Insulin Sensitivity in Postmenopausal Women

Independent and combined associations with hormone replacement, cardiovascular fitness, and body composition

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OBJECTIVE — The effects of combined physical activity and hormone replacement therapy (HRT) on insulin sensitivity in postmenopausal (PM) women are unclear. The purpose of the study was to test the following hypotheses: 1) PM women who have undergone vigorous exercise training have greater insulin sensitivity than PM women who are physically active and PM women who are sedentary, and 2) PM women using HRT have greater insulin sensitivity than PM women not using HRT. We also sought to determine whether body composition or cardiovascular fitness was the stronger predictor of insulin sensitivity in these women.

RESEARCH DESIGN AND METHODS — Three groups of PM women classified as sedentary (n = 18), physically active (n = 19), and athletic (n = 23) underwent an insulin-modified frequently sampled intravenous glucose tolerance test to determine the insulin sensitivity index (SI) and dual-energy X-ray absorptiometry to determine body composition.

RESULTS — There was a significant association between both physical activity (P = 0.036) and HRT (P = 0.007) and fasting plasma insulin levels. The athletic PM women had the lowest plasma insulin levels and the highest SI. Across all physical activity levels, PM women using HRT (n = 29) had significantly lower fasting plasma insulin levels and a lower SI than PM women not using HRT (n = 31). HRT was significantly (P = 0.025) associated with intravenous glucose tolerance (Kg); the women not using HRT had a higher Kg than the PM women using HRT (0.83 ± 0.08 vs. 0.60 ± 0.05% per minute). Percent body fat (r = −0.37, P = 0.004) and VO2max (r = 0.35, P = 0.007) were similar predictors of SI.

CONCLUSIONS — We conclude that, although overall HRT was associated with an attenuated SI, vigorous exercise training was independently associated with the greatest SI. In addition, PM women using HRT may benefit from having lower plasma insulin levels, but they may also have a lower SI.

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Loss of ovarian function is associated with an increased risk for coronary artery disease (CAD) (1). One possible reason for this increased CAD risk after menopause may be a decrease in glucose tolerance and insulin sensitivity and an increase in plasma insulin levels, all of which may be the result of increased total body and abdominal adiposity that begins to occur at menopause (2–5). Results from studies in animals and humans suggest that estrogen replacement may improve insulin sensitivity and reduce plasma insulin levels (6–8). Exercise training has also been shown to improve insulin sensitivity and reduce fasting and glucose-stimulated plasma insulin levels in young, old, diabetic, and hypertensive individuals (9–12). However, the combined effect of hormone replacement therapy (HRT) and increased physical activity on insulin sensitivity and plasma insulin levels in postmenopausal (PM) women is unclear.

We hypothesized that PM women who have undergone prolonged vigorous exercise training would have greater insulin sensitivity than PM women who were physically active and PM women who were sedentary. In addition, because of the reported beneficial effects of HRT on glucose and insulin metabolism, we hypothesized that PM women on HRT would have greater insulin sensitivity and lower plasma insulin levels than PM women not on HRT. We also sought to determine whether body composition or cardiovascular fitness was the strongest predictor of insulin sensitivity in healthy PM women.

RESEARCH DESIGN AND METHODS — We recruited 60 healthy PM women to participate in the study based on their HRT status and exercise history. These women were classified as PM by self-reported lack of menses for >2 years and elevated levels of follicle-stimulating hormone and luteinizing hormone. Eighteen of the women had not participated in a regular exercise program for at least 2 years and were classified as sedentary. Nineteen...
Exercise and insulin sensitivity in PM women

Women who participated in regular aerobic exercise, but who were not training for endurance-based competitive events, were classified as physically active. Of 60 recruited subjects, 23 were competitive distance runners who were vigorously training and regularly placed in regional, national, and international competitions. We recruited the sedentary and physically active women from the Pittsburgh metropolitan area by media advertisements and personal contacts. We recruited women athletes from across the U.S. by advertisements in master's running communications and personal contacts. Approximately half of the women (n = 29) were undergoing HRT; the other half (n = 31) were not on HRT. Of the women on HRT, 66% was using combined oral estrogen and progesterone medication (approximately equal numbers were on continuous and cyclic progesterone). Women on cyclic progesterone were studied for 7–10 days without progesterone. The remaining women (34%) were using only oral estrogen. The range of estrogen and progesterone dosages was similar in all groups. All women on estrogen were taking dosages <1.0 mg/day. The sedentary group consisted of 9 women on HRT (6 on combined estrogen/progesterone and 3 on only estrogen) and 9 women not on HRT. The physically active group consisted of 9 women on HRT (6 on combined estrogen/progesterone and 3 on only estrogen) and 10 women not on HRT. And, the athletic group consisted of 11 women on HRT (7 on combined estrogen/progesterone and 4 on only estrogen) and 12 women not on HRT. The physical activity level and HRT status of all subjects had been constant for at least 2 years before the study. All subjects provided their written informed consent before any testing; the study was approved by the Institutional Review Board of the University of Pittsburgh.

Subjects with known CAD and those who were taking medications affecting glucose metabolism or the cardiovascular system or subjects who had conditions that affected their ability to perform maximal exercise were excluded from the study after the initial interview and review of their medical history. Sedentary subjects first underwent a physical examination, resting electrocardiogram (ECG), and blood pressure measurement, and if no abnormalities were present, a screening graded maximal exercise test according to a modified Naughton protocol as previously described (13). A second exercise test was administered to the sedentary and physically active subjects to measure their VO2max. The procedures for the VO2max test have been described previously (14). Women athletes completed a single maximal treadmill exercise test for both screening and measuring VO2max. The VO2max data have been published previously (15). To qualify for the study, each subject's exercise tests must have been stopped because of exhaustion with no evidence of clinically significant ECG changes or cardiovascular decompensation (16). Thus, only healthy subjects without cardiovascular disease and other conditions that may influence glucose and insulin metabolism were studied.

Frequently sampled intravenous glucose tolerance test
To assess whole-body insulin sensitivity, subjects underwent an insulin-modified frequently sampled intravenous glucose tolerance test (FSIVGTT), according to the methods of Bergman et al. (17). The FSIVGTT was performed at the General Clinical Research Center starting between 7:00 A.M. and 8:00 A.M. All subjects ingested a diet containing 250–300 g carbohydrate/day for each of the 3 days before the FSIVGTT study and fasted for 12 h before the start of the test. The women in the physically active and athletic groups underwent the FSIVGTT 15–24 h after their last exercise session. Indwelling catheters were inserted into the antecubital veins bilaterally. One catheter was used for administration of glucose and insulin, and the other was used for drawing blood samples; both were maintained patent with a slow saline drip. After a 30-min equilibration period, three basal blood samples for glucose and insulin were drawn. d-Glucose (300 mg glucose/kg as 50% dextrose) was injected over a 1-min period. Insulin (0.02 U/kg) (Humulin-Regular; Eli Lilly, Indianapolis, IN) was injected 20 min after the glucose injection to augment the insulin response. Sufficient saline flush was used to guarantee total delivery of the glucose and insulin doses. Blood samples for glucose and insulin were drawn at 28 standard time points for 3 h after the glucose injection. Blood samples were placed in a glycolytic inhibitor and anticoagulant, stored temporarily on ice, and then centrifuged at 4°C. Plasma samples for insulin were stored at −70°C. Insulin was measured by radioimmunoassay, and glucose was measured by the glucose oxidase method (YSI Glucose Analyzer, Yellow Springs Instruments, Yellow Springs, OH). The glucose and insulin data were analyzed using the Bergman minimal model (MINMOD) program (Version 2, 1989) to determine the insulin sensitivity index (S) (18). S is a measure of an increment in plasma insulin to enhance the fractional disappearance of glucose. Intravenous glucose tolerance (Kg) was calculated as the slope of the regression line relating the logarithm of glucose concentration to the time between 10 and 19 min after the glucose injection (18). The acute insulin response to glucose (AIRg) was calculated as the mean plasma insulin concentration during the first 10 min after glucose injection minus the basal plasma insulin concentration (22).

Body composition
Body composition was determined using dual-energy X-ray absorptiometry (DPX-L software version 1.3; Lunar Radiation, Madison, WI). All measurements were performed after an overnight fast with the subject lying comfortably wearing standard hospital issue clothing. All scans were performed at medium scan speed and were analyzed with DPX-L. BMI was determined as weight (kg) divided by height (m) squared. More detailed body composition data from these women have been published previously (19).

Statistical analyses
Data were analyzed using Statview software (Abacus Concepts, Berkeley, CA). Characteristics of the subjects as well as the dependent variables were analyzed using a two-way analysis of variance with physical activity status as one variable and HRT status as the other variable. When indicated, appropriate variables were used as covariates. An α level of 0.05 was accepted for statistical significance. In addition, VO2max and measures of body composition were used as continuous variables to assess their correlation with the different components of glucose and insulin metabolism. All data are reported as means ± SEM.

RESULTS — The 60 PM healthy women had an average age of 64 ± 5 years (Table 1). Among the groups, there were no significant differences in the number of years they had been PM. For those women on HRT, there were no significant differences in the length of time they had been on HRT. The physically active and athletic groups averaged 5–6 h of physical activity/week. They also had been physically active or athletic for the same number of years (12–16 years).
associations with physical activity were significant association between fasting plasma glucose levels. There was a significant association between physical activity and fasting plasma glucose, with the sedentary group having the lowest glucose levels compared with the physically active and sedentary groups.

There was a significant association ($P = 0.008$) between physical activity and fasting plasma glucose, with the sedentary group demonstrating the lowest glucose levels (Table 2). However, the differences between the groups were small, and all the groups had similar fasting glucose values within the normal range. HRT status did not affect fasting plasma glucose levels. There was a significant association between fasting plasma insulin levels and both physical activity ($P = 0.036$) and HRT ($P = 0.007$), and the lowest fasting plasma insulin levels were observed in the athletic group. The associations with physical activity were independent of differences in body composition and BMI. Across all physical activity levels, PM women on HRT demonstrated significantly lower fasting insulin levels and a significantly lower $K_G$ than women not on HRT. There was no significant difference in measures of body composition between women on and not on HRT. Thus, the associations with HRT were also independent of body composition. There were no significant interactive relationships between physical activity and HRT and parameters of glucose and insulin metabolism.

The $S_i$, as determined from modeling of the FSIVGTT results by the MINMOD program, tended to be higher in the athletic group than the sedentary and physically active groups by 44 and 42%, respectively ($P = 0.060$). Unexpectedly, the women not on HRT tended to have a higher $S_i$ ($5.86 \pm 0.61 \mu U \times 10^{-4} \cdot \text{min}^{-1} \cdot \text{ml}^{-1}$) than women on HRT ($4.41 \pm 0.50 \mu U \times 10^{-4} \cdot \text{min}^{-1} \cdot \text{ml}^{-1}, P = 0.069$). Thus, the athletic women not on HRT had the highest $S_i$, although it was not significantly higher than that of the athletic women on HRT, and the sedentary women on HRT had the lowest $S_i$ ($6.61 \pm 1.26$ vs. $3.65 \pm 0.40 \mu U \times 10^{-4} \cdot \text{min}^{-1} \cdot \text{ml}^{-1}$, respectively). These associations with physical activity and HRT were independent of differences in body composition and BMI.

Physical activity status did not significantly affect $K_G$. However, the women not on HRT had a significantly higher $K_G$ than those women on HRT ($0.83 \pm 0.08$ vs. $0.60 \pm 0.05$% per minute, $P = 0.025$), independent of body composition. All of the groups in the present study would be categorized as having a less than normal $K_G$ (20). Neither physical activity status nor HRT status was significantly related to $A_I$.

To further elucidate the influence of HRT on glucose and insulin metabolism, the 60 PM women were divided into three groups: women using only estrogen ($n = 10$), women using combined estrogen and progesterone ($n = 19$), and women not on HRT ($n = 31$). These three groups had similar percentages of sedentary, physically active, and athletic women. There was a trend ($P = 0.052$) for HRT status to be associated with $S_i$: the women using only

### Table 1—Characteristics of the different groups of PM women

<table>
<thead>
<tr>
<th>Variable</th>
<th>Not on HRT</th>
<th>On HRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Age (years)</td>
<td>$66 \pm 2$</td>
<td>$62 \pm 2$</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>$160 \pm 2$</td>
<td>$158 \pm 2$</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>$58.9 \pm 1.6^{*}$</td>
<td>$59.2 \pm 2.8^{*}$</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>$23.1 \pm 1.1^{*}$</td>
<td>$23.8 \pm 0.9^{*}$</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>$36.9 \pm 1.1^{*}$</td>
<td>$35.9 \pm 2.4^{*}$</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>$21.8 \pm 1.2^{*}$</td>
<td>$21.7 \pm 2.2^{*}$</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>$37.1 \pm 0.7^{*}$</td>
<td>$37.6 \pm 1.2^{*}$</td>
</tr>
<tr>
<td>VO₂ max (ml · kg⁻¹ · min⁻¹)</td>
<td>$22.3 \pm 0.7^{*}$</td>
<td>$24.4 \pm 1.6^{*}$</td>
</tr>
<tr>
<td>Years on HRT</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Years PM</td>
<td>$15.2 \pm 2.5$</td>
<td>$11.1 \pm 1.2$</td>
</tr>
</tbody>
</table>

Data are means ± SEM. Like symbols indicate values within the same variable. $P < 0.05$ vs. different variables.

The athletic women on and not on HRT had similar training mileage, averaging $31.2 \pm 3.2$ and $28.7 \pm 2.7$ miles/week of running, respectively. There were no statistically significant differences in age or height among these six groups. The physically active group was heavier and had a significantly greater BMI than both the sedentary and athletic groups. The athletic group had the lowest BMI and percent body fat and the highest VO₂max compared with the physically active and sedentary groups.

There was a significant association ($P = 0.008$) between physical activity and fasting plasma glucose, with the sedentary group demonstrating the lowest glucose levels (Table 2). However, the differences between the groups were small, and all the groups had similar fasting glucose values within the normal range. HRT status did not affect fasting plasma glucose levels. There was a significant association between fasting plasma insulin levels and both physical activity ($P = 0.036$) and HRT ($P = 0.007$), and the lowest fasting plasma insulin levels were observed in the athletic group. The associations with physical activity were independent of differences in body composition and BMI. Across all physical activity levels, PM women on HRT demonstrated significantly lower fasting insulin levels and a significantly lower $K_G$ than women not on HRT. There was no significant difference in measures of body composition between women on and not on HRT. Thus, the associations with HRT were also independent of body composition. There were no significant interactive relationships between physical activity and HRT and parameters of glucose and insulin metabolism.

The $S_i$, as determined from modeling of the FSIVGTT results by the MINMOD program, tended to be higher in the athletic group than the sedentary and physically active groups by 44 and 42%, respectively ($P = 0.060$). Unexpectedly, the women not on HRT tended to have a higher $S_i$ ($5.86 \pm 0.61 \mu U \times 10^{-4} \cdot \text{min}^{-1} \cdot \text{ml}^{-1}$) than women on HRT ($4.41 \pm 0.50 \mu U \times 10^{-4} \cdot \text{min}^{-1} \cdot \text{ml}^{-1}, P = 0.069$). Thus, the athletic women not on HRT had the highest $S_i$, although it was not significantly higher than that of the athletic women on HRT, and the sedentary women on HRT had the lowest $S_i$ ($6.61 \pm 1.26$ vs. $3.65 \pm 0.40 \mu U \times 10^{-4} \cdot \text{min}^{-1} \cdot \text{ml}^{-1}$, respectively). These associations with physical activity and HRT were independent of differences in body composition and BMI.

Physical activity status did not significantly affect $K_G$. However, the women not on HRT had a significantly higher $K_G$ than those women on HRT ($0.83 \pm 0.08$ vs. $0.60 \pm 0.05$% per minute, $P = 0.025$), independent of body composition. All of the groups in the present study would be categorized as having a less than normal $K_G$ (20). Neither physical activity status nor HRT status was significantly related to $A_I$.

To further elucidate the influence of HRT on glucose and insulin metabolism, the 60 PM women were divided into three groups: women using only estrogen ($n = 10$), women using combined estrogen and progesterone ($n = 19$), and women not on HRT ($n = 31$). These three groups had similar percentages of sedentary, physically active, and athletic women. There was a trend ($P = 0.052$) for HRT status to be associated with $S_i$: the women using only

### Table 2—Glucose and insulin metabolism characteristics of the different groups of PM women

<table>
<thead>
<tr>
<th>Variable</th>
<th>Not on HRT</th>
<th>On HRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>$4.39 \pm 0.11^{*}$</td>
<td>$4.55 \pm 0.11^{*}$</td>
</tr>
<tr>
<td>Fasting insulin (pmol/l)</td>
<td>$23.4 \pm 2.4^{+}$</td>
<td>$19.2 \pm 3.0^{*}$</td>
</tr>
<tr>
<td>$S_i$ ($\mu U \times 10^{-4} \cdot \text{min}^{-1} \cdot \text{ml}^{-1}$)</td>
<td>$5.14 \pm 0.92^{*}$</td>
<td>$3.65 \pm 0.40^{+}$</td>
</tr>
<tr>
<td>AIR (pmol/l)</td>
<td>$253.4 \pm 90.5$</td>
<td>$202.3 \pm 52.4$</td>
</tr>
<tr>
<td>$K_G$ (%/min)</td>
<td>$0.68 \pm 0.12^{+}$</td>
<td>$0.57 \pm 0.08^{+}$</td>
</tr>
</tbody>
</table>

Data are means ± SEM. Like symbols indicate values within the same variable. $P < 0.05$ vs. different variables.
estrogen had the lowest value (Table 3). There were also trends for HRT status to be associated with fasting plasma insulin levels (P = 0.070) and K_s (P = 0.086). Post hoc analyses revealed that the women using only estrogen had significantly higher fasting plasma glucose and lower fasting plasma insulin levels, S_g and K_s than the women not on HRT.

\[
\text{Fasting Insulin (pmol/l)} = 17.4 \pm 3.0^* \quad 21.6 \pm 1.8^* \quad 23.0 \pm 2.4^*
\]

\[
\text{Fasting glucose (mmol/l)} = 5.0 \pm 0.2^* \quad 4.7 \pm 0.1^* \quad 4.7 \pm 0.1^*
\]

Data are means ± SEM. Like symbols indicate values within the same range.

The primary findings of this study are that 1) the highest physical activity levels are associated with a significantly greater insulin sensitivity, 2) HRT is associated with an attenuated insulin sensitivity, but is also associated with lower plasma insulin levels, and 3) percentage of body fat and VO_2max are similar predictors of insulin sensitivity. To our knowledge, this is the first study to assess differences in insulin sensitivity in three groups of PM women with different levels of habitual physical activity.

Previous studies have found that menopause and aging are each associated with a reduction in insulin sensitivity (4,21). The increased insulin resistance associated with menopause may be due, in part, to the tendency to be more sedentary with advancing age. Previous studies have shown that exercise training improves insulin sensitivity and reduces fasting and glucose-stimulated insulin levels in middle-aged and older individuals (11,22,39). In agreement with our first hypothesis, the PM women with the highest levels of physical activity had the greatest insulin sensitivity regardless of HRT status. When the groups on and not on HRT were combined within activity groups, the S_g for the athletic PM women averaged 6.31 μU × 10^{-4} · min^{-1} · ml^{-1}, a value comparable with that of young lean healthy women (18). The sedentary and physically active PM women had an average S_g of 4.40 and 4.57 μU × 10^{-4} · min^{-1} · ml^{-1}, respectively, which is comparable with S_g values of lean individuals with impaired glucose tolerance (18).

A previous study in older men found that insulin sensitivity increased by 36% in older men with 6 months of exercise training (22). Pratley et al. (23) used a three-dose hyperinsulinemic-euglycemic glucose clamp to assess insulin sensitivity in male master athletes and sedentary control subjects. The glucose infusion rate was 30% higher in the master athletes than the low insulin dose, indicating a greater sensitivity.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Not on HRT</th>
<th>On HRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>31</td>
<td>29</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>60.5 ± 1.5</td>
<td>58.2 ± 1.7</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>23.4 ± 0.5</td>
<td>23.2 ± 0.5</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>33.7 ± 1.3</td>
<td>30.9 ± 1.7</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>20.8 ± 1.2</td>
<td>18.4 ± 0.9</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>39.8 ± 0.7</td>
<td>39.8 ± 1.0</td>
</tr>
</tbody>
</table>

Data are means ± SEM.
Although results of previous studies have been inconsistent, HRT has been shown to influence glucose and insulin metabolism (8,13,24,31–34,41). We found a significant relationship between HRT use and both fasting plasma insulin levels and $K_G$. Those women on HRT had significantly lower fasting plasma insulin levels across the three physical activity groups. Unexpectedly, it was the PM women on HRT who had the lowest $K_G$, although both groups had an average $K_G < 1.0\%$ per minute, which would be categorized as poor intravenous $K_G$ (20). We also found that the PM women on HRT had an average $S_I$ that was 25% lower than women not on HRT. HRT use in sedentary and physically active women was associated with a significantly lower $S_I$, but the differences were not as substantial and not statistically significant between women athletes on and not on HRT. Thus, it appears that the effects of intense and prolonged endurance training override the effects of HRT on insulin sensitivity in postmenopausal women. As in the sedentary and physically active groups, women athletes on HRT had lower fasting insulin levels than athletes not on HRT; however, the differences were not statistically significant in the athletes. It is also not surprising that there are somewhat different relationships between fasting insulin levels and insulin sensitivity among the groups; although there is generally a strong relationship between fasting insulin levels and insulin sensitivity, the correlation does not approach unity.

HRT may also affect body composition and thereby indirectly affect glucose and insulin metabolism. Recently, Samaras et al. (42) found that HRT significantly reduced abdominal fat mass. We did not find any differences in body weight, BMI, or body composition between women on and not on HRT. Therefore, it is unlikely that the observed differences in glucose and insulin metabolism parameters between these groups were due to differences in body weight or composition. We also found that percent body fat and VCO$_{max}$ were similar predictors of insulin sensitivity. Together, these results suggest that cardiovascular fitness, percent body fat, and HRT are independently associated with glucose and insulin metabolism in healthy PM women with varying levels of habitual physical activity.

Because estrogen and progesterone may differentially affect glucose and insulin metabolism, we also assessed the influence of estrogen and estrogen plus progesterone on insulin sensitivity. Women on only estrogen had the lowest fasting and glucose-stimulated plasma insulin values. These results agree with previous studies that show higher plasma insulin levels in healthy PM women not on HRT (5) and reduced fasting plasma insulin levels after 24 months of HRT in PM women (8). In a prospective study, Samaras et al. (42) found that 2 months of estrogen therapy decreased fasting insulin levels, whereas fasting insulin levels increased when progesterone was added. In the present study, women on only estrogen had the worst insulin sensitivity and intravenous $K_G$. The average $S_I$ value for the group using only estrogen was comparable to that of elderly nonobese individuals (18). Women using combined estrogen and progesterone and women not on HRT had comparable $S_I$ values. Thus, those on only estrogen may benefit from having lower fasting and glucose-stimulated insulin levels, but may have worse insulin sensitivity and intravenous $K_G$.

Previous intervention studies of the effects of HRT on glucose and insulin metabolism have provided mixed results. Some studies have found that adding progesterone to the estrogen therapy attenuated the beneficial effects of estrogen on insulin sensitivity (7,21,33,35), whereas other studies did not find this attenuating effect (8,40). The results of the present study agree with those of Elkind-Hirsch et al. (35); we found that the women not on HRT had a higher $S_I$ than women on estrogen alone or combined estrogen and progesterone therapy. However, our results differ from those of Elkind-Hirsch et al.; the women in the present study using estrogen alone had the lowest $S_I$, whereas those women using combined estrogen and progesterone in the study by Elkind-Hirsch et al. had the lowest $S_I$.

The estrogen dosage has also been shown to have substantial effects on carbohydrate metabolism (7,32,34,36,37,40). Lindeheim et al. (7,21) found that 2 months of a low dose (0.625 mg/day) of estrogen improved the $S_I$ in healthy PM women, but that a higher dose (1.25 mg/day) worsened insulin sensitivity in healthy PM women. The PM women in the present study were receiving estrogen doses $\leq 1$ mg/day. Thus, it is unlikely that the dosage of estrogen played a major role in the present study.

Guidelines previously reported by the Centers for Disease Control and Prevention and the American College of Sports Medicine indicated that 30 min of physical activity on most days of the week reduces all-cause and cardiovascular disease mortality (38). In the present study, we found that the $S_I$ values were similar in the sedentary and physically active groups. However, the women who had been training rigorously for competitive events had the highest $S_I$ values, suggesting that it may take more vigorous exercise training to derive benefits in insulin sensitivity.

In conclusion, our results indicate that physical activity and HRT may differentially and independently affect fasting levels of plasma glucose and insulin as well as parameters of glucose kinetics in healthy PM women. Both physical activity and HRT were positively associated with fasting plasma insulin levels, but vigorous physical activity was associated with improved insulin sensitivity, and HRT was associated with worsened insulin sensitivity. Our results also indicate a strong influence of body fat percentage on insulin sensitivity in PM women.

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References
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