Depressive Symptoms and Changes in Body Weight Exert Independent and Site-Specific Effects on Bone in Post-Menopausal Women Exercising For One Year

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Running Head: Depressive Symptoms, Body Weight & Bone
Abstract

Background: Lower bone mineral density (BMD) has been documented in clinically depressed populations and depression is the second most common chronic medical condition in general medical practice. Therefore, the purpose of this study was to determine whether depressive symptoms, vitality, and body weight changes were related to one-year BMD changes after accounting for covariates.

Methods: Healthy postmenopausal women (n = 320; 40-65 years) were recruited and 266 women completed the study. Participants were 3-10 years postmenopausal, sedentary, and either taking HRT (1-3.9 years) or not taking HRT (at least 1 year). Exclusion criteria were: smoking, history of fractures, low BMD, body mass index >32.9 or <19.0, or bone altering medications. Regional BMD was measured from dual-energy x-ray absorptiometry at baseline and one year. Self-reported depressive symptoms and vitality were measured using standard questionnaires.

Results: Both the vitality and depressive symptoms scores were related to BMD changes at the femur but not at the greater trochanter or spine. Weight change was a predictor of BMD changes in the trochanter and spine but not the femoral neck. Weight change and vitality / depressive symptoms had differential and site specific effects on BMD changes at the hip. Vitality and depressive symptoms related to femoral neck changes and weight change related to greater trochanter changes.

Conclusions: The negative impact of depressive symptoms on BMD in this population of postmenopausal women was independent of body weight or other behavioral factors such as calcium compliance or exercise.
Introduction

The loss of bone mineral density (BMD) with aging is a result of the complex interactions of hormonal, environmental, nutritional and genetic factors. In recent years, psychological status has been identified as another factor possibly related to the loss of BMD (1,2). In clinically depressed populations, significantly lower BMD has been found compared to non-depressed controls (3-7). Lower BMD in depressed populations could be related to depression itself or to other behavioral disturbances that occur as a result of depression. Factors sometimes associated with depression such as lower levels of physical activity, changes in body weight, lower calcium compliance, or anti-depressant medications have been postulated as underlying causes of bone loss (8). It is also possible that the depressed state alters the metabolic hormonal milieu resulting in bone mineral loss (9).

The difference in BMD between depressed and non-depressed populations has been documented in both medicated and non-medicated individuals, in males and females, and in those who were clinically depressed as well as in those with undiagnosed but severe depressive episodes (3-7). Despite these findings, there have been no large prospective trials examining bone loss and depressive symptoms. Additionally, no studies have focused on depressive symptoms measured in an apparently healthy population nor have studies accounted for the potential behavioral factors (changes in body weight or low calcium compliance) that are likely to also contribute to bone loss. The clinical relevance is unambiguous considering that depression is the second most common chronic condition encountered in general medical practice (10). Therefore, the purpose of this study was to determine whether depressive symptoms, indicators of well being, and changes in body weight were significantly related to one-year BMD changes after accounting for behavioral factors (e.g. calcium compliance,
exercise and use of hormone replacement) and other related factors (baseline BMD, age). In addition, in a subset of women who were exercising, we sought to determine whether depressive symptoms were associated with bone changes after accounting for body weight change, exercise compliance and the cumulative amount of weight lifted over one year of training, as well as other important covariates.

Methods

Three hundred and twenty postmenopausal women aged 40-65 years were recruited and 266 women completed the one-year study. Women were 3-10 years past menopause (natural or surgical), participated in less than 120 minutes of exercise per week, and were willing to be randomized to an exercise or control group. Exclusion criteria included: smokers, those with a history of fractures, low BMD (Z score of −3.0 or less), body mass index (kg/m²) >32.9 or <19.0, or those taking any bone altering medication (except HRT). At the study’s start, subjects were either taking HRT (for 1-3.9 years) or not taking HRT (for at least 1 year) and were randomized within group to either a 1-year supervised exercise training program or the control group (Figure 1). All subjects received 800 mg of calcium citrate daily (Citrical®, Mission Pharmacal, San Antonio, TX) and compliance was measured through pill counts. Exercise compliance and weight lifted throughout one year were monitored using workout logs. All protocols were approved by the University of Arizona’s Institutional Review Board and informed consent was obtained from each participant. The main effects of exercise with and without HRT on BMD have been published (11). The present study is a secondary analysis of the original database. Two women were excluded from analyses due to noncompliance to the study protocol and their sizable influence on the regression results. Both women lifted 30% more than the next highest
lifters, one by attending 50% more sessions and the other by performing up to 75% more repetitions on most exercises. The final sample size was 264.

Lumbar spine, femoral neck and greater trochanter BMDs (g/cm²) were measured in duplicate (within 7 days) on medium speed at baseline and at one year using a Lunar DPX-L (version 1.3y, Lunar Radiation Corporation, Madison, WI) dual-energy x-ray absorptiometer (DXA). The average of the two scans was used in all analyses. Scan analysis was performed by one certified technician using the extended research analysis feature. DXA calibration was performed daily using a calibration block supplied by the manufacturer. The coefficient of variation for this block was 0.6%. BMD precision, expressed as a percent of mean BMD, was less than 2.4% for each BMD site.

Subjects completed several questionnaires at baseline including the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) (12) and the 21 item Beck Depression Inventory (BDI) (13). Demographic information was also collected through a questionnaire.

Body weight (kg) was measured to the nearest 0.1 kg at baseline and at one year using a digital scale (SECA, Model 770, Hamburg, Germany) and height was measured to the nearest 0.1cm with a Schorr measuring board.

**Statistical Analysis**

Multiple regression was used to determine whether one year changes in body weight and baseline BDI, vitality (from SF-36), or general well-being (from SF-36) could significantly account for variability in one year changes in femoral neck, greater trochanter, and spine BMD. After adjusting for covariates (baseline BMD, baseline body weight, age, exercise group assignment, HRT use and calcium compliance), changes in body weight plus either BDI, vitality or general well-being variables were added to predict the one-year changes in regional BMD.
For the subset of women who exercised, the impact of the cumulative amount of weight lifted during the one-year exercise program, exercise compliance, changes in body weight along with BDI or vitality were tested, adjusted for the above covariates except exercise group assignment. All analyses were carried out using the Statistical Package for Social Sciences (SPSS, v 11.5, Chicago, IL).

**Results**

Subject physical characteristics for body mass index (BMI), regional BMD and baseline values for vitality and depressive symptoms are given in Table 1. Bone density values for our sample of postmenpausal women are similar to others measured using similar technology (14-17). Figures 2 and 3 show frequency distributions for BDI and changes in body weight. Table 2 shows the standardized regression coefficients for the 3 models predicting one-year changes in each regional BMD site with the change in body weight plus either vitality or depressive symptoms as predictors. Both the vitality and BDI scores were significantly related to BMD changes at the femur but not at the greater trochanter or spine. Vitality was a positive predictor of femoral BMD changes over one year (p = 0.034). BDI was a negative predictor of one-year BMD changes at the femoral neck (p = 0.026). General well-being (from the SF-36) was not a significant predictor of BMD changes. The results for depressive symptoms were substantiated by replacing BDI in the regression model with either the probability of depression (calculated using the Women’s Health Initiative’s formula) or a single question about depressive symptoms (“Have you felt depressed or sad much of the time in the past year?”). These alternate variables also significantly predicted femoral neck BMD changes (p = 0.09 and 0.01, respectively).

After accounting for the effects of baseline bone density, baseline body weight, age, calcium compliance, HRT use and exercise group assignment, weight change was a predictor of
1-year BMD changes in the trochanter (p < 0.01), and spine (p < 0.10) but not the femoral neck.

Weight change after one year and vitality or BDI had differential and site specific effects on bone density changes at the hip, with vitality and BDI related to femoral neck changes and weight change related to BMD changes in the greater trochanter. When comparing the standardized regression coefficients (β), we found that the magnitude of the effect for BDI (β = -0.139) exceeded the effects of exercise in HRT users and non-users (β = 0.070 and 0.101, respectively). At the greater trochanter, the change in body weight (β = 0.211) was a more powerful predictor of BMD change than HRT use (β = 0.085) and exercise group assignment in HRT users and non-users (β = 0.131 and 0.190, respectively). Weight increases were associated with a greater change in trochanter BMD while weight decreases were associated with a smaller change in trochanter BMD. Figures 3 and 4 illustrate the result on bone in response to arbitrarily selected high and low values of BDI, vitality, and body weight changes.

In the subset of women who exercised (n = 140), the effects of vitality and BDI were examined after accounting for age, baseline BMD, HRT use, the change in body weight, baseline body weight, exercise compliance, calcium compliance and the cumulative amount of weight lifted over one year (Table 3). Increased vitality was associated with greater BMD changes at the femoral neck (p = 0.065). At all other sites, neither vitality nor BDI (or alternate depression indices) were related to BMD changes. Changes in body weight also were not related to BMD changes at any BMD site. The cumulative amount of weight lifted during the one year program predicted BMD changes (p < 0.01) at the greater trochanter.

**Discussion**

Factors that affect the loss of BMD in postmenopausal women are numerous and include age, exercise, HRT use, calcium intake, the loss of body weight and psychological factors. The
link between depression and bone loss has been documented in clinically depressed populations, mostly based on cross-sectional studies examining either those acutely ill with a major depressive episode (3,7,18) or those identified as depressed using standardized diagnostic checklists or interviews (3-5,19,20). In each case, lower regional BMD or elevated bone remodeling, a precursor to bone loss, was found in the depressed versus controls. Robbins (21) found a significant negative association between depression and hip BMD (measured once 2 years after the assessment of depression) in a large (n = 1566) random sample of males and females aged 65 – 100 years, 16% of whom were clinically depressed. In a sample of 102 Portuguese white women selected for elevated depression, those with osteoporosis were significantly more depressed (BDI = 16.6) than women without osteoporosis (BDI = 13) (22). In the only prospective study, Schweiger (6) found greater 2-year spine BMD loss in 18 depressed patients (receiving medication and outpatient treatment) compared to 21 controls. In contrast to most studies, Amsterdam (23) and Reginster (24) did not find a BMD depression relationship. However, in both studies, most (24) or all (23) of the analyses may have been limited due to low statistical power. Unique to our longitudinal study was an association between one-year BMD changes and initial levels of self-reported depressive symptoms and vitality, after accounting for several important covariates.

The present results, a secondary analysis of data from a previously published clinical trial (11), provide evidence that this link between depressive symptoms and bone loss exists in a population that exhibited much lower levels of depressive symptoms than those in previous studies (Figure 2). For example, the mean score on the BDI was 4.5 with a range of 0-27. The percent of individuals who scored greater than 9 on the BDI in the present study was 12.5% whereas 64.7% scored >9 in the Coehlo (22) study. We found that depressive symptoms were
significantly related to BMD changes at the femoral neck and accounted for an additional 2.2% of variation in that site. This is consistent with Michelson (4) and Reginster (24) who reported that the largest differences between the BMD of the depressed and non-depressed occurred at the femur. Also consistent with the present study, Robbins (21) reported that depression accounted for an additional 2% of the variability in the total hip BMD in a regression model accounting for age, race, gender, alcohol use, smoking, estrogen use and body mass index. Similar to both Amsterdam (23) and Reginster (24), we did not find significant effects of depressive symptoms on the BMD loss at the lumbar spine.

Depression is often associated with behavioral factors such as low activity levels or changes in body weight that could influence bone independently of other depressive symptomatology. While these behavioral factors contribute to bone loss in individuals who are depressed, depressive symptoms increase the one-year loss of BMD even after accounting for the influence of behavioral factors such as exercise group assignment, calcium supplement compliance, and changes in body weight. Hence, depression may exert its negative effect on bone through mechanisms that are, at least in part, unrelated to behavior. In addition, the influence of depressive symptoms on femoral neck BMD was larger than the exercise effect (Figure 4). Though one-year effects are generally small, the negative impact may become substantial if this depression-related loss persists long-term or if it is combined with other negative factors affecting BMD.

Sub-analyses performed on the women who exercised (n = 140) showed the impact of depressive symptoms or vitality on BMD changes after accounting for exercise compliance and weight lifted, rather than simply the exercise group assignment. BMD changes at the femoral neck were associated with self-reported vitality (p = 0.065), but not depressive symptoms (p =
Noteworthy was the persistence of vitality as a predictor of BMD changes even after accounting for the effects of HRT use, exercise program compliance, calcium supplement compliance, and the amount of weight lifted over the one-year program. The effect of low vitality on changes in BMD was not a function of poor program compliance or performance.

Although the present study was not designed to reduce body weight and the average body weight change was negligible (0.22 kg), there was a considerable range of changes in weight (-13.9 to +12.2 kg) (Figure 3) and these changes in weight had moderate effects on BMD changes. The effect of weight change was a more important factor affecting femoral neck bone changes than both exercise and HRT use (Figure 5). When only the exercisers were examined (Table 3), the amount of weight lifted was the most important factor affecting trochanter BMD changes and changes in body weight were not significant.

The phenomenon of weight loss associated bone loss has been reported consistently (25-31). Because of this, bone density clinical trials generally attempt to minimize weight loss throughout the intervention. Despite any investigators best efforts, moderate weight changes may occur and will confound the overall results. As covariates of bone density changes are identified, such as depressive symptoms or weight loss, investigators should account for their confounding effects when interpreting the final results of long-term exercise trials. Also, because weight loss and depression have differential site-specific effects, it is important for investigators to examine the femoral neck and greater trochanter areas rather than only “total hip” BMD.

In summary, the negative impact of depressive symptoms on BMD in this population of postmenopausal women was independent of changes in body weight and varying calcium
compliance, and was not ameliorated by assignment to a strength-training program. Further, the impact of depressive symptoms (at the femoral neck) and weight change (at the greater trochanter) was comparable to or exceeded the impact of hormone use and exercise training. These results suggest that the presence of depressive symptoms may be clinically relevant with regard to bone health. Future bone density clinical trials should control for the change in body weight and for depressive symptoms when assessing the osteogenic potential of any intervention.

Acknowledgements: Supported by the National Institute for Arthritis, and Musculoskeletal and Skin Diseases, National Institutes of Health (AR39559) and by Mission Pharmacal (San Antonio, TX). Address correspondence to: Laura A. Milliken, PhD., Department of Exercise and Health Sciences, University of Massachusetts Boston, 100 Morrissey Blvd., Boston, MA 02125 Email: laurie.milliken@umb.edu
References


Table 1: Subject Physical Characteristics (n = 264).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>55.6</td>
<td>4.8</td>
<td>40.2</td>
<td>66.3</td>
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<tr>
<td>Baseline BMI (kg/m$^2$)</td>
<td>25.6</td>
<td>3.8</td>
<td>17.9</td>
<td>35.5</td>
</tr>
<tr>
<td>Baseline Weight (kg)</td>
<td>68.3</td>
<td>11.5</td>
<td>46.1</td>
<td>110.7</td>
</tr>
<tr>
<td>Baseline Height (cm)</td>
<td>163.3</td>
<td>6.6</td>
<td>144.0</td>
<td>185.6</td>
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<tr>
<td>1 Year Weight Change (kg)</td>
<td>0.22</td>
<td>3.1</td>
<td>-13.9</td>
<td>12.2</td>
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<tr>
<td>1-Year Calcium Compliance (%)</td>
<td>91.2</td>
<td>14.3</td>
<td>4</td>
<td>114</td>
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<tr>
<td>Baseline Vitality Score (SF-36)</td>
<td>68.13</td>
<td>17.7</td>
<td>5</td>
<td>100</td>
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<td>Baseline BDI</td>
<td>4.52</td>
<td>4.5</td>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td>Baseline BMD (g/cm$^2$)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femur Neck</td>
<td>0.873</td>
<td>0.121</td>
<td>0.616</td>
<td>1.291</td>
</tr>
<tr>
<td>Trochanter</td>
<td>0.745</td>
<td>0.110</td>
<td>0.490</td>
<td>1.194</td>
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<tr>
<td>Spine (L2-4)</td>
<td>1.130</td>
<td>0.155</td>
<td>0.739</td>
<td>1.719</td>
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<tr>
<td>1 Year Change in BMD (g/cm$^2$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femur Neck</td>
<td>0.0056</td>
<td>0.033</td>
<td>-0.0960</td>
<td>0.0940</td>
</tr>
<tr>
<td>Trochanter</td>
<td>0.0063</td>
<td>0.028</td>
<td>-0.1060</td>
<td>0.0810</td>
</tr>
<tr>
<td>Spine (L2-4)</td>
<td>0.0034</td>
<td>0.027</td>
<td>-0.0730</td>
<td>0.0890</td>
</tr>
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</table>
Table 2: Standardized regression coefficients for the prediction of BMD changes over one year for covariates plus the change in body weight and either vitality or depressive symptoms (n = 264). Adjusted $R^2$ is for the variables indicated plus age, baseline BMD, and baseline body weight.

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Femoral Neck Models</th>
<th>Trochanter Models</th>
<th>Spine Models</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise effect (for HRT users)</td>
<td>0.053</td>
<td>0.070</td>
<td>0.061</td>
</tr>
<tr>
<td>Exercise effect (for HRT non-users)</td>
<td>0.105‡</td>
<td>0.101‡</td>
<td>0.078</td>
</tr>
<tr>
<td>Calcium Compliance</td>
<td>-0.014</td>
<td>-0.031</td>
<td>-0.031</td>
</tr>
<tr>
<td>HRT Use</td>
<td>0.171*</td>
<td>0.162*</td>
<td>0.143*</td>
</tr>
<tr>
<td>$R^2$ (for Covariates)</td>
<td>5.5</td>
<td>5.5</td>
<td>4.3</td>
</tr>
<tr>
<td>Change in body weight</td>
<td>0.020</td>
<td>0.022</td>
<td>0.011</td>
</tr>
<tr>
<td>Vitality</td>
<td>0.130†</td>
<td>-0.017</td>
<td></td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>-0.139‡</td>
<td></td>
<td>0.027</td>
</tr>
<tr>
<td>“Depressed Much of Past Year” (n = 243)</td>
<td></td>
<td>-0.175*</td>
<td></td>
</tr>
<tr>
<td>$R^2$ (Overall)</td>
<td>6.5</td>
<td>6.7</td>
<td>6.4</td>
</tr>
</tbody>
</table>

* $p < 0.01$
† $p < 0.05$
‡ $p < 0.10$
Table 3: Standardized regression coefficients for the prediction of BMD changes over one year for exercisers including the change in body weight and either vitality or depression (n = 140). Adjusted $R^2$ is for the variables indicated plus age, baseline BMD, and baseline body weight.

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Femoral Neck Models</th>
<th>Trochanter Models</th>
<th>Spine Models</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRT Use</td>
<td>0.112 0.122</td>
<td>0.108 0.106</td>
<td>0.179† 0.178†</td>
</tr>
<tr>
<td>Calcium Compliance</td>
<td>0.191‡ 0.160</td>
<td>0.103 0.127</td>
<td>0.157 0.125</td>
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<tr>
<td>Exercise Compliance</td>
<td>-0.144 -0.136</td>
<td>-0.280‡ -0.291‡</td>
<td>-0.012 0.010</td>
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<tr>
<td>Weight Lifted</td>
<td>0.041 0.051</td>
<td>0.444* 0.464*</td>
<td>0.057 0.013</td>
</tr>
<tr>
<td>$R^2$ (for Covariates)</td>
<td>1.0 1.0</td>
<td>8.4 8.4</td>
<td>4.3 4.3</td>
</tr>
<tr>
<td>Change in Body Weight</td>
<td>0.107 0.100</td>
<td>0.113 0.117</td>
<td>0.028 0.020</td>
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<tr>
<td>Vitality</td>
<td>0.162‡</td>
<td>0.010</td>
<td>-0.069</td>
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<tr>
<td>Beck Depression Inventory</td>
<td>-0.121</td>
<td>0.090</td>
<td>-0.115</td>
</tr>
<tr>
<td>$R^2$ (Overall)</td>
<td>3.2 1.9</td>
<td>8.1 8.8</td>
<td>3.4 4.1</td>
</tr>
</tbody>
</table>

* p < 0.01
† p < 0.05
‡ p < 0.10
Figure 1: Participant recruitment and randomization.
Figure 2: Frequency distribution for the Beck Depression Inventory (n = 264).
Figure 3: Frequency distribution for the one year change in body weight (n = 264)
Figure 4: Changes in BMD for high and low depression and vitality scores and exercise group status.
Figure 5: Changes in femur and trochanter BMD for the mean and 2 SDs above and below the mean for the change in weight.