Effect of a lifestyle intervention on bone mineral density in premenopausal women: a randomized trial


ABSTRACT

Background: The positive association between body weight and bone mineral density (BMD) is well documented; in contrast, the effect of changes in body weight on BMD is not well understood, particularly, in normal-weight populations.

Objective: We examined the effect of a lifestyle intervention aimed at lowering dietary fat intake and increasing physical activity to produce modest weight loss or prevent weight gain on BMD in a population of 236 healthy, premenopausal women aged 44–50 y.

Design: All women were participating in a clinical trial known as The Women’s Healthy Lifestyle Project and were randomly assigned to intervention or control groups. Dual-energy X-ray absorptiometry of BMD at the lumbar spine and proximal femur were made before and after 18 mo of participation in the trial.

Results: The intervention group (n = 115) experienced a mean (±SD) weight loss of 3.2 ± 4.7 kg over the 18 mo compared with a weight gain of 0.42 ± 3.6 kg in the control group (n = 121) (P < 0.001). The annualized rate of hip BMD loss was 2-fold higher (P < 0.015) in the intervention group (0.81 ± 1.3%) than in the control group (0.42 ± 1.1%); a similar, although nonsignificant pattern was observed for the loss in spine BMD: 0.70 ± 1.4% and 0.37 ± 1.5% (P = 0.093) in the intervention and control groups, respectively. Large increases in physical activity attenuated spine BMD loss, but had no significant effect on BMD loss at the hip.

Conclusions: The intervention group, who modified their lifestyle to lose weight, had a higher rate of BMD loss at the hip and lumbar spine than did the weight-stable control group. Recommendations for weight loss must be made with consideration that such an endorsement may result in BMD loss.

KEY WORDS Bone mineral density, premenopausal women, body weight, weight loss, osteoporosis, physical activity, bone markers, osteocalcin, N-telopeptides, The Women’s Healthy Lifestyle Project

INTRODUCTION

Greater body weight is associated with greater bone mineral density (BMD), particularly at the weight-bearing sites of the axial skeleton (1–4). Heavier women tend to have a lower risk of osteoporosis and related fractures than do slender women (5–8). There is little consensus, however, on whether changes in body weight are related to changes in BMD. Earlier studies examining weight loss and bone loss largely focused on obese subjects who were undergoing severe dietary restriction or gastrointestinal surgery, thereby limiting the generalizability of the results (9, 10). Moreover, less accurate and precise methods of measuring BMD, such as photon absorptiometry, were used (9). More recently, Compston et al (11) reported a 2.5% total-body bone loss after 11 wk of a severely energy-restrictive diet (1693 kJ/d) in pre- and postmenopausal women. Similarly, in moderately overweight, premenopausal women, a mean weight loss of 3.4 kg after 6 mo of dietary restriction was accompanied by significant bone loss at the total body and lumbar spine (12). There are limited data on whether similar changes occur when exercise is included as a component of the intervention. Svendsen et al (13) compared an energy-restrictive dietary intervention with and without aerobic exercise and weight training and found no additional benefit of exercise on weight-loss-induced changes in BMD.

Recent public health efforts have advocated low-fat diets and increased physical activity as effective lifestyle changes for preventing cardiovascular disease. There is essentially, however, no information on the effect of this recommendation on other important health conditions influencing women’s health, such as osteoporosis. The objective of this study was to examine the effect of a lifestyle intervention, aimed at modest weight loss and prevention of weight gain through a low-fat diet and exercise program, on changes in BMD at the lumbar spine and total hip in healthy, free-living, premenopausal women.

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SUBJECTS AND METHODS

Subjects

Five hundred thirty-five premenopausal women aged 44–50 y were recruited from August 1992 to March 1994 to participate in The Women’s Healthy Lifestyle Project, a randomized clinical trial designed to test the hypothesis that an increase in LDL cholesterol and body weight in women as they traverse menopause can be prevented by a low-fat diet and exercise intervention (14, 15). Participants were recruited from a random sample of registered voters by selected zip codes in Allegheny County, PA. The protocol was approved by the Human Investigation Review Board at the University of Pittsburgh and written, informed consent was obtained from each participant.

To be eligible for this study, the women had to be in good general health; be aged 44–50 y; be <3 mo amenorrheic in the 6 mo before the initial telephone interview (in nonsurgically induced menopause); not be receiving hormone replacement therapy; have a diastolic blood pressure <95 mm Hg; have a body mass index (BMI; in kg/m²) between 20 and 34; have a fasting glucose concentration <7.7 mmol/L; have an LDL-cholesterol concentration between 2.1 and 4.1 mmol/L; have a total cholesterol concentration between 3.6 and 6.7 mmol/L; not be taking any lipid-lowering, insulin, thyroid, antihypertensive, or psychotropic medications; not have received any treatment for cancer in the past 5 y; and not have participated in a commercial weight-reduction program within the past 4 mo.

We measured BMD in 513 women at the baseline clinic exam or within 6 mo of their baseline exam. Thirty-three women were excluded from the BMD study because they were not white and we had limited power to examine racial differences in BMD. We excluded 48 women who started hormone replacement therapy, 14 women who became perimenopausal, and 10 women who were perimenopausal, leaving 408 women. A total of 172 women had recently undergone menopause; not be receiving hormone replacement therapy; be aged 44–50 y; be <3 mo amenorrheic in the 6 mo before the initial telephone interview (in nonsurgically induced menopause); not be receiving hormone replacement therapy; have a diastolic blood pressure <95 mm Hg; have a body mass index (BMI; in kg/m²) between 20 and 34; have a fasting glucose concentration <7.7 mmol/L; have an LDL-cholesterol concentration between 2.1 and 4.1 mmol/L; have a total cholesterol concentration between 3.6 and 6.7 mmol/L; not be taking any lipid-lowering, insulin, thyroid, antihypertensive, or psychotropic medications; not have received any treatment for cancer in the past 5 y; and not have participated in a commercial weight-reduction program within the past 4 mo.

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Study design

Participants were randomly assigned to a lifestyle intervention group or a control group. Participants in the intervention group attended 15 group meetings during the first 20 wk and both groups received clinic assessments 6 and 18 mo after their group attended 15 group meetings during the first 20 wk and use of the DXA software were used. The scans were analyzed with Hologic software version 7.10 with the compare feature. The within-subject CVs with a similar protocol were 1.5% and 1.3% for the spine and femoral neck, respectively (18). BMD data are presented as annualized percentage changes.

Markers of bone turnover

Of the 236 women, only 134 had complete serum and urine samples at both baseline and 18 mo. Osteocalcin was measured with a solid-phase sandwich-type immunochemiluminometric assay that used 2 antibodies, 1 polyclonal and 1 monoclonal antibody, in a 12-h fasting serum sample collected by venipuncture and stored at −70°C. N-Telopeptide was measured from a fasting urine sample stored at −70°C by using an enzyme-linked immunoassay assay with a monoclonal antibody to N-telopeptide labeled with peroxidase. The assay is sensitive to 20 nmol bone collagen equivalents/L. All measurements were performed in duplicate and in batches by Endocrine Sciences Laboratory, Los Angeles.
TABLE 1
Characteristics at enrollment of women in the intervention and control groups

<table>
<thead>
<tr>
<th></th>
<th>Intervention (n = 115)</th>
<th>Control (n = 126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>46.7 ± 1.7†</td>
<td>46.8 ± 1.8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.5 ± 9.7</td>
<td>66.6 ± 10.0</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.8 ± 3.3</td>
<td>25.1 ± 3.4</td>
</tr>
<tr>
<td>BMI category (%)</td>
<td>≤ 24.44</td>
<td>54.8 [63]</td>
</tr>
<tr>
<td></td>
<td>24.45–26.44</td>
<td>48.8 [59]</td>
</tr>
<tr>
<td></td>
<td>≥ 26.45</td>
<td>18.3 [21]</td>
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<tr>
<td></td>
<td></td>
<td>22.3 [27]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>27.0 [31]</td>
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<tr>
<td></td>
<td></td>
<td>28.9 [35]</td>
</tr>
<tr>
<td>Dietary intake</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total energy intake (kJ/d)</td>
<td>6220 ± 2315</td>
<td>5863 ± 1960</td>
</tr>
<tr>
<td>Total fat (%)</td>
<td>32.2 ± 6.5</td>
<td>32.9 ± 8.0</td>
</tr>
<tr>
<td>Saturated fat (%)</td>
<td>11.7 ± 2.9</td>
<td>11.7 ± 3.1</td>
</tr>
<tr>
<td>Calcium (mg/d)</td>
<td>804 ± 416</td>
<td>825 ± 486</td>
</tr>
<tr>
<td>Suplemental calcium (mg/d)</td>
<td>96 ± 179</td>
<td>114 ± 235</td>
</tr>
<tr>
<td>Physical activity (kJ/wk)²</td>
<td>4224</td>
<td>3432</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>5.2 [6]</td>
<td>8.3 [10]</td>
</tr>
<tr>
<td>Bone mineral density (g/cm²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumbar spine (L1–L4)</td>
<td>1.037 ± 0.11</td>
<td>1.031 ± 0.11</td>
</tr>
<tr>
<td>Total hip</td>
<td>0.925 ± 0.12</td>
<td>0.917 ± 0.11</td>
</tr>
<tr>
<td>Body composition (kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total fat mass</td>
<td>24.6 ± 7.7</td>
<td>25.6 ± 7.6</td>
</tr>
<tr>
<td>Trunk fat mass</td>
<td>9.6 ± 3.8</td>
<td>10.1 ± 4.1</td>
</tr>
<tr>
<td>Total nonfat mass</td>
<td>40.3 ± 4.4</td>
<td>40.0 ± 4.6</td>
</tr>
<tr>
<td>Markers of bone turnover</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-telopeptides (nmol BCE/L)</td>
<td>31.0 [68]</td>
<td>35.0 [66]</td>
</tr>
<tr>
<td>Osteocalcin (µg/L)</td>
<td>9.2</td>
<td>9.4</td>
</tr>
</tbody>
</table>

† Median. § Mean. | SD; † in brackets. There were no significant differences between groups. BCE, bone collagen equivalents.

Statistical analyses

SAS software (version 6.12; SAS Institute Inc, Cary, NC) was used for all analyses (19). Results are presented as means ± SDs unless otherwise indicated. Percentage weight change was calculated over the entire 18-mo period. Comparisons between the intervention and control groups were conducted using an intention-to-treat analysis. Pearson product-moment correlations were used to examine the relation between change in weight and activity. The strength of association between percentage changes in body wt and change in BMD was examined. The association between percentage changes in weight and activity was dichotomized as follows: 1) an increase of ≥4180 kJ/wk (approximately the upper 25th percentile) and 2) an increase from baseline to follow-up of < 4180 kJ/wk.

Within the intervention group, simple linear regression was performed to examine the relation between the change in weight and change in BMD. The association between changes in weight and BMD were similar whether weight was expressed as either a percentage change or absolute change. Separate analyses were performed for baseline BMI categories: (≤ 24.44 compared with ≥ 24.45). Multiple regression analyses were conducted with baseline BMD and activity levels and changes in both weight and activity as the independent variables and with percentage change in BMD as the dependent variable. General linear models were used to test for differences in BMD by changes in weight and activity categories. Adjustment for significant covariates, including baseline BMD and activity, were made. The significance level was 0.05 and Bonferroni adjustments were made for multiple comparisons.

RESULTS

Characteristics of the subjects

There were no significant differences in baseline characteristics for age, weight, BMI, or dietary intake between the intervention and control groups (Table 1). The total percentage fat in the diet was 32% for both groups, with 12% derived from saturated fat. Dietary calcium intake was not significantly different between the 2 groups, with 39% of women in the intervention group and 46% of women in the control group having intakes at or above the recommended dietary allowance of 800 mg/d (20). There were no significant differences in baseline BMD, fat mass, or nonfat mass between the 2 groups. The median baseline measurements of urinary N-telopeptide, a marker of bone resorption, and serum osteocalcin, a marker of bone formation, were not significantly different between the intervention and control groups.

Weight change: efficacy of intervention

Women in the intervention group lost 3.2 ± 4.7 kg (4.5 ± 6.4% of body wt) over the 18-mo period, whereas the control subjects gained 0.42 ± 3.6 kg (0.69 ± 5.2% of body wt) (Table 2). There were also significant decreases in total fat mass, but not in total nonfat mass, in the intervention and control groups. The increase in total energy expenditure was significantly greater from baseline to 18 mo in the intervention group than in the control group. Dietary calcium intake increased in the intervention group, but declined in the control group over the 18-mo study period. Mean energy intakes at 18 mo were virtually identical in the intervention and control groups: 5408 ± 1723 and 5407 ± 1076 kJ/d, respectively. Total dietary fat intake was significantly lower in the intervention group than in the control group at 18 mo.

Weight change and BMD change

Annualized rates of BMD loss at the spine and hip were almost twice as high in the intervention group as in the control group (Figure 1). Adjustment for baseline BMD did not significantly alter these results.
and −0.20 ± 1.8%/y, respectively). Correlations between changes in body weight and composition with changes in BMD over the 18-mo period ranged from r = 0.02 to r = 0.30.

**Determinants of BMD loss**

Percentage weight change from baseline to 18 mo explained 9.8% and 7.7% of the variance in spine and hip BMD changes, respectively (P < 0.005). When we examined the association between percentage weight change and BMD change within baseline BMI categories (≤24.44 (n = 63) and ≥24.45 (n = 52)), there were no significant differences in the strength of the association between weight loss and BMD loss across BMI categories.

Within the intervention group, we compared women who experienced the greatest percentage weight loss over the 18-mo period with all others: upper quartile (≥ 8.0%; n = 29) compared with the lower 75th percentile (< 8.0%; n = 85). Women in the top quartile for weight loss experienced > 3 times the rate of BMD loss of all other women, even after adjustment for baseline BMI (β = 0.26%/y) than those who increased their activity levels by < 4180 kJ/wk (−0.14%/y), even after adjustment for baseline energy expenditure and BMD and percentage change in weight. When we entered the change in energy expenditure and the percentage change in weight over the 18-mo period as dichotomous variables into a multiple regression model predicting spine BMD loss, both had significant main effects, after adjustment for baseline BMD and activity level. Women who experienced a loss in body weight of ≥8.0% and who increased their energy expenditure by < 4180 kJ/wk (n = 21) had significantly greater spine BMD loss than both women with a weight loss of ≥8.0% who increased their energy expenditure by ≥4180 kJ/wk (n = 68) and women with a weight loss of < 8.0% and an increase in activity of ≥4180 kJ/wk (n = 17) (Figure 3). Similar findings, however, were not observed at the hip.

**DISCUSSION**

In this population of healthy women, a lifestyle intervention aimed at diet- and exercise-induced weight loss was associated with a 2-fold greater rate of loss in hip BMD (P = 0.015); a similar, although nonsignificant, pattern was observed for spine BMD. Women who lost the most weight tended to lose the most BMD; these women also experienced the greatest increases in urinary N-telopeptide, a marker of bone resorption. The strength of the association between weight loss and BMD loss was independent of baseline body weight, BMI, or BMD. The modest increments in activity levels from baseline to follow-up had an attenuating effect on BMD loss at the spine, but not at the hip.

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**TABLE 2**

Changes in body size and lifestyle factors during the 18-mo study in the intervention and control groups

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>−3.2 ± 4.7†</td>
<td>0.42 ± 3.6</td>
</tr>
<tr>
<td>Total fat mass (kg)</td>
<td>−3.5 ± 4.2‡</td>
<td>−0.93 ± 3.9</td>
</tr>
<tr>
<td>Total nonfat mass (kg)</td>
<td>0.55 ± 1.5</td>
<td>0.58 ± 3.3</td>
</tr>
<tr>
<td>Physical activity (kJ/d)</td>
<td>1618 ± 5855‡</td>
<td>262 ± 4225</td>
</tr>
<tr>
<td>Dietary calcium (mg/d)</td>
<td>31.9 ± 433</td>
<td>−54.1 ± 416</td>
</tr>
<tr>
<td>Supplemental calcium (mg/d)</td>
<td>121 ± 325‡</td>
<td>25 ± 226</td>
</tr>
<tr>
<td>Total energy intake (kJ/d)</td>
<td>−722 ± 2122</td>
<td>−421 ± 1976</td>
</tr>
<tr>
<td>Total dietary fat (g/d)</td>
<td>−19.9 ± 21.4‡</td>
<td>−6.2 ± 21.7</td>
</tr>
<tr>
<td>(%)</td>
<td>−8.6 ± 6.2‡</td>
<td>−1.5 ± 6.0</td>
</tr>
</tbody>
</table>

†SE: ‡Significantly different from the control group: †P = 0.0001, ‡P = 0.039, †P = 0.0002.

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**FIGURE 1.** Mean (±SE) annualized percentage changes in lumbar spine and total hip bone mineral density (BMD) in the intervention (shaded bars ■; n = 115) and control (open bars □; n = 121) groups. *Nearly significantly different from the control group, P = 0.093; †significantly different from the control group, P = 0.015.
perhaps reflecting differences in the proportion of trabecular and cortical bone at these sites. It is possible that the intensity of the physical activity intervention was not sufficient to exert an independent effect on BMD or to overcome the negative effect of weight loss. Numerous studies have shown that moderate aerobic physical activity can increase BMD, reduce the rate of BMD loss, or both (21–25); however, these studies were not specifically aimed at successful weight loss. Additional prospective studies should examine the effects of weight loss on BMD with and without a physical activity intervention.

Results of previous cross-sectional studies are not directly comparable with the results of the present study because they relied on self-report of weight change over a period of time in the past (26, 27). Moreover, results of previous longitudinal studies are not directly comparable either because of their limited generalizability and the short duration of the study (9–13, 28, 29).

Several mechanisms may explain the loss of BMD with weight loss. First, with weight loss there is a decline in the mechanical stress on the weight-bearing skeleton that could influence bone remodeling. For example, nonsignificant reductions in markers of bone formation (13) and elevations in markers of bone resorption (30) have been reported among women consuming an energy-restrictive diet compared with control subjects. Similar results were shown in our study. Accordingly, women who lost the most weight experienced the largest increase in the percentage change in $N$-telopeptide, a marker of...

**FIGURE 2.** Median annualized percentage changes in markers of bone turnover (shaded bars ■, $N$-telopeptides; open bars □, osteocalcin) in women in the intervention group who lost $\geq 5.3\%$ of body weight ($n = 17$) and $< 5.3\%$ of body weight ($n = 51$) and in the control group ($n = 66$). *Significantly different from the intervention group who lost $< 5.3\%$ of body weight and the control group, $P = 0.052$.

**FIGURE 3.** Mean (±SE) annualized percentage changes in lumbar spine bone mineral density (BMD), adjusted for baseline BMD, baseline physical activity levels (low: < 4180 kJ/wk; high: $\geq 4180$ kJ/wk), and the interaction between percentage weight change and the change in activity level from baseline to follow-up (18 mo). Shaded bars ■ represent high weight loss ($\geq 8\%$ of body wt) and open bars □ represent low weight loss ($< 8\%$ of body wt). *Significantly different ($n = 21$) from those with low physical activity and low weight loss ($n = 68$) and those with high physical activity and low weight loss ($n = 17$), $P = 0.0001$. 

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bone resorption. These parallel changes in bone resorption and BMD loss support the hypothesis that weight-loss induced BMD loss may be mediated, at least in part, by alterations in bone remodeling.

Second, the association between BMD loss and weight may reflect a physiologic adaptation to a more normal weight and perhaps to a more appropriate BMD; this is not a likely explanation, however, given the modest weight loss (3.2 kg) observed in the intervention group. Third, declines in fat mass with weight loss may result in lower concentrations of androgen precursors for conversion to estrogens in peripheral tissues. Finally, weight-control programs may compromise the adequacy of calcium intake, although dietary calcium intake in this population was similar between intervention and control women; of interest, supplemental calcium intake was significantly higher in intervention than control women over the 18-mo study period.

This study had several limitations. There was no objective assessment of the women’s adherence to the intervention program other than their ability to achieve the weight-loss goals. In addition, sex hormone data were not available in this study, which would have ensured that the observed increase in bone resorption was not influenced by subtle changes in sex hormones. The fan-beam densitometer used in this study may have caused inherent magnification of scanned structures (31). This magnification, however, occurs in the mediolateral direction and not in the cranio-caudal direction, and hence, should not affect bone measurements (32, 33). Annualized changes in BMD may be artifactual because of compromises in both the accuracy and precision of DXA measurements; however, the parallel changes in the bone resorption markers indicated that this was unlikely. Recent improvements in DXA software, particularly for the hip and spine, support the reduced dependence on adjacent soft tissues and the ability of DXA to more reliably measure changes in BMD (34). Truncal fat may also effect the accuracy of spine measurements, although in a small study by Tothill and Pye (35), alterations in fat distribution during weight loss were independent of changes in spine BMD.

BMD was not measured at the 6-mo examination, limiting our ability to examine the effect of initial weight loss on BMD. In a study by Compston et al (11) in the 10-mo after the cessation of a dietary intervention, there were parallel regains in body weight and BMD. In contrast, Avenell et al (29) did not observe parallel gains in weight and BMD in the second 6-mo of a 1-y study. These observations raise several important questions about whether weight regain is accompanied by BMD regain and whether the BMD regained is of similar quality.

In summary, premenopausal and early perimenopausal women who were randomly assigned to a lifestyle intervention lost 3.2 kg over 18 mo and experienced rates of BMD loss at the hip that were 2-fold higher than those of weight-stable control subjects. About 50% of American women consume weight-reduction diets at some point (36); hence, the consequence of intentional and typically modest weight loss on BMD has widespread implications. Evaluation of the overall risks and benefits of weight reduction among overweight women needs to include effects on BMD and risks of osteoporosis as well as the consideration of the type, duration, and intensity of physical activity that may attenuate BMD loss. Achievement of weight loss while maintaining skeletal integrity is ideal. At present, recommendations for weight loss must be made with consideration that such an outcome may increase BMD loss.

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REFERENCES