Alendronate for the Treatment of Osteopenia in Anorexia Nervosa: A Randomized, Double-Blind, Placebo-Controlled Trial


Osteoporosis is a serious medical complication of anorexia nervosa, with no known effective treatment. We conducted a double-blinded, randomized trial comparing alendronate (10 mg daily) with placebo in 32 adolescents with anorexia nervosa (mean age, 16.9 ± 1.9 yr). All subjects received 1200 mg elemental calcium and 400 IU vitamin D daily and received the same multidisciplinary treatment for their eating disorder. Bone mineral densities (BMDs) of the lumbar spine and femoral neck were measured by dual energy x-ray absorptiometry at baseline and after 1 yr of treatment. Twenty-nine subjects completed the study. Femoral neck and lumbar spine BMDs increased 4.4 ± 6.4% and 3.5 ± 4.6% in the alendronate group compared with increases of 2.3 ± 6.9% and 2.2 ± 6.1% in the control group (P = 0.41, femoral neck; P = 0.53, lumbar spine). From baseline to follow-up, BMD increased significantly at the femoral neck (P = 0.02) and lumbar spine (P = 0.02) in those receiving alendronate, but did not increase in those assigned placebo (P = 0.22, femoral neck; P = 0.18, lumbar spine). At follow-up, body weight was the most important determinant of BMD. BMD was significantly higher in subjects who were weight-restored compared with those who remained at low weight (P = 0.002, femoral neck; P = 0.04, lumbar spine). After controlling for body weight, treatment group assignment still had an independent effect at the femoral neck. We conclude that in adolescents with anorexia nervosa, weight restoration is the most important determinant of BMD, but treatment with alendronate did increase the BMD of the lumbar spine and femoral neck within the group receiving alendronate, but not compared with placebo in the primary analysis. Until additional studies have demonstrated efficacy and long-term safety, the use of alendronate in this population should be confined to controlled clinical trials. (J Clin Endocrinol Metab 90: 3179–3185, 2005)

Osteoporosis is a major health problem worldwide. In the United States an estimated 25–30 million people suffer from osteoporosis at an estimated annual cost to the U.S. Health Care System in excess of $13.8 billion (1, 2). The development of osteoporosis in later life depends not only on the rate of bone loss in adulthood, but also on the amount of bone present at skeletal maturity. According to a recent National Institutes of Health consensus statement, “the bone mass attained early in life is perhaps the most important determinant of life-long skeletal health” (3). Peak bone mass is achieved during the late stages of pubertal development (4–9), and approximately 40–60% of peak bone mass is acquired during the adolescent years (7).

Anorexia nervosa in adolescence interferes with peak bone mass acquisition (10), thereby increasing the risk for osteoporosis. Although approximately one of 200 adolescent females develops anorexia nervosa, much larger numbers of adolescents have disordered eating without necessarily meeting the full criteria for anorexia nervosa (11) and may be at risk for reduced bone mass. Osteoporosis, or reduced bone mineral density (BMD), is a precursor of osteoporosis, and more than 90% of adolescents and young women with anorexia nervosa have reduced BMD at one or more sites (12, 13). In anorexia nervosa, reduction in bone mass can develop after a relatively short duration of illness (14), and the degree of osteopenia is more severe than that found in women with hypothalamic amenorrhea who are of normal weight (15). Despite intervention, osteopenia in anorexia nervosa is persistent and sometimes progressive (10, 13, 16–18) and is associated with increased long-term risk of fracture (19).

Alendronate, a potent aminobisphosphonate that inhibits osteoclast-mediated bone resorption, increases BMD and reduces fracture risk in postmenopausal women (20) and in men with osteoporosis (21) and increases bone mass in glucocorticoid-induced osteoporosis (22). Bisphosphonates have recently been studied in children and adolescents with a number of conditions associated with severe osteoporosis and increased fracture risk (23–25). To our knowledge, the use of alendronate in adolescents with anorexia nervosa has not been evaluated.

We chose to study the use of this medication in adolescents with anorexia nervosa because of the long-lasting morbidity associated with reduced bone mass in this condition and the relatively short window of opportunity for effective intervention. The aim of our randomized, double-blind, placebo-controlled pilot study was to test the hypothesis that, compared with placebo, treatment with oral alendronate would
increase the BMD of the lumbar spine and femoral neck in adolescents with anorexia nervosa.

Subjects and Methods

Subjects

Subjects were 32 adolescent females between the ages of 12 and 21 yr, who met Diagnostic and Statistical Manual for Mental Disorders-IV criteria for anorexia nervosa (26). Eligible subjects had either primary amenorrhea or secondary amenorrhea of greater than 6-months duration and had a lumbar vertebral spine BMD more than 1 sd below the age-matched mean (z-score, <−1.0). All subjects had a negative pregnancy test. Subjects were excluded from participation if they were already receiving hormone therapy (such as steroids or injectable or oral contraceptives) or if they had received such medication within 90 d of enrollment, if they had a history of self-induced vomiting, if they had a coexistent medical condition that could contribute to the osteopenia, or if they had any medical condition that precluded the administration of alendronate. Subjects with primary amenorrhea who had a bone age less than 13.0 yr were also excluded.

Power analysis

Sample size was estimated assuming an α of 0.05 with 80% power of finding a 4% difference in percent change in lumbar spine BMD between the groups over a 1-yr follow-up period. Our preliminary data showed that the mean percent change in spinal BMD after 12 months of follow-up in 28 adolescents with anorexia nervosa who did not receive pharmacological treatment was −0.03 ± 3.5%. Using a pooled sd of 3.5 and a two-tailed t test, a sample size of 15 in each group would be necessary to detect a 4% difference in percent change in lumbar spine BMD between the two groups.

Experimental protocol

Subjects were randomly assigned to receive either alendronate (Fosamax, Merck & Co., Inc., Rahway, NJ; 10 mg daily by mouth) or placebo in an identical capsule prepared by the hospital pharmacy. The randomization code was predetermined by the pharmacy, and randomization assignments were made in sequential order as subjects were enrolled. The randomization code was stored in a sealed envelope in the pharmacy until completion of the study. All study personnel and participants were blinded to treatment assignment for the duration of the study.

Patients were instructed to take the medication in the morning after rising and at least 30 min before the first food, drink, or medication of the day. All subjects received a daily multivitamin containing 400 IU vitamin D and a calcium supplement containing 1200 mg elemental calcium/d. Patients were instructed about the risks of becoming pregnant while on the medication, and those subjects who were sexually active were advised to use nonhormonal contraception to protect against pregnancy.

The study was approved by the North Shore-Long Island Jewish Health System human subjects review committee. Risks associated with the use of alendronate were carefully discussed with the adolescent and her family. Written informed consent was obtained from each subject. For those under 18 yr, written consent was obtained from a parent, and assent was obtained from the subject.

Baseline and follow-up studies

All subjects underwent a comprehensive medical, nutritional, and psychiatric evaluation. Subjects were weighed after voiding, wearing only underwear and a hospital gown. Body weight was measured to the nearest 0.1 kg using a digital scale. Height was measured with the patient barefoot, using a wall-mounted stadiometer. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared. The percentage of standard body weight (SBW) was determined from the National Center for Health Statistics tables (27), where SBW was defined as the median weight for age and height. Bone age of the left wrist was determined in subjects with primary amenorrhea.

Subjects underwent a semistructured clinical interview conducted by a child psychiatrist to confirm the diagnosis of anorexia nervosa according to Diagnostic and Statistical Manual for Mental Disorders-IV criteria. Seven-day diet records were analyzed by a registered dietician to determine daily calcium, phosphorus, magnesium, vitamin D, and total caloric intake using the University of Minnesota Nutrient Data System computer program (version 4.06, Minneapolis, MN). Blood was obtained for measurement of serum chemistries (including serum electrolytes, calcium, phosphorus, alkaline phosphatase, albumin, and liver function tests), estradiol, cortisol, IGF-I, and markers of bone formation [osteocalcin (OC) and bone-specific alkaline phosphatase (BSAP)]. Urine was obtained for a urine pregnancy test and measurement of urinary deoxypyridinoline (DPD), a marker of bone resorption. A second-void specimen of the day was collected to avoid diurnal variation. Urine and serum specimens were batched and frozen until assay in the pediatric endocrinology research laboratory.

Subjects were followed at 6 wk, 3 months, 6 months, 9 months, and 1 yr after initiation of treatment to check for side effects and monitor compliance by pill count. Subjects were asked to return bottles of medication with any remaining pills at each study visit. Subjects were considered to be compliant if they took the medication 90% or more of the days between visits. Serum chemistries, estradiol, cortisol, OC, BSAP, IGF-I, and urinary DPD were repeated at 6 and 12 months, and a urine pregnancy test was repeated at the end of the study. Bone densitometry was repeated after 12 months of treatment.

Measurement of BMD

BMD of the lumbar spine (L1-L4) and left hip (femoral neck, trochanter, Ward’s triangle, and total hip) was measured by dual energy x-ray absorptiometry using a QDR-4500 x-ray bone densitometer (Hologic, Inc., Waltham, MA). The coefficient of variation of repeated measurements using this equipment was less than 1%. The densitometer was calibrated every week using a phantom of known density, and daily calibrations checks were performed.

To correct for the confounding effect of changes in bone size, volumetric BMD (vBMD; in grams per cubic centimeter) of the lumbar spine and femoral neck was calculated using the formulas described by Katzman and Carter (7, 28). The t- and z-scores of the spine were calculated using Hologic software. For those under 20 yr of age, z-scores of the femoral neck were calculated from the applet of Bachrach, Hastie, and Narasimhan (http://stat-class.stanford.edu/pediatric-bones/).

One patient, who had moved out of state, had her repeat bone density study performed on a bone densitometer (Lunar Corp., Madison, WI). For this single patient, BMD scores were converted to standardized scores, and then percent increases were calculated using the method of Genant et al. (29).

Laboratory assays of hormones

Serum levels of estradiol and cortisol were measured by RIA using kits from Diagnostic Products Corp. (Los Angeles, CA). IGF-I was extracted from plasma using ethanol before its measurement using RIA kits (Nichols Institute Diagnostics, San Juan Capistrano, CA). Serum OC was measured using immunoradiometric assay kits (Diagnostic System Laboratories, Inc., Webster, TX). BSAP activity in the serum was measured using enzyme immunoassay kits (Metrabiosystems, Inc., Mountain View, CA). Urinary DPD was measured using an enzyme immunoassay-based Immulite instrument (Diagnostic Products Corp.). Intraassay coefficients of variation were less than 10%.

Statistical analysis

The primary hypothesis of this study was that patients treated with alendronate would have a greater percent change in lumbar spine and femoral neck BMD than those receiving placebo. The independent groups t test was used to detect differences in percent increases of lumbar spine and femoral neck BMD between groups. Our secondary hypothesis was that those subjects receiving alendronate would have a greater within-group change in BMD over time compared with those receiving placebo. The paired t test was used to detect changes in BMD of the lumbar spine and femoral neck within groups from baseline to follow-up. The independent groups t test was used to analyze clinical
and BMD variables between groups at baseline and follow-up. Repeated measures ANOVA was used to detect changes in markers of bone formation and bone resorption at baseline, 6 months, and 1 yr. All participants who underwent randomization were analyzed according to group assignment.

Pearson’s correlation coefficient was used to examine the relationships among BMD and the following predefined variables: body weight, BMI, caloric intake, calcium intake, vitamin D intake, and serum IGF-I, cortisol, and estradiol levels. A subgroup analysis was performed on weight restoration using ANOVA on BMD with treatment group, category of weight restoration (<85% and ≥85% SBW), and the interaction between treatment group and weight restoration category. A second subgroup analysis was performed on resumption of menses, adjusting for treatment group. Those variables found to be significant at \( P \leq 0.05 \) were then entered into a stepwise regression analysis to determine the relative influences of drug treatment, changes in body weight, resumption of menses, hormonal status, and nutritional intake on BMD. The 95% confidence intervals were computed for a number of variables, and the data are expressed as the mean ± SD (with a 95% confidence interval for selected variables). Data were analyzed using SPSS for Windows (version 10.0, SPSS, Inc., Chicago, IL).

### Results

#### Enrollment and retention of subjects

One hundred and eighteen subjects were assessed for eligibility for the study. Fifty-five did not meet study criteria, and 31 refused to participate. Thirty-two subjects were enrolled in the study, and of these, 15 were assigned active medication, and 17 were given placebo.

Three subjects withdrew from the study within 1 wk of enrollment (one from the active medication group and two from the placebo group). Two of the subjects withdrew before starting the medication. The other withdrew because of gastrointestinal complaints (dyspepsia), presumed, by the patient, to be caused by the medication. When the randomization code was subsequently revealed, that patient had been assigned placebo. Twenty-nine subjects completed the study protocol.

#### Clinical and anthropometric data

Subjects were all female and predominantly Caucasian. One subject was Hispanic. The mean age was 16.9 ± 1.9 yr (range, 13–21 yr). As expected, the subjects were malnourished (77.1 ± 6.6% of SBW; BMI, 16.4 ± 1.3 kg/m²). Five of 32 subjects (15.6%) had primary amenorrhea (three from the placebo group and two from the alendronate group). The remainder had secondary amenorrhea, with a mean duration of 20.8 ± 16.8 months.

The baseline demographic and clinical characteristics of each group are shown in Table 1. Subjects in the intervention and placebo groups were similar with respect to age, duration of illness, amount of weight lost, duration of amenorrhea, nutritional intake, amount of exercise performed, and degree of malnutrition. Twelve of the 32 subjects (six from each group) had been hospitalized within the month before enrollment and had already initiated nutritional rehabilitation.

#### Bone density data

The baseline and follow-up bone densitometry results are summarized in Table 2. At baseline, the intervention and control groups were similar with respect to baseline bone mineral content, BMD, t-scores, z-scores, and vBMD values.

### Table 1. Baseline demographic and clinical variables

<table>
<thead>
<tr>
<th></th>
<th>Alendronate (n = 15)</th>
<th>Placebo (n = 17)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>16.9 ± 1.6</td>
<td>16.9 ± 2.2</td>
<td>0.98</td>
</tr>
<tr>
<td>Duration illness (months)</td>
<td>25.7 ± 14.6</td>
<td>34.7 ± 28.0</td>
<td>0.28</td>
</tr>
<tr>
<td>Weight loss (kg)</td>
<td>14.2 ± 6.6</td>
<td>16.9 ± 8.3</td>
<td>0.33</td>
</tr>
<tr>
<td>Duration of amenorrhea (months)*</td>
<td>20.1 ± 17.5</td>
<td>19.9 ± 17.3</td>
<td>0.98</td>
</tr>
<tr>
<td>Caloric intake (kcal/24 h)</td>
<td>2025 ± 802</td>
<td>2431 ± 748</td>
<td>0.26</td>
</tr>
<tr>
<td>Calcium intake (mg/24 h)</td>
<td>996.1 ± 474</td>
<td>1348 ± 360</td>
<td>0.07</td>
</tr>
<tr>
<td>Vitamin D intake (µg/24 h)</td>
<td>5.2 ± 2.9</td>
<td>6.8 ± 4.1</td>
<td>0.31</td>
</tr>
<tr>
<td>Exercise (h/wk)</td>
<td>3.0 ± 4.8</td>
<td>1.2 ± 2.3</td>
<td>0.89</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>42.6 ± 4.28</td>
<td>42.9 ± 3.94</td>
<td>0.86</td>
</tr>
<tr>
<td>% Standard body weight</td>
<td>76.9 ± 7.1</td>
<td>77.3 ± 6.2</td>
<td>0.84</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>16.3 ± 1.4</td>
<td>16.4 ± 1.3</td>
<td>0.77</td>
</tr>
<tr>
<td>Estradiol (pg/ml)</td>
<td>43.4 ± 27.2</td>
<td>38.6 ± 16.8</td>
<td>0.58</td>
</tr>
<tr>
<td>Cortisol (µg/dl)</td>
<td>15.2 ± 7.4</td>
<td>14.4 ± 6.2</td>
<td>0.76</td>
</tr>
<tr>
<td>IGF-I (ng/ml)</td>
<td>229.3 ± 138</td>
<td>251.0 ± 114</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Values are the mean ± SD. Conversion to Systeme International units: estradiol: to obtain pmol/liter, multiply by 3.67; cortisol: to obtain nmol/liter, multiply by 27.586; IGF: to obtain nmol/liter, multiply by 0.1307.

* By independent groups t test.

** For those with secondary amenorrhea.

Our primary outcome measure was the difference in percent increase in BMD between the two groups over the 1-yr study period. BMD of the femoral neck increased 4.4 ± 6.4% in the alendronate group compared with a 2.3 ± 6.9% increase in the control group (\( P = 0.41 \)). Although these results did not reach statistical significance, there is a trend in favor of a positive effect of alendronate. Similarly, for the lumbar spine, BMD increased 3.5 ± 4.6% in the alendronate group vs. 2.2 ± 6.1% in the control group (\( P = 0.53 \)). In nine of 14 subjects (64.3%) who received alendronate, BMD of the hip increased 4% or more over the study period compared with such an increase in five of 15 (33.3%) who received placebo (\( P = 0.10 \)).

For our secondary analysis, both lumbar spine and femoral neck BMD increased significantly in the alendronate group from baseline to follow-up [for the spine: 0.788 ± 0.09 to 0.815 ± 0.10; mean difference, 0.027; 95% confidence interval (CI), 0.006–0.048; \( P = 0.02 \); for the femoral neck: 0.721 ± 0.10 to 0.753 ± 0.11; mean difference, 0.032; 95% CI, 0.005–0.059; \( P = 0.02 \)]. In contrast, there was no significant increase in the group that received placebo (for the spine: 0.783 ± 0.06 to 0.800 ± 0.08; mean difference, 0.017; 95% CI, 0.009–0.043; \( P = 0.18 \); for the femoral neck: 0.671 ± 0.10 to 0.687 ± 0.11; mean difference, 0.016; 95% CI, -0.01 to 0.042; \( P = 0.22 \); Fig. 1). Similarly, there were significant increases in BMD of the trochanter (\( P = 0.04 \)) and Ward’s triangle (\( P = 0.004 \)) in the alendronate group, with no significant changes in the control group.

At 1-yr follow-up, vBMD of the femoral neck was significantly higher in the group that received alendronate (0.184 ± 0.05 vs. 0.151 ± 0.03; \( P = 0.04 \); Fig. 2), but there were no significant differences in absolute values of bone mineral content, BMD, t-scores, or z-scores of the lumbar spine or hip between the two groups (Table 2). The absolute change in vBMD of the femoral neck was significantly greater in those receiving alendronate (\( P < 0.05 \)).

Both groups gained weight during the study period (13.5 ± 9.9% for the intervention group and 16.2 ± 16.4% for...
TABLE 2. Baseline and follow-up bone densitometry data by treatment group

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline (n = 15)</th>
<th>1 yr (n = 14)</th>
<th>Change</th>
<th>Baseline (n = 17)</th>
<th>Follow-up (n = 15)</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lumbar spine</strong></td>
<td></td>
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<tr>
<td>BMC (g)</td>
<td>42.1 ± 8.9</td>
<td>43.2 ± 9.2</td>
<td>2.0 ± 3.0</td>
<td>42.3 ± 5.9</td>
<td>42.9 ± 5.3</td>
<td>0.5 ± 3.4</td>
</tr>
<tr>
<td>BMD (g/cm²)</td>
<td>0.795 ± 0.09</td>
<td>0.815 ± 0.10</td>
<td>0.027 ± 0.04</td>
<td>0.780 ± 0.07</td>
<td>0.800 ± 0.08</td>
<td>0.017 ± 0.05</td>
</tr>
<tr>
<td>t-Score</td>
<td>-2.3 ± 0.82</td>
<td>-2.2 ± 0.87</td>
<td>0.19 ± 0.28</td>
<td>-2.4 ± 0.60</td>
<td>-2.2 ± 0.68</td>
<td>0.16 ± 0.43</td>
</tr>
<tr>
<td>z-Score</td>
<td>-1.9 ± 0.81</td>
<td>-1.9 ± 0.87</td>
<td>0.14 ± 0.35</td>
<td>-2.0 ± 0.69</td>
<td>-1.9 ± 0.69</td>
<td>0.04 ± 0.50</td>
</tr>
<tr>
<td>vBMD (g/cm³)</td>
<td>0.110 ± 0.009</td>
<td>0.103 ± 0.03</td>
<td>-0.007 ± 0.03</td>
<td>0.107 ± 0.009</td>
<td>0.110 ± 0.01</td>
<td>0.003 ± 0.01</td>
</tr>
<tr>
<td>% Increase in BMD</td>
<td>3.5 ± 4.6</td>
<td></td>
<td></td>
<td>2.2 ± 6.1</td>
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<tr>
<td><strong>Femoral neck</strong></td>
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<tr>
<td>BMC (g)</td>
<td>3.52 ± 0.74</td>
<td>3.26 ± 0.92</td>
<td>-0.2 ± 0.6</td>
<td>3.14 ± 0.49</td>
<td>3.17 ± 0.64</td>
<td>0.05 ± 0.5</td>
</tr>
<tr>
<td>BMD (g/cm²)</td>
<td>0.725 ± 0.09</td>
<td>0.753 ± 0.11</td>
<td>0.032 ± 0.05</td>
<td>0.672 ± 0.09</td>
<td>0.687 ± 0.11</td>
<td>0.016 ± 0.05</td>
</tr>
<tr>
<td>t-Score</td>
<td>-1.1 ± 0.83</td>
<td>-0.98 ± 0.90</td>
<td>0.25 ± 0.42</td>
<td>-1.6 ± 0.80</td>
<td>-1.49 ± 0.94</td>
<td>0.127 ± 0.43</td>
</tr>
<tr>
<td>z-Score</td>
<td>-1.4 ± 0.87</td>
<td>-1.3 ± 1.09</td>
<td>0.16 ± 0.43</td>
<td>-1.8 ± 0.62</td>
<td>-1.8 ± 0.86</td>
<td>-0.01 ± 0.41</td>
</tr>
<tr>
<td>vBMD (g/cm³)</td>
<td>0.152 ± 0.02</td>
<td>0.184 ± 0.05</td>
<td>0.034 ± 0.05</td>
<td>0.146 ± 0.03</td>
<td>0.151 ± 0.03ab</td>
<td>0.004 ± 0.02ab</td>
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<tr>
<td>% Increase in BMD</td>
<td>4.4 ± 6.4</td>
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<td>2.3 ± 6.9</td>
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<tr>
<td><strong>Trochanter</strong></td>
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<tr>
<td>BMC (g)</td>
<td>0.621 ± 0.07</td>
<td>0.637 ± 0.08</td>
<td>0.016 ± 0.03</td>
<td>0.569 ± 0.08</td>
<td>0.575 ± 0.08</td>
<td>0.018 ± 0.03</td>
</tr>
<tr>
<td>BMD (g/cm²)</td>
<td>0.698 ± 0.12</td>
<td>0.737 ± 0.13</td>
<td>0.045 ± 0.05</td>
<td>0.640 ± 0.11</td>
<td>0.649 ± 0.13</td>
<td>0.011 ± 0.07</td>
</tr>
<tr>
<td>% Increase in BMD</td>
<td>2.67 ± 4.4</td>
<td></td>
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<td>0.01 ± 2.7</td>
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<tr>
<td>Ward’s triangle</td>
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<tr>
<td>BMD (g/cm²)</td>
<td>3.66 ± 6.6</td>
<td>3.73 ± 6.9</td>
<td>0.045 ± 0.05</td>
<td>0.640 ± 0.11</td>
<td>0.649 ± 0.13</td>
<td>0.011 ± 0.07</td>
</tr>
<tr>
<td>% Increase in BMD</td>
<td>3.66 ± 6.6</td>
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<td></td>
<td>1.9 ± 11.4</td>
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<tr>
<td><strong>Total hip</strong></td>
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<tr>
<td>BMC (g)</td>
<td>0.783 ± 0.11</td>
<td>0.813 ± 0.11</td>
<td>0.026 ± 0.06</td>
<td>0.735 ± 0.10</td>
<td>0.742 ± 0.12</td>
<td>0.011 ± 0.06</td>
</tr>
<tr>
<td>% Increase in BMD</td>
<td>3.6 ± 8.5</td>
<td></td>
<td></td>
<td>1.6 ± 8.7</td>
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</tbody>
</table>

BMC, Bone mineral content.
* P < 0.05, alendronate vs. placebo at 1-yr follow-up (by independent groups t test).
* P < 0.05, analysis of change in BMD, alendronate vs. placebo (by independent groups t test).

...and femoral neck (r = 0.66; P < 0.002). At 1 yr, for both the spine and femoral neck, there was no significant correlation between BMD and caloric intake, calcium intake, vitamin D intake, or estradiol or cortisol levels. Baseline IGF-I, cortisol, and estradiol levels did not predict responses. Using stepwise regression analysis for follow-up BMD at the femoral neck, body weight and treatment group contributed 30.7% and 14% of the variance in BMD, respectively. After controlling for body weight, treatment with alendronate still had an independent effect on BMD of the femoral neck (P = 0.02). Treatment with alendronate resulted in a 0.002 g/cm² or 14.3% increase in BMD at the femoral neck. For the lumbar spine, body weight at follow-up and change in body weight over the year were the most important determinants of BMD at 1-yr follow-up, accounting for 47.3% of the variance. Treatment group assignment did not add significantly to this model.

At the end of the study period, 15 of 29 subjects (51.7%), were weight-restored, defined as at or above a weight 85% of SBW. BMDs of the hip and spine were significantly higher in those who were weight restored compared with those whose weight remained less than 85% SBW (Fig. 3). This finding was true for each of the treatment groups. Using ANOVA and stratifying for treatment group, weight restoration had a significant effect at both the hip (P = 0.006) and spine (P = 0.06). However, despite weight gain and nutritional rehabilitation, at the end of the study period, only five of 29 subjects (17.2%) had a BMD of the spine in the normal range for age (z-score > 1.0). Three of these subjects received alendronate. Similarly, for the femoral neck, only nine of 29 subjects (31.0%) had a BMD within the normal range for age. Five of the nine had received alendronate.

Nineteen of 29 subjects (65.5%) resumed menses during the study period. Subjects who resumed menses during the
study were equally distributed between the placebo and alendronate groups (P = 0.45, by Fisher’s exact test). Re-
sumption of menses did not predict any of the outcome variables at the hip. At the lumbar spine, resumption of menses and treatment with alendronate accounted for 36% of the variance in percent change in BMD (P = 0.01 and P = 0.06, respectively, by ANOVA). In those who remained a-
menorrheic, BMD of the spine increased by 3.3 ± 5.9% in the alendronate group, whereas in the placebo group, BMD de-
creased by 4.9 ± 5.5% over the study period. In those who
had resumed menses, there was no additional benefit at the lumbar spine of treatment with alendronate.

Biochemical markers of bone metabolism

Measurement of markers of bone formation and degradation at baseline, 6 months, and 1 yr demonstrated that BSAP, a
marker of bone formation, increased in both groups, but not significantly (P = 0.23, by repeated measures analysis; P = 0.08,
between-group analysis). There was no significant change in OC levels over time in either group. Urinary DPD, a marker of
bone resorption, decreased significantly from baseline to follow-up (P = 0.04, by repeated measures analysis), but did not
differ between groups (P = 0.47). For both the femoral neck and the lumbar spine, at the end of the study there was an inverse
correlation between BMD and urinary DPD levels (P = 0.004
and P = 0.05, respectively). Levels of IGF-1 increased in both
groups, but not significantly.

Safety

Four subjects, two from each group, complained of nausea and abdominal bloating attributed to the medication. The
symptoms were mild and lasted from 1–7 d. One additional subject discontinued the medication because of dyspepsia.
She had been assigned placebo. There were no adverse ef-
facts on serum chemistries. During the study period, three
subjects sustained fractures: one from the placebo group
(multiple nontraumatic stress fractures of the tibia) and two
from the alendronate group (a traumatic fracture of the hu-
merus and a traumatic fracture of the radius).

Discussion

Osteopenia is a serious and potentially irreversible compi-
cation of anorexia nervosa, for which there is no known effec-
tive treatment. In our study, BMD of the lumbar spine and
femoral neck increased in both the intervention group and the
control group with weight gain, but increased relatively more
in the group receiving alendronate. Body weight and changes
in body weight were the most important determinants of BMD

Fig. 2. Mean ± so vBMD of the femoral neck and lumbar spine after 12 months of treatment: alendronate vs. placebo.

Fig. 3. The effect of weight restoration on BMD of the lumbar spine and femoral neck. Comparison between those who are weight restored (>85% of SBW; n = 15) and those who are still of low weight (<85% of SBW; n = 14). Those who were weight restored gained 8.7 ± 5.5 kg, whereas those who were not weight restored only gained 3.6 ± 4.0 kg during the study period. Values are the mean ± so.
at 1-yr follow-up, but treatment with alendronate had an independent positive effect at the femoral neck.

All of our subjects were actively being treated for their eating disorder. They were monitored by a physician, were in psychotherapy, and were seeing a nutritionist at frequent intervals. Sixteen of the 29 subjects were hospitalized for nutritional rehabilitation at some time during the year of study. Most gained weight, and approximately two thirds resumed menses during the study period. Both groups received calcium and vitamin D supplementation. The fact that BMD increased with weight gain is consistent with the findings of other longitudinal studies of anorexia nervosa (16, 30). In our study, although bone mass increased in both groups despite intervention, it remained low at the end of the study period. In fact, less than a third of subjects were able to restore their bone mass to the normal range, and three sustained a fracture during the study period.

Other agents that either increase bone formation or reduce bone resorption have had limited success in anorexia nervosa. Earlier studies conducted in both adults and adolescents have shown that hormone replacement therapy does not increase BMD in this condition (13, 31). Dehydroepiandrosterone (DHEA) is a precursor of both estrogens and androgens, and levels of DHEA are low in anorexia nervosa. Theoretically, administration of DHEA could inhibit bone resorption and stimulate bone formation. Gordon et al. (30) studied 61 women with anorexia nervosa, randomly assigned to receive either 50 mg/d DHEA or a combination estrogen-progestin pill. Over a 1-yr follow-up period, total hip BMD increased 1.7% in both groups, but after controlling for weight gain, no treatment effect was detected. In 60 osteopenic women with anorexia nervosa, Grinspoon et al. (32) compared the use of recombinant human IGF-I, a nutritionally dependent hormone that promotes bone formation, with oral contraceptives alone and in combination and found that treatment with IGF-I or the oral contraceptive alone had no significant effect on BMD of the lumbar spine, but that their combination increased BMD by 1.8%. In contrast, in the current study, subjects who received alendronate increased BMD of the femoral neck by 4.4% and that of the lumbar spine by 3.5%. The control group who underwent nutritional rehabilitation without active medication increased BMD of the femoral neck by 2.3% and that of the lumbar spine by 2.2%.

In recent years, bisphosphonates have been used successfully in children and adolescents with osteogenesis imperfecta, juvenile idiopathic osteoporosis, juvenile rheumatoid arthritis, steroid-induced osteoporosis, and cerebral palsy (23–25, 33, 34). All of these conditions are associated with severe osteoporosis and fractures. The only double-blind, randomized trial in a pediatric population was conducted on six pairs of children (aged 6–16 yr) with cerebral palsy who randomly received either saline or iv pamidronate every 3 months for 1 yr (25). In that study, over an 18-month period, BMD of the metaphyseal region of the distal femur increased 89% in the group receiving pamidronate compared with a 9% increase in the control group. As expected, the effect of bisphosphonates on BMD in anorexia nervosa is not as dramatic as that seen in cerebral palsy or in other conditions where the prime mechanism of low bone mass is increased bone resorption. In anorexia nervosa, in addition to increased bone resorption, reduced bone formation contributes to the low bone mass.

In a recent nonrandomized study, Miller et al. (35) administered another bisphosphonate, risedronate, to 10 adult women with anorexia nervosa for 9 months and compared the results with published data for 14 control women studied by the same group of investigators. They found that BMD of the lumbar spine increased significantly in those who received risedronate, whereas it decreased in the controls. Unlike our study, there was no change at the hip. The magnitude of the change at the spine was similar to our findings, but the major difference was that in our study, BMD also increased in the placebo group. There are two major reasons for this difference. Firstly, we studied adolescents, and during adolescence, BMD is expected to increase. Secondly, our patients were receiving active treatment for their eating disorder. Approximately half of them were hospitalized for nutritional rehabilitation during the study period. Both the expected changes during adolescence and nutritional rehabilitation in the control group decreased the discriminatory capacity to discern the effect of alendronate. We believe that, especially in adolescents, before recommending a bisphosphonate, it is important to demonstrate the efficacy of this treatment over and above that of nutritional rehabilitation.

Anorexia nervosa is associated with increased bone resorption and reduced bone formation. Treatment with alendronate decreases bone turnover. In addition to a reduction in bone resorption, there can be a reduction in bone formation, although to a lesser degree. In our study, neither marker of bone formation (BSAP or osteocalcin) showed significant change over the study period. As expected, urinary DPD levels (a surrogate marker of bone resorption) decreased in both groups, but what was surprising is that there was no significant difference between the groups. We would have expected the degree of reduction to be greater in the alendronate group. The lack of difference may be due to the small sample size in this pilot study.

We found alendronate to be well tolerated and safe. Subjects took the medication as prescribed, and the only patient who complained of clinically significant side effects actually had been assigned placebo. The long-term side effects of alendronate in the adolescent age group still need to be evaluated in larger numbers of patients. Earlier concerns about possible effects on linear growth have not been substantiated (24, 33, 36). One issue of importance to adolescents is that the bisphosphonates remain in the skeleton for many years, and there are concerns about potential teratogenicity. To our knowledge, there have been no reports of adverse effects of bisphosphonates on the fetuses of humans or animals (36). Alendronate is not Food and Drug Administration-approved for use in women of child-bearing age and should not be used in women who are at risk of becoming pregnant.

In summary, we found that in a population of adolescents with anorexia nervosa, treatment with alendronate significantly increased BMD of the lumbar spine and femoral neck of the hip, but these results were not statistically significant compared with placebo. The effect, however, was modest, and body weight and amount of weight gained were the most important determinants of BMD at the end of the study. The results of this pilot study indicate that alendronate may
have beneficial effects on BMD in adolescents with anorexia nervosa. The drug appears to be more active at the femoral site than at the lumbar spine. Weight restoration remains the major clinical factor determining BMD, but despite weight gain, BMD remains low in the majority of patients. In view of the favorable safety profile in this patient cohort, we recommend a larger, randomized, controlled trial to test the efficacy of alendronate in anorexia nervosa using the data from this pilot study to guide the formulation of a definitive trial. Until additional studies have demonstrated efficacy and long-term safety, the use of alendronate should be confined to controlled clinical trials.

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