Gender differences in glucose kinetics and substrate oxidation during exercise near the lactate threshold

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Although the majority of previous research has suggested that substrate utilization during moderate-intensity exercise is different between genders (12, 13, 36–38), some research has demonstrated minimal differences (5, 16, 31). Previous research has also suggested that women may rely more heavily on lipid metabolism while preserving muscle glycogen (36–38).

The mechanisms responsible for these gender-dependent differences in fuel selection appear to be correlated with the complex hormonal milieu surrounding ovulation in women.

Some recent investigations have attempted to study a gender-specific response in glucose kinetics to exercise using stable isotope-tracer methodologies (8, 12, 28). Friedlander et al. (12) demonstrated similar rates of glucose appearance (Ra) and glucose disposal (Rd) after training at the same exercise intensity relative to peak \( V_{O_2} \) uptake \( (V_{O_2 \text{peak}}) \) in women and men. When data from women were compared with previously collected data from men during an identical training program, women tended to have a lower respiratory exchange ratio (RER), despite similar rates of glucose flux. Friedlander et al. further suggested that this might indicate a higher relative contribution from blood glucose as a percentage of total carbohydrate (CHO) oxidation.

Previous research has attempted to increase the level of experimental control by matching men and women on several training characteristics, including weekly mileage and average training intensity (36–38). These studies have continually demonstrated that women have a lower RER, rely less on muscle glycogen, and oxidize proportionately more lipid than similarly trained men (36–38) during exercise relative to \( V_{O_2 \text{peak}} \). However, previous research has not determined whether men and women demonstrate different patterns of substrate oxidation and glucose kinetics during exercise relative to the lactate threshold (LT).

Coggan et al. (3) demonstrated that glucose kinetics during exercise were most related to the LT, even when subjects were matched on \( V_{O_2 \text{peak}} \), fiber type distribution, and capillary density. During exercise at 55% of \( V_{O_2 \text{peak}} \), glucose Ra and Rd were significantly lower for the high- than for the low-LT subjects. Therefore, normalizing the exercise intensity relative to the LT may reduce the variability in substrate oxidation between the genders. The rationale for selecting an exercise intensity relative to the LT stems from previous re-

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search that has demonstrated the concept that exercise performance is more related to the ventilatory threshold (21, 27) and LT (6, 7) than to a percentage of V̇\textsubscript{O2 peak}. We hypothesized that, during cycle ergometer exercise at the same percentage of the LT, gender differences in glucose Ra and Rd and total CHO oxidation would be minimized.

The purpose of the present study was to compare glucose kinetics and substrate utilization in men and women during exercise at two intensities: 70 and 90% of \textit{FFM}, fat-free mass (FFM) or total body weight
differences in glucose Ra and Rd during exercise at the same percentage of the LT, gender

Table 1. Physical characteristics of the subjects

<table>
<thead>
<tr>
<th></th>
<th>Men (n = 5)</th>
<th>Women (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>25.0 ± 2.0</td>
<td>23.6 ± 1.1</td>
</tr>
<tr>
<td>Height, cm</td>
<td>173.9 ± 1.8</td>
<td>163 ± 3*</td>
</tr>
<tr>
<td>Body mass, kg</td>
<td>68.2 ± 2.7</td>
<td>60.1 ± 3.7</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>8.8 ± 1.4</td>
<td>14.5 ± 1.4*</td>
</tr>
<tr>
<td>Fat body mass, kg</td>
<td>5.9 ± 0.8</td>
<td>8.9 ± 1.3</td>
</tr>
<tr>
<td>Fat-free mass, kg</td>
<td>62.3 ± 3.1</td>
<td>51.2 ± 2.6*</td>
</tr>
<tr>
<td>Maximum HR, beats/min</td>
<td>191 ± 2.4</td>
<td>186 ± 2.0</td>
</tr>
<tr>
<td>V̇\textsubscript{O2 peak} l/min</td>
<td>4.20 ± 0.23</td>
<td>2.86 ± 0.17*</td>
</tr>
<tr>
<td>ml·kg\textsuperscript{−1}·min\textsuperscript{−1}</td>
<td>61.7 ± 1.3</td>
<td>48.2 ± 1.1*</td>
</tr>
<tr>
<td>ml·kg·FFM\textsuperscript{−1}·min\textsuperscript{−1}</td>
<td>67.4 ± 1.3</td>
<td>55.4 ± 1.4*</td>
</tr>
<tr>
<td>%V̇\textsubscript{O2 peak} at LT</td>
<td>68.9 ± 2.6</td>
<td>62.1 ± 1.5</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>46.2 ± 2.1</td>
<td>38.9 ± 0.5*</td>
</tr>
<tr>
<td>Hb, mg/dl</td>
<td>14.4 ± 0.2</td>
<td>12.3 ± 0.4*</td>
</tr>
</tbody>
</table>

Values are means ± SE. HR, heart rate; V̇\textsubscript{O2 peak}, peak O\textsubscript{2} uptake; FFM, fat-free mass; LT, lactate threshold. *P < 0.05 vs. men.
GLUCOSE KINETICS DURING EXERCISE IN MEN AND WOMEN

The ratio of [6,6-²H]glucose to unlabeled glucose (isotopic enrichment) was determined by forming the pentaacetate derivative of glycogen use. There is no evidence to suggest that there are differences between genders in the percentage of glucose oxidized in the working muscle.

Table 2. Workload intensities for the two-stage submaximal exercise trials

<table>
<thead>
<tr>
<th>Workload Intensity</th>
<th>Men</th>
<th>Women</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>70% LT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%VO₂ at LT</td>
<td>68.7±0.9</td>
<td>69.0±1.9</td>
<td>90.1±1.1</td>
<td>88.7±1.2</td>
</tr>
<tr>
<td>%VO₂peak</td>
<td>47.3±1.5</td>
<td>39.2±2.9*</td>
<td>62.2±2.6</td>
<td>50.4±3.6*</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>129±5</td>
<td>116±4*</td>
<td>156±7</td>
<td>139±4*</td>
</tr>
</tbody>
</table>

Values are means ± SE. *P < 0.05 vs. men at 70% LT; †P < 0.05 vs. men at 90% LT.
CHO oxidation with no change in fat oxidation from 70 to 90% LT. Figure 1 demonstrates the differences between genders for CHO oxidation expressed relative to FFM.

Plasma metabolites and insulin. Table 4 summarizes the plasma metabolite and hormone response to the two-stage experimental protocol. Although there were no differences in plasma glucose concentration at rest, the women maintained a higher blood glucose concentration at 70% LT. However, there was no difference in the plasma glucose concentration between the men and women at 90% LT. The men showed a significant difference in the plasma glucose concentration between 70 and 90% LT. However, there were no differences in the plasma glucose concentrations across the workloads in the women. Plasma insulin concentration was significantly higher for the women at rest and during the 70 and 90% LT workloads. The women showed a significant increase in blood lactate concentration from 70 to 90% LT. However, there were no differences between the 70 and 90% LT workloads in the men. There were no differences in plasma lactate concentrations between the men and women at either workload.

Plasma glucose kinetics. Figures 2 and 3 summarize the glucose $R_a$ and $R_d$ at rest and during the 70 and 90% LT workloads relative to FFM (\(\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\)). There were no differences between men and women in glucose $R_a$ at rest and during the 70 and 90% LT workloads. Although the means demonstrate a trend toward higher values in the men, calculated-effect size using Cohen’s $d$ demonstrated a moderate effect ($d = 0.506$). With the use of Cohen’s $d$, it was calculated that, even with a sample size $>15$, similar results would be obtained. The same results were observed for glucose $R_d$. Metabolic clearance of glucose was not significantly different between the men and women for either workload: 5.1 $\pm$ 0.7 and 7.9 $\pm$ 1.1 \(\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\) at 70 and 90% LT, respectively, for men and 4.2 $\pm$ 0.6 and 6.5 $\pm$ 1.3 \(\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\) at 70 and 90% LT, respectively, for women.

However, when glucose $R_a$ and $R_d$ were expressed relative to total body mass (\(\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\)), there were subtle differences between the men and women. Although there were no differences in $R_a$ at 70% LT (20.7 $\pm$ 1.9 and 18.9 $\pm$ 2.2 \(\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\) for men and women, respectively), men demonstrated a significantly higher $R_a$ at 90% LT (36.4 $\pm$ 3.7 and 28.9 $\pm$ 4.8 \(\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\) for men and women, respectively). Glucose $R_d$ was not different between genders at 70% LT (19.4 $\pm$ 1.8 and 18.5 $\pm$ 2.3 \(\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\) for men and women, respectively). However, glucose $R_d$ was significantly higher for the men at 90% LT (34.7 $\pm$ 3.4 and 28.4 $\pm$ 4.8 \(\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\) for men and women, respectively).

Figure 4 summarizes the relative contribution of plasma glucose and muscle glycogen to the total CHO oxidation for both workloads. For both workloads, the relative contribution of plasma glucose was significantly higher in the women than in the men at the same intensity relative to the LT. Consequently, the relative contribution of muscle glycogen was significantly lower in the women than in the men at both workloads. There were no significant changes in the relative contribution of plasma glucose or muscle glycogen across the two workloads for the men and women.

**DISCUSSION**

The purpose of this investigation was to determine whether plasma glucose $R_a$ and $R_d$ and CHO oxidation...
varied between recreationally trained men and women at exercise intensities relative to the LT. Although the present group of men demonstrated a higher glucose Ra and Rd expressed relative to total body weight, when the data were expressed relative to FFM, there were no differences between the groups. The most notable finding in the present investigation was that the relative contribution of blood glucose (to total CHO oxidation) was considerably higher in the women with a concomitant decrease in the contribution of muscle glycogen (Fig. 4).

Previous research has suggested that the reproductive hormone 17β-estradiol (E2) may suppress glycogen utilization (19, 24, 25, 33). Consistently, it was demonstrated that women use less muscle glycogen than similarly trained men during submaximal endurance exercise (19, 24, 25, 33). Kendrick et al. (24, 25) also demonstrated suppression in muscle glycogen use during exercise in rats treated with E2. Although it is an indirect measure of glycogen utilization, Friedlander et al. (12) suggested that the relative contribution of blood glucose may be higher in women. Tarnopolsky et al. (37) also demonstrated that women have a limited ability to maximize glycogen stores in response to a 4-day CHO-loading protocol and that this limitation may be related to a lower energy intake in women (39). Collectively, the human data suggest less reliance on muscle glycogen by women than by men. However, whether the decrease in glycogen utilization is due to limitations in muscle glycogen availability (or storage) or some other mechanism associated with stimulation of glycogenolysis remains unclear. Although our data do not show direct measures of glycogen depletion, they demonstrate an increased relative contribution of blood glucose to total CHO oxidation in women. The increased reliance on blood glucose in women requires further investigation.

Research by Hansen et al. (18) may in part explain the differences in the relative contribution of CHO sources in women. Ovariectomy in female rats did not change muscle glycogen or GLUT-4 concentration in the skeletal muscle (soleus, epitrochlearis, and flexor digitorum brevis) at rest or in response to insulin-stimulated glucose transport. In contrast, when muscle tissue was subjected to in vitro electrical stimulation, ovariectomy resulted in decreased glucose transport. However, total GLUT-4 protein content was similar between the sham and ovariectomized animals. Although the total GLUT-4 protein content and insulin-stimulated glucose uptake may be unaffected by abnormally low concentrations of ovarian hormones, the translocation of the GLUT-4 proteins to the plasma membrane may be altered. This mechanism requires further investigation. The possibility that E2 and progesterone may enhance or inhibit the translocation process may provide insight into metabolic regulation during pregnancy.

Table 4. Plasma metabolite and insulin concentrations during rest and exercise

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest 70% LT 90% LT</td>
<td>Rest 70% LT 90% LT</td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>4.2 ± 0.2 3.9 ± 0.3 4.5 ± 0.2</td>
<td>4.5 ± 0.1 4.4 ± 0.1* 4.5 ± 0.1</td>
</tr>
<tr>
<td>Lactate, mmol/l</td>
<td>1.5 ± 0.1 2.0 ± 0.2 2.0 ± 0.2</td>
<td>1.1 ± 0.1 1.6 ± 0.1 2.3 ± 0.4‡</td>
</tr>
</tbody>
</table>
| Insulin, IU/ml | 4.2 ± 0.4 3.9 ± 0.5 3.5 ± 0.4 | 5.2 ± 0.3§ 4.9 ± 0.2* 4.5 ± 0.5†  

Values are means ± SE. *P < 0.05 vs. men at 70% LT; †P < 0.05 vs. men at 90% LT; ‡P < 0.05 vs. 70% LT (within gender); §P < 0.05 vs. men at rest.
Campbell and Febbraio (2) demonstrated an E2-dependent increase in 2-[1-14C]-deoxy-D-glucose uptake in ovariectomized rats treated with subcutaneous E2 pellets (timed release of E2) compared with untreated and progesterone-treated animals. Interestingly, glucose uptake by the muscle was only increased with E2 administration. Administration of progesterone alone resulted in rates of glucose uptake similar to those in untreated ovariectomized animals. These recent data indicate that circulating levels of E2 may stimulate GLUT-4 translocation and promote glucose uptake during contraction. Consequently, the effects of progestosterone apparently antagonize elevated rates of glucose uptake by the muscle. These results also suggest that the mechanisms for disparity in glucose metabolism at rest between men and women are controlled differently compared with exercise and may further emphasize the importance of blood glucose maintenance in women.

Our glucose kinetic data are in agreement with a recent study by Marliss et al. (28). Regardless of the possible differences in the LT among subjects, glucose Rg (mg·min^{-1}·kg^{-1}) was similar between men and women during exercise at 88% of V\textsubscript{O2peak}. However, glucose Rd (mg·min^{-1}·kg^{-1}) was lower in the women. When Rg and Rd were expressed relative to FFM (mg·kg·FFM^{-1}·min^{-1}), there were no differences between men and women during the short exercise trial. Our present data show a trend identical to that of Marliss et al. for glucose Rg and Rd expressed relative to FFM (no difference between men and women). Marliss et al. also quantified glucose kinetics during a 120-min recovery period. Although there were no differences during exercise, during the recovery period, women exhibited higher circulating insulin and glucose Rd (relative to FFM) than men. The authors suggest that women may be more efficient at restoring muscle glycogen from endogenous glucose after exercise. The hyperinsulinemic response noted by Marliss et al. during recovery is also of interest given the present data. The women in our study demonstrated a higher circulating insulin concentration at rest and during both exercise intensities than the men. However, circulating insulin levels remained consistently low during exercise. Therefore, it is not likely that the circulating insulin contributed significantly to the dominant contraction-mediated glucose uptake during exercise. Although this did not translate to a higher glucose Rd in the women, it may have contributed to the larger relative contribution of blood glucose to total CHO oxidation.

The majority of past research that has described gender variation in substrate utilization has relied heavily on indirect calorimetry. The present data are in agreement with previous research reporting no difference in RER between men and women (5, 8, 16, 31) but are in disagreement with other reports demonstrating that women have a lower RER during exercise (1, 13, 14, 22, 30, 36–38). One possible explanation for the observed lower RER in women in other studies may be related to differences in LT between the male and female subjects. Coyle et al. (6) and Coggan et al. (3) reported that cyclists with high LT have lower RER values than those with lower LT at a given percentage of V\textsubscript{O2peak}. It is possible that the female subjects in some of the studies that reported lower RER had higher LT and thus exercised at a lower percentage of LT than the men when exercised at a given percentage of V\textsubscript{O2peak}. Although Phillips et al. (30) showed similar LT between men and women after matching subjects on training and competitive habits (including training intensity, duration, frequency, common competitive distances, and years of training), the possible discrepancies in LT among subjects are not discussed in the previous literature. Interestingly, Davis et al. (8) also compared men and women in the follicular phase at the same percentage of the anaerobic threshold (as calculated from the V-slope method) and observed similar RER values between men and women, which supports the present findings.

Previous literature has suggested that, for an adequate comparison of substrate utilization between men and women, subjects should be carefully selected and equated on detailed training and competitive histories (30, 36–38). However, matching similarly trained men and women without subjecting them to similar training regimens has also been criticized, in that it does not adequately allow for the collection of directly comparable data in men and women (12). Furthermore, a similar V\textsubscript{O2peak} does not guarantee a similar metabolic response to exercise above and below a subject’s LT (3). Other studies that have compared men and women have noted a significant difference in the V\textsubscript{O2peak} values of the subjects. Even when V\textsubscript{O2peak} is expressed relative to FFM, women demonstrated values 13.5% lower than men (8). Skinner et al. (34) describe the gender differences across 20 wk of cycle ergometer training in the HERITAGE Family Study. Before training, women (n = 346) demonstrated a 13% lower V\textsubscript{O2peak} (ml·kg·FFM^{-1}·min^{-1}) than men (n = 287). The difference in V\textsubscript{O2peak} between the men and women in the present study was 19%.

On the basis of the recent work cited above, matching men and women using the criteria established by...
Phillips et al. (30) has advantages in terms of maximizing internal validity. However, it is unclear how this may suppress external validity and act to minimize the sexual dimorphisms during moderate-intensity exercise. If the data of Skinner et al. (34) represent an average gender difference in the population, an argument could be made that, to maximize external validity, subjects who demonstrate a similar discrepancy in \(^{\text{\textit{VO}}}_2\) \text{peak} \text{(relative to FFM)} should be selected. The rationale for selecting an exercise intensity relative to the LT was taken from previous research that has demonstrated that exercise performance is more related to ventilatory threshold (21, 27) and LT (6, 7) than to \(^{\text{\textit{VO}}}_2\) \text{peak}. Similarly, the data of Coggan et al. (3) support the concept that glucose \(R_a\) and \(R_d\) are related to LT. Without controlling for the LT, some subjects may be performing the experimental trial well below LT, whereas others may be forced to work above the LT.

Female subjects in the present study were tested in the late-follicular phase of the menstrual cycle. CHO oxidation (9, 10, 15, 17, 40, 43) and lactate concentrations (23, 26, 29) are lower during the luteal phase. In a recent study from our laboratory, we noted pronounced differences in fuel utilization and glucose kinetics across the menstrual cycle in fasted female subjects (43). Indirect calorimetry data demonstrated a significantly lower total CHO oxidation for the luteal than for the follicular phase of the cycle during exercise at 90% LT: 82.0 ± 12.3 vs. 93.8 ± 9.7 \(\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\). Glucose \(R_a\) and \(R_d\) were also significantly lower during the luteal than during the follicular phase of the cycle at 90% LT. Although our previous study indicated higher circulating E2 and, consequently, lower glucose \(R_a\) and \(R_d\) during the luteal phase, the relative contribution of muscle glycogen was similar for both phases of the menstrual cycle and consistently lower than that of the men. The data of Tarnopolsky et al. (36) demonstrating decreased glycogen depletion in women are in agreement with this observation (although women were tested in the early-midfollicular phase of the menstrual cycle).

In the previous research by Romijn et al. (32), the relative contribution of glucose and glycogen to total CHO oxidation changed in response to the intensity and duration of the exercise. However, Romijn et al. studied glucose kinetics at 25, 65, and 85% of \(^{\text{\textit{VO}}}_2\) \text{peak}. In the present investigation, the two exercise intensities were different by ~10–12% \(^{\text{\textit{VO}}}_2\) \text{peak}, which, in part, explains the similar RER and relative contribution of CHO sources at 70 and 90% LT in the female subjects. In contrast, the men demonstrated an increase of ~15% \(^{\text{\textit{VO}}}_2\) \text{peak} between the two intensities. This is closer to the 20% difference built into the design of Romijn et al. and may explain the intensity-dependent increase in RER noted in the men.

In conclusion, the results of this study indicate that at exercise intensities near the LT, glucose \(R_a\) and \(R_d\) expressed relative to FFM (\(\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{FFM}^{-1} \cdot \text{min}^{-1}\)) are similar in men and women. There were also no significant gender differences in total CHO and fat oxidation relative to total energy expenditure. The most notable finding in the present study indicates that the relative contribution of blood glucose to total CHO oxidation is higher in women. The precise mechanism(s) associated with the increased relative contribution of glucose in women may include but may not be limited to E2- or progesterone-mediated alterations in GLUT-4 translocation or muscle glycogenolysis and decreased muscle and/or hepatic glycogen stores. These results also suggest the need to reevaluate the importance of CHO feedings and the maintenance of blood glucose during exercise in women.

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REFERENCES

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