

Effects Of Exercise Training On Bone Remodeling, Insulin-Like Growth Factors And Bone Mineral Density In Post-Menopausal Women With And Without Hormone

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Running Title: **Exercise Training, Hormone Replacement Therapy and Bone Remodeling**

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Abstract

The purpose of this study was to determine the effects of 12 months of weight bearing and resistance exercise on bone mineral density (BMD) and bone remodeling (bone formation and bone resorption) in 2 groups of postmenopausal women either with or without hormone replacement therapy (HRT). Secondary aims were to characterize the changes in insulin-like growth factors-1 and -2 (IGF-1 and -2) and IGF binding protein 3 (IGFBP3) in response to exercise training.

Women who were three to ten years postmenopausal (aged 40 - 65 years) were included in the study. Women in HRT and no HRT groups were randomized into the exercise intervention resulting in four groups: 1) women not taking HRT, not exercising; 2) women taking HRT, not exercising; 3) women exercising, not taking HRT; and 4) women exercising, taking HRT. The number of subjects per group after one year was 27, 21, 25, and 16, respectively.

HRT increased BMD at most sites whereas the combination of exercise and HRT produced increases in BMD greater than either treatment alone. Exercise training alone resulted in modest site-specific increases in BMD. Bone remodeling was suppressed in the groups taking HRT regardless of exercise status. The bone remodeling response to exercise training in women not taking HRT was not significantly different from those not exercising. However, the direction of change suggests an elevation in bone remodeling in response to exercise training, a phenomenon usually associated with bone loss. No training induced differences in IGF-1, IGF-2, IGF-1:IGF-2, and IGFBP3 were detected.

Key Words: Bone remodeling - exercise training – hormone therapy

Introduction

The positive effect of high intensity resistance exercise on bone mineral density (BMD) in postmenopausal women has been previously demonstrated [1,2]. However, to begin to understand the potential effectiveness of exercise training as an adjunct therapy to decrease bone loss in postmenopausal women, it is helpful to examine the mechanisms by which BMD is increased or maintained. The intracellular post-loading cascade of events, which presumably can alter the rates of bone formation and resorption, have not been clearly identified. However, calcium, prostacyclin, prostaglandin E₂, and insulin-like growth factor -1 (IGF-1) have been detected, *in vivo*, following a mechanical stimulus [3]. In efforts to elucidate the post-loading responses in bone, insulin-like growth factors (IGFs) have received much attention because they are involved in longitudinal bone growth prenatally and during puberty [4,5] and age-related decreases in both systemic and bone tissue levels have been shown [6,7].

Ultimately, the mechanical loads imposed on bone will influence changes in bone mass through bone remodeling, a coupled process whereby formation follows resorption. Though the suppression of bone remodeling in response to hormone replacement therapy (HRT) is well documented [8-11], the response to exercise and exercise plus HRT in post-menopausal women is unclear. Studies in postmenopausal women have been inconsistent with authors reporting decreases [12], no change [8,13] and increases [14] in bone formation in response to various types of exercise training interventions which all resulted in increases in BMD. The effects of low impact exercise, low impact exercise plus calcium supplementation, and low impact exercise plus HRT on BMD was examined by Prince [9] who showed lower levels of resorption, measured by urinary hydroxyproline, in the exercise plus calcium and the exercise plus HRT groups vs. exercise alone. Hatori [13] showed that 7 months of high intensity walking in a

sample of postmenopausal women resulted in increases in BMD with no significant change in osteocalcin and hydroxyproline. The control group in this study lost bone and experienced significantly higher osteocalcin and hydroxyproline levels.

In spite of these studies, few comprehensive efforts have been made to characterize the effects of exercise and exercise plus HRT on BMD and bone remodeling. Therefore, the purpose of this study was to determine the effects of exercise training on BMD, osteocalcin (OC) (marker of bone formation), and deoxypyridinoline crosslinks (Dpd) (marker of bone resorption) in postmenopausal women either with or without HRT. A secondary aim was to determine the effects of exercise training on IGF-1, insulin-like growth factor-2 (IGF-2), insulin-like growth factor binding protein-3 (IGFBP3) and the ratio of IGF-1 to IGF-2 in the same samples of postmenopausal women to determine their role in the regulation of bone remodeling.

Experimental Subjects

Ninety four postmenopausal women who were either with HRT (for at least 1 year but not longer than 3.9 years) or without HRT (not taking hormone for at least one year) enrolled in the study. Any physician prescribed HRT regimen and formulation was accepted. Regimens included the estrogen transdermal patch ($n = 3$), unopposed estrogen ($n = 10$), estrogen plus progesterone taken orally ($n = 23$) and oral estrogen plus testosterone ($n = 2$). Women were three to ten years postmenopausal (natural or surgical), aged 40 - 65 years, sedentary (less than 120 minutes of regular weight-bearing exercise per week for at least one year), and were not taking any drugs that altered BMD except HRT. Potential subjects were excluded if they were smokers, had osteoporosis (initial spine or hip BMD less than a T score of -3.0), were obese or very lean (body mass index > 32.9 or < 19.0 from self-reported weight and height), were undergoing cancer treatment or had treatment within the past 5 years, or were unable or unwilling to be randomly assigned to the exercise or no-exercise group. Physical examinations were performed and subjects were excluded if they had a history of an eating disorder, a musculoskeletal condition such as muscular dystrophy or rheumatoid arthritis, a history of bone fractures, or conditions which contraindicate exercise training.

Qualified participants agreed not to change their dietary habits or their initial levels of physical activity except as required by the exercise intervention. All subjects agreed to take 800 mg of calcium citrate daily which, in conjunction with dietary calcium intake, was intended to minimize the confounding effects of low calcium intakes to adequately test the effects of the exercise intervention. Subjects also agreed to have all laboratory measurements performed at baseline, 6 months and at 1 year. Informed and written consent was obtained from each subject

prior to participation and all study procedures have been approved by the University of Arizona's Human Subjects Review Board.

Materials and Methods

Intervention

Women with HRT and those without HRT were randomized into the exercise or non-exercise groups resulting in four groups: Exercisers and non-exercisers who were not taking HRT (Ex, No HRT, n = 26 and No Ex, No HRT, n = 30, respectively); and exercisers and non-exercisers who were taking HRT (Ex, HRT, n = 17 and No Ex, HRT, n = 21, respectively). The 12 month exercise training program involved both resistance and weight-bearing exercises to maximize the potential bone loading effects. Supervised exercise sessions lasting 75 minutes were performed three times per week on alternating days at local fitness centers. Each session consisted of three components: 20 minutes of aerobic weight bearing activity (jumping, skipping while wearing weight vests), 35 minutes of resistance exercises (small and large muscle weight lifting), and 10 minutes of stretching and balance.

Aerobic weight bearing activity began with walking and then a circuit for 10 - 20 minutes which progressed to include stair stepping and walking with weight vests. The circuit included higher impact activities such as skipping, high stepping, and side stepping interspersed with walking performed for 15 minutes per session. The frequency and duration of the higher impact activities in the circuit were increased upon adaptation to maintain an intensity of 50% - 70% of maximal heart rate. Stair stepping was introduced at month three and was performed for 10 - 15 minutes per session. Beginning with month four, 10 pound weight vests were worn during walking twice per week. The amount of weight was increased throughout the remainder of the exercise intervention.

Resistance training was composed of exercises targeting large muscle groups and small muscle groups including abdominals. The leg press, squat, seated one-arm dumbbell (alternating

arms) presses, back extension, rotary torso, seated rows, and lateral pull-downs were performed to focus on the large muscles of the legs, shoulders, arms, and back. Subjects performed two sets (6 - 8 repetitions per set) at 70 - 80% of a one repetition maximum for each exercise. The one repetition maximum was assessed every 6 weeks in order to adjust the exercise intensity for strength gains throughout the training program. Small muscle groups involved in the maintenance of proper posture were targeted using therabands for resistance and physioballs for support and balance. These exercises included adduction/retraction of the scapula, scapular depression/elevation, and external rotation of the humerus. Exercises for the abdominals and obliques were also performed.

Height and Weight

Standing height was measured in duplicate using a wall mounted stadiometer. Weight was measured in duplicate using an Accu-weigh Model 150 TK/A-58 beam scale (Metro Equipment Corp., Sunnyvale, CA). Height and weight were measured to the nearest tenth of a cm or kg, respectively.

Bone Densitometry

Regional and total body BMD (g/cm^2) measurements were obtained using dual-energy x-ray absorptiometry (DXA). Whole body, anteroposterior lumbar spine, and right proximal femur scans were performed in duplicate on medium speed using the Lunar Radiation Corporation DXA scanner, model DPX-L with software version 1.3y. Duplicate scans were performed on separate days within 2 weeks for baseline, 6 months and 1 year visits. Duplicate scans were highly correlated ($r_{1,2}$) ($r = 0.94 - 0.99$) and had coefficients of variation ranging from 1.6 % - 4.0 %. The average of the two scans was used in all subsequent analyses. Follow-up scans were

performed on the same settings as the baseline scans. All analyses were performed using the extended research analysis feature.

Blood and Urine Sample Collections

Blood and urine specimens were collected after an overnight (12h) fast. All follow-up samples were taken during the same phase of the cycle as the baseline sample (i.e. estrogen alone or estrogen plus progesterone for those women who were prescribed a cyclic HRT regimen). Each subject was instructed not to consume any medication including HRT, calcium supplements, or multivitamins the morning of their blood draw. Blood specimens were collected at the laboratory between 0600 h and 0900 h, were aliquotted into cryovials and transferred into -80° C for storage until assayed. Also, a single first morning void urine sample was collected by the subject immediately upon waking and returned to the laboratory the same morning. Urine samples were transferred into -80° C for storage until assayed. Urine collection procedures used herein were consistent with those recommended by Metra Biosystems (Mountain View, CA) for the measurement of Dpd.

Biochemical Assays

Immunoradiometric assays (IRMA) were performed to determine serum levels of OC, IGF-1, IGF-2 and IGFBP3 and competitive enzyme-linked immunoabsorbant assays (ELISA) were performed for the measurement of Dpd corrected for creatinine excretion. All assays were performed using commercially available assay kits from Diagnostic Systems Laboratories (Webster, TX), Nichols Institute Diagnostics (San Juan Capistrano, CA), and Metra Biosystems (Mountain View, CA). Immunofit EIA/RIA software v4.0 (Beckman Instruments, Fullerton, CA), a curve fitting software package capable of cubic spline and 4 parameter logistic curve fits, was used for the calculation of the unknown sample concentrations.

All samples, standards, and controls were assayed in duplicate and samples from all time points during the first year for any given subject were included in the same assay to eliminate the impact of inter-assay variation. Also, each assay contained subjects from each of the treatment groups. Any sample with a concentration higher than the highest standard was diluted and reassayed. Samples with high variation (greater than $\sim 10.0\%$) between duplicate tubes, assessed using CVs and standard deviations, were also reassayed. To evaluate assay accuracy, high and low controls provided with each kit were assayed. All high and low control values fell within the acceptable ranges provided by each company. The low and high controls were also used to determine the interassay variability. The coefficients of variation (CV) ranged from 2.0 to 14.5%.

Statistical Analyses

Eighty four of the original 94 subjects completed one year of the study and were able to provide adequate fasting serum and urine samples for analysis. A priori built-in comparisons were performed because the exercise intervention was randomized within HRT groups, which was self-selected. Therefore, the comparisons made for each independent variable were: exercise versus control for the group with HRT; exercise versus control for the group without HRT; and HRT versus no HRT. These comparisons were dictated by the partially randomized design of the study. Self-selected HRT use by the subjects increases the external validity and generalizability of the study and the built-in comparisons (versus performing all possible comparisons) minimize the possibility of inflating the Type I error. All statistical analyses were performed using Statistical Package for the Social Sciences software version 7.0 (Chicago, IL). Significance levels of $p < 0.05$ were used.

To determine baseline differences among groups, multiple regression was used with each baseline variable as the dependent variable and categorical variables representing coded contrasts comparing the Ex group to the no-Ex group within each HRT group and comparing HRT users with non-HRT users entered as the independent variables. Adjusted mean values for baseline data were subsequently calculated.

To determine the effect of exercise training on BMD and the biochemical variables, the differences between baseline and 6 months or 12 months values for each variable were calculated and used as the dependent variables in multiple regression analyses. Independent variables for each analysis were the baseline values to account for the potential influence of the baseline value on the change from baseline to 6 or 12 month, the number of years postmenopausal, and the three coded contrasts denoting the comparisons between the HRT and no HRT groups, the exercise effect in women with HRT, and the exercise effect of women without HRT. Adjusted means and adjusted percent changes from baseline were subsequently calculated from the multiple regression results.

Results

There were significant ($p < 0.05$) baseline differences between the HRT and non HRT groups in age, OC, Dpd, IGF-1, estrone, and estradiol (Table 1). The HRT group was younger, had lower serum levels of OC and IGF-1, higher serum levels of estrone and estradiol, and lower urinary excretion of Dpd. There were no differences in BMD between the HRT and the no HRT groups.

Adjusted mean percent changes in BMD from baseline to 6 and 12 months are presented in Table 2. There were significant differences between the HRT and non-HRT groups in the percent change in BMD of the lumbar spine ($p = 0.01$) and Ward's triangle ($p = 0.02$) from baseline to 6 months. Percent changes from baseline to 12 months were significantly different between the HRT and non-HRT groups in the femoral neck ($p = 0.02$), Ward's triangle ($p = 0.01$), lumbar spine ($p = 0.05$), and total body ($p = 0.009$). In the group of women taking HRT, there was a significant exercise effect at the greater trochanter ($p = 0.03$) at 12 months. In the group of women not taking HRT, there was a significant exercise effect at the Ward's triangle ($p = 0.04$) at 12 months.

Adjusted mean percent changes in OC and Dpd between baseline and 6 and 12 months of the intervention are shown in Figure 1. Decreases in Dpd at 6 months were significantly greater ($p = 0.003$) in women taking HRT compared to those without HRT. Dpd decreases from baseline to 12 months were not different between women using HRT versus those not using HRT ($p = 0.084$). Though not statistically significantly different between HRT groups ($p = 0.062$), OC decreased more from baseline to 6 months in women on HRT than women not on HRT. OC changes from baseline to 12 months were also not different between groups. There were no significant exercise effects in either HRT group but, for women without HRT, 9.1 % and 11.8 %

increases in OC and Dpd, respectively, were observed in response to exercise training compared to 2.1 % and 0.3 % increases for OC and Dpd, respectively, in the control group.

The effects of exercise training on IGF-1, IGF-2 and IGFBP3 in postmenopausal women taking or not taking HRT are presented in Table 3. Percent changes in the ratio of IGF-1 to IGF-2 were also examined. No significant differences between groups were found. The largest change occurred in IGF-1 for the group exercising and on HRT (-8.2%) vs. the group not exercising and on HRT (-1.9%).

Discussion

The baseline differences between the HRT and no HRT groups in OC and Dpd were consistent with the well-documented [8-11] suppression of bone remodeling in the HRT group (Figure 1). It is possible that women with HRT in the present study were still adjusting to the HRT upon entering the study due to the decrease in bone remodeling that continued to occur (for the non-exercisers) over the first six months. During estrogen withdrawal (i.e. menopause), bone remodeling becomes elevated and this is usually associated with bone loss [15]. Women without HRT in the present study who did not exercise experienced no changes in bone remodeling suggesting these women had already adjusted to the withdrawal of estrogen. Baseline IGF-1 levels were also lower in the HRT group than in the non HRT group (Figure 1). This is consistent with research in postmenopausal women [16,17] suggesting that a suppression of bone remodeling reduces the IGF-1 production from osteoblasts. These baseline differences between HRT and no HRT groups limit any meaningful comparisons that can be made regarding HRT. Based on these differences, the effect of exercise on BMD and bone remodeling was examined in two different postmenopausal populations.

The BMD changes from baseline to 12 months for all sites except the greater trochanter were significantly larger for the HRT group compared to the no HRT group. The group not exercising and without HRT experienced decreases in BMD at all sites. The largest increases in BMD were found in the group who exercised and were on HRT except for the femoral neck where the group on HRT alone showed the largest increase. These results are similar to the findings of Kohrt [8] who showed additive or synergistic effects of exercise training and HRT in postmenopausal women and in older postmenopausal women not on HRT who were performing weight bearing exercises [18]. In the present study, there were no significant increases in BMD

at the lumbar spine in response to exercise in those women not on HRT whereas increases at this site in response to exercise alone have been previously documented [18]. These data suggest that either exercise alone or HRT alone can retard bone loss or increase BMD, although this varies by site, whereas the combination of the two therapies may provide the largest and most consistent increases in BMD.

This study is unique because we have included measurements of both bone formation and bone resorption. Decreases in Dpd at 6 and 12 months ($p < 0.05$) and decreases in OC at 6 months ($p = 0.06$) were observed in the HRT group versus the non HRT group (Table 3). For women not using HRT, exercisers showed a trend toward larger positive changes in both formation and resorption over 12 months versus the control group. Kohrt [8] studied the interactive effects of HRT and weight-bearing exercise on BMD and bone remodeling and reported decreases in osteocalcin in the HRT and HRT plus exercise groups compared to the exercise alone group where no change was observed. Prince [9] reported decreased hydroxyproline levels, a marker of bone resorption, in women who were exercising and taking HRT or exercising and taking Ca^{++} . However, Hatori [13] found that the nonexercising control group exhibited elevated OC and hydroxyproline levels versus no changes in the exercise group even though increases in BMD were documented. In the present study, though there were no significant exercise effects, there were larger increases in bone remodeling for exercisers compared to non-exercisers, which is contrary to the findings of others [8, 9, 13]. It is important to note that the power to detect these differences due to exercise is low because of the high day to day variability that exists in these markers.

Women in those groups taking HRT, regardless of their exercise status, achieved an increase in BMD by a suppression of bone remodeling, which is consistent with previous reports

[8,9]. In contrast, our data suggest that the exercise group achieved an increase in BMD by a potential increase in bone remodeling, a phenomenon usually associated with bone loss. It is thought that estrogen alters the set point of bone mechanosensors [15,19] requiring a smaller mechanical stimulus to produce an osteogenic response similar to conditions without estrogen. The changes observed in BMD in the Ex, HRT group (larger increases than either Ex or HRT groups) support the set point altering function of estrogen (Table 2). However, the changes in bone remodeling for the Ex alone group versus the HRT alone group were opposite in direction. Recognizing the limitations of the present study design, this may suggest that exercise and HRT may function to increase BMD through different mechanisms.

One of the difficulties in assessing markers of bone remodeling as well as growth factors is that serum or urine samples reflect systemic levels of these biochemical variables, whereas the BMD changes that occurred in this study are site specific. A significant increase in BMD was observed in the greater trochanter for women exercising whereas, at the Ward's Triangle, there was a significant decrease in BMD that was smaller than in the control group. There were also no significant changes in the lumbar spine and femoral neck BMD in the Ex, No HRT group. Since there are site-specific effects on BMD, the utility of changes in systemic levels of OC and Dpd may not reflect changes at a given BMD site. Therefore, it is not surprising that significant changes in OC and Dpd occurred in the groups who showed the most consistent regional and total body response in BMD (HRT vs. no HRT). However, markers of bone remodeling may still be useful tools to help identify whether exercise and HRT function through different mechanisms. Future studies should incorporate a substantial exercise intervention targeting both strength and weight-bearing types of activities (as was done herein) that last for longer durations than are typically studied (> 1 year). The usefulness of bone markers in long-term exercise

studies (where bone changes may be larger) has not been investigated. In addition, to minimize the impact of high day to day variability in bone remodeling markers, samples should be measured in duplicate at each time-point tested. This would reduce the technical error involved with the measurement of remodeling, increase statistical power, and allow smaller changes over time to be detected.

No significant changes in the IGFs were found in response to exercise training in the samples of women taking or not taking HRT. Day to day variability of IGF-1, which was measured at baseline using 2 blood samples collected within 2 weeks, was 14%. This high variability does not allow the detection of small changes over time. However, we can not rule out the possibility that changes in bone remodeling or IGFs were transient in nature either as an acute exercise effect or with a time course that could not be detected in a six month sample. In addition, many different HRT regimens were present in this study. Oral and transdermal HRT have been shown to have differential effects on IGF-1 levels [16,17]. Differential effects on IGF-1 may also exist between unopposed estrogen, estrogen opposed with progesterone, or estrogen plus testosterone. We are aware of no study that has examined the effects of different hormone regimens on bone remodeling.

We conclude that HRT resulted in favorable changes in BMD at most sites and the combination of exercise training and HRT results in more favorable changes in BMD than either treatment alone (except at the femoral neck). Exercise training in women who did not take HRT resulted in only modest nonsignificant increases in BMD (except at the Ward's triangle). Additionally, bone remodeling was suppressed in the groups with HRT regardless of exercise status. The bone remodeling changes in women exercising without HRT were not significantly different from those not exercising but the direction of change suggests an increase in bone

remodeling in those who exercised and did not take HRT. No significant exercise effects were detected in IGF-1, IGF-2, IGF-1:IGF-2, and IGFBP3 in postmenopausal women with HRT or without HRT.

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Table 1: Means (\pm SD) for baseline values in the HRT and non HRT groups.

Variable	Non HRT Group	HRT Group
Age (yrs)	56.9 \pm 4.6 ^a	54.4 \pm 4.4
Years past menopause	6.05 \pm 2.9 ^a	4.75 \pm 2.5
Height (cm)	162.4 \pm 6.1	162.8 \pm 7.6
Weight (kg)	68.4 \pm 10.6	68.8 \pm 11.7
BMD (g/cm ²)		
Greater Trochanter	0.739 \pm 0.109	0.752 \pm 0.116
Ward's Triangle	0.743 \pm 0.119	0.764 \pm 0.141
Femoral Neck	0.836 \pm 0.109	0.864 \pm 0.121
Lumbar Spine	1.104 \pm 0.159	1.144 \pm 0.134
Total body	1.096 \pm 0.080	1.131 \pm 0.082
Osteocalcin (ng/ml)	8.04 \pm 2.09 ^a	5.18 \pm 1.52
Deoxypyridinoline crosslinks (mM/nM)	6.93 \pm 2.77 ^a	5.17 \pm 1.79
Insulin-like growth factor-1 (ng/ml)	146.4 \pm 42.8 ^a	119.2 \pm 45.8
Insulin-like growth factor-2 (ng/ml)	855.5 \pm 128.6	836.7 \pm 123.0
IGF binding protein 3 (ng/ml)	300.0 \pm 47.0	295.3 \pm 50.9
Estrone (pg/ml)	17.9 \pm 10.5 ^a	142.1 \pm 76.5
Estradiol (pg/ml)	10.9 \pm 8.6 ^a	61.1 \pm 28.7

a = Significantly different between HRT and non HRT groups ($p < 0.05$).

Table 2: Adjusted^a percent changes (mean \pm standard error of the mean^b) in bone mineral density from baseline to six (A) and twelve months (B) for each intervention group.

A) Six Months		No HRT Group		HRT Group	
Bone Density Site	Control	Exercise	Control	Exercise	
Total Body	-0.1 ± 1.7	0.1 ± 1.8	0.2 ± 2.0	0.4 ± 2.2	
Femoral Neck	-0.8 ± 4.9	0.6 ± 5.1	-0.6 ± 5.7	-0.5 ± 6.5	
Greater Trochanter	-0.8 ± 5.3	1.3 ± 5.5	-0.1 ± 6.1	3.0 ± 7.0	
Ward's Triangle	-1.2 ± 6.4	-0.1 ± 6.6	1.4 ± 7.4 ^c	2.2 ± 8.4 ^c	
Lumbar Spine (L2-4)	-0.4 ± 4.0	0.3 ± 4.2	1.2 ± 4.6 ^c	1.4 ± 5.2 ^c	

B) Twelve Months		No HRT Group		HRT Group	
Bone Density Site	Control	Exercise	Control	Exercise	
Total Body	-0.4 ± 2.4	0.2 ± 2.5	0.5 ± 2.7 ^c	0.7 ± 3.0 ^c	
Femoral Neck	-0.5 ± 6.7	1.1 ± 6.9	2.8 ± 7.5 ^c	2.0 ± 8.5 ^c	
Greater Trochanter	-0.8 ± 6.0	1.3 ± 6.3	-0.1 ± 6.8	3.0 ± 7.7 ^d	
Ward's Triangle	-4.3 ± 8.4	-1.0 ± 8.7 ^e	-0.7 ± 9.5 ^c	2.0 ± 10.8 ^c	
Lumbar Spine (L2-4)	-0.2 ± 5.0	-0.2 ± 5.1	0.9 ± 5.6 ^c	1.5 ± 6.4 ^c	

a = Percent changes were adjusted for the number of years past menopause and the baseline value of each variable.

b = SEM are 10^{-3} .

c = HRT different than no HRT ($p < 0.05$)

d = Ex different than Control in HRT group ($p < 0.05$)

e = Ex different than Control in no HRT group ($p < 0.05$)

Table 3: Adjusted^a percent changes (mean and standard error of the mean (SEM)) in biochemical variables from baseline to six (A) and twelve months (B) for each intervention group.

A) Six Months		No HRT Group		HRT Group	
Biochemical Variable	Control	Exercise	Control	Exercise	
Osteocalcin	-2.8 ± 0.24	1.0 ± 0.25	-9.7 ± 0.26	-11.4 ± 0.29	
Dpd	0.3 ± 0.29	8.3 ± 0.28	-12.7 ± 0.31 ^b	-16.2 ± 0.35 ^b	
IGF-1	-3.5 ± 5.27	2.7 ± 5.47	-3.8 ± 5.83	-2.3 ± 6.64	
IGF-2	-0.5 ± 14.78	-1.7 ± 15.38	-0.08 ± 16.07	-1.5 ± 18.28	
IGFBP3	-0.6 ± 0.47	-1.1 ± 0.49	-1.4 ± 0.52	-3.1 ± 0.59	

B) Twelve Months		No HRT Group		HRT Group	
Biochemical Variable	Control	Exercise	Control	Exercise	
Osteocalcin	2.1 ± 0.33	9.1 ± 0.36	1.9 ± 0.36	-7.7 ± 0.42	
Dpd	0.3 ± 0.27	11.8 ± 0.31	-2.8 ± 0.32	-6.2 ± 0.35	
IGF-1	-0.4 ± 5.23	-0.3 ± 5.79	-1.9 ± 5.79	-8.2 ± 6.79	
IGF-2	-0.8 ± 15.27	-3.2 ± 16.28	-0.6 ± 16.28	-1.8 ± 18.52	
IGFBP3	-0.5 ± 0.58	-2.3 ± 0.65	0.1 ± 0.65	-2.3 ± 0.76	

a = Percent changes were adjusted for the number of years past menopause and the baseline value of each variable.

b = HRT different than no HRT (p<0.05)

Figure Legends

Figure 1: Adjusted percent changes from baseline to six months (A) and twelve months (B) for bone remodeling markers in response to exercise in women taking or not taking HRT. Error bars are standard errors of the mean.

a = HRT different than no HRT ($p < 0.05$)

