The Inability of Hormone Replacement Therapy or Chronic Running to Maintain Bone Mass in Master Athletes

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Background. Previous studies have demonstrated equivocal findings on the effect of chronic running on bone mass in postmenopausal women. The purpose of this study was to determine the effect of chronic running alone and in conjunction with hormone replacement therapy (HRT) on bone mineral density (BMD) in postmenopausal women.

Methods. Forty-three women [15 premenopausal 48.1 ± 4 yrs (Pre); 13 postmenopausal 57.3 ± 2.3 yrs (Post); and 15 HRT-treated postmenopausal 56.8 ± 1.5 yrs (PostE)] served as subjects. All were chronic runners (duration >5 yrs, >10 miles per week). BMD was determined by dual energy x-ray absorptiometry, VO2max on a treadmill, body composition by hydrostatic weighing, knee strength by KinCom dynamometer, and training and menstrual history by questionnaire. Analysis of covariance with Tukey post hoc tests was utilized to compare the groups.

Results. The groups were similar in body weight, VO2max, years training, and miles run per week. Pre and PostE did not differ in total or spine BMD. However, Pre had greater hip BMD than PostE (0.973 ± 0.03 vs. 0.876 ± 0.03 g/cm²; p < 0.05). As well, Pre had greater BMD of the hip (0.973 ± 0.03 vs. 0.805 ± 0.03 g/cm²; p < 0.05), spine (1.047 ± 0.04 vs 0.870 ± 0.04 g/cm²; p < 0.05), and total body (1.115 ± 0.02 vs 0.996 ± 0.03 g/cm²; p < 0.05) than Post.

Conclusions. These results suggest that (a) chronic running + HRT is insufficient to protect hip BMD and (b) chronic running alone provides no protection for bone mass in postmenopausal women.

The early years after menopause are characterized by an accelerated rate of bone turnover resulting in a significant loss of bone. Heaney and colleagues (1) have suggested that 15–20% of the skeleton may be lost by 10 years following menopause. However, treatments exist that have been shown to oppose this accelerated bone loss. It is clear that hormone replacement therapy (HRT) begun at menopause either reduces or abolishes the accelerated bone turnover in most women, maintaining bone density for up to a decade (2). In addition, weight-bearing exercise begun after menopause has been shown to reduce bone loss or even increase bone mass in estrogen-deficient women (3,4). It has also been suggested that estrogen and weight-bearing exercise begun postmenopause have an additive effect in increasing bone mass (5). Thus, it appears that weight-bearing exercise begun following menopause is beneficial to the skeleton either alone or in conjunction with HRT.

However, it is presently unclear how chronic weight-bearing exercise (specifically running) begun prior to menopause affects bone mineral density (BMD), as studies utilizing this population group have been equivocal. Lane and coworkers (6) demonstrated 40% greater bone mineral in the lumbar vertebrae of chronic runners compared to controls. However, these results were based on only six subjects per group. In contrast, Kirk and associates (7) found no difference in bone mass between runners and closely matched controls, whereas Nelson and coworkers (8) found that bone mass was lower in runners compared to slightly heavier sedentary subjects. The latter results suggest that chronic endurance exercise might not be beneficial to bone, and there is evidence that this type of exercise can create an environment that could be harmful to the skeleton (9). Unfortunately, comparisons of chronic exercisers and sedentary subjects can be confounded by body weight, body composition, and hormonal differences related to activity. We have proposed a model that would be useful in determining the effects of chronic running on bone following menopause, utilizing a cross-sectional comparison of premenopausal and postmenopausal master athletes. Use of this sample group reduces the confound of differences in body weight and hormonal status related to chronic endurance training, as all have similar body mass and training background. Utilizing this model, we hypothesized that postmenopausal women runners on HRT would maintain bone mass at levels similar to those in the premenopausal group, but that postmenopausal women runners not on HRT would have significantly lower BMD than either estrogen-replete group. Further, we hypothesized that the rate of bone loss in the postmenopausal, nonestrogen-treated runners—predicted by the expected differences in bone mass between pre- and postmenopausal groups—would differ from those expected in untreated sedentary women, suggesting a protective effect of running exercise despite the absence of estrogen.

Therefore, the purpose of this study was to determine the effect of chronic running exercise alone, and in conjunction with HRT, on BMD in postmenopausal women.

METHODS

Subjects.—Forty-three women [15 premenopausal (Pre); 13 untreated postmenopausal (Post); 15 HRT-treated postmenopausal (PostE)] were studied after giving their informed consent in accordance with the guidelines established by the
Institutional Review Board of the University of Southern California. Subjects were free from diseases known to affect bone, and were similar in caloric and calcium consumption as determined by 3-day dietary records. The Post and PostE women were at least one year postmenopausal, as evidenced by the absence of menstruation in the previous 12 months. All participants were chronically active endurance athletes, running a minimum of 5 years and an average of 24 miles per week, and competing in races at least once per year. General characteristics of the subject groups are given in Table 1.

**Hydrostatic weighing.**—Body composition was estimated by hydrodensitometry. Residual lung volume was determined by the oxygen dilution method of Wilmore at the time of underwater weighing. Underwater weight was measured with a minimum of 3 trials, and the highest value attained was used in the calculations. Body fat was calculated from total body density using the equation of Siri.

**Maximal aerobic capacity.**—A modified Balke protocol was performed on a treadmill to determine each subject’s maximal aerobic capacity (VO2max). After an initial 2 minutes at 2.5 mph and 0% grade, speed and grade were increased by 0.5 mph and 2% at 2-minute stages until the subjects reached volitional fatigue. Volume of expired ventilation was determined by a pneumotach, and expired volume of oxygen (VO2) and carbon dioxide (VCO2) was measured via open-circuit indirect calorimetry using a Parvomedics system (Consentius Technologies, Sandy, Utah). The analyzers were calibrated prior to testing for volume and concentration with known gases. Twelve-lead EKG (Quinton Q750B, Bothell, WA) was monitored throughout exercise, and a board-certified physician of internal medicine was present during the testing.

**Bone densitometry.**—The BMD of the lumbar spine (L1-L4) (SBD) and nondominant proximal femur (HBD), and BMD and bone mineral content (BMC) of the total body (TBD and TBC) were measured by dual energy x-ray absorptiometry (DEXA) using a Hologic QDR-1500 system, software version 7.10 (Hologic, Waltham, MA). Quality control was ensured daily by use of a phantom, and the measurements were maintained within the manufacturer’s precision standards of ≤1.0% for the spine and ≤1.5% for the total hip. Reproducibility, assessed in 10 healthy volunteers, ranged from 0.8–2.0%. Subjects’ z scores (comparison to predicted peak bone mass) and t scores (comparison to age-predicted bone mass) were obtained using normative values provided by the software manufacturer. These scores are ± standard deviations from predicted values, representing a value of zero.

**Muscle strength.**—Isokinetic knee extension strength and isometric knee extension strength of the right knee were assessed using a KinCom dynamometer (Chattecx Corp., Hixson, TN). Strength testing was preceded by the VO2max test in all cases, serving as the warmup. Following adequate recovery, subjects received instruction, including practice efforts, on the test procedures. Three maximal repetitions of each exercise were performed, with 1-minute recovery between repetitions. Isokinetic extension strength was measured concentrically at 60°·s⁻¹ between 15–80° of knee flexion (0° = full extension). Strength is reported as the peak torque achieved in Newton-meters (N·m). Isometric extension strength was measured at 60, 45, and 30° (0° = full extension). The peak torque (in N·m) achieved among the three angles is reported.

**Training history.**—Subjects’ training history was self-reported by questionnaire. Subjects were asked for years of training, miles run per week, training pace, personal best and most recent times for competitions, and a sample training week. Reported values were confirmed by oral interview.

**Menstrual history.**—Subjects completed a menstrual history questionnaire, including age at menarche, current menstrual history, age at menopause (if relevant), and current and past oral contraceptive (OC) and HRT use. Reported values were confirmed by oral interview.

**Statistics.**—Data were analyzed using the Statistical Package for Social Sciences (SPSS) software, version 8.0. Comparisons among the three groups were done by analysis of covariance (ANCOVA), with body weight as the covariate. Follow-up tests were conducted to evaluate pairwise differences among the adjusted means, with Holm’s sequential Bonferroni procedure used to control for Type I error. Independent sample t tests were used to compare the Post and PostE groups on variables unique to those two groups. Pearson correlations were utilized to examine relationships between variables for all groups combined. Significance was predetermined at p < .05.

**RESULTS**

General characteristics of subjects are shown in Table 1. Age did not differ between Post and PostE, whereas Pre was significantly younger than both postmenopausal groups (F = 11.27; p < .05). The groups did not differ in body weight, although Pre was significantly taller (F = 3.13; p < .05), had significantly lower body fat (F = 3.55, p < .05), and significantly greater total lean mass (F = 8.29, p < .05) than Post. Although body weight did not differ statistically, we utilized ANCOVA to control for body weight in comparing the three groups, due to the slightly higher body weight in the Pre group, and the finding of significant correlations between bone mass and body weight (described below). Years of training, miles run per week, and maximal aerobic capacity were not different for the three groups, as shown in Table 2.

Menstrual history data are shown in Table 3. The groups were not different for age at menarche. Ten Pre, 8 PostE, and 6 Post subjects reported previous OC use; years of OC use and years since OC use were not different between the three groups. Years

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**Table 1. Subject Characteristics (Mean ± SEM)**

<table>
<thead>
<tr>
<th></th>
<th>Premenopausal</th>
<th>Postmenopausal + HRT</th>
<th>Postmenopausal</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 15)</td>
<td>(n = 15)</td>
<td>(n = 13)</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>48.1 ± 4.4</td>
<td>56.8 ± 1.5*</td>
<td>57.3 ± 2.3*</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>58.5 ± 1.2</td>
<td>55.1 ± 1.1</td>
<td>55.5 ± 2.1</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165.9 ± 1.5</td>
<td>163.3 ± 1.1</td>
<td>161.1 ± 1.4*</td>
</tr>
<tr>
<td>% Body fat</td>
<td>21.3 ± 1.2</td>
<td>22.3 ± 1.1</td>
<td>26.0 ± 1.6*</td>
</tr>
<tr>
<td>Total lean mass (kg)</td>
<td>46.0 ± 0.9</td>
<td>42.9 ± 0.8</td>
<td>40.5 ± 1.2*</td>
</tr>
</tbody>
</table>

* p < .05, significantly different from Pre.
past menopause did not differ between Post and PostE. However, statistical power for this comparison was inadequate given the wide variance and small number of subjects. For PostE, years past menopause and years on HRT were not significantly different, and only two of the PostE group did not begin HRT immediately at menopause. Two forms of estrogen replacement were used by the subjects in the PostE group. Twelve women took conjugated estrogen, 10 at a dosage of 0.625 mg and 2 at a dosage of 0.3 mg. The remaining 3 women in the PostE group used estradiol at a dosage of 0.05 mg. The HRT utilized by 7 of the PostE group included dosages of progesterone (2.5–5.0 mg).

Data on BMD and BMC are presented in Table 4 and Figure 1. The hip measure reported is the Hologic total hip value. Pre and PostE did not differ significantly for THD, TBG, and SBG. However, Pre had significantly greater HBD than PostE (F = 3.91; p < .05), a difference that equaled 10%. In comparing Pre to Post, Pre had significantly greater values for all BMD and BMC measures (F = 13.31, 8.16, 8.39, and 5.23 respectively for HBD, SBG, TBG, and THD; p < .05). These differences equaled 17%, 17%, 11%, and 16%, respectively. PostE had significantly greater TBG than Post (F = 6.79, p < .05), and approached significance for HBD (p = .06).

In comparison to age-predicted norms (z scores), Pre was 0.5 to 0.75 standard deviations greater than predicted for THD, HBD, and SBG. The BMD values for PostE ranged from 0.1 to 0.5 standard deviations greater than age-predicted, whereas for Post the range was from −0.2 to −0.5 standard deviations less than age-predicted. None of these values differed significantly from the population norms as determined by one-sample t tests.

Strength data are presented in Table 2 and Figure 2. Isokinetic knee extension strength was significantly greater in Pre compared to Post, a difference of 23%. Although not reaching statistical significance, Pre also had 16% greater mean isometric knee extension strength than Post. In contrast, Pre did not differ from PostE in muscle strength, nor did PostE differ from Post.

Pearson correlations revealed significant inverse relationships with age for HBMD (r = −0.30, p < .05), isometric knee extension strength (r = −0.32, p < .05), total lean mass (r = −0.34, p < .05) and maximal aerobic capacity (Absolute: r = −0.49, p < .05; Relative: r = −0.38, p < .05). The relationships between age and BMD are plotted in Figure 3. Age was not related to body weight, and none of the BMD values were related to muscle strength, aerobic fitness, or training history. However, HBD and THD were significantly related to body weight and total lean mass. These relationships are plotted in Figure 4.

**DISCUSSION**

The comparison of BMD in pre-, post-, and postmenopausal estrogen-replete women runners is an important source of informa-

### Table 2. Training and Strength Characteristics of the Subject Groups (Mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>Premenopausal (n = 15)</th>
<th>Postmenopausal + HRT (n = 15)</th>
<th>Postmenopausal (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miles/Week</td>
<td>22.8 ± 3.0</td>
<td>27.3 ± 3.2</td>
<td>21.5 ± 2.8</td>
</tr>
<tr>
<td>Training intensity</td>
<td>10.3 ± 1.0</td>
<td>9.3 ± 0.3</td>
<td>10.3 ± 0.7</td>
</tr>
<tr>
<td>Years training</td>
<td>16.4 ± 2.1</td>
<td>15.4 ± 1.2</td>
<td>15.9 ± 1.7</td>
</tr>
<tr>
<td>VO₂ (L/min)</td>
<td>2.58 ± 0.11</td>
<td>2.47 ± 0.12</td>
<td>2.20 ± 0.13</td>
</tr>
<tr>
<td>VO₂ (ml-kg⁻¹·min⁻¹)</td>
<td>44.2 ± 2.0</td>
<td>45.1 ± 2.4</td>
<td>40.2 ± 2.5</td>
</tr>
<tr>
<td>Isokinetic knee</td>
<td>99.1 ± 5.3</td>
<td>87.8 ± 5.4</td>
<td>76.4 ± 7.5*</td>
</tr>
<tr>
<td>Isometric knee</td>
<td>129.0 ± 6.3</td>
<td>110.1 ± 5.5</td>
<td>109.2 ± 8.3</td>
</tr>
</tbody>
</table>

*p < .05, significantly different from Pre.

### Table 3. Menstrual History of the Subject Groups (Mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>Premenopausal (n = 15)</th>
<th>Postmenopausal + HRT (n = 15)</th>
<th>Postmenopausal (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at menarche (yrs)</td>
<td>13.7 ± 0.4</td>
<td>12.9 ± 0.6</td>
<td>12.7 ± 0.5</td>
</tr>
<tr>
<td>Years past menopause</td>
<td>8.5 ± 1.6</td>
<td>8.3 ± 1.6</td>
<td>12.3 ± 2.6</td>
</tr>
<tr>
<td>Years on HRT</td>
<td>7.6 ± 1.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects reporting</td>
<td>10</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>previous OC use</td>
<td>7.0 ± 2.4</td>
<td>7.6 ± 1.7</td>
<td>6.2 ± 1.8</td>
</tr>
<tr>
<td>Years on OC</td>
<td>19.4 ± 2.6</td>
<td>25.0 ± 5.5</td>
<td>23.1 ± 2.1</td>
</tr>
<tr>
<td>Years since OC</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note: HRT = hormone replacement therapy; OC = oral contraceptive.

Figure 1. Bone mineral density of the hip, spine, and total body by group.
tion regarding the interaction between chronic running and bone. Both body mass (10,11) and aerobic capacity (12) have been shown to predict bone mass in older women. Given the similarity between our groups in these variables, and the chronic nature of the training undertaken by our subjects, we were able to control for the influence of body weight and training history on the determination of how chronic running affects BMD after menopause.

The key finding of this study was that chronic running in the presence of HRT appeared unable to maintain BMD of the hip in postmenopausal women. These data indicate that the level of physical activity undertaken by these subjects, even in the presence of HRT, is not an adequate stimulus to maintain hip bone mass. In contrast, HRT and exercise maintained $T_{	ext{no}}$ and $T_{	ext{inc}}$ at levels similar to those of premenopausal women runners.

The finding of differences in BMD between Pre and PostE was unexpected. The literature is clear that estrogen replacement can almost completely abolish bone loss associated with menopause in most women. The work of Lindsay and colleagues (2) demonstrated long-term conservation of bone with estrogen treatment, begun at the onset of menopause, that lasted at least up until the age of 70 years. The estrogen-treated women in our study began treatment at menopause, yet they had significantly lower BMD of the hip, and a trend toward lower BMD of the spine, than premenopausal women of similar weight and training history. The reasons for these differences are unclear, as the interaction between chronic exercise and HRT has not been well studied. Some data suggest that weight-bearing exercise enhances the effect of estrogen to increase bone mass (5), but these results were established in women who began HRT and exercise several years after menopause. It has been suggested that there might be more potential to add bone mass once postmenopausal loss has already occurred (13), making it likely that the additive effect of estrogen and exercise was in part due to a more responsive skeleton. In contrast, our subjects had been chronically training from several years prior to menopause, suggesting they may be acclimated to the exercise stimulus. Moreover, Mosekilde (14) suggested that chronic exer-

cisers experience any skeletal gains during the early years of training, after which bone mass would be expected to plateau with no further increase from the chronic exercise. Thus, although the combination of running and HRT might not be expected to increase BMD in this group of women, it would be expected to maintain bone mass at nearly premenopausal levels. The fact that our data suggest a loss of bone mass despite HRT is as yet unexplained.

It remains possible that the dosage of estrogen utilized by the subjects in our study was insufficient to protect bone. Lindsay (15) has stated that not all patients treated with the minimum dose of estrogen conserve bone. Whether this is due to estrogen resistance, interference from other factors, or lack of compliance with treatment has not been reported. Certainly, delayed onset of HRT following menopause, and/or poor compliance with the medication, could provide an explanation for our findings if these data were incorrectly reported by our subjects. Additionally, the postmenopausal athletes may have had a lower peak bone mass, or they may have experienced greater premenopausal bone loss due to premenopausal bouts of amenorrhea. However, only one athlete in the postmenopausal group reported an amenorrheic event during her lifetime. Thus, it is difficult at best to determine precisely the influence of these factors on our results.

Finally, it is possible that some aspect created by the chronic nature of the exercise undertaken by these subjects created an environ-

Figure 2. Isometric and isokinetic knee extension strength by group.

Figure 3. Relationship between age and bone mineral density for all subjects.

Figure 4. Relationship between body weight and bone mineral density for all subjects.
ment detrimental to bone even in the presence of HRT. Risk factors for osteoporosis that are known to be prominent in female athletes include low body weight, low body fat, high cortisol levels, and low estrogen levels (9). As well, Nelson and coworkers (8) demonstrated lower serum estrogen in non-HRT treated, chronically trained postmenopausal women runners when compared to sedentary controls, likely due to lower body fat percentage. An adverse effect of chronic running on bone mass in men has also been suggested (16); this was attributed to hormonal changes associated with endurance training, and certainly warrants further investigation.

The second major finding of this study was that exercise alone was not able to reduce the expected rate of bone loss in postmenopausal women. The Post group had 17% lower BMD of the hip and the lumbar spine when compared to Pre, similar to the predicted 15–20% loss in bone mass during the first 10 years following menopause (1). T_BD was also significantly lower in the Post group, although the difference amounted to only 11%. The finding of a slower rate of loss in T_BD than H_BD and S_BD is not surprising. Cortical bone, which is primarily reflected by TBD, is affected more slowly by menopause than trabecular bone, of which HBD and SBD are more reflective (17).

We did not expect that exercise alone would be a sufficient stimulus to completely maintain bone mass in the absence of estrogen. There is no evidence to date in humans that suggests otherwise. However, in young women who are amenorrheic, studies have shown a skeletal benefit to running exercise in comparison with sedentary subjects (18). Thus, it could be expected that exercise would slow the rate of bone loss in postmenopausal women not utilizing HRT. Our data, although not conclusive due to the cross-sectional nature of the comparison, suggests that it does not in chronic exercisers. This supports the work of Kirk and associates (7), who found no decrease in bone mass between chronic runners and closely matched sedentary controls. These findings call into question the benefit of chronic running exercise to the skeleton in postmenopausal women, and warrant further investigation.

In conclusion, the results of this study suggest that HRT and chronic running exercise are unable to maintain hip bone mass in postmenopausal women, whereas total body bone mass is maintained at nearly premenopausal levels. Moreover, the results suggest that chronic running alone is unable to prevent or reduce the bone loss associated with menopause.

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REFERENCES