Effects of Exercise Mode on Postprandial Metabolism in Humans with Chronic Paraplegia

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[1]*The Miami Project to Cure Paralysis, University of Miami Miller School of Medicine, Miami FL;* [2]*Department of Physical Medicine and Rehabilitation, University of Miami Miller School of Medicine, Miami FL;* [3]*Department for Health, University of Bath, Bath, Somerset, UNITED KINGDOM;* [4]*Department of Kinesiology and Sport Sciences, University of Miami, Miami, FL; and* [5]*Division of Endocrinology, Diabetes and Metabolism, University of Miami Miller School of Medicine, Miami, FL*

ABSTRACT

MCMILLAN, D. W., J. L. MAHER, K. A. JACOBS, A. J. MENDEZ, M. S. NASH, and J. L. J. BILZON. Effects of Exercise Mode on Postprandial Metabolism in Humans with Chronic Paraplegia. *Med. Sci. Sports Exerc.*, Vol. 53, No. 7, pp. 1495–1504, 2021. **Purpose:** The purpose of this study was to assess the acute effects of exercise mode and intensity on postprandial macronutrient metabolism. **Methods:** Ten healthy men age 39 ± 10 yr with chronic paraplegia (13.2 ± 8.8 yr, ASIA A–C) completed three isocaloric bouts of upper-body exercise and a resting control. After an overnight fast, participants completed circuit resistance exercise (CRE) first and the following conditions in a randomized order, separated by >48 h: i) control (CON), ~45-min seated rest; ii) moderate-intensity continuous exercise (MICE), ~40-min arm cranking at a resistance equivalent to ~30% peak power output (PPO); and iii) high-intensity interval exercise (HIIE), ~30 min arm cranking with resistance alternating every 2 min between 10% PPO and 70% PPO. After each condition, participants completed a mixed-meal tolerance test consisting of a 2510-kJ liquid meal (35% fat, 50% carbohydrate, 15% protein). Blood and expired gas samples were collected at baseline and regular intervals for 150 min after a meal. **Results:** An interaction ($P < 0.001$) was observed, with rates of lipid oxidation elevated above CON in HIIE until 60 min after a meal and in CRE at all postprandial time points up to 150 min after a meal. Postprandial blood glycerol was greater in MICE ($P = 0.020$) and CRE ($P = 0.001$) compared with CON. Furthermore, nonesterified fatty acid area under the curve had a moderate-to-strong effect in CRE versus MICE and HIIE (Cohen's $d = -0.76$ and -0.50, respectively). **Conclusions:** In persons with paraplegia, high-intensity exercise increased postprandial energy expenditure independent of the energy cost of exercise. Furthermore, exercise combining resistance and endurance modes (CRE) showed the greater effect on postprandial lipid oxidation. **Key Words:** SPINAL CORD INJURY, INTERVAL EXERCISE, CIRCUIT RESISTANCE EXERCISE, UPPER-BODY EXERCISE, EXERCISE INTENSITY, MIXED-MEAL TOLERANCE TEST

Spinal cord injury (SCI) results in dysregulation of energy metabolism that increases the risk of cardiometabolic disease (CMD) (1). The Consortium for Spinal Cord Medicine's Clinical Practice Guidelines recommends exercise as primary management strategy for combating CMD in SCI (1). Furthermore, recent AGREE II evidence-based guidelines found moderate to high GRADE confidence ratings for the effect of exercise on cardiometabolic health in persons with SCI (2). Specifically, circuit resistance training has been shown to improve the clinical lipid profile (3) and high-intensity interval training is an emerging exercise strategy to target CMD (4) in persons with SCI. Although the aforementioned guidelines and evidence highlight the importance of exercise for metabolic health in SCI, it is possible that lifestyle monotherapies are insufficient to modify the component risks of cardiometabolic syndrome (5). Considered in conjunction with the unique nutritional considerations in SCI (6), a further understanding of the interaction of nutrition and physical activity is warranted in this population.

Clinical and laboratory tests of macronutrient handling have shown glycemic and lipemic dysregulation in persons with SCI. Oral glucose tolerance testing (OGTT) (7–9) has shown that persons with SCI who have "normal" fasted blood glucose (<5.5 mmol·L^{-1}) likely still experience impaired glycemic regulation. The finding of dysglycemia despite normal fasted glucose levels demonstrates how metabolic changes after SCI seem dormant until the system is presented with a challenge. Similarly, dyslipidemia can occur in SCI despite a "normal" serum triglyceride (TG) concentration (10), whereas laboratory postprandial lipemia (PPL) tests have consistently shown an impaired ability to handle an oral lipid challenge (11–14). When also considering obesity and intermuscular fat accumulation (15) in this population, it seems that disorders of fat

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metabolism are paramount in the development of CMD in SCI. Evidence for disordered macronutrient handling in SCI is based primarily on single-nutrient (e.g., 75 g glucose) feeding challenges. Dysglycemia after consumption of a liquid mixed macronutrient meal has been documented in persons with tetraplegia (16), but evidence is lacking in persons with paraplegia. Further evidence is required to understand the effect of SCI on substrate handling after consumptions of a mixed meal and to identify ways to influence postprandial metabolism in this population.

In noninjured humans, premeal exercise has a robust effect on postprandial glycemia (17) and lipemia (18). To our knowledge, only one study has looked at the acute interaction of feeding and exercise in persons with SCI (19). Twenty persons with and without chronic SCI (85% motor complete, 90% paraplegia) consumed a high-fat meal (48 g fat, 37% fat by kcal) and, 30 min later, performed ~50 min of aerobic exercise. A blood sample was obtained ~4 h after a meal that showed no difference in 4-h blood glucose or TG concentrations between people with and without SCI. However, a single blood draw is insufficient to quantify the dynamic glycemic and lipemic response to feeding. Furthermore, rates of postprandial substrate oxidation were not measured. It is possible that the exercise used in this study (19) was of an insufficient energy cost to modify postprandial metabolism. However, it is also possible that the mode and/or intensity of exercise was not optimal for influencing energy expenditure (EE) during recovery from exercise. Previous studies have determined that, independent of total energy cost, exercise mode (20) and intensity (21) modulate changes in postexercise metabolism in noninjured individuals. However, the optimal exercise mode and intensity for influencing postprandial metabolism in persons with SCI have yet to be determined.

It remains unknown whether, in persons with SCI, the mode or intensity of exercise influences the metabolic handling and oxidation of macronutrients during a mixed-meal tolerance test (MMTT). The objectives of this study were therefore to compare the effects of resting control (CON), moderate-intensity continuous exercise (MICE), high-intensity interval exercise (HIIE), and continuous resistance exercise (CRE) on 1) fasting systemic concentrations of metabolites and hormones, 2) postprandial systemic concentrations of metabolites and hormones, and 3) postprandial EE and whole-body substrate oxidation rates. We hypothesized that higher-intensity modes of intermittent upper-body exercise (i.e., HIIE and CRE) will enhance measures of fasting and postprandial insulin sensitivity, compared with moderate-intensity exercise (MICE) or rest (CON).

METHODS

This study is a partially randomized repeated-measures counterbalanced design. It is registered with ClinicalTrials.gov (NCT03545867), and procedures were in accordance with the Human Subjects Research Office, University of Miami Miller School of Medicine. The protocol has been published in full (22), with trial enrollment and eligibility testing all conducted in accordance with Standard Protocol Items: Recommendations for Interventional Trials guidelines (22). A flow diagram has been provided (Fig. 1).

Participants. We aimed to recruit 11 participants, based on an *a priori* sample size calculation (Cohen's d = 1.0, α = 0.05, ß = 0.90) to detect a significant difference in the change in insulin area under the curve (AUC) between HIIE and CRE compared with MICE and CON (22). Eleven individuals with chronic SCI provided written consent to participate in this study, which was approved by institutional ethical authorities. Participants were men age ≥18 yr with neurologically stable spinal cord injury (ASIA Impairment Scale A–C) at T1 and lower spinal levels for >1 yr who were able and willing to comply with study procedures. Exclusion criteria included American College of Sports Medicine contraindication to exercise; lower extremity fracture or dislocation within 6 months of participation; inability to provide informed consent; restrictions in upper extremity range of motion that would prevent an individual from achieving an unhindered arm cycling motion or moving throughout a range needed to perform resistance maneuvers; pressure ulcer at ischial/gluteus, trochanteric, sacral, or heel sites within the last 3 months; taking any medication that might interfere with the study outcomes; or having been diagnosed with an illness/condition that might interact with study measures (e.g., diabetes and heart disease) or pose undue personal risk.

Baseline assessments and HIIE familiarization. Participants attended two preliminary sessions including baseline assessments and an HIIE familiarization session before completing the four experimental conditions. Participants were instructed to refrain from exercise/alcohol/caffeine for 24 h before testing and to arrive at the laboratory normally hydrated (500 mL of water within 1 h of testing). During their first preliminary visit, participants' cardiorespiratory fitness and muscular strength were assessed via an arm cycle–graded exercise test and a one-repetition maximum text, respectively, as previously described (22).

During their second preliminary visit to the laboratory, participants were fitted with a Hans–Rudolph Softmask, and expired gases were collected and analyzed throughout arm cycle exercise (as described previously). Participants conducted ACE on the same device/position as described previously. The arm ergometer was programmed to vary power output so that a warm-up and cool-down (2 min) and the active recovery intervals were completed at 10% PO_{peak}, and the working intervals completed at 70% PO_{peak}. The ratio of work to recovery intervals was 1:1. The EE data were used to calculate the duration of HIIE required to elicit an isocaloric challenge to CRE.

Experimental exercise and feeding trials. Participants completed the CRE condition first, allowing for the intensity and/or duration of the HIIE and MICE protocols to be adjusted to deliver an isocaloric exercise challenge. Before the first trial, participants were provided with a food journal and asked to record their dietary intake for the 24 h before the CRE trial. After completion of CRE, one of the study team

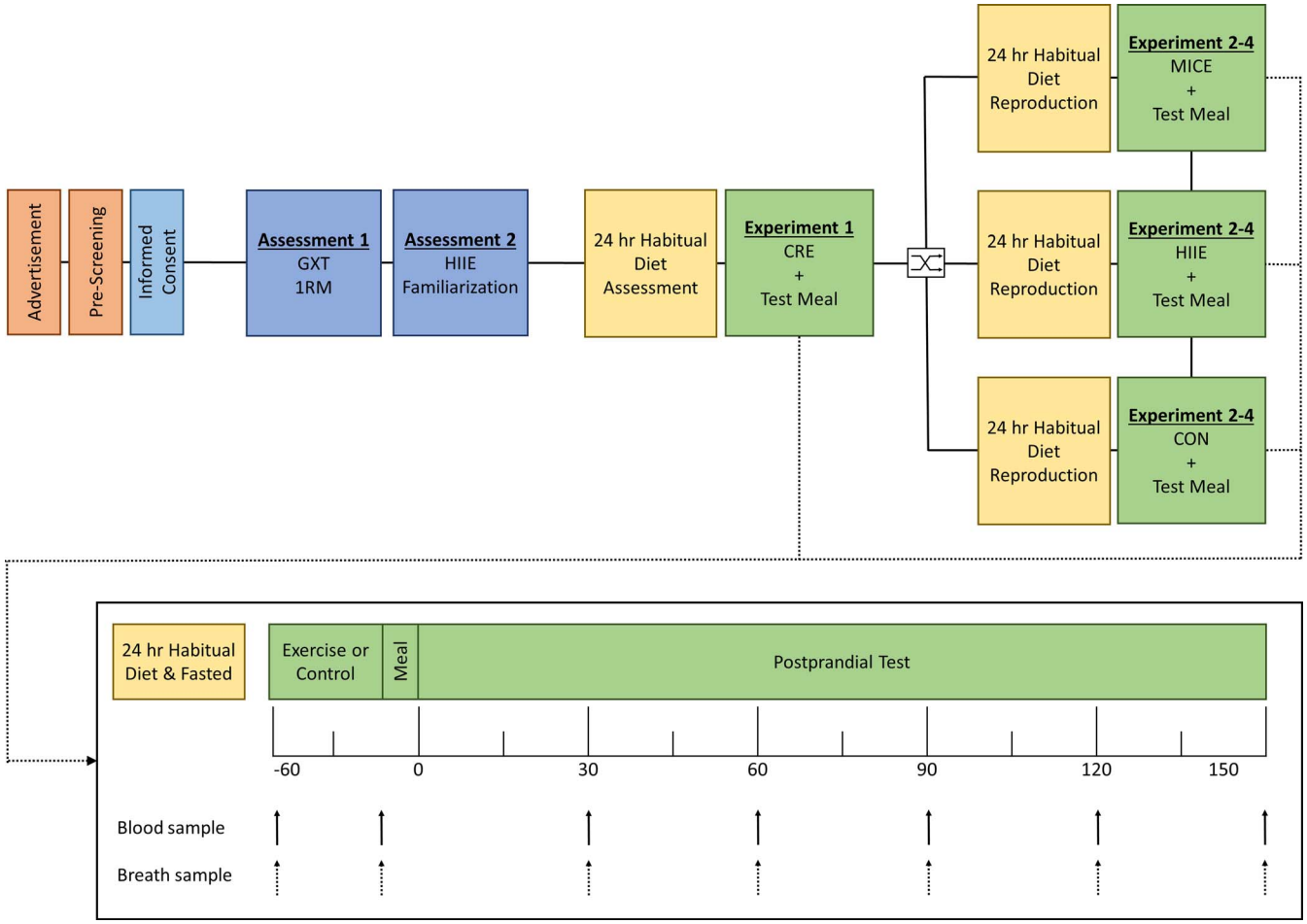

FIGURE 1—Flowchart of study and timeline of individual experiments. CRE, circuit resistance exercise; GXT, graded exercise test; HIIE, high-intensity interval training exercise; 1RM, one-repetition maximum; MICE, moderate intensity continuous exercise.

(J.L.M. or D.W.M.) reviewed the food journal with the participant and the provided them with a copy of the journal that would then serve as their dietary plan for the subsequent main trials. Regardless of their ability to successfully follow the plan, they were instructed to record their actual dietary intake preceding the subsequent trials, and these food journals were reviewed and analyzed. A commercial food analysis software (Food Processor v11.6; ESHA Research, Salem, OR) was used to quantify participant's macronutrient intake. After CRE, the remaining CON, MICE, and HIIE conditions were completed in a randomized order, at least 48 h apart, with all four trials completed within a 1-month period.

Twenty-four hours before each main laboratory trial, participants were asked to abstain from caffeine, alcohol ingestion, and strenuous exercise. However, physical activity habits on the days before the trials were not recorded or controlled. On the morning of the main trials, participants were instructed to consume ~10 $mL \cdot kg^{-1}$ of water on waking and report to the laboratory after an overnight fast (≥10 h). Upon arrival, participants were fitted with the mask for indirect calorimetry (as described previously) and remained seated in their wheelchair for 20 min to assess resting energy expenditure. The final 10 min of this baseline measurement was used to determine premeal resting energy expenditure. Immediately after this, an initial 10 mL venous blood sample (T_{-45}) was drawn to determine the insulin and metabolite concentrations (see discussion hereinafter). For the next ~30–50 min (depending on condition), expired gases and heart rate were collected while the participants rested (CON) or exercised (MICE, HIIE, or CRE). Immediately after this period, an indwelling cannula was inserted into an antecubital vein as previously described (22) and kept patent with sterile saline. An initial sample (T_0) was drawn before participants consumed a 600-kcal liquid test meal (to be ingested in ≤6 min) consisting of a macronutrient distribution equal to *ad libitum* published norms in SCI (35% fat, 50% CHO, 15% protein) (23). Further 10 mL venous blood samples were drawn 30 min after the meal (T_{30}) and at 30-min intervals after that (T_{60}, T_{90}, T_{120}, T_{150}) until 150 min after a meal. Expired gases were collected throughout the postprandial period.

Continuous resistance exercise. After baseline measurements, participants conducted 40.0 ± 4.6 min of CRE consisting of resistance maneuvers (weightlifting) and low-resistance, high-speed endurance activities (ACE). Each session was preceded by 2 min of ACE. Participants then performed one set of 10 repetitions for two of the following

resistance maneuvers: 1) military press, 2) horizontal rows, 3) pectoralis ("pec") deck, 4) preacher curls (elbow flexion), 5) wide-grip latissimus pull-down, and 6) seated dips. A detailed pictorial guide to the CRE is available in Ref. (22) (Fig. 3). Resistance maneuvers were performed in pairs and followed by 2 min of ACE without applied resistance. Every time participants completed two resistance exercises, they performed low-resistance, high-speed arm exercise for 2 min on a stationary cycle. Transitions between equipment occurred as quickly as possible, and a complete session involved three rounds of the cycle of six exercises. Resistive loads for the CRE session were 60% one-repetition maximum as determined during strength testing. The EE response to CRE (methods hereinafter) was used as a calorie target for the other exercise trials. The duration of CRE was used as the duration of seated rest in CON.

Resting control (CON). During the resting control (CON) condition, participants remained seated in their wheelchair for the same duration as the CRE condition (38.9 ± 4.3 min). If they required the bathroom during this period, they were pushed to and from the room and the time was recorded.

Moderate-intensity continuous exercise. The graded exercise test was used to generate a PO versus oxygen consumption ($\dot{V}O_2$) regression equation. This individualized equation was used to estimate a power output during MICE that would elicit the same relative intensity (percent peak rate of $\dot{V}O_2$ (% $\dot{V}O_{2peak}$)) and duration as the CRE trial. The relationship between PO and $\dot{V}O_2$ estimated that 26.1% ± 7.3% PO_{peak} would elicit the 53.5% ± 7.0% $\dot{V}O_{2peak}$ observed during CRE. Participants conducted 39.8 ± 4.6 min of ACE on the same device/position as described previously.

High-intensity interval exercise. After baseline measurements, participants conducted ACE for a duration (32.2 ± 6.2 min) estimated to achieve a calorie expenditure during HIIE equal to CRE. The arm ergometer was programmed to vary the resistance to produce a power output for the warm-up, cool-down (2.5 min), and active recovery intervals equivalent to 10% PO_{peak}, and the working intervals completed at 70% PO_{peak}. The ratio of work to recovery intervals was 1:1. The energetic response to the HIIE familiarization trial was used to estimate the number of bouts required so that total EE during HIIE was equivalent to the CRE condition.

EE, substrate oxidation, and blood analytes. EE and substrate oxidation rates were determined from expired gas analysis averaged over each exercise bout and in 20-min bins between postprandial blood draw time points. For example, indirect calorimetry data labeled "$Post_{0–30}$" are an average of 20 min of expired gas data between the blood draw T_0 and T_{30}. The appropriate stoichiometric equations were used (24) to calculate EE and substrate oxidation from indirect calorimetry data. These updated equations are calibrated for high-intensity exercise where an estimated 80% of carbohydrate oxidation is assumed to come from intramuscular glycogen stores (24). Biochemical assays were performed by the Biomarker and Immunoassay Laboratory at the Diabetes Research Institute, University of Miami. Insulin, glucose, and TG measurements were performed by automated analyzer on a Roche Cobas 6000 analyzer (Roche Diagnostics, Indianapolis, IN) using the manufacturer's reagents and following all instructions for instrument maintenance and assay calibration and test procedures. Intra-assay and interassay percent coefficients of variation for insulin, glucose, and TG were 1.2 and 3.8, 1.1 and 2.4, and 1.6 and 2.1, respectively. Nonesterified fatty acids (NEFA) were measured using reagents from Sekisui Diagnostics (Burlington, MA) and glycerol using kits form Millipore Sigma (St. Louis, MO) adapted for use in the Roche analyzer. Intra-assay and interassay percent coefficients of variation were 4.1 and 6.5 for NEFA and 3.8 and 5.9 for glycerol determinations. American Diabetes Association (ADA) guidelines for using OGTT to determine dysglycemia (any postprandial (glucose) > 11.1 $mmol \cdot L^{-1}$) (25) were used to identify exaggerated postprandial glucose excursions. Expert panel guidelines for using oral fat tolerance test (OFTT) to determine dyslipidemia (any postprandial (TG) > 2.5 $mmol \cdot L^{-1}$) (26) were used to identify exaggerated postprandial lipid excursions.

Statistical analysis. Expired gas data during exercise and pretrial nutritional data were analyzed using a one-way ANOVA to detect differences between experimental conditions. Postprandial expired gas and blood analyte data were analyzed using a two-way (condition–time) repeated-measures ANOVA to detect differences between experimental conditions (CON, MICE, HIIE, and CRE) and across time (dependent on variable). Where significant interactions and main effects were observed, simple effects analysis was used to determine the location of variance. Asphericity was determined with Greenhouse–Geisser epsilon; all values were <0.75 and were corrected for with Greenhouse–Geisser correction. Serial measurements of glucose and insulin responses at baseline and in response to the rest/exercise challenge were converted into simple summary statistics (27), such as insulin sensitivity index (ISIMatsuda) (28) and the Homeostasis Model Assessment (HOMA) calculator, incorporating the updated HOMA-2 model (28). Individual metabolite AUC (GraphPad Prism v5; GraphPad Software, La Jolla, CA) was calculated for 150 min of the MMTT. Standardized effect sizes (Cohen's *d*) were calculated for AUC. Based on the magnitude of correlation between trials, thresholds of >0.2 (small), >0.5 (moderate), and >0.8 (large) were used. For all the aforementioned statistical approaches, statistical significance was set at an α level of $P \leq 0.05$, and data are presented as mean ± SD.

RESULTS

Participant characteristics. Descriptive characteristics and basic injury characteristics of the 10 men with chronic SCI who completed the trial are presented in Table 1. After baseline assessments and HIIE familiarization, one participant was withdrawn from the study having been prescribed medication for type 2 diabetes by his physician. Participants were, on average, of "good" cardiorespiratory fitness (19.2 ± 5.2 $mL \cdot kg^{-1} \cdot min^{-1}$) based on a normative classification

TABLE 1. Participant characteristics.

Habitus			Injury			Fitness			
Age, yr	Height, m	Body Mass, kg	Duration, yr	Level	AIS	HR_{peak}, bpm	$\dot{V}O_{2peak}$, mL·min^{-1}	$\dot{V}O_{2peak}$, mL·kg^{-1}·min^{-1})	Classification (Ref. 29)
28	1.68	72.6	10	T2	A	160	1304	18.0	Good
45	1.73	78.4	16	T6	A	172	1369	17.5	Good
37	1.88	99.5	19	T4	A	181	1615	16.2	Average
28	1.70	51.2	8	T6	A	180	1079	21.1	Good
51	1.65	65.6	8	T10	A	159	1537	23.4	Excellent
32	1.83	67.6	15	T3	A	188	2150	31.8	Excellent
35	1.78	80.8	3	T4	B	165	1332	16.5	Average
38	1.74	106.5	13	T6	C	171	1365	12.8	Fair
57	1.70	64.9	34	T8	B	182	1118	17.2	Average
38	1.73	62.5	6	T9	A	134	1104	17.7	Average
39 ± 10	1.74 ± 0.07	75.0 ± 17.0	13.2 ± 8.8			169 ± 16	1397 ± 319	19.2 ± 5.2	

Values are mean ± SD.
AIS, American Spinal Injury Association impairment scale; HR = heart rate.

for persons with SCI (29), but fitness varied within the group. Peak heart rate (169 ± 16 bpm) suggests that injury did not result in disruption of sympathetic output to the myocardium.

Dietary intake. Participant's average pretrial habitual dietary intake was 1942 ± 15 kcal·d^{-1} at 37% fat, 39% CHO, and 22% protein (Table 2). There were no differences in participant reported caloric intake ($P = 0.653$) or dietary macronutrient content (fat, $P = 0.184$; CHO, $P = 0.729$; protein, $P = 0.537$) in the 24 h preceding each experiment (Table 2).

EE and substrate oxidation rates at baseline and during exercise. There were no significant differences between conditions in rates of EE or substrate oxidation at baseline (Fig. 2). All exercise conditions were matched for total energy cost (116 ± 22, 117 ± 35, and 118 ± 22 kcal, respectively; $P = 0.982$). However, rates of EE were significantly greater in HIIE compared with MICE and CRE ($P = 0.01$; Table 2). Participants achieved a significantly greater % $\dot{V}O_{2peak}$ ($P < 0.001$) in HIIE compared with MICE and CRE (Table 2). Respiratory exchange ratio (RER) was lower ($P < 0.001$) in MICE (0.90 ± 0.08) compared with HIIE and CRE (1.01 ± 0.07 and 1.05 ± 0.04, respectively; Table 2).

Postprandial EE and substrate oxidation rates. There was a significant main effect of time ($P = 0.039$) and condition ($P = 0.024$) on rates of EE during recovery (Fig. 2). However, the time–condition interaction term did not reach statistical significance ($P = 0.374$). Pairwise tests indicated that postprandial EE were significantly greater at $Post_{30–60}$ ($P = 0.050$) and $Post_{60–90}$ ($P = 0.039$) compared with baseline, and that EE during the HIIE condition was significantly greater than the CON ($P = 0.038$) condition.

There was a significant main effect of time ($P = 0.020$), condition ($P = 0.000$), and time–condition interaction ($P = 0.000$) for lipid oxidation (Lox; Fig. 2). Pairwise tests indicate that the rate of Lox in CRE was significantly greater than CON at all time points ($Post_{0–30}$, $P = 0.000$; $Post_{30–60}$, $P = 0.002$; $Post_{60–90}$, $P = 0.019$; $Post_{90–120}$ $P = 0.027$; $Post_{120–150}$, $P = 0.044$), significantly greater than MICE at $Post_{0–30}$ ($P = 0.030$) and $Post_{30–60}$ ($P = 0.039$), and significantly greater than HIIE at $Post_{60–90}$ ($P = 0.014$). Lox in HIIE was significantly greater than CON at $Post_{0–30}$ ($P = 0.007$) and $Post_{30–60}$ ($P = 0.015$).

For carbohydrate oxidation, there was a significant main effect of time ($P = 0.000$) and a time–condition interaction ($P = 0.006$). Rate of oxidation was significantly lower at $Post_{0–30}$ compared with all time points (all, $P = 0.000$) and $Post_{30–60}$ was significantly lower than time $Post_{60–90}$ ($P = 0.000$), $Post_{90–120}$ ($P = 0.000$), and $Post_{120–150}$ ($P = 0.003$).

Metabolite concentrations in the fasted and postprandial states. Metabolite concentrations measured in the fasted state ($T_{–45}$) and postexercise (T_0) are shown in Table 3. There was no significant main effect of condition or time–condition interaction for concentrations of glucose, insulin, TG, and NEFA. There was a significant main effect of time in which glucose concentration at T_0 was significantly greater than $T_{–45}$ ($P = 0.023$). There was a significant main effect of time ($P = 0.015$), condition ($P = 0.000$), and a time–condition interaction ($P = 0.040$) for glycerol. Simple effects analysis indicated a significant increase from $T_{–45}$ to T_0 in the MICE ($P = 0.008$) and HIIE ($P = 0.004$) conditions only. There were no differences observed in HOM2-IR insulin sensitivity (Table 3).

Based on ADA guidelines for OGTT (25), no participants displayed signs of postprandial dysglycemia (any postprandial (glucose) > 11.1 mmol·L^{-1}). Based on expert panel guidelines for OFTT (26), 3 of 10 participants displayed signs of PPL (any postprandial (TG) > 2.5 mmol·L^{-1}).

Postprandial metabolite responses. Figures 3A–E show the 2-h MMTT AUC across all conditions representing changes in postload concentrations of glucose (A), insulin (B), TG (C), NEFA (D), and glycerol (E). Considering the

TABLE 2. Pretrial 24-h diet and average metabolic responses during seated control and different exercise conditions.

	CON	MICE	HIIE	CRE
24-h pretrial diet				
Total, kcal	1909 ± 707	1947 ± 666	1887 ± 739	1806 ± 716
Carb, kcal	770 ± 375	715 ± 308	786 ± 423	739 ± 387
Fat, kcal	666 ± 334	753 ± 355	628 ± 318	627 ± 310
Prot, kcal	428 ± 151	444 ± 167	429 ± 157	404 ± 149
Alc, kcal	45 ± 98	35 ± 74	45 ± 98	36 ± 75
Exercise				
EE, kcal·min^{-1}	0.98 ± 0.20	2.90 ± 0.44	3.60 ± 0.66*	2.86 ± 0.38
RER	0.82 ± 0.04	0.90 ± 0.08**	1.01 ± 0.07	1.05 ± 0.04
% $\dot{V}O_{2peak}$	18.1 ± 4.6	53.0 ± 6.6	66.1 ± 5.2*	53.5 ± 7.0

Values are mean ± SD ($n = 10$).
*$P < 0.01$ vs MICT and CRT.
**$P < 0.001$ vs HIIE and CRE.
Alc, alcohol; Carb, carbohydrate; Prot, protein.

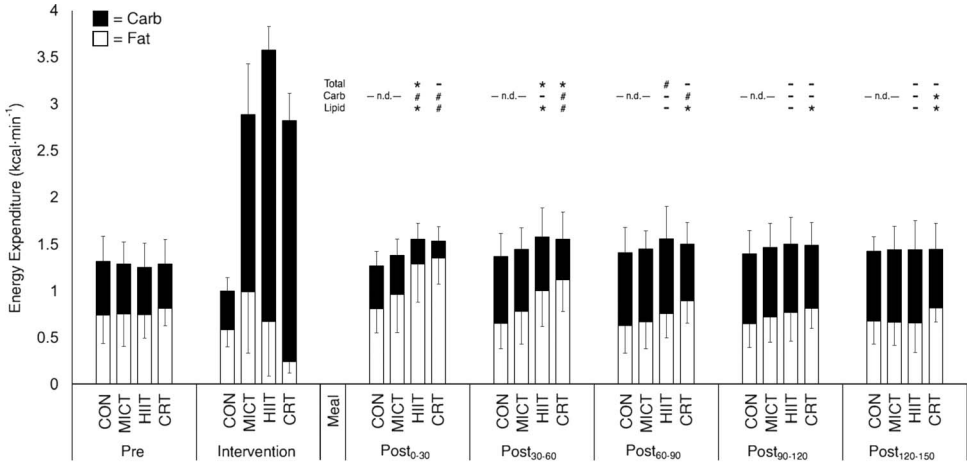

FIGURE 2—Carbohydrate and fat use before, during, and after a meal preceded by sitting or various forms of exercise. A, $P < 0.05$ vs CON for total EE; B, $P < 0.05$ vs CON and MICT for total EE; a, $P < 0.05$ vs CON for fat expenditure; b, $P < 0.05$ vs CON and MICT for fat expenditure.

whole 150-min postload experiment, there were no significant differences in AUC in any metabolite between conditions (data not shown). Cohen's *d* effect sizes showed a moderate-to-strong effect for comparisons between conditions for TG (CRE vs HIIE, −0.44), NEFA (CRE vs MICE = −0.76; CRE vs HIIE = −0.50), and glycerol (MICE vs CON, −0.49; CRE vs CON, −0.71). All other comparisons had a weak (Cohen's $d < \pm 0.40$) effect size.

DISCUSSION

The primary finding of this study is that, independent of total exercise energy cost, exercise intensity and mode modulate postprandial EE and Lox in persons with paraplegia. Secondarily, our data provide provisional evidence suggesting that exercise mode modulates the postprandial lipemic response. There were no differences between conditions in terms of postprandial glucose or insulin responses.

Postprandial metabolism. This is one of the few scientific studies examining postprandial macronutrient metabolism in response to MMTT in persons with chronic paraplegia. Previous studies of postprandial metabolism in SCI used OGTT or OFTT that have atypical macronutrient compositions, often relying on a single macronutrient as the sole stimulus. In contrast, our MMTT was designed to reflect the energy and macronutrient content of an *ad lib* meal in persons with SCI (23).

Based on ADA guidelines for OGTT (25), no participants displayed signs of postprandial dysglycemia. Compared with a standard 75 g OGTT (25), the MMTT used in the current study contained a similar total carbohydrate load (75.5 g) but comprised different carbohydrate (glucose polymer from the carbohydrate powder and a mix of sucrose/fructose/glucose from the banana) as opposed to homogeneous anhydrous glucose in an OGTT. Furthermore, the insoluble fiber and other macronutrients in our meal likely reduced the peak amplitude of the postprandial glucose and insulin response compared with OGTT (30). However, although absolute values differ, peak glucose excursions after OGTT and MMTT are well correlated (30) and insulin resistance calculated from MMTT can be effectively compared with insulin sensitivity during OGTT (31). Moreover, MMTT has a similar C-peptide response (30) and might therefore reflect pancreatic functions better compared with OGTT (31). Therefore, because our MMTT has a similar total carbohydrate content to an OGTT, the results of postprandial glucose metabolism in this study indicate that none of our participants had impaired glucose handling.

Based on expert panel guidelines for OFTT (26), 3 of 10 participants displayed signs of PPL. This impaired postprandial fat metabolism was seen, although the MMTT used in the current study contained ~250 less kilocalories and ~50 g less fat than the OFTT upon which the guidelines are based (26). These postprandial fat excursion data indicate that

TABLE 3. Markers of metabolic regulation and CMS risk.

	CON		MICE		HIIE		CRE	
	BL (T_{-45})	Postsitting (T_0)	BL (T_{-45})	Postexercise (T_0)	BL (T_{-45})	Postexercise (T_0)	BL (T_{-45})	Postexercise (T_0)
Fasting measures								
Glucose, mmol·L^{-1}	5.0 ± 0.5	4.9 ± 03	5.1 ± 0.5	4.9 ± 0.5	4.9 ± 0.5	4.6 ± 0.5	4.9 ± 0.3	4.7 ± 0.4
Insulin, pmol·L^{-1}	63.6 ± 31.7	55.81 ± 31.69	61.6 ± 27.9	94.22 ± 47.52	77.4 ± 51.4	89.51 ± 38.74	64.4 ± 38.7	53.41 ± 22.26
TG, mmol·L^{-1}	1.35 ± 0.49	1.28 ± 0.48	1.43 ± 1.02	1.43 ± 0.93	1.55 ± 0.70	1.62 ± 0.68	1.24 ± 0.34	1.21 ± 0.33
NEFA, mmol·L^{-1}	0.49 ± 0.14	0.45 ± 0.10	0.58 ± 0.25	0.77 ± 0.40	0.55 ± 0.24	0.68 ± 0.70	0.57 ± 0.12	0.39 ± 0.07
Glycerol, mmol·L^{-1}	0.020 ± 0.011	0.016 ± 0.008	0.025 ± 0.017	0.052 ± 0.034	0.025 ± 0.015	0.037 ± 0.012	0.030 ± 0.018	0.045 ± 0.019
Indices of insulin sensitivity								
HOMA2-IR	1.18 ± 0.59	0.95 ± 0.47	1.16 ± 0.51	1.71 ± 0.82	1.43 ± 0.95	1.63 ± 0.66	1.18 ± 0.70	0.98 ± 0.39
C-ISI$_{Matsuda}$	5.2 ± 2.2		5.7 ± 3.0		6.0 ± 4.3		6.3 ± 3.5	

Values are mean ± SD ($n = 10$).
BL = baseline; C-ISI$_{Matsuda}$ = Matsuda's insulin sensitivity index; HOMA2-IR, second homoeostatic model assessment of insulin resistance.

postprandial fat metabolism was relatively more impaired than postprandial glucose metabolism in our sample.

Premeal exercise and postprandial energy utilization. Exercise performed before a meal has the ability to increase postprandial EE (32). Without prior feeding, exercise intensity is the primary determinant of postexercise EE, especially when an exercise session is limited in duration (33). For example, in noninjured cyclists, sprint interval training lasting 14 min and costing 132 kcal elicited a total postexercise EE equal to that seen after 30 min of continuous exercise at 85% $\dot{V}O_{2peak}$ costing 493 kcal (34). The effects of premeal exercise on postprandial EE are also intensity dependent, with previous studies suggesting a minimum intensity threshold of ~60% $\dot{V}O_{2peak}$ (35). In the current study, HIIE was above the posited % $\dot{V}O_{2peak}$ threshold, contributing to why postprandial EE was elevated above CON in the HIIE condition. The % $\dot{V}O_{2peak}$ intensities of MICE and CRE (53.0% ± 6.6% and 53.5% ± 7.0% $\dot{V}O_{2peak}$, respectively) in the current study were below this threshold. However, at $Post_{30–60}$, EE was elevated in CRE versus CON (Fig. 2). This finding can be explained by the intensity of contraction during the resistance maneuvers, which resulted in local cellular stress that is not fully reflected in % $\dot{V}O_{2peak}$. Given that the total cost of exercise was similar in all conditions and the % $\dot{V}O_{2peak}$ intensity was similar in MICE and CRE, our findings show that in persons with paraplegia, exercise that is more reliant on carbohydrate oxidation has a great effect on postprandial EE.

Exercise mode and intensity had robust effects on postprandial substrate oxidation (Fig. 2). During exercise, rates of carbohydrate and Lox can be changed dramatically, with HIIE and CRE having a greater carbohydrate oxidation (36). During recovery from exercise, the body transitions to an increased reliance on fat that persists for hours (37) to days (38). Kuo et al. (37) showed that in noninjured persons, exercise EE during MICE determined postexercise fat use independent of exercise intensity. MICE can only be conducted within a limited range of intensities, and thus, when compared with HIIE, it is often found that MICE has a lesser effect on postexercise metabolism (21). Furthermore, in noninjured persons, a session of resistance exercise with approximately half the energy cost as MICE resulted in similar attenuation of PPL due, in part, to increasing exogenous Lox (39). However, the effect of premeal exercise on postprandial fuel partitioning had yet to be determined in persons with SCI. In our study, postprandial Lox was greater in CRE and HIIE compared with MICE and CON, and only CRE resulted in elevated Lox at the 2-h postprandial time point. Similar to postprandial EE, our data show that that premeal exercise influences postprandial substrate oxidation in a manner dependent on the degree of carbohydrate oxidation during exercise.

Premeal exercise and postprandial metabolite concentrations. Our data show little effect of premeal exercise on postprandial glucose concentration after MMTT (Fig. 3). The circulating concentrations of glucose and insulin in all conditions, including CON, show that glucose homeostasis was well maintained. The participants in this study were

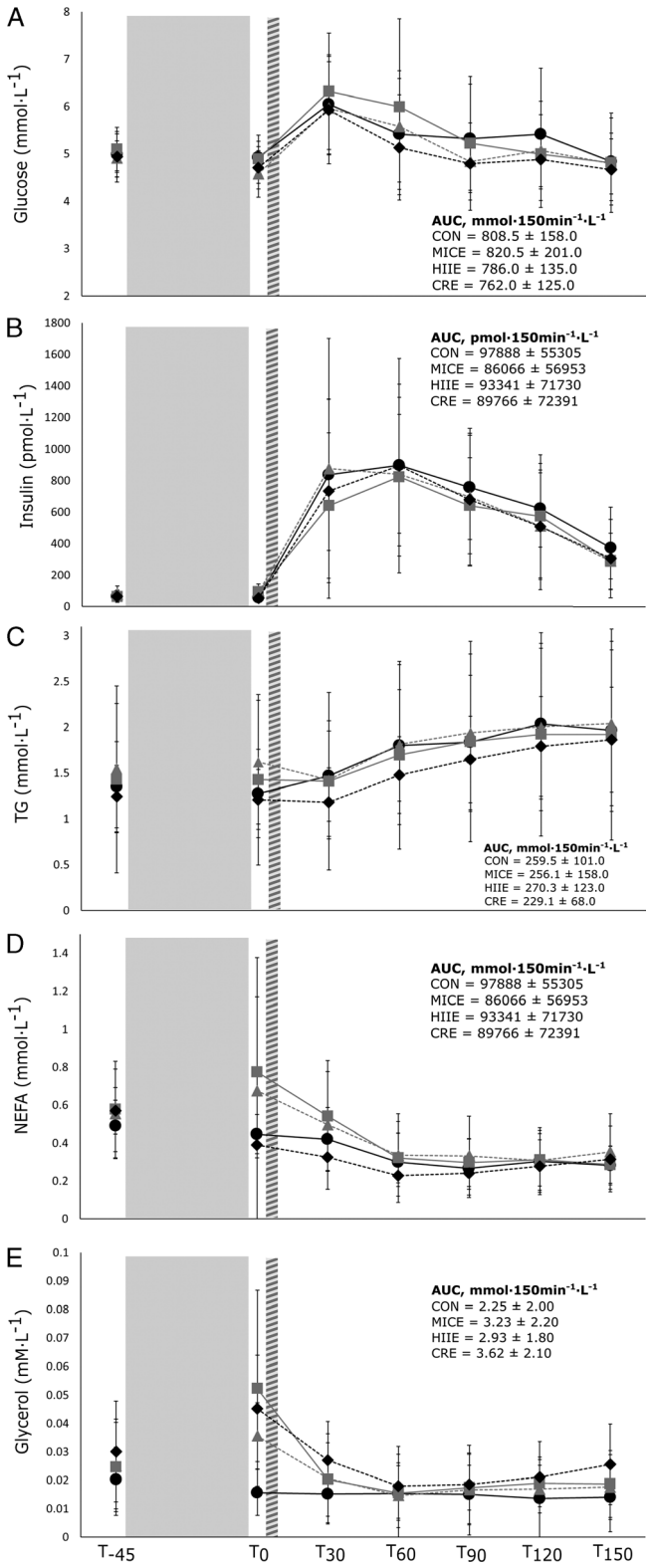

FIGURE 3—A–E, Concentration and AUC plasma glucose (A; in millimoles per liter), plasma insulin (B; in picomoles per liter), TG (C; in millimoles per liter), NEFA (D; in millimoles per liter), and glycerol (E) in response to 120-min MMTT under CON (-●-), MICT (-■-), HIIT (-▲-), and CRT (-▼-) conditions. ▓ exercise or rest; ▒, MMTT.

relatively fit and did not have evidence of glycemic dysregulation based on fasted and postprandial glucose concentration (Table 3, Fig. 3). Thus, the finding that exercise had little effect on circulating glucose and insulin might be due to a floor effect due to the lower peak glycemic response to the MMTT and the lack of glycemic dysregulation in our participants. Furthermore, compared with a standard bout of exercise in noninjured persons where 45 min of exercise results in ~200–600 kcal expenditure (40), the energy cost of our exercise was relatively low (~120 kcal). The results of our study may suggest that there is a minimum EE threshold required for premeal exercise to influence postprandial metabolite concentrations. This possibility needs to be considered in the context of exercise as a strategy for improving cardiometabolic health in persons with SCI. Obligatory upper extremity exercise and increased potential for overuse injuries in persons with SCI place a practical limit on the total exercise EE. These limitation suggest that electrically stimulated lower extremity exercise has the greatest potential as an exercise intervention for benefitting CMD in SCI (41).

With respect to postprandial circulating lipids and their metabolites, statistical differences were observed only for glycerol where MICE (P = 0.020) and CRE (P = 0.001) were greater than CON. PPL based on peak TG ≥2.5 mmol·L^{-1} (26) was observed after CON (three participants), MICE (two participants), and HIIE (three participants). After CRE, no participants had TG concentration greater than 2.5 mmol·L^{-1}. Therefore, CRE seemed to partially accommodate for the disordered postprandial fat metabolism inherent to SCI and observed in the current study. This response might be explained by an increased catecholamine response to CRE compared with other modes of exercise, although these were not measured. Only four of our participants had SCI above the neurological level whereby the catecholamine response to exercise is impaired (<T4) (42), and all of these participants had normal cardioacceleratory capacity (Table 1) suggesting intact sympathetic nervous system signaling. Beyond endocrine signaling, our results could be explained by endogenous factors originating from within skeletal muscle cells and released during exercise. Greater skeletal muscle glycogen use during exercise results in increased Lox during postexercise recovery, as glucose is preferentially used for glycogen resynthesis, requiring the use of fats for fuel (43). Although we did not measure glycogen use, it is well established that HIIE resulted in greater glycogen reductions than steady-state moderate-intensity activity (43). It is also possible that contraction resulted in the release of myogenic signaling molecules (44) labeled for specific target tissues related to energy metabolism (45).

Methodological considerations. The purpose of this study was to identify the optimal exercise strategies for influencing metabolic function in persons with SCI. We aimed to control for nutritional intake for 24 h before each trial to isolate the effects of select exercise parameters. Our strategy utilized a self-reported food journal, completed before the first trial and then reproduced before the following experimental trials. Participants reported similar energy and macronutrient intake before each trial; however, there is an inherent source of error associated with self-reported food journals. Furthermore, it is possible that nutritional differences in the >24 h preceding the trials may influence metabolism during our testing. Although the HIIE prescription is not conventional (10:70 %PO_{peak}), the physiological response confirms that HIIE occurred at a high intensity, as 29.4% ± 7.7% of the duration of the session was spent at or greater than 80% $\dot{V}O_{2peak}$. Finally, one further methodological consideration should be considered when interpreting our results. Our previous data indicate that CRE will elicit a mean exercise EE of ~170 kcal in persons with paraplegia (46), whereas the data from the current study show an expenditure of ~120 kcal. Most importantly, all previous CRE studies in SCI (3,46,47) calculated EE using stochiometric equations (24) that assume that the blood glucose is the only type of carbohydrate contributing to carbohydrate oxidation. In the current study, we used more appropriate calculations for glycolytic exercise (24) that assume 80% of carbohydrate use is due to utilization of muscle glycogen. Muscle glycogen utilization is energetically more efficient, thus yielding a calculation of carbohydrate oxidation that is approximately 10% lower than the calculations applied to the previous data. Given the average RER of 1.01 in the CRE condition, carbohydrate oxidation accounts for nearly all of the total EE, thus exacerbating the difference in the calculations. Furthermore, the participants in the previous study (46) were ~4 kg heavier, and assuming this difference was related to lean tissue mass, this likely contributed to a greater total EE.

Limitations. One participant was withdrawn from the study after being prescribed medication for type 2 diabetes, and therefore, we failed to reach our target sample size of 11. However, based on the observed effect size (d = 0.013–0.12) for our primary outcome, change in insulin AUC, between HIIE and CRE compared with MICE and CON, one extra participant would not have meaningfully changed our findings regarding postprandial insulin response. We used stoichiometric equations to calculate EE that were designed to be used with steady-state indirect calorimetry data (24). However, the CRE and HIIE conditions were not steady state. Accordingly, it is possible that EE was underestimated in these conditions. This difference in exercise EE is an important consideration. However, studies that have combined blood lactate and excess postexercise oxygen consumption with indirect calorimetry during resistance exercise suggest that underestimation of EE during resistance exercise is relatively small (48). Based on current ADA (25) guidelines, neither fasted blood glucose nor TG (Table 3) was elevated. Furthermore, HOMA-IR was within a "normal" range. These findings of a "healthy" fasted metabolic profile in our participants means that the results of our study are not generalizable to the large portion of the SCI population that live with stark diabetes and dyslipidemia (1). Furthermore, 40% of our participants classified as having "good" or better CRF (29), limiting the application of our results to the considerable portion of the SCI population that exists at the lowest end of the spectrum of CRF (29). Future studies should aim to understand the interaction of feeding and exercise in a population of persons

with SCI who have greater metabolic impairments and thus are more representative candidates for lifestyle interventions targeting metabolic health.

CONCLUSIONS

This study is the first to demonstrate that premeal exercise influences postprandial metabolism in persons with SCI. Exercise intensity and mode modulate postprandial EE and substrate utilization independent of the energy cost of exercise. Our data also demonstrate that premeal exercise has a limited effect on macronutrient handling in paraplegics with good fitness and relatively healthy postprandial glycemic and lipemic responses. However, circuit-style exercise resulted in peak postprandial TG concentrations that fell below the PPL (2.5 mmol·L^{-1}) cut-off for all participants.

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