peak per unit fat-free mass (Table 1). In both men and women, $\dot{V}O_2$peak and body composition did not vary significantly between assessments carried out before enrolling study participants and after completing the final tracer infusion trial. Habitual exercise habits of ≈7 h per week of moderate exertion (more intense than walking and less intense than competitive sporting competition) were reported by both the men and women. Body fat percent was significantly greater in women than in men ($P < 0.05$). Habitual dietary energy intake and macronutrient composition, as determined by multiple 3-d diet records, did not vary significantly between the 3 separate assessments and, therefore, averaged values are reported. Habitual dietary energy intake was significantly larger in men than women (men, 2537 ± 118 kcal/d; women, 1854 ± 48 kcal/d; $P < 0.05$). Habitual dietary macronutrient composition was not significantly different between sexes for carbohydrate (men, 53.2 ± 1.9%; women, 53.5 ± 1.6%), lipid (men, 30.5 ± 1.6%; women, 29.3 ± 1.3%), and protein (men, 16.3 ± 0.9%; and women, 17.2 ± 0.8%).

Characteristics of exercise bouts

Exercise sessions were described in a previous report (3). EEEs were significantly greater in men than women ($P < 0.05$). EEE was calculated by subtracting the resting energy expenditure, calculated from the C trial, from the energy expenditure of the exercise sessions. Within men and within women, the EEE was matched between exercise trials in that there was no significant difference between the EEE for E45 (men, 693.2 ± 40.3 kcal; women, 444.7 ± 31.9 kcal) and E65 (men, 703.6 ± 41.5 kcal; women, 440.3 ± 51.4 kcal) (3). As physical fitness level ($\dot{V}O_2$peak per unit fat free mass) was similar between men and women, $\dot{V}O_2$ was not significantly different between sexes during exercise when expressed per unit fat-free mass in either E45 or E65, and relative exercise intensities were also similar between sexes in E45 (men, 46.7 ± 0.4% $\dot{V}O_2$peak; women, 45.1 ± 0.8% $\dot{V}O_2$peak) and E65 (men, 66.1 ± 1.1% $\dot{V}O_2$peak; women, 65.0 ± 0.5% $\dot{V}O_2$peak) (3).

TABLE 1
Characteristics of the study participants[1]

	Men (n = 10)	Women (n = 8)
Age (y)	24.5 ± 1.1	25.4 ± 2.0
Height (cm)	178.5 ± 1.6[2]	162.0 ± 2.2
Weight (kg)	73.1 ± 2.4[2]	58.3 ± 1.9
BMI (kg/m^2)	22.9 ± 1.6	22.2 ± 0.4
Body fat (%)	10.4 ± 1.2[2]	22.2 ± 1.0
FFM (kg)	65.4 ± 2.2[2]	45.3 ± 1.7
$\dot{V}O_2$peak (L/min)	4.1 ± 0.2[2]	2.8 ± 0.2
$\dot{V}O_2$peak (mL · kg^{-1} · min^{-1})	56.6 ± 2.0[2]	48.9 ± 2.6
$\dot{V}O_2$peak (mL · kg FFM^{-1} · min^{-1})	63.0 ± 2.2	62.7 ± 3.2
Exercise (h/wk)	6.9 ± 0.9	7.0 ± 1.0

[1] All values are $\bar{x}$ ± SE. $\dot{V}O_2$peak, peak O_2 consumption; FFM, fat-free mass.

[2] Significantly different from women, $P < 0.05$ (unpaired t test).

Hormones

Serum insulin concentration results were reported previously (3). Plasma glucagon concentrations decreased significantly in men and women from the pre-exercise time points to those corresponding to the postexercise recovery period ($P < 0.05$), but insulin decreased to a greater extent such that the insulin/glucagon molar ratio (I/G) decreased ($P < 0.05$) ≈2-fold during C. In men, glucagon concentrations were significantly elevated above C during exercise in E45 and E65. At individual time points glucagon concentrations remained significantly elevated through 30 min of recovery in E45 and 60 min of recovery in E65 for men. The average postexercise glucagon concentrations, calculated from 30 to 180 min after exercise, were significantly elevated above C (Control, 11.9 ± 0.5 pmol/L) by 12 ± 3% in E65 ($P < 0.05$) but the 8 ± 3% elevation of E45 above C approached but did not reach significance ($P = 0.06$). In women, compared with their corresponding control (14.2 ± 1.2 pmol/L), the average postexercise glucagon concentrations were not significantly elevated (E45, 2 ± 2%; E65, 5 ± 3%; NS).

Metabolite concentrations

Blood glucose concentrations decreased slightly, but significantly ($P < 0.05$), in both men and women by the end of the 2 exercise challenges. Subsequently, blood glucose concentrations remained significantly depressed ($P < 0.05$) in men (**Figure 1**) but not women (Figure 1) during the postexercise recovery period. There were no significant differences between men and women in C or during exercise for glucose concentrations. Blood lactate concentrations decreased significantly ($P < 0.05$) in men (Figure 1) and women (Figure 1) over the course of observations in C. In men, during exercise and for 1 h after exercise, lactate concentrations were significantly elevated above C in both E45 and E65 ($P < 0.05$). In women, lactate concentrations were significantly elevated during exercise and for 15 min after exercise in E65 ($P < 0.05$), but was not significantly different from C at any time points in E45. In neither men nor women was the average postexercise lactate concentrations significantly different from C. In C and during exercise in E65, lactate concentrations were not significantly different between men and women, but were significantly higher in men during exercise in E45 ($P < 0.05$).

Glucose kinetics

Glucose Ra and Rd decreased significantly in both sexes over the course of observations in C (**Figure 2**; $P < 0.05$). In both sexes, glucose Ra and Rd were significantly higher than C during exercise in E45 and E65 and higher in E65 than E45 ($P < 0.05$).

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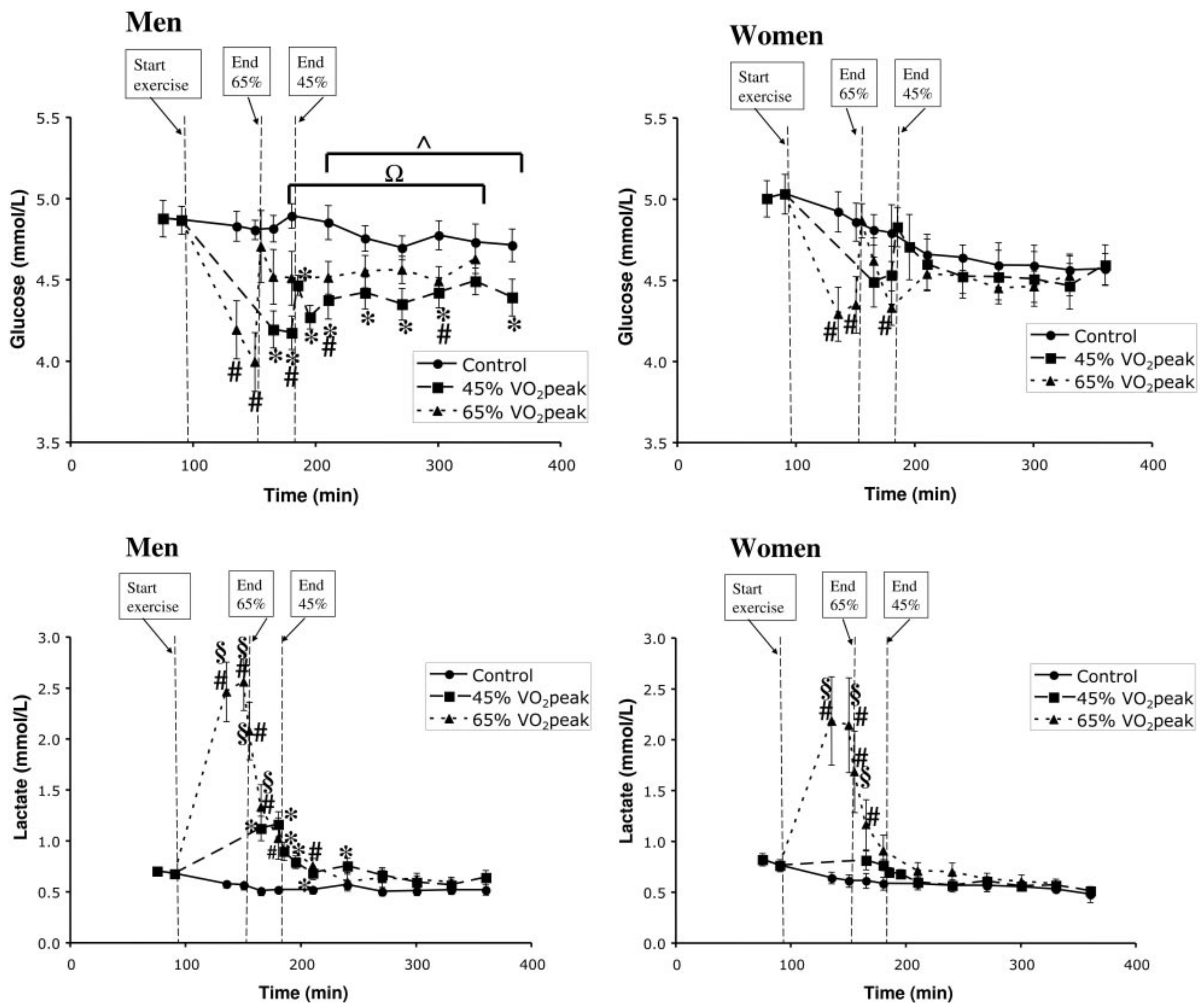

FIGURE 1. Mean (± SE) blood glucose and lactate concentrations in men (n = 10) and women (n = 8). $\dot{V}O_2$peak, peak oxygen consumption; time (min), duration elapsed since beginning tracer infusion. *45% $\dot{V}O_2$peak trial significantly different from corresponding time points in control trial, $P < 0.05$. #65% $\dot{V}O_2$peak trial significantly different from corresponding time points in control trial, $P < 0.05$. §45% $\dot{V}O_2$peak trial significantly different from corresponding time point in 65% $\dot{V}O_2$peak trial, $P < 0.05$. ^Average postexercise value (30 to 180 min after exercise) in 45% $\dot{V}O_2$peak trial significantly different from corresponding average in control trial, $P < 0.05$. ΩAverage postexercise value (30 to 180 min after exercise) in 65% $\dot{V}O_2$peak trial significantly different from corresponding average in control trial, $P < 0.05$. Statistical analysis by ANOVA with Fischer's LSD post hoc text. Time × trial interactions for all panels were significant, $P < 0.05$.

The average postexercise glucose Ra and Rd in men were significantly elevated above C in E45 and E65 ($P < 0.05$), but there were no significant differences between average postexercise glucose Ra or Rd between E45 and E65 (**Table 2**). The average postexercise glucose Ra and Rd in women were not significantly different between trials (Table 2). There were no significant differences between men and women in C or during exercise for glucose Ra or Rd (Table 2).

Glucose MCR in men and women (Figure 2) decreased significantly over the course of observations in C ($P < 0.05$). In both sexes, glucose MCR was significantly higher than C during exercise at either intensity and higher in E65 than E45 ($P < 0.05$). MCR remained significantly elevated at individual time points in men ($P < 0.05$) through 90 min after exercise in E45 and 120 min after exercise in E65 ($P < 0.05$), but the only individual postexercise time point at which MCR was significantly elevated in women was 30 min after exercise in E65 ($P < 0.05$). The average postexercise glucose MCR in men was significantly elevated above C in E45 and E65 ($P < 0.05$), but not different between E45 and E65 in recovery (Table 2). The average postexercise glucose MCR in women was not significantly elevated above C in E45 but in E65 was significantly higher ($P < 0.05$) than both C and E45 (Table 2). The relative elevation of MCR above C in the postexercise recovery period was significantly higher ($P < 0.05$) in men than women in both E45 (men, 30 ± 9%; women, 2 ± 4%) and E65 (men, 37 ± 8%; women, 16 ± 5%). There were no significant differences between men and women in C or during exercise in E65, but MCR was significantly higher in men than women during exercise in E45 ($P < 0.05$).

DISCUSSION

During exercise tasks of similar relative intensity and the same duration, women display greater capacity for lipid oxidation and

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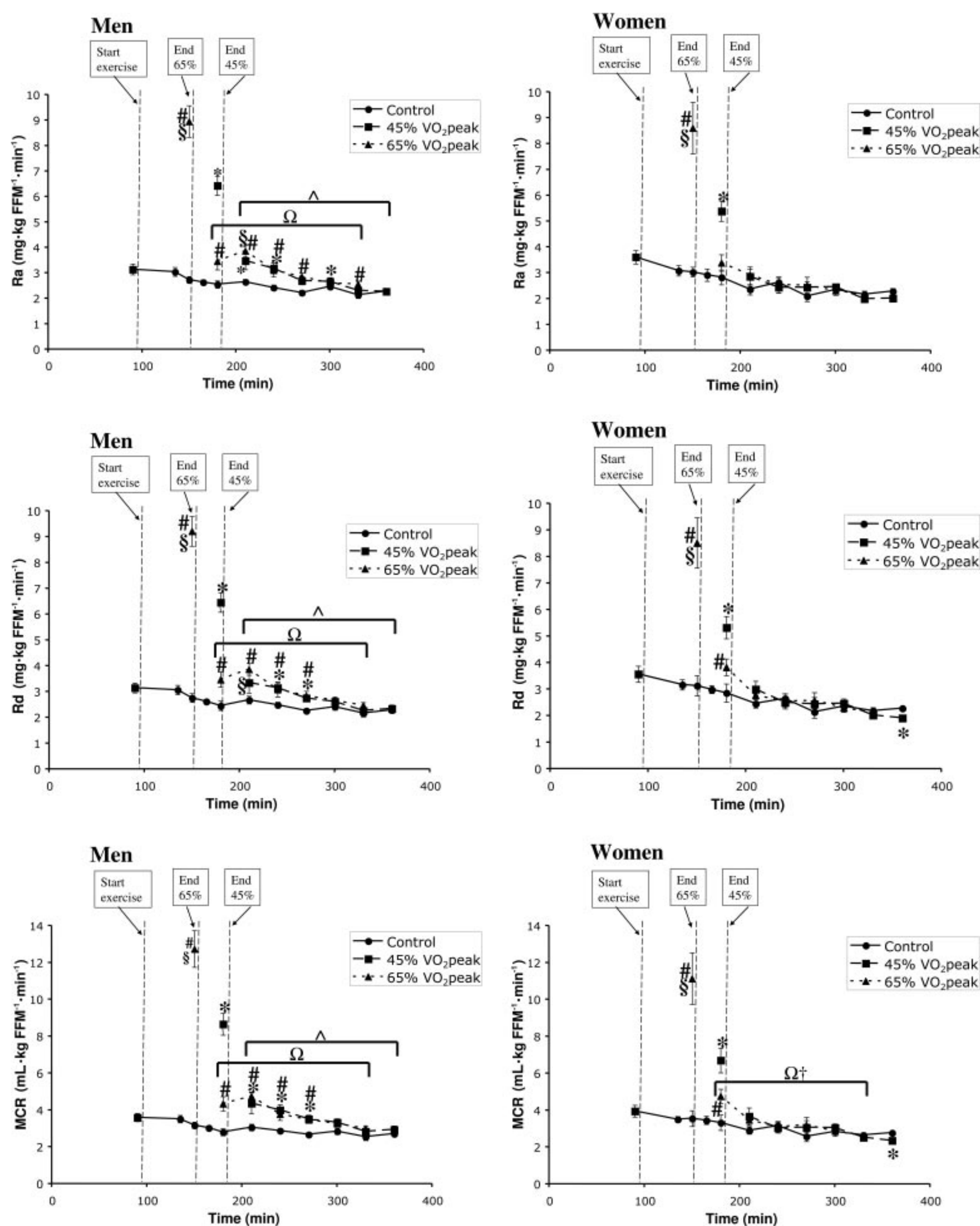

FIGURE 2. Mean (± SE) glucose rate of appearance (Ra), rate of disappearance (Rd), and metabolic clearance rate (MCR) in men ($n = 10$) and women ($n = 8$). $\dot{V}O_2$peak, peak oxygen consumption; time (min), duration elapsed since beginning tracer infusion. *45% $\dot{V}O_2$peak trial significantly different from corresponding time points in control trial, $P < 0.05$. #65% $\dot{V}O_2$peak trial significantly different from corresponding time points in control trial, $P < 0.05$. §45% $\dot{V}O_2$peak trial significantly different from corresponding time point in 65% $\dot{V}O_2$peak trial, $P < 0.05$. ^Average postexercise value (30 to 180 min after exercise) in 45% $\dot{V}O_2$peak trial significantly different from corresponding average in control trial, $P < 0.05$. ΩAverage postexercise value (30 to 180 min after exercise) in 65% $\dot{V}O_2$peak trial significantly different from corresponding average in control trial, $P < 0.05$. †Average postexercise value (30 to 180 min after exercise) in 45% $\dot{V}O_2$peak trial significantly different from that in 65% $\dot{V}O_2$peak trial, $P < 0.05$. Statistical analysis by ANOVA with Fischer's LSD post hoc text. Time × trial interactions for all panels were significant, $P < 0.05$.

women regain control over glycemia and glucose flux more rapidly in recovery than do men. Therefore, women do not require the same degree of augmentation of lipid mobilization and utilization in postexercise recovery (3). These results present differences as well as similarities in comparison to previously reported results. Seemingly, consistency among results from diverse laboratories is improved if sex, dietary, and time-of-day comparisons are made.

In the present study, glucose Ra, Rd, and MCR each decreased by approximately one third in men and women during the course of the C trial (Figure 2). This shift in glucose kinetics reflects transition toward a more fasted state over time that occurs between meals (20–23). As glucose flux declines substantially over time in a sedentary condition, we believe that inclusion of a resting time-of-day control trial is crucial and that comparison of postexercise recovery with pre-exercise rest might lead to inaccurate depiction of postexercise metabolism. Furthermore, while we find the average postexercise elevation of glucose Ra, Rd, and MCR to be significant in men, the elevation appears to gradually diminish over the 3 h of postexercise recovery. Therefore, a

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TABLE 2
Glucose kinetics[1]

Time and trial	Men (n = 10)			Women (n = 8)		
	Ra	Rd	MCR	Ra	Rd	MCR
Pre-exercise, pooled	3.1 ± 0.2	3.1 ± 0.2	3.6 ± 0.2	3.6 ± 0.3	3.6 ± 0.3	4.0 ± 0.3
Exercise						
45%	6.4 ± 0.4[2,3]	6.5 ± 0.4[2,3]	8.7 ± 0.6[2–4]	5.4 ± 0.4[2,3]	5.3 ± 0.4[2,3]	6.7 ± 0.7[2,3]
65%	9.0 ± 0.6[2]	9.2 ± 0.6[2]	12.7 ± 1.0[2]	8.6 ± 1.0[2]	8.5 ± 0.9[2]	11.1 ± 1.4[2]
Recovery						
Control	2.4 ± 0.1	2.4 ± 0.1	2.8 ± 0.1	2.4 ± 0.1	2.4 ± 0.1	2.9 ± 0.1
45%	2.8 ± 0.1[2]	2.7 ± 0.2[2]	3.5 ± 0.2[2]	2.4 ± 0.1	2.4 ± 0.1	3.0 ± 0.2[3]
65%	3.1 ± 0.2[3]	3.1 ± 0.2[2]	3.8 ± 0.2[2]	2.6 ± 0.2	2.7 ± 0.2	3.3 ± 0.2[2]

[1] All values are $\bar{x}$ ± SE. Exercise and recovery control were compared between men and women. 45%, 45% $\dot{V}O_2$peak trial; 65%, 65% $\dot{V}O_2$peak trial; recovery, average from 30 min after exercise to 180 min after exercise; Ra, glucose rate appearance in mg · kg FFM^{-1} · min^{-1}; Rd, glucose rate of disappearance in mg · kg FFM^{-1} · min^{-1}; MCR, glucose metabolic clearance rate in mL · kg FFM^{-1} · min^{-1}. Statistical analysis by ANOVA with Fischer's LSD post hoc text. Time × trial interaction, $P < 0.05$.

[2] Significantly different from corresponding time points in control trial, $P < 0.05$.

[3] Significantly different from corresponding time points in 65% $\dot{O}_2$peak trial, $P < 0.05$.

[4] Significantly different from women, $P < 0.05$.

measurement at a single time point would not be representative of the overall effect of exercise on postexercise glucose kinetics.

It is likely that our finding of no sex difference in glucose flux during exercise is related to the fact that we provided our volunteers with a light breakfast 3 h before exercise, because it has been shown that men have higher glucose flux than women during exercise in the fasted (10), but not in the fed state (8). Of importance though, it is noteworthy that a significant elevation of glucose flux above control levels occurred during the postexercise recovery period in men, but not women. The higher-intensity exercise bout (E65) did promote an increase in MCR in women at 30 min after exercise as well as for the overall average of the postexercise recovery period ($P < 0.05$), but the relative elevation above C was significantly less than in men (men, 37 ± 8; women, 16 ± 5%; $P < 0.05$). Comparing metabolic responses in individuals of differing body sizes and compositions is always difficult, particularly when they differ in sex as well. However, because male and female study participants were well matched on fitness and habitual physical activity (Table 1), because women were studied in the follicular menstrual cycle phase, and because the duration and relative intensity of the exercise bouts were matched, we believe that the findings of a sex difference in postexercise glucose kinetics are robust. This conclusion is not based on isolated findings, but rather our conclusion is based in patterns of differences in the circulating fuel supply and the endocrine environment and collectively represent a sex-related difference in postexercise glucoregulation. Insulin was not different between C and postexercise recovery in men and women (3), but in men the average postexercise glucagon was significantly elevated in E65 and tended to be elevated in E45 (P = 0.06). As well, we previously reported that the average plasma norepinephrine concentration was significantly elevated above C in men during the postexercise recovery period in both E45 and E65 (3), but the relative increase in norepinephrine concentration required to alter glucose Ra may be substantially larger than the subtle (but statistically significant) elevation of ≈15–30% that we observed (34), and so we focus on glucagon as a possible cause of the elevated glucose Ra in men after exercise. As glucagon is known to stimulate glucose production via enhanced hepatic glycogenolysis and gluconeogenesis (35, 36), we conclude that the elevated glucose Ra in recovery in men may have been related to the effect of glucagon on stimulating hepatic glucose production.

As occurs when energy intake is lowered without changing physical activity, when activity is increased without a change in energy intake (as done in this study), a challenge is imposed on energy homeostasis. Glucose concentrations were significantly lower than C in men ($P < 0.05$), but not women during postexercise recovery (Figure 1), and this may represent a physiologic benefit of the lower exercise respiratory quotient achieved in women as seen in this (3) and other studies (4–12). Blood glucose concentrations were depressed in men during recovery despite the fact that glucose Ra was elevated. As such, depressed glucose concentrations in men during the postexercise recovery period appears to be related to elevated clearance. The elevated glucose Ra in men is likely an attempt (although not completely successful) at restoring blood glucose homeostasis in response to a counter-regulatory endocrine response (elevated glucagon). Elevated glucose Rd might be driven by an enhanced rate of glycogen synthesis (37–39) in exercised skeletal muscle, especially in men in which glycogen depletion may be expected to be greater than women (4) and therefore the rate of glycogen resynthesis also greater (37). In opposition to this concept though, Devries at al showed no sex difference in glycogen utilization during cycling exercise in the fasted state (10). While it is conceivable that running exercise (4) and cycling exercise (10) affect carbohydrate metabolism differently, it is likely that fed state glucose flux in women (8) spares net muscle glycogen degradation and that the sex difference in glycogen utilization is more apparent in the fed state. As our participants exercised 3 h after breakfast (in the fed state), it is in fact plausible that the higher carbohydrate oxidation that we found in men during exercise (3) and has been shown in other studies (4–12) did lead to greater depletion of glycogen in skeletal muscle. What's more, while women normalize blood glucose more rapidly than men in postexercise recovery, men may synthesize muscle glycogen more rapidly, thereby suggesting a sex-related difference in the prioritizing of the repletion rate of different carbohydrate pools within

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the body. Muscle glycogen synthesis (or non-oxidative glucose disposal in other peripheral tissues) in men may be at the expense of blood glucose homeostasis. Meanwhile, women are better able to normalize blood glucose, even though the state of negative energy balance caused by the EEE persists during the recovery period.

When different glucose flux rates are reported to occur in men and women following exercise, a temptation is that readers may classify one group as 'higher' and the other as 'lower.' For example, Horton et al (25) reported that women had lower glucose flux than men during postexercise recovery. In concert, here we report elevated glucose Ra in men, but not women, during postexercise recovery. However, our conclusion is based on both male-female as well as matched time-of-day resting control value comparisons in the same subjects. As carbohydrate storage depots are much smaller than those for lipid, it may be that carbohydrate sparing in women during exercise allows for carbohydrate fuel homeostasis to be less challenged following exercise in women in which greater glycogen stores could remain and blood glucose concentrations (Figure 1) would remain closer to that of a sedentary condition. It appears to be that women re-establish baseline fuel mobilization rates more readily than men following exercise bouts. We previously reported that men, but not women, display elevated glycerol Ra in recovery and that, compared with men, women have a relatively smaller elevation of FFA flux in recovery (3). The inferior postexercise defense of glycemia in men is likely the reason that men have a greater elevation of glucose, glycerol, and FFA flux rates in recovery. That is, elevated mobilization of fuels in recovery can be considered to be a counter-regulatory response to challenged blood glucose homeostasis.

In this report, we focus on postexercise glucose kinetics, and we have previously reported the data on postexercise lipolysis and fatty acid kinetics (3). Taken together, the results indicate that the relation between fuel mobilization, and oxidation differs between lipid and carbohydrate, and between men and women. FFA mobilization and oxidation were elevated in men and women during the postexercise recovery period (3). Therefore, FFA mobilization tracked changes in lipid oxidation. On the other hand, glucose flux was elevated (in men) or maintained at C levels (in women) during the postexercise recovery period in which carbohydrate oxidation was depressed (3). During the postexercise recovery period, total lipid oxidation and oxidation of plasma FFA are enhanced (3, 19, 40), and meanwhile, glucose and glycogen are likely spared until full repletion is achieved following rest and carbohydrate nutrition. As such, up-regulation of postexercise lipid metabolism is likely driven by depletion of carbohydrate (especially blood glucose) and represents counter-regulation, acting through alternative non-glucose fuel mobilization and use.

In considering how metabolism is modified following activities of daily life, an excess postexercise oxygen consumption (EPOC) value of 15% of the EEE is typical (30). However, we now know that glucose and lipid flux and oxidation rates shift over the course of a day and differ between men and women. Further, as already discussed women defend glycemia more successfully following physical activity, but men experience a greater elevation of glucose and lipid flux as well as lipid oxidation after exercise. Whether these findings complicate the ability to make dietary predictions is yet to be determined as unknowns arise. For example, should nutritional strategies be aimed at improving the precision of postexercise glucoregulation in men, or should they be aimed at elevating substrate mobilization and lipid oxidation in women? Or, does simply estimating EEE and assuming an EPOC of 15% cover energy and macronutrient needs on a balanced diet containing the AMDR for carbohydrate, even though carbohydrate is the predominant fuel for exercise?

In conclusion, we studied isoenergetic exercise bouts of 2 intensities in which short-term negative energy balance was achieved. Novel results are that when compared with time-of-day background, glucose concentration and flux are altered to a greater extent in men than women, and that men require a greater postexercise counter-regulatory response to maintain blood glucose concentrations. Furthermore, glucose clearance is elevated in recovery in women only following hard exercise, but glucose clearance is elevated in men to a greater extent following exercise of either moderate or hard intensity. Glucoregulation is more precisely maintained following exercise in women than men, and this difference in maintenance of glycemia underlies the sex differences in postexercise energy substrate metabolism.

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