HRT preserves increases in bone mineral density and reductions in body fat after a supervised exercise program

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Kohrt, Wendy M., Ali A. Ehsani, and Stanley J. Birge, Jr. HRT preserves increases in bone mineral density and reductions in body fat after a supervised exercise program. J. Appl. Physiol. 84(5): 1506–1512, 1998.—The aims of this study were to confirm our previous finding that hormone-replacement therapy (HRT) augments exercise-induced increases in bone mineral density (BMD) in older women and to determine whether HRT preserves the adaptations when exercise is reduced or discontinued. The study included an 11-mo treatment phase and a 6-mo follow-up phase. Participants, aged 66 ± 3 yr, were assigned to control (Con; n = 10), exercise (Ex; n = 18), HRT (n = 10), and Ex+HRT (n = 16) groups. HRT was continued during the follow-up. After the treatment phase, changes in total body BMD were −0.5 ± 1.7, 1.5 ± 1.4, 1.2 ± 0.8, and 2.7 ± 1.2% in Con, Ex, HRT, and Ex+HRT, respectively. Ex+HRT was more effective than HRT in increasing BMD of the total body and tended (P = 0.08) to be more effective at the lumbar spine. Ex+HRT was more effective than Ex in increasing BMD of the total body, lumbar spine, and trochanter. Exercise-induced gains in BMD were preserved during the follow-up only in those individuals on HRT. HRT also attenuated fat accumulation, particularly in the abdominal region, after the exercise program. These findings suggest that HRT is an important adjunct to exercise for the prevention not only of osteoporosis but also of diseases related to abdominal obesity.

EXERCISE TRAINING has been shown to result in increased bone mineral density (BMD) in older women (7, 15, 16, 18), but little is known regarding the extent to which the adaptation persists when exercise is reduced or discontinued. In postmenopausal women who increased lumbar spine BMD by ~6% in response to a weight-bearing exercise program, there were little or no residual effects of exercise on bone mass 13 mo after the completion of the training program (7). The increase in BMD in response to exercise training in postmenopausal women appears to be brought about through a suppression of bone resorption (16, 18). It therefore seems likely that the reduction in BMD that occurs when exercise is reduced or discontinued is due to an acceleration of bone resorption and that use of an antiresorptive agent, such as estrogen, may help to preserve exercise-induced gains in BMD.

The aims of the present study were to confirm our previous finding in a small group of postmenopausal women that weight-bearing exercise and hormone-replacement therapy (HRT) result in independent and additive increases in BMD at some skeletal sites (18) and to determine whether HRT helps to preserve exercise-induced gains in BMD when the exercise is reduced or discontinued. Changes in BMD were also evaluated in nonexercising women who were or were not on HRT.

METHODS

Subjects

The 54 women who completed the study were nonsmokers, aged 60–72 yr, who had not used estrogen for at least 2 yr and did not participate in regular exercise. Volunteers were assigned to the following treatment groups: control (n = 10), exercise (n = 18), HRT (n = 10), and exercise+HRT (n = 16). Random assignment to treatment arms was not performed because the exercise training sessions had to be coordinated with other exercise studies being conducted within our division; the number of exercisers that could be accommodated at any point in time was limited by availability of equipment and personnel. Decisions made by members of the research team regarding group assignment were based on the intent to try to match the study groups on the basis of body weight because it is an important determinant of skeletal loading. Importantly, to minimize the limitations imposed by nonrandom assignment to treatment arms, all participants were willing and able to participate in an exercise program and to go on HRT, and all met the inclusion criteria for the study.

Data from five participants in each of the exercise groups were included in a previous report on the effects of exercise and HRT on BMD (18). Data from nine participants in each of the exercise groups and from five nonexercising subjects were included in a previous paper on the effects of exercise and HRT on muscle strength and fat-free mass (6). All of the participants provided written informed consent to participate in the study, which was approved by the Human Studies Committee.

Screening tests included a medical history, physical examination, chest X-ray, blood and urine chemistries, graded exercise test with monitoring of blood pressure and electrocardiogram, gynecological examination, mammogram, and a 24-h urinary calcium and creatinine evaluation. Volunteers were excluded from participation if they had medical problems that contraindicated HRT or exercise.

The study was composed of two phases: an 11-mo treatment period and a 6-mo follow-up period. Women assigned to the two HRT groups started HRT at the beginning of the treatment period and continued it through the follow-up period. Women assigned to the two exercise groups were required to attend supervised exercise sessions during the treatment period and were encouraged to continue exercising during the follow-up but were left to choose how much exercise they performed.

Diet Evaluation and Calcium Supplementation

Participants completed 7-d food records at the beginning and end of the treatment period and at the end of the follow-up period. A registered dietician instructed the subjects on the procedures for weighing and recording foods in household measures and conducted interviews after food
records were completed to validate their accuracy. Records were analyzed by using Nutritionist IV (N-Squared Computing, Salem, OR). Calcium intake was adjusted to ~1,500 mg/day in all participants after the initial dietary assessment.

HRT

HRT consisted of continuous conjugated estrogens (0.625 mg/day; Wyeth-Ayerst, Philadelphia, PA) and medroxyprogesterone acetate (5 mg/day; Upjohn, Kalamazoo, MI) for 13 consecutive days every third month. In the exercise + HRT group, HRT was initiated at the start of the exercise program.

Exercise Program

The exercise program consisted of 2 mo of flexibility exercise training followed by 9 mo of weight-bearing exercise training. Subjects were required to attend an average of at least three exercise sessions per week. The 2-mo flexibility exercise program included exercises to improve flexibility and range of motion of all major muscle groups and joints, with the intent of reducing the likelihood of injury in the subsequent, more vigorous, weight-bearing exercise program.

The 9-mo weight-bearing exercise program consisted of walking, jogging, and stair climbing/descending. Exercise prescriptions were individualized and updated on a weekly basis. The initial goal for all participants was to walk 30 min at a moderate intensity corresponding to ~70% of maximal heart rate. Thereafter, the rates at which the duration and intensity were increased depended on the extent to which each individual tolerated the exercise. At the beginning of the third month, stairs and jogging were included in the exercise prescriptions. All women jogged at least intermittently (e.g., jog 1 out of every 5 laps) to increase the magnitude of the ground-reaction forces (21).

Maximal Aerobic Power (V\textsubscript{O\textsubscript{2}}\text{max})

V\textsubscript{O\textsubscript{2}}\text{max} was assessed as described previously (17). In all subjects, V\textsubscript{O\textsubscript{2}}\text{max} was assessed before and after the treatment period. In exercising subjects, additional assessments were made at 3-mo intervals during the treatment period and at the end of the follow-up period.

BMD and Body Composition

BMD of the total body, lumbar spine (L\textsubscript{2}–L\textsubscript{4}), and proximal femur (neck, trochanter, Ward's triangle) was measured by dual-energy X-ray absorptiometry (DXA) by using a Hologic QDR-1000/W instrument (Hologic, Waltham, MA). BMD was measured with ~3-mo intervals. Also, a DXA procedure was also used to assess body composition (v5.64, enhanced whole body analysis). Waist circumference was measured in all subjects before and after the treatment period and after the follow-up period in exercising subjects. All measurements were made by the same person at the midpoint of the vertical distance between the top of the iliac crest and the bottom of the rib cage with the subject in a standing position. The intraclass correlation for repeated measures of waist circumference was r = 0.98.

Bone turnover rate was assessed by measuring serum osteocalcin levels before and after the treatment period and at the end of the follow-up period. Blood samples were obtained in the morning after an overnight fast, processed immediately, and stored at ~80°C for subsequent batch analysis by radioimmunoassay (24).

Statistical Analyses

Differences among groups in baseline measurements were evaluated using one-way analyses of variance (ANOVA) and the Student-Newman-Keuls post hoc test. ANOVA was also used to evaluate changes in outcome variables from baseline to the end of the treatment period and to the end of the follow-up period. These analyses included contrast statements to determine whether differences between the following groups were significant: 1) exercise vs. control, 2) HRT vs. control, 3) exercise + HRT vs. exercise, and 4) exercise + HRT vs. HRT. Statistical significance was defined as an alpha level ≤0.05, and all data are reported as means ± SD.

RESULTS

Baseline

There were no significant differences among the groups at baseline in parameters of interest with the exception of total body BMD, which was higher in the exercise-only group than in controls (Table 1). There were no significant differences among the groups in calcium intake, energy intake, or the composition of the diet. Total energy intake averaged 1,128 ± 676, 957 ± 281, 1,077 ± 300, and 847 ± 293 mg/day in the control, exercise, HRT, and exercise + HRT groups, respectively. Total energy intake averaged 1,669 ± 272, 1,784 ± 245, 1,908 ± 340, and 1,769 ± 320 kcal/day in the control, exercise, HRT, and exercise + HRT groups, respectively.

Treatment

Exercise training. The two exercise groups performed a similar amount of exercise. During the weight-bearing exercise program, subjects in the exercise-only group attended 3.3 ± 0.7 sessions/wk and exercised 45 ± 7 min/day at a heart rate of 126 ± 10 beats/min, or 79 ± 6% of maximal heart rate. Subjects in the exercise + HRT group attended 3.3 ± 0.6 sessions/wk and exercised 46 ± 6 min/day at a heart rate of 132 ± 9 beats/min, or 80 ± 5% of maximal heart rate. The exercise energy expenditure averaged 1,013 ± 324 and 997 ± 333 kcal/wk in the exercise and exercise + HRT groups, respectively.

Body composition, energy intake, and V\textsubscript{O\textsubscript{2}}\text{max}. The exercise and exercise + HRT groups had reductions in body weight (~2.3 ± 2.0 and ~2.7 ± 3.9 kg, respectively; both P < 0.01), fat mass, and waist girth and increases in fat-free mass (Fig. 1) and V\textsubscript{O\textsubscript{2}}\text{max} (0.20 ± 0.13 and 0.13 ± 0.18 l/min, respectively; both P < 0.01) during the treatment period. HRT alone had no significant effects on body composition or V\textsubscript{O\textsubscript{2}}\text{max}. There were no significant changes in body composition of control subjects, but there was a decrease in V\textsubscript{O\textsubscript{2}}\text{max} (~0.10 ± 0.13 l/min; P < 0.05). Energy intake was not significantly changed at the end of the treatment period in any of the groups. The average changes in energy intake relative to the baseline assessment were 153 ± 251, −2 ± 242, 1 ± 188, and 22 ± 251 kcal/day in the control, exercise, HRT, and exercise + HRT groups, respectively. Calcium intake during the treatment period
was not significantly different among the groups, averaging 1,226 ± 384, 1,452 ± 178, 1,674 ± 232, and 1,352 ± 210 mg/day in the control, exercise, HRT, and exercise+HRT groups, respectively.

BMD and osteocalcin. Both exercise alone and HRT alone brought about significant increases in BMD of the total body, lumbar spine, and neck and Ward's triangle regions of the proximal femur (Figs. 2–5). There was a significant increase in BMD of the trochanter region of the femur in response to HRT.

The combination of exercise and HRT increased BMD at all sites of interest (Figs. 2–5). Exercise+HRT was more effective than HRT alone in increasing BMD of the total body (P < 0.01) and lumbar spine (P < 0.08) and was more effective than exercise alone in increasing BMD of the total body, lumbar spine, and trochanter.

Serum osteocalcin levels were significantly and similarly reduced in response to HRT alone and exercise+HRT (Fig. 6). There were no significant changes in osteocalcin levels in the control or exercise-only groups.

Follow-up

Exercise training. According to self-reports, participants in the exercise-only group exercised an average of 1.2 ± 1.1 days/wk for 39 ± 11 min/day during the 6-mo follow-up period. Participants in the exercise+HRT group exercised an average of 1.5 ± 1.3 days/wk for 47 ± 8 min/day. Few of the women recorded heart rates from their exercise sessions, but the available data on walking speed suggested that the intensity of exercise during the follow-up was also reduced.

Body composition, energy intake, and \( \text{VO}_{2\max} \). There were no significant changes in calcium intake or total energy intake in any of the groups. As a result of the reduction in training volume, there were partial reversals during the follow-up period of the exercise-induced reductions in body weight, fat mass, and waist girth and increases in \( \text{VO}_{2\max} \) and fat-free mass. In the exercise-only group, the changes in body weight (−0.7 ± 2.1 kg) and composition (Fig. 1) at the end of the follow-up period relative to baseline were no longer significant. In the exercise+HRT group, the reductions in body weight (−2.3 ± 4.1 kg; P < 0.05), fat mass, and waist girth and the increase in fat-free mass (Fig. 1) relative to baseline remained significant after the follow-up period. The small increase in waist circumference that occurred in the exercise+HRT group during the follow-up period was significantly less than the increase that occurred in the exercise-only group. \( \text{VO}_{2\max} \) remained significantly elevated after the follow-up period in the exercise group (0.08 ± 0.13 l/min; P < 0.05) but not in the exercise+HRT group (0.02 ± 0.13 l/min).

BMD and osteocalcin. At the end of the follow-up period, BMD of the total body and lumbar spine remained significantly elevated relative to baseline in the exercise-only group, and the increases in total body and Ward's triangle BMD were significantly different from the reductions that occurred in the control subjects (Figs. 2–5). In the HRT-only and exercise+HRT groups, BMD tended to continue to increase during the follow-up period. Increases in BMD at the end of follow-up in the exercise+HRT group were significantly greater than those in the exercise-only group at all sites except Ward's triangle. Increases in the exercise+HRT group also tended to be larger than in the HRT-only group, but only the increase in total body BMD was significantly larger.

Serum osteocalcin levels remained suppressed in response to HRT to the same extent after follow-up as after the treatment period (Fig. 6). Osteocalcin levels remained unchanged in the exercise-only and control groups.

**DISCUSSION**

The results of this study confirmed previous findings that the combination of weight-bearing exercise and...
HRT was more effective than either exercise alone (18) or HRT alone (18, 22) in increasing BMD of the total body and lumbar spine. An important new finding was that HRT preserved gains in BMD when the exercise was reduced or discontinued. In women who exercised but were not on HRT, 60–93% of the exercise-induced gains in BMD of the total body, lumbar spine, and Ward's triangle were retained 6 mo after the exercise. Nearly the entire exercise-induced increase in BMD of the femoral neck was lost during the follow-up period. In contrast, BMD values at all sites remained the same or continued to increase during the follow-up period in women who exercised and were on HRT.

Studies in animals and humans suggest that the magnitude of mechanical loading forces is an important determinant of the osteogenic response (15, 27, 28). This was supported in the present study by the finding of abrupt increases in BMD of the whole body and lumbar spine in women in the exercise+HRT group after the initiation of the more vigorous, weight-bearing exercise portion of the training program (i.e., between the 3- and 6-mo assessments). The fact that this occurred only in women on HRT supports the theory that estrogen potentiates the bone modeling/remodeling responses to a given loading force. It has been suggested that estrogen reduces the degrees of strain necessary to bring about more favorable coupling between the rates of bone resorption and formation in the remodeling process and to induce formation in the bone modeling process (10, 19, 30). According to this hypothesis, the same loading forces would have more favorable effects on the skeleton in the estrogen-sufficient, compared with the estrogen-deficient, state.

The purported effect of estrogen on effective strain thresholds may explain, in part, the trends for BMD values to continue to increase in estrogen-treated women after 17 mo of HRT. As an antiresorptive agent, estrogen would be expected to induce a transient increase in bone mass by suppressing the activation of new bone remodeling units while units activated before estrogen exposure continued to accrue mineral. This...
Bone remodeling transient occurs over one remodeling period, which has a normal average duration of 40 wk (14). Because there is evidence that the duration of the remodeling period is reduced in postmenopausal women with elevated rates of bone turnover (4), it is unlikely that the gains in BMD in estrogen-treated women in the present study were attributable only to the bone remodeling transient. Rather, it seems plausible that estrogen potentiated the osteogenic responses to the mechanical loading forces acting on the skeleton on a day-to-day basis, in both the exercise + HRT and the HRT-only groups. Differences in the net gain in BMD values between these two groups would presumably reflect differences in mechanical loading histories over the duration of the study (i.e., effects of the exercise program).

What remains perplexing is why the potentiating effect of estrogen on exercise-induced gains in BMD would be apparent for the whole body and some regional sites but not for others. Although the loading characteristics of the exercise program were sufficient to induce an increase in BMD of the femoral neck, there was no augmentation of BMD at that site by estrogen in the exercise + HRT group. This was in sharp contrast to the additive effects of exercise and HRT on BMD of the lumbar spine and whole body. One possibility is that, in the estrogen-deficient state, the strains engendered by the exercise program were sufficiently high to have a favorable effect on bone remodeling but not on modeling (10). Presuming that estrogen does indeed act by lowering the strain threshold for modeling, the same strains generated by exercise in the estrogen-replete state could have exceeded the minimal effective strain for modeling at some skeletal sites, thereby resulting in greater gains in BMD at those sites, but not at others. Further studies are clearly necessary to delineate the mechanisms by which exercise and estrogen regulate bone metabolism.

In addition to its well-established effects on bone, estrogen has been suggested to play a role in the regulation of body composition and fat distribution. Results from cross-sectional and prospective studies indicate that menopause is associated with an acceleration of bone loss. However, evidence for the role of estrogen in the regulation of body composition is less compelling. Although estrogen may have effects on body weight and fat distribution, the mechanisms by which it acts are not well understood. Further research is needed to clarify the role of estrogen in the regulation of body composition and fat distribution.
ated loss of fat-free mass (1, 9, 23) and an increase in abdominal adiposity (20, 23). Although HRT alone does not appear to either increase fat-free mass (2, 6, 18) or decrease abdominal adiposity (2) in postmenopausal women, there is evidence that estrogen may prevent or attenuate the accumulation of abdominal fat (11–13, 26).

In the present study, there were significant increases in fat-free mass after 17 mo of HRT in both exercisers and nonexercisers. Because body composition was assessed by DXA, it was not possible to determine whether the increase in fat-free mass was due to an increase in extracellular fluid, skeletal muscle, or other tissues. HRT alone did not cause a decrease in either total or abdominal adiposity. However, there was a tendency for HRT to augment the reduction in fat mass in response to exercise and to attenuate the subsequent gain during the follow-up period. Whereas the exercise-only group gained back 57% of the fat lost during the supervised exercise training program, the exercise+HRT group gained back only 26%. Similarly, the exercise-only group gained back 76% of the exercise-induced reduction in waist circumference, compared with only 14% for the exercise+HRT group. It cannot be ruled out that the differential changes in body composition and fat distribution in the exercise and exercise+HRT groups during the follow-up period were due to differences in the amount of exercise performed. However, this seems unlikely because differences in self-reported measurements of exercise were small and changes in VO₂max were similar in the two groups. The notion that sex hormones independently modulate energy balance is supported by the study by Poehlman and colleagues (23), who found that women progressing through menopause gained more total and abdominal fat and lost more lean body mass over a 6-yr period than did age-matched women who remained premenopausal over the same time period. Others have also shown that the accumulation of abdominal fat in women tends not to occur until after the menopause (8, 29). In this context, it seems plausible that HRT attenuated the accumulation of fat, particularly in the abdominal region, that occurred subsequent to the exercise program in the present study. The mechanisms by which female sex hormones independently modulate energy balance are not clear but appear to be indirect, given the absence of estrogen and progesterone receptors in adipose tissue (5, 25). It has been postulated that estrogens may downregulate androgen receptors, thereby diminishing androgen-related regulation of adipose tissue metabolism, or exert effects on the secretion or activity of other hormones involved in the regulation of fat metabolism (3). Another possibility is that progestins, which interact with the glucocorticoid receptors that are particularly abundant in visceral adipose tissue, protect against the cortisol-induced activation of lipoprotein lipase (3).

In summary, weight-bearing exercise resulted in significant increases in BMD at clinically relevant sites in older postmenopausal women not on HRT, but
adaptations tended to reverse during a 6-mo follow-up period when the amount of exercise performed was reduced. The concomitant use of HRT not only augmented the osteogenic response to exercise but also preserved the gains in BMD after the exercise program. Exercise was also effective in reducing total and abdominal adiposity, and HRT had an attenuating effect on these findings imply that HRT may enhance the beneficial effects of exercise on reducing risk not only for osteoporosis but also for the diseases associated with abdominal obesity, including atherosclerosis, noninsulin-dependent diabetes, and hypertension.

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