Hormone Replacement Therapy Does Not Augment Gains in Muscle Strength or Fat-free Mass in Response to Weight-Bearing Exercise

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Lower extremity strength and fat-free mass were examined in 58 postmenopausal women aged 60–72 yr. Subjects were studied before and after an 11-mo control period (n = 16) or before and after an 11-mo weight-bearing exercise training program designed to generate relatively high ground reaction forces (n = 42). Twenty-two of the exercisers initiated hormone replacement therapy (HRT) at the outset of exercise and continued HRT for 11 mo. Hip extension and abduction strength were assessed using a hand-held dynamometer. Force production during knee extension and flexion was evaluated on an isokinetic dynamometer at 60, 90, and 180°/s. Simultaneous knee and hip extension strength was also assessed on a leg press machine. Total body and lower extremity fat-free mass were determined using dual-energy x-ray absorptiometry. There were no significant changes in muscle strength or body composition in control subjects. Both exercise groups had significant increases in fat-free mass and in all strength measures. Fat-free mass increased from 38.8 ± 4.3 to 39.7 ± 4.3 kg in the exercise group and from 37.7 ± 3.9 to 38.9 ± 4.6 kg in the exercise-plus-HRT group. The average relative increase in strength was 16.2 ± 11.0% in the exercise group and 17.0 ± 13.0% in the exercise-plus-HRT group. Women receiving HRT did not have a gain in fat-free mass or in strength over and above that demonstrated by the women not on HRT. Our results provide evidence that HRT does not augment the increases in muscle mass or strength that occur in response to weight-bearing exercise in older women.

E STROGEN receptors were identified on skeletal muscle membrane several decades ago (Dube et al., 1975; Vanbrocklin et al., 1992), but the role of estrogen in the regulation of muscle metabolism and/or maintenance of muscle mass remains unclear. Estrogen has been reported to stimulate muscle growth in developing sheep and cattle (Trenkle, 1976) and to hinder the growth of skeletal muscle in developing rodents (Ishmelandu, 1980, 1981; Suzuki and Yamamuro, 1985). In women, estrogen has been reported to promote or enhance muscle strength (Cauley et al., 1987; Phillips et al., 1993; Sarwar et al., 1995) and to have no effect on muscle mass or strength (Petrofsky et al., 1976; Seeley et al., 1995). For example, Phillips et al. (1993) found that sex hormone-deficient women had less specific strength (force/muscle cross-sectional area) in the adductor pollicis muscle than age-matched women who were receiving hormone replacement therapy (HRT). In contrast, Seeley et al. (1995) found that postmenopausal women currently using estrogen and age-matched women who had never used estrogen were similar in strength, had the same incidence of falls, and performed comparably on physical performance measures.

The decline in strength in older women has been associated with an increased incidence of falling (Whipple et al., 1987), loss of functional capacity (Bassey et al., 1992), and the need for nursing home placement (Guralnik et al., 1994). Given the importance of strength in older women and the paucity of information concerning the relationship of sex hormones, muscle mass, and strength, it was the purpose of this investigation to examine the effects of exercise training, alone and in combination with HRT, on muscle strength and fat-free mass in postmenopausal women. The primary objective was to determine if gains in strength and fat-free mass in response to exercise training are augmented in women who also initiate HRT.

METHODS

Subjects. — Fifty-eight women between the ages of 60 and 72 years were studied: controls (CON, n = 16), exercise subjects (EX, n = 20), and exercisers who initiated HRT (EX + HRT, n = 22). Control subjects were individuals interested in and eligible for participation in the supervised exercise training program but unable to do so because of time constraints, travel distance, etc. All subjects were nonsmokers, in good general health, and free of orthopedic problems that would interfere with testing and exercise training. All subjects were eligible for HRT (i.e., no contraindications), but initiation of HRT was by choice of the individual.

Volunteers were examined by a physician and underwent an exercise stress test with blood pressure and electrocardiogram monitoring using the Bruce protocol. Additional screening tests included a medical history, chest x-ray, and blood and urine chemicals, which were performed using standard automated laboratory techniques. Subjects were excluded from the study if they had any medical problems that could contraindicate exercise, interfere with performance of vigorous exercise, or interfere with interpretation of results. The study was thoroughly explained to all subjects, who subsequently gave written consent to participate. All protocols were approved by the Human Studies Committee of Washington University.
Exercise training. — The first 2 months of the exercise program were spent performing exercises designed to enhance flexibility, balance, reaction time, and, to a modest degree, strength. These exercises were intended to counteract some of the age-related decline associated with an inactive lifestyle and to prepare subjects for the subsequent, more vigorous weight-bearing exercise program. The exercises were performed while supine, prone, side lying, sitting, and standing, using body weight, the weight of the extremity, Theraband, and/or gravity as resistance. This exercise program has been described in detail by Brown and Holloszy (1991).

After the initial 2-mo exercise program, participants began a 9-mo weight-bearing exercise training program that consisted of walking, jogging, and stair climbing. This exercise training program was chosen to accomplish multiple exercise-related goals, one of which was the enhancement of bone mass (Kohrt et al., 1995) through the generation of relatively high ground reaction forces. The initial goal was to walk for 30 min (excluding warm-up and cooldown) at an intensity of 60–70% of maximal heart rate. All participants met this goal within 4 weeks. Thereafter, the rates at which exercise intensity and duration were increased were determined by measured improvements in \( V_{O2\text{max}} \) (measured every 3 mo) and by the ability of the individual to tolerate the prescription in terms of fatigue and musculoskeletal symptoms. At the beginning of the third month, stair climbing and/or jogging were incorporated into the exercise program. Intensity was determined by comparing the exercise session heart rate with the individual’s heart rate maximum. Throughout the endurance training program, stretching was performed at least twice daily as exercise intensity and duration were increased during the first 3 mo was strongly encouraged. Subjects were required to attend a minimum of three exercise sessions/wk but were encouraged to attend five sessions/wk.

Maximal aerobic power (\( V_{O2\text{max}} \)) was assessed in exercising subjects before and after the 2-mo exercise program and at 3-mo intervals thereafter; controls were assessed at 3-mo intervals. \( V_{O2\text{max}} \) was tested isometrically using a hand-held Micro-Fet dynamometer (Hoggan Health Industries, Draper, UT). To test the hip extensors, subjects were placed prone on an unpadded plinth. The hip was brought actively into full extension while the knee was held in slight flexion (~20°). The dynamometer was placed on the posterior thigh, just above the popliteal fossa. Subjects held the extended hip posture (break test) while the tester pushed the thigh into flexion. Three maximal efforts were performed, and the highest two values were averaged. For the hip abductors, subjects were side-lying and the tester positioned the hip in neutral or a few degrees of extension, ~20° of abduction, and ~5° of external rotation. The knee was positioned in ~45° of flexion. The dynamometer was placed on the lateral thigh, ~2 in above the femoral epicondyle, and the tester attempted to break the hold of the subject by pressing the thigh down toward the horizontal resting surface. When muscle substitution was apparent, such as moving the thigh out of the desired position, the trial was disregarded. Rests of 30–60 s were given between trials. Three to 5 trials were performed, and the highest two values were used in the data analysis. Although bilateral strength assessments were made, data are presented for the right lower extremity only as there were no side-to-side differences.

For assessment of the hip extensors and abductors, women were seated on a Cybex II isokinetic dynamometer (Cybex, Ronkonkoma, NY), which fully supported the back and positioned the hip at 90°. Velcro straps were tightened across the pelvis and thigh to maintain the test position. The arm of the dynamometer was positioned as closely to the anatomical axis of the knee as possible. The leg was then secured to the movement arm of the dynamometer using Velcro straps placed just above the ankle. After four to five practice efforts at 60%/s, the subject was asked to move the dynamometer as quickly and forcefully as possible at angular velocities of 60, 90, and 180%/s. Three or four maximal efforts were performed at each speed, and the two highest efforts were recorded. Two to 3 min of rest were given between bouts. The dam setting on the dynamometer was kept at 2 for all speeds tested. Torque data for the knee flexors and extensors are presented as absolute values and were not gravity-compensated. Simultaneous hip and knee extension were also assessed using a Nautilus leg press machine (Nautilus, Huntersville, NC). The machine was adjusted to the appropriate seat height for each individual. A seat belt was applied, both feet were placed on the leg press plate, and subjects pushed the plate until the knees were fully extended. The maximal number of plates that each woman could press once (one repetition maximum) was recorded.

Hormone replacement therapy. — HRT consisted of continuous conjugated estrogens (Wyeth–Ayerst Laboratories, Philadelphia), 0.625 mg/d, and trimonthly medroxyprogesterone acetate (The Upjohn Company, Kalamazoo, MI), 5 mg/d for 13 days. The duration of HRT was 11 mo and was concurrent with the 11-mo exercise program. Twenty of the participants had used estrogen previously, for an average duration of 6.3 ± 6.0 yr. None had used estrogen for at least 1 year, and the average duration since previous use was 9.8 ± 7.6 yr.

Strength testing. — Muscle strength measures were taken for the hip extensors and abductors and knee flexors and extensors. These muscles were chosen because of their importance in functional activities such as walking, stair climbing, and rising from a seated position. Hip musculature was tested isometrically using a hand-held Micro-Fet dynamometer (Hoggan Health Industries, Draper, UT). To test the hip extensors, subjects were placed prone on an unpadded plinth. The hip was brought actively into full extension while the knee was held in slight flexion (~20°). The dynamometer was placed on the posterior thigh, just above the popliteal fossa. Subjects held the extended hip posture (break test) while the tester pushed the thigh into flexion. Three maximal efforts were performed, and the highest two values were averaged. For the hip abductors, subjects were side-lying and the tester positioned the hip in neutral or a few degrees of extension, ~20° of abduction, and ~5° of external rotation. The knee was positioned in ~45° of flexion. The dynamometer was placed on the lateral thigh, ~2 in above the femoral epicondyle, and the tester attempted to break the hold of the subject by pressing the thigh down toward the horizontal resting surface. When muscle substitution was apparent, such as moving the thigh out of the desired position, the trial was disregarded. Rests of 30–60 s were given between trials. Three to 5 trials were performed, and the highest two values were used in the data analysis. Although bilateral strength assessments were made, data are presented for the right lower extremity only as there were no side-to-side differences.

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Test-retest reliability (intraclass correlation or ICC) was established for some of the strength measures on 17 women.
tested 1–2 wk apart. For hip extension, the ICC was \( r = .89 \) and for hip abduction the ICC was \( r = .86 \). Test-retest ICCs were \( r = .96 \) for the knee extensors (\( n = 10 \)) and \( r = .87 \) for the knee flexors on the Cybex at 60°/s.

**Body composition.** — Total body dual-energy x-ray absorptiometry (DXA) was used to assess changes in body composition over 11 mo, using version 5.64 of the enhanced whole body software (Kohrt et al., 1995). Lower extremity soft lean mass was determined by subtracting bone mineral content from total lower extremity fat-free mass. Coefficients of variation (CVs) for the assessment of body composition by DXA were established by assessing 13 women, aged 60–74 yr, on three occasions at 1-wk intervals. The CVs for body weight, fat-free mass, fat mass, and percent body fat were 0.9 ± 0.4%, 1.9 ± 0.9%, 1.4 ± 1.1%, and 1.7 ± 1.1%, respectively.

**Statistical analyses.** — Individual changes in strength and body composition over the treatment/observation period were determined by subtracting baseline measures from those obtained at the completion of the study. Within each treatment group, changes were evaluated to determine if they were statistically different from zero. One-way analyses of variance, in conjunction with the Duncan post-hoc test, were used to determine if there were significant differences among the groups in baseline measures and in changes over the treatment/observation period. Data are presented as mean ± SD, and the level of significance was \( p < .05 \).

In previous studies of older women (Brown and Holloszy, 1991), we have found that changes in isokinetic strength in control subjects averaged 0 ± 10 nm at speeds of 0, 60, 120, and 300°/s. Based on this, the power to detect differences among the groups of 10 nm in isokinetic strength in the EX and EX + HRT groups was exercising 3.1 ± 1.0 vs 3.2 ± 1.3 d/wk for 49 ± 9 vs 47 ± 8 min/d at an intensity of 79 ± 10% vs 82 ± 4% of maximal heart rate; caloric expenditure was 1171 ± 497 vs 1215 ± 787 kcal/wk.

There were no significant differences among the groups in age, body composition, or \( \text{VO}_2\text{max} \) at the beginning of the study (Table 1). Both the EX and EX + HRT groups had significant increases in \( \text{VO}_2\text{max} \) and fat-free mass and decreases in fat mass in response to exercise training (all \( p < .01 \)); there was no apparent effect of HRT on these responses. There were no changes in body composition or \( \text{VO}_2\text{max} \) in control subjects.

There were no significant differences among the groups in measures of strength at the beginning of the study. Both exercise groups had significant increases in all measures of isometric, concentric, and isokinetic strength following the exercise program (Table 2). The increases were significantly different from changes in the control group for all strength measures except for hip abduction. However, women in the EX + HRT group did not experience a gain in strength over and above that demonstrated by the women who were not on HRT. When the percent improvement in all strength measures was averaged, there was an increase of 16.2 ± 11.0% in response to exercise and 17.0 ± 13.0% in response to EX + HRT. Because the increases in strength and lower extremity soft lean mass (lean mass minus bone mineral) were comparable for both exercise groups, strength measures relative to lean mass were comparable. Strength was unchanged in the controls (1.3 ± 9.7%).

**DISCUSSION**

As expected, the exercise program resulted in significant gains in strength, a finding consistent with previous results from this laboratory (Brown and Holloszy, 1991, 1993). The major observation of note in the current investigation is that, under the conditions of study, HRT did not augment the gains in muscle strength beyond those that occurred in response to exercise alone.

There is evidence that menopause is associated with an accelerated loss of muscle mass. Aloia et al. (1991) measured total body potassium levels in 304 women aged 20–80 yr, and they found that the rate of potassium loss was –0.2 mmol/yr and –8.4 mmol/yr in pre- and postmenopausal women, respectively. From these data, it is not possible to

<table>
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<tr>
<th>Table 1. Subject Characteristics</th>
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<tr>
<td><strong>Age (yr)</strong></td>
</tr>
<tr>
<td>Initial</td>
</tr>
<tr>
<td>Final</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
</tr>
<tr>
<td><strong>Fat-free mass (kg)</strong></td>
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<tr>
<td><strong>Soft LE lean mass (kg)</strong></td>
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<tr>
<td><strong>Fat mass (kg)</strong></td>
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<tr>
<td><strong>VO\text{max} (mL/kg/min)</strong></td>
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*Notes: Change from initial to final different from controls, \( *p < .01 \), \( **p < .001 \); values are means ± SD.

*Soft lower extremity lean mass (lean leg mass minus bone mineral).
determine if the faster rate of potassium loss in the older women was a menopause- or an age-related event. However, Wang and colleagues (1995) found that lean body mass was significantly and inversely related to years since menopause, but not to age, in 373 postmenopausal women, aged 49–60 yr. Furthermore, Poehlman et al. (1995) found that the decline in lean body mass over a 6-yr period was significantly greater in women who became postmenopausal (−3.0 ± 1.1 kg) than in age-matched women who remained premenopausal (−0.5 ± 0.5 kg). Although these data suggest that there is an accelerated loss of muscle mass at the time of the menopause, the mechanism is unknown.

Also unclear is whether HRT can prevent or attenuate the menopause-related loss of nonbone lean tissue. Haarbo et al. (1991) reported a tendency for fat-free mass to be maintained in women after 2 yr of HRT (−0.01 ± 0.30) when compared with changes in women not on HRT (−0.64 ± 0.40 kg). Conversely, Aloia et al. (1995) found that the rapid loss of lean mass in early postmenopausal women was not prevented by HRT. In the present study, there was an increase in fat-free mass in response to exercise plus HRT, but this was not significantly greater than the increase that occurred in response to exercise alone.

It is possible that estrogen affects muscle function independently of changes in muscle mass. In support of this, Sarwar et al. (1995) found isometric quadriceps strength to vary with the monthly estrous cycle in 10 women between the ages of 19 and 24 yr. Quadriceps strength was significantly higher during the ovulatory phase when estrogen levels were relatively high than during the early and mid-follicular phases when estrogen levels were lower. Women in this same study who were taking oral contraceptives did not show monthly variations in strength. Additional support for an effect of estrogen on muscle function comes from the study by Phillips et al. (1993), who measured specific muscle force (force per cross-sectional area) of the adductor pollicis muscle in men, premenopausal women, and postmenopausal women who were or were not on HRT. Their cross-sectional data suggested that muscle-specific force was similar in young men and women, and that muscle specific force was maintained in men until the age of ~60 yr, after which it declined. However, in women there was a marked reduction in muscle-specific force after the age of 45 yr that appeared to be prevented in women receiving HRT. Mechanisms underlying the hypothesized estrogen effects have not been elucidated.

Not all investigators have found beneficial effects of estrogen on muscle function. Cauley et al. (1987) measured grip strength in 310 postmenopausal women, 55 of whom were on estrogen replacement therapy. Although grip strength was significantly higher in women using estrogen than in those not on estrogen, this effect was not independent of differences between the groups in such factors as age, body size, and physical activity. In a study involving 9,704 women aged 65 yr and older, Seeley et al. (1995) compared muscle strength, the incidence of falls, and other functional measures in current users of estrogen, former users of estrogen, and women who never used estrogen. After controlling for a number of factors that might have affected the outcome measures, these investigators found no evidence that estrogen plays a role in preserving muscle strength or function in older women. Results of the present study further suggest that increases in muscle strength in response to weight-bearing exercise are not augmented by HRT.

In summary, there were no apparent effects of HRT on gains in muscle strength in older postmenopausal women, as similar improvements occurred in response to weight-bearing exercise alone and exercise plus HRT. HRT also had no apparent effect on the small, but significant, increase in fat-free mass that occurred in response to weight-bearing exercise training. However, it should be noted that previous studies (Brown and Holloszy, 1991, 1993) that utilized a similar exercise training regimen as the present study found that most of the gains in muscle strength occurred in the first 3 mo of training, despite progressive increments in exercise duration and intensity. This suggests that the increases in strength were probably not mediated by muscle hypertrophy. The results of the current study do not rule out a possible role of estrogen in the hypertrophic response of skeletal muscle to an exercise training program specifically designed to induce muscle hypertrophy (i.e., high intensity resistance training).

### Table 2. Maximal Force and Torque Values

<table>
<thead>
<tr>
<th>Muscle Action</th>
<th>Control</th>
<th>Exercise</th>
<th>EX + HRT</th>
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<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Final</td>
<td>Initial</td>
</tr>
<tr>
<td>Leg press (n)</td>
<td>384 ± 80</td>
<td>381 ± 79</td>
<td>389 ± 60</td>
</tr>
<tr>
<td>Hip extension (n)</td>
<td>156 ± 38</td>
<td>154 ± 40</td>
<td>180 ± 51</td>
</tr>
<tr>
<td>Hip abduction (n)</td>
<td>227 ± 65</td>
<td>219 ± 36</td>
<td>263 ± 57</td>
</tr>
<tr>
<td>Knee extension (nm)</td>
<td>60%</td>
<td>90 ± 21</td>
<td>95 ± 16</td>
</tr>
<tr>
<td></td>
<td>90%</td>
<td>80 ± 17</td>
<td>85 ± 15</td>
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<tr>
<td></td>
<td>180%</td>
<td>59 ± 14</td>
<td>61 ± 11</td>
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<tr>
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<td>60%</td>
<td>62 ± 15</td>
<td>64 ± 10</td>
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<tr>
<td></td>
<td>90%</td>
<td>58 ± 11</td>
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Notes: Change from initial to final different from controls, *p < .05; values are means ± SD.
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