Hormone-replacement therapy use, but not race, impacts the resting and exercise-induced GH response in postmenopausal women

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Abstract
Objective: This study examined the effect of hormone-replacement therapy (HRT) use on the incremental GH response to aerobic exercise in postmenopausal women and established whether racial differences in the GH response were seen at rest and in response to exercise.
Methods: 13 white (n = 6, HRT; n = 7, no HRT) and seven black women (no HRT) were studied on two occasions, a control day and an exercise day (30 min at 70% VO2max on a cycle ergometer). Blood was sampled every 10 min for a 4-h period and analyzed for GH using an ultrasensitive chemiluminescent assay.
Results: The mean 4-h GH concentration was higher on both study days in the HRT women than the non-HRT users. The integrated GH concentrations were greater in the HRT women both at rest and in response to exercise (rest, 352 ± 53 mIU/l; exercise, 711 ± 57 mIU/l; P < 0.01) than in the non-HRT women (rest, 157 ± 87 mIU/l; exercise, 248 ± 94 mIU/l). The incremental GH response was greater in the HRT users than in the non-HRT women (358 ± 130 versus 90.8 ± 94 mIU/l, respectively; P < 0.05). GH-production rate during the 4-h period was greater in the HRT women than in the non-HRT women (358 ± 130 versus 90.8 ± 94 mIU/l, respectively; P < 0.05). GH-production rate during the 4-h period was greater in the HRT women than in the non-HRT women (P < 0.01), due to an increase in the GH mass secreted/pulse (P < 0.05), with no change in GH pulse number or GH half-life. No racial differences in the mean 4-h GH concentrations or integrated GH concentrations were found at rest or in response to exercise.
Conclusion: HRT use resulted in a greater incremental exercise response compared with non-HRT users, due to changes in the secretory pulse characteristics in the HRT users. This study also demonstrated that no racial differences exist at rest and in response to exercise in the morning hours.

Introduction
With aging there is a decrease in growth hormone (GH) concentrations and this decline is more dramatic at menopause, when there is a concomitant decline in circulating estradiol levels (1). Numerous studies have reported increases in GH concentrations with oral administration of ethinyl estradiol (2, 3) or transdermal administration (4), resulting in levels above the deficient state. This rise in GH in estrogen-supplemented women has been attributed to increased levels of GH-binding protein (GHBP) and decreases in serum insulin-like growth factor I (IGF-I) levels (5). The suppressed IGF-I levels would minimize IGF-I’s negative feedback on the pituitary and hypothalamus resulting in increased GH production and secretion (2).

It is unclear if the elevated resting GH levels seen in hormone-replacement therapy (HRT) users results in a greater GH response to a physiological stressor. Only one study has examined the exercise-induced GH responses in women on HRT and reported that the exercise-induced integrated GH levels were higher in women using HRT (6). These authors, however, did not examine whether the magnitude of the exercise-induced GH response or the GH secretory pulsatility were different between HRT users and non-users.

Furthermore, potential variation in the GH response to exercise may also occur between races because of differences in estradiol levels. Black men, who were observed to have higher estradiol levels than white men (7), have also been shown to have higher 24-h integrated GH concentrations and GH secretory burst amplitude. Subsequent research (8) on premenopausal black and white women found no differences in the 17β-estradiol concentrations or the 24-h GH profile. No studies, however, have focused on the racial differences in the GH response to exercise between individuals who potentially have different estradiol levels.

Therefore the purpose of this study was twofold: (1) to examine the effect of HRT use on the incremental...
GH response to moderate-intensity aerobic exercise and (2) to investigate whether differences exist in the GH concentrations of black and white postmenopausal women at rest and during a submaximal bout of aerobic exercise. Based on previous work where differences in resting estradiol and GH concentrations were observed (9), we speculated that exercise is a potent-enough stimulus to override the differences in circulating estradiol levels between HRT and non-HRT users. We also hypothesized that resting GH levels would be lower in the black women than in white women but that the exercise-induced GH response would not be different between races.

Methods

Study subjects

Thirteen white (n = 6 HRT, n = 7 no HRT) and seven black (no HRT) postmenopausal women, 50–61 years old, volunteered to participate in this research study, and signed an informed consent approved by the Institutional Review Boards of Syracuse University and SUNY Upstate Medical University, Syracuse, NY, USA. The subjects had been postmenopausal for a minimum of 1 year (mean, 4.61 ± 0.5 years) as diagnosed by their own physician. Both parents and grandparents of the subjects had to be American-born and both parents and grandparents were either Caucasian or African-American. All subjects were healthy, with no major chronic diseases. No subjects were smokers or on β-blocker medications. Subjects were physically inactive, with no recent participation in a regular exercise program. The women who were on HRT were using Premarin (0.625 mg; Wyeth Pharmaceuticals, Philadelphia, PA, USA; n = 4 also used medroxyprogesterone; HRT use, 4.9 ± 0.5 year). Since body composition has been shown to impact the GH levels, the black and white women were matched on percentage of body fat.

Experimental procedures

Subjects visited the Human Performance Laboratory at Syracuse University on three occasions. A medical history and a physical activity questionnaire were completed on the first visit and then the subject underwent an exercise stress test on a cycle ergometer (10). During visits two and three, subjects were required to come to the Human Performance Laboratory for a control or an exercise study day; the order of the study days was randomized. The study day was 4 h in length and blood samples were drawn every 10 min during this period.

Exercise stress test

The exercise protocol has been described previously (10). Briefly, the protocol consisted of 2-min exercise stages on a cycle ergometer, starting at 50 W, and increased 15 W every 2 min until volitional fatigue. O₂ consumption (VO₂) and CO₂ production were monitored using a Sensormedics 2900 metabolic cart (Diagnostic Products and Diagnostic Systems, Yorba Linda, CA, USA). VO₂ peak was determined as the highest oxygen consumption attained during the exercise test. Heart rate and blood pressure were measured at rest and at the end of each 2-min exercise stage, and continuous 12-lead electrocardiogram (ECG) recording was performed throughout the exercise stress test.

Body composition

At the completion of the stress test, total body fat was measured using hydrostatic weighing. Body density was measured with the underwater weight taken simultaneously with measurement of residual lung volume (11). Percentage body fat was calculated using age-specific equations (12).

In addition, all women also underwent magnetic resonance imaging (MRI) to determine the abdominal fat distribution patterning. These methods and findings have been reported previously (13). Briefly, the MRI images were obtained using a GE Signa 1.5 T MRI scanner with standard T1-weighted spin-echo imaging with respiratory compensation. Images were acquired beginning at the superior portion of the head of the femur and inclusive to the most superior portion of the kidneys. The total visceral fat volume subtracted from the total fat (visceral adipose tissue (VAT) plus subcutaneous adipose tissue (SAT)) of that slice determined the total subcutaneous fat of that slice level and all slices were added together to calculate total abdominal fat volume (14).

Study day

During visits two and three, subjects came to the Human Performance Laboratory at 0700 h, after a 12-h overnight fast. A heparin lock was placed in the antecubital vein of the subjects’ arm and kept patent by a saline flush. 30 min after the heparin lock was placed, blood samples were drawn every 10 min over the next 4 h. On the exercise study day, after 60 min of resting blood sampling subjects exercised on a cycle ergometer for 30 min at 70% VO₂ peak. After the exercise, subjects sat quietly as they did on the control day. Subjects were not allowed to sleep or eat during the recovery period.

Blood sampling and analysis

Each blood sample was collected in an EDTA tube, centrifuged and the plasma aliquotted and frozen at a temperature of −80°C and later assayed for estradiol, estrone, IGF-I and GH concentrations. Estradiol, estrone and IGF-I concentrations were performed
Statistical analysis

An independent t-test was used to compare the physical characteristics of the groups. Calculation of the integrated GH hormone concentration (area under the curve; baseline hormone concentration: \( y = 0 \)) was determined by using GraphPad Prism (version 2.01; San Diego, CA, USA). A multiple-parameter deconvolution method was employed to determine the quantitative estimates of attributes of GH secretion from the measured GH concentrations during the 4-h period. This method uses validated two-component endogenous GH kinetics (15) comprised of a rapid GH half-life of 3.5 min and a slow-phase GH half-life of 20.8 min. A fractional (slow/total) decay amplitude of 0.63 was used (15).

A 2 × 2 analysis of variance (ANOVA) with repeated measures was performed (HRT use or race × study day) to determine the effects of exercise on the GH concentrations. An independent t-test was conducted to determine whether the incremental GH response was different by race or HRT use. Since previous reports (16) have indicated that total body fat, abdominal fat or aerobic capacity may alter the GH response, we used these variables as covariates in an analysis of covariance (ANCOVA) to determine whether they may have affected our results. Although there were no racial differences in percentage body fat, this was done to control for the potential differences in fat mass between the two races. For those variables where significance was not found, the effect size (\( \eta^2 \)) was calculated using the formula by Cohen (17). The data are reported as means ± S.E. and significance was determined at an \( \alpha \) level of 0.05.

Results

Table 1 shows the subject characteristics of the black and white women who participated in both study days. There were no differences in any of the subject characteristics for the women on HRT and those who were not. As expected, the women on HRT had significantly higher estradiol levels (\( P < 0.05 \)) than the non-HRT women, while the estrone levels were higher but not significantly (\( P = 0.08 \)). IGF-I levels were higher, but not significantly, in the non-HRT women. The black and white women were similar in age, height and percentage body fat (white, 38.6 ± 3.9%; black, 37.8 ± 3.2%), but the black women were heavier, and had a greater fat mass and body mass index (\( P < 0.01 \)). Aerobic capacity (VO₂ peak) was greater in the white than in the black women when expressed in terms of body mass, but no differences were observed when expressed relative to fat free mass (data not shown).

Comparison between HRT and non-HRT users

The mean 4-h GH concentration on the resting day was higher in the HRT women than the non-HRT users (1.4 ± 1.1 versus 0.7 ± 0.8 µg l⁻¹; \( P < 0.05 \)). Similarly, a greater mean 4-h GH concentration was found on the exercise day in the HRT women (2.4 ± 1.1 µg l⁻¹) compared with the non-HRT women (1.0 ± 0.5 µg l⁻¹).

Table 1 Subject characteristics.

<table>
<thead>
<tr>
<th>Measure</th>
<th>White, HRT (n = 6)</th>
<th>White, no HRT (n = 7)</th>
<th>Black, no HRT (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55.1 ± 1.4</td>
<td>54.3 ± 1.2</td>
<td>53.4 ± 1.4</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163.2 ± 3.8</td>
<td>160.1 ± 2.6</td>
<td>162.6 ± 2.2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.9 ± 4.9</td>
<td>68.2 ± 3.6</td>
<td>88.6 ± 7.5†</td>
</tr>
<tr>
<td>BMI (kg m⁻²)</td>
<td>26.5 ± 2.1</td>
<td>26.5 ± 0.7</td>
<td>33.3 ± 2.4†</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>33.1 ± 1.8</td>
<td>38.6 ± 2.9</td>
<td>37.8 ± 3.2</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>22.8 ± 3.6</td>
<td>26.6 ± 2.4</td>
<td>34.7 ± 5.0†</td>
</tr>
<tr>
<td>Total abdominal fat (cm²)</td>
<td>7729 ± 1690</td>
<td>8794 ± 1195</td>
<td>13550 ± 1813†</td>
</tr>
<tr>
<td>Visceral fat (cm³)</td>
<td>2272 ± 484</td>
<td>2543 ± 423</td>
<td>2512 ± 424</td>
</tr>
<tr>
<td>VO₂ peak (m/1 kg⁻¹ min⁻¹)</td>
<td>26.7 ± 1.6</td>
<td>24.4 ± 0.7</td>
<td>18.0 ± 0.9†</td>
</tr>
<tr>
<td>Estrone (pM)</td>
<td>447.8 ± 162.3</td>
<td>125.8 ± 44.6</td>
<td>162.0 ± 67.8</td>
</tr>
<tr>
<td>Estradiol (pM)</td>
<td>60.7 ± 7.9*</td>
<td>22.7 ± 10.5</td>
<td>65.6 ± 26.5</td>
</tr>
<tr>
<td>IGF-I (µg l⁻¹)</td>
<td>95.5 ± 25.4</td>
<td>158.6 ± 42.9</td>
<td>157.1 ± 38.5</td>
</tr>
</tbody>
</table>

*\( P < 0.05 \) between HRT and no HRT; †\( P < 0.05 \) between blacks and white, no HRT.
The pattern of GH response was similar between groups on both study days (Fig. 1), with higher peak GH levels in the HRT users (rest, 4.8±1.3 μg·l⁻¹; exercise, 12.1±1.4 μg·l⁻¹) than was found in the non-HRT users (rest, 2.8±1.4 μg·l⁻¹; exercise, 4.7±0.8 μg·l⁻¹). The integrated GH concentrations were greater in the HRT women \((P < 0.01)\) than in the non-HRT women both at rest and in response to exercise, and both groups showed a significant increase in GH concentrations in response to exercise \((P < 0.01; \text{Fig. 2, top panel})\). The incremental GH response was almost 4-fold greater in the HRT users \((P < 0.05; \text{Fig. 2, top panel})\).

Table 2 shows the results of the deconvolution analysis of GH concentrations for the 4-h period on both the control and exercise days. The total amount of GH secreted during the 4-h period (production rate) was significantly greater in the HRT women than in the non-HRT women \((P < 0.01)\). This could be accounted for by the increase in the mass of GH secreted per pulse \((P < 0.05)\), with no change in the number of GH pulses or in the GH half-life. Additionally, the secretory pulse amplitude and pulse half-duration were both greater \((P < 0.01)\) in the HRT women than in the non-HRT women. We found no change in the GH secretory parameters between the control day and the exercise day in either group of women.

Although the HRT women had higher estradiol and estrone levels than the non-HRT women, adjusting the GH concentrations for these hormonal differences did not alter the reported findings between groups.

**Comparison between black and white women**

Comparison of the white women (non-HRT) with the black women revealed no differences in the mean 4-h GH concentrations between groups either at rest or in response to exercise (white rest, 0.7±0.3 μg·l⁻¹; white exercise, 1.0±0.2 μg·l⁻¹; black rest, 0.8±0.2 μg·l⁻¹; black exercise, 1.0±0.3 μg·l⁻¹; \(\eta = 0.03\)), or in the pattern of response (Fig. 1). With exercise both groups had a similar peak height (white, 4.7±1.3 μg·l⁻¹; black, 4.5±1.3 μg·l⁻¹; \(\eta = 0.098\)). No group differences were observed in the integrated GH concentrations at rest or in response to exercise (Fig. 2, bottom panel; \(\eta = 0.087\)), nor were there differences in the incremental response \((P = \text{not significant}; \eta = 0.05)\).

Neither the estrone or estradiol levels were significantly different between the black and white women. The estrone and estradiol levels were 23 and 65% higher, respectively, in the black women than in the white women; however, these differences were not statistically different (Table 1). Adjusting the GH concentrations for estrone levels, estradiol levels, total
Table 2 Comparison of deconvolution GH variables for the HRT and non-HRT women, as well as comparison between non-HRT, white women and black women.

<table>
<thead>
<tr>
<th>Variable</th>
<th>White, HRT</th>
<th>White, non-HRT</th>
<th>Black, no HRT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control day Exercise day</td>
<td>Control day Exercise day</td>
<td>Control day Exercise day</td>
</tr>
<tr>
<td>Basal GH secretion rate (min•μg·l⁻¹)</td>
<td>0.016±0.005* 0.013±0.002</td>
<td>0.008±0.005 0.003±0.002</td>
<td>0.006±0.002 0.006±0.002</td>
</tr>
<tr>
<td>GH secretory pulse half-duration (min)</td>
<td>24.3±6.6 19.8±4.7</td>
<td>20.0±6.0 13.5±4.3§</td>
<td>26.8±6.5 10.7±2.4‡</td>
</tr>
<tr>
<td>GH half-life (min)</td>
<td>14.7±2.3 16.4±1.7</td>
<td>16.5±2.1 19.4±1.6</td>
<td>21.8±3.9 18.6±1.4</td>
</tr>
<tr>
<td>GH secretory pulses per 4 h</td>
<td>2.0±0.6 1.6±0.4</td>
<td>1.8±0.5 2.3±0.3</td>
<td>2.0±0.4 2.0±0.3</td>
</tr>
<tr>
<td>Mass of GH secreted/pulse (μg·l⁻¹)</td>
<td>17.1±7.7* 22.7±5.1*</td>
<td>4.2±7.2 3.3±4.6</td>
<td>2.5±1.2 4.8±2.0</td>
</tr>
<tr>
<td>GH pulse amplitude (min•μg·l⁻¹)</td>
<td>0.48±0.14* 1.89±0.49*</td>
<td>0.25±0.13 0.26±0.44‡</td>
<td>0.16±0.7 5.3±3.8‡</td>
</tr>
<tr>
<td>Pulsatile GH production rate (μg·h·l⁻¹)</td>
<td>22.2±7.6* 27.0±4.3</td>
<td>6.3±6.9 7.2±4.0</td>
<td>4.0±1.7 6.3±2.3</td>
</tr>
</tbody>
</table>

Means±S.E. are shown; n = 6 white, HRT, n = 7 white, non-HRT, n = 7 black, non-HRT. *P < 0.01 between HRT and non-HRT women; †P < 0.05 between HRT and non-HRT women; ‡P < 0.05 from rest to exercise in the black, non-HRT and white, non-HRT women.

abdominal fat or fat mass did not result in any racial differences. In the sample of black and white women, we observed no significant correlation between the mean resting GH concentration or the GH area under the curve and any of the measures of abdominal fat (data not shown).

The deconvolution analysis revealed no differences in the GH secretory pulse characteristics between groups (Table 2). Both the black and white women had a similar basal secretion, production rates, pulse amplitudes and secretory half-duration. A significant decrease in the GH secretory half-duration and pulse amplitude was observed in both groups between the control and exercise day.

Discussion

This study examined whether HRT affects the GH response to exercise in postmenopausal women, and whether racial differences existed in the exercise responses. This is the first study to demonstrate that during exercise differences exist in the pulsatile GH release between women using HRT and those women who do not. The women using HRT had a greater basal GH secretion in response to exercise and the women on HRT had greater increment of GH than non-HRT women. These differences in GH secretion with HRT use are in agreement with earlier studies (2, 6) examining 24-h GH secretion under resting conditions only. We have also demonstrated that no racial differences in GH secretory variables were observed at rest or in response to exercise.

Effects of HRT

Differences in estradiol levels have been shown to account for differences in 24-h GH release (18). Likewise, in the present study in the non-HRT women, we observed a lower resting GH secretory half-duration (18%), pulse mass (75%), pulse amplitude (52%) and GH-production rate (72%) than the HRT women. Both at rest and during exercise, the higher GH area under the curve and calculated GH-production rate in women on HRT reflected a greater mean mass of GH secreted per burst compared with the non-HRT women. In response to exercise the women on HRT had almost a 4-fold greater GH level, which could be explained by the substantially greater pulse mass (83%) than found in the women not on HRT. The higher GH secretion in the HRT users is consistent with earlier findings. Friend et al. (4) reported that at rest both oral and transdermal estrogen supplementations increased GH concentrations in postmenopausal women and this increase was due to larger GH pulses and higher basal GH levels. Similarly there was no difference in pulse frequency.

The regulatory augmentation mechanism of estrogen on GH secretion is not clear. Veldhuis and colleagues (19–21) postulate that estrogen facilitates the upstroke and IGF-I enforces the downstroke of high-amplitude GH secretory bursts in estrogen-replete individuals. IGF-I can exert autoinhibitory effects on both the hypothalamus and pituitary gland (5). Whether estrogen facilitates hypothalamic secretion of GH-releasing hormone is not clear, but estrogen’s stimulation of more irregular GH release may reflect its ability to mute GH autonegative feedback and/or reduce IGF-I negative feedback (5). Thus during exercise this mechanism may be enhanced in estrogen-replete individuals. We found lower, but not significantly lower, IGF levels, which supports the previous studies that attenuated IGF-I levels decrease the negative feedback.

Effects of race on GH concentrations

Our data add to the limited research available concerning racial differences in GH levels. Wright and colleagues (7) demonstrated that there was a greater 24-h GH secretion in black men than in white men, and hypothesized that the higher circulating
17β-estradiol levels in black men may contribute to the higher GH secretion. Subsequent research by this group (8) reported no differences in 17β-estradiol levels and a lack of racial difference in GH secretion between black and white premenopausal women. Recently, however, Manson and colleagues (22) observed that perimenopausal black women have low β-estradiol, leading to the speculation that GH levels may vary between black and white postmenopausal women. There has been no prior research examining whether there are racial differences in response to a profound, physiologically relevant stimulus. We found higher estradiol levels in the black women and adjusting for the difference in fat mass did not alter our findings. These higher estradiol levels appeared to have little impact on resting GH levels, which is consistent with previous findings in premenopausal women (8). Using moderate intensity submaximal exercise, we clearly demonstrated that there were no racial differences in the GH response. Both groups demonstrated an increase in GH concentrations that followed a similar time frame as well as similar changes in secretory variables. Although we found no differences between black and white women, there may be racial differences in the GH response during the evening hours when the most spontaneous GH bursts are typically observed, and the estradiol levels may have a greater impact on these levels. This study provides preliminary data for future research.

These data add to the aging literature by showing that 30 min of moderately intense exercise does modify GH levels. Earlier work (23, 24) has demonstrated that GH secretion increased during either short-duration maximal or prolonged submaximal exercise, but was significantly blunted in older men in comparison with their younger counterparts. Likewise we revealed that 30 min of exercise results in a significant increase in GH levels in postmenopausal black and white women, but compared with 20 min of submaximal exercise in younger premenopausal women this response is substantially lower than what we have reported previously (25). Although exercise appears to result in a significant increase in GH levels, it should be noted that 25% of the women had less than a 25% increase in the integrated GH concentrations over the resting day regardless of race or HRT use. This lack of response with aging has been attributed primarily to alterations in hypothalamic control of GH release, with a decreased nocturnal GH pulse amplitude (26) as well as an age-related increase in somatostatin (27).

There are important experimental considerations regarding the present study that should be acknowledged. There is a large inter-individual variability when working with humans and frequently there is the constraint of having a small sample size. We calculated the effect size to estimate the risk of type II errors. Overall the effect sizes were low, indicating that a substantially greater number of subjects would have been needed to distinguish significant differences, providing evidence that we most likely did not compromise our findings. Additionally, the level of fitness and body composition could have affected the results when comparing the black and white women, but our ANCOVA did not reveal any differences in the GH or estradiol levels. In men, it has been shown that age and physical fitness are more important than body fat when looking at the exercise-induced GH secretion (28). Although we had differences in the fitness levels between groups, these differences were not dramatically different, and thus probably had only minimal impact on our findings. Likewise the estradiol and estrone levels had no impact on our findings, lending support to the findings of Holt et al. (28) that age may be more important in determining the GH response in these women. Further, the estradiol and estrone levels may have been affected by sex hormone-binding globulin; we did not measure this and in itself this may have affected how the estrogens can alter the hypothalamic-pituitary axis. Likewise the IGF-I levels were not substantially higher in the women on HRT, as would be expected, but it is possible that IGF-binding protein 3 or IGF-I proteolysis is different in these women, resulting in a different IGF-I bioavailability, which may affect the axis. Since these binding globulins were not measured, we can only speculate that they may have affected the circulating levels of estrogens.

In conclusion, the present study demonstrates that HRT use results in a greater incremental GH response to exercise compared with non-HRT users, and this response is due to changes in the secretory pulse characteristics in the HRT users. Also, no racial differences in GH levels exist at rest and in response to exercise in the morning hours. This study demonstrates that there is a clinical advantage to using HRT in increasing exercise GH levels compared with non-HRT users and this may provide protection from other age-related health changes.

Acknowledgements

This project was funded in part by the National Institute of Aging 1RO3AG16370-01.

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