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Bone Size and Volumetric Density in Women with Anorexia Nervosa Receiving Estrogen Replacement Therapy and in Women Recovered from Anorexia Nervosa

MAGNUS K. KARLSSON*, SUSAN J. WEIGALL, YUNBO DUAN, AND EGO SEEMAN

Department of Endocrinology, Austin and Repatriation Medical Center, and Department of Psychiatry, Royal Melbourne Hospital (S.J.W.), University of Melbourne, Melbourne 3084, Australia

ABSTRACT

Anorexia nervosa is associated with bone loss during adulthood, but may also delay skeletal growth and mineral accrual during growth. We asked the following questions. 1) Is anorexia nervosa associated with reduced bone size and reduced volumetric bone mineral density (vBMD)? 2) Is estrogen replacement therapy (ERT) or recovery from anorexia nervosa associated with normal bone size and vBMD?

Using dual-energy x-ray absorptiometry, we measured bone size and vBMD of the third lumbar vertebra and femoral neck in a cross-sectional study of 161 female patients: 77 with untreated anorexia nervosa, 58 with anorexia nervosa receiving ERT, 26 recovered from anorexia nervosa, and 205 healthy age-matched controls. Results were expressed as the SD or z-score (mean ± SEM).

Deficits in vertebral body and femoral neck width in untreated women were −1.0 ± 0.1 and −0.3 ± 0.1 SD ($P < 0.001$ and $P < 0.05$, respectively). Deficits in bone width were less in the ERT-treated women than in untreated women at the vertebral body (−0.6 ± 0.1 SD; $P < 0.001$), but not at the femoral neck (−0.4 ± 0.2 SD; $P < 0.05$). There were no significant deficits in vertebral body and femoral neck width in recovered women (both −0.3 ± 0.2 SD; P = NS). In untreated women, vertebral and femoral neck vBMD were −1.6 ± 0.1 and −1.1 ± 0.1 SD, respectively (both $P < 0.001$), less severely reduced in ERT-treated women (−1.2 ± 0.2 and −0.6 ± 0.2 SD, respectively; both $P < 0.001$), and least reduced in recovered women (−0.6 ± 0.1 and −0.5 ± 0.2 SD; $P < 0.01$ and $P < 0.05$, respectively). After adjusting for differences in fat and lean mass, vertebral body and femoral neck width were no longer reduced in untreated, ERT-treated, and recovered women. Adjustment for body composition had little effect on group difference in vBMD.

Bone fragility in anorexia nervosa is due to reduced bone size and reduced vBMD. Although causality cannot be inferred in cross-sectional studies, the data are consistent with the view that malnutrition may contribute to reduced bone size, whereas estrogen deficiency may reduce vBMD. The use of ERT early in disease is a reasonable component of management if the chance of recovery appears remote. (*J Clin Endocrinol Metab* **85:** 3177–3182, 2000)

ANOREXIA NERVOSA is a chronic illness affecting 1% of adolescent females and is characterized by a fear of fatness, self-imposed semistarvation, and weight loss (1). The illness has a high morbidity and is fatal in 6% of cases (2). Estrogen deficiency is an important risk factor for bone loss and osteoporosis, whereas malnutrition and low body weight may also increase the risk for osteoporosis by estrogen-dependent and nonestrogen-dependent mechanisms (3–10).

Although the reduced bone mass that characterizes the secondary osteoporosis of anorexia nervosa is commonly attributed to bone loss, this illness begins during the first 3 decades of life, a period of rapid growth in skeletal size and mineral accrual, particularly during puberty (11, 12). Consequently, estrogen deficiency and malnutrition during adolescence may result in reduced growth, reduced peak bone size, and reduced mineral accrual within the periosteal envelope of the smaller bone (vBMD).

As bone mineral content (BMC) and areal bone mineral density (aBMD), the two most commonly used expressions of bone mass or density in clinical practice, do not fully adjust for bone size, finding smaller bone size in anorexia nervosa will exaggerate the deficit in BMC and aBMD relative to that in controls (with bigger bones) (13). Likewise, if estrogen replacement therapy (ERT) or spontaneous recovery from anorexia nervosa produces periosteal growth as well as increased mineral accrual within the growing bone, the larger bone size will exaggerate the increase in mineral accrual within the bone relative to that in women with untreated anorexia nervosa (with smaller bones) when bone mass is expressed as BMC or aBMD.

We measured the effects of anorexia nervosa, ERT, or spontaneous remission from anorexia nervosa on bone size, BMC, aBMD, and vBMD to test the following hypotheses. 1) Bone size is reduced in women with untreated active anorexia nervosa. 2) Deficits in bone size exaggerate the deficit in BMC and aBMD in untreated women with anorexia nervosa relative to that in controls. 3) Bone size will be more completely restored in recovered women than in ERT-treated women. 4) vBMD (a measurement independent of bone size) will be restored in women receiving ERT and in women recovered from anorexia nervosa.

Subjects and Methods

Subjects

We studied 161 patients: 135 women with active anorexia nervosa [77 women with untreated anorexia nervosa, 58 women with active anorexia

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Address all correspondence and requests for reprints to: Ego Seeman, M.D., Department of Endocrinology, Austin and Repatriation Medical Center, Heidelberg, Melbourne 3084, Australia. E-mail: ego@austin.unimelb.edu.au.

* Present address: Department of Orthopedic Surgery, University Hospital UMAS, S-205 02 Malmo, Sweden.

nervosa treated with ERT for a mean of 4.3 yr (range, 1–16)], 26 women recovered from anorexia nervosa, and 205 premenopausal healthy female volunteers with normal menstrual cycles who received no drugs and suffered no diseases known to affect bone. As most of the effects of antiresorptive agents such as ERT occur within the first 2 yr of treatment, among the 58 women with active anorexia nervosa treated with ERT, we compared the results in the 32 women who received ERT for more than 2 yr (mean, 6.6 yr; range, 2.1–16 yr) and the 26 women who received ERT for less than 2 yr (mean, 1.4 yr; range, 1–2 yr) to determine whether there may be an additional benefit beyond 2 yr. Conjugated equine estrogen (Premarin, 0.3–0.625 mg daily) was used in the majority of patients. Of the 26 recovered women, 17 received ERT at some time during the illness. Seven women were still taking ERT for a mean of 6.8 yr (range, 2–11). The diagnosis of anorexia nervosa was based on ICD-10 criteria (14). Women with recovered anorexia nervosa had body mass index above 19, regular monthly menstrual cycles for at least 6 months, and no evidence of bulimia. All subjects gave informed consent. The study was approved by the ethics committee of the Austin and Repatriation Medical Center.

Measurements of bone mass and size

Total body and regional bone BMC (grams) and aBMD (BMC/projected area of the region scanned, grams per cm^2) were measured by dual energy x-ray absorptiometry (DPX-L, version 1.3z, Lunar Corp., Madison, WI) (15). Coefficients of variation ranged between 1.5–2.4%. The height and width of the body of the third lumbar (L3) vertebra were determined from the posteroanterior scan of the lumbar spine. vBMD (grams per cm^3) of L3 was calculated by the method of Carter (BMC/volume, where volume = scanned $area^{3/2}$) (16). Femoral neck width was calculated as scanned area/scanning length. Femoral neck vBMD was calculated as BMC/femoral neck volume ($\pi \times$ [femoral neck width/2]^2 $\times$ scanning height) (17). The coefficient of variation ranged between 0.9–2.9%. Total body fat (grams) and lean mass (grams) were derived from the total body scan, with coefficients of variation of 0.6% and 4.1%, respectively.

Statistical analysis

Bone volume-adjusted BMC and aBMD were derived by regressing BMC (and aBMD) on bone volume in the controls using BMC = C + k $\times$ volume (13). Volume-adjusted BMC was: observed BMC + (mean volume − observed volume) $\times$ k (13, 18, 19). Comparison of the deficits in unadjusted and volume adjusted BMC to healthy controls apportions the deficit due to size and that due to reduced vBMD (13). Similar analyses were performed for aBMD.

Unpaired and paired Student's *t* tests were used to compare the same region between groups and different regions within a group, respectively. Analysis of covariance, adjusting for fat and lean mass, was used to compare untreated, ERT-treated, and recovered women with controls; ERT-treated and recovered women with untreated women; and recovered women with ERT-treated women. The z-scores (the number of SD above or below the age-predicted mean) were derived by linear regression using data in the controls.

Results

Table 1 shows the results in absolute terms and z-scores expressed as the mean ± SEM with *P* values. For the sake of clarity, only means are reported in the text below, except for data not shown in the table.

Bone size and BMC unadjusted for bone size

As shown in Table 1 and Fig. 1, vertebral body and femoral neck width were reduced in untreated women relative to those in controls (−1.0 and −0.3 SD, respectively) and were less reduced in ERT-treated women at the vertebral body (−0.6 SD), but no different from untreated women at the femoral neck (−0.4 SD). Vertebral body and femoral neck width were not reduced in the recovered women (both −0.3 SD; P = NS). Vertebral body height was not reduced in any group (Table 1). The 32 women treated with ERT for 6.6 yr (range, 2.1–16) did not have a more modest deficit in bone width than the 26 women treated with ERT for 1.4 yr (range, 1–2 yr; vertebral body, both −0.6 ± 0.2 SD; femoral neck, −0.3 ± 0.2 *vs.* −0.4 ± 0.2 SD; P = NS, respectively).

Vertebral and femoral neck BMC were reduced in untreated women (both −1.6 SD), less reduced in ERT-treated women (both −1.1 SD), and least reduced in recovered women (−0.7 and −0.9 SD, respectively). Results expressed as aBMD were similar (Table 1).

Effect of differences in bone size on differences in BMC

The smaller vertebral body volume in the untreated, ERT-treated, and recovered women (relative to controls) accounted for 35–44% of the deficit in vertebral BMC (Fig. 2, *shaded regions*). Likewise, the larger vertebral body volume in the ERT and recovered women (relative to untreated women) accounted for 37–56% of their higher vertebral BMC. The larger vertebral body volume in the recovered women (relative to ERT-treated women) accounted for 21% of their higher vertebral BMC. Differences in femoral neck width accounted for only 1–16% of between-group differences in femoral neck BMC.

Volumetric BMD

Vertebral and femoral neck vBMD were reduced in untreated women (−1.6 and −1.1 SD, respectively), less reduced in ERT-treated women (−1.2 and 0.6 SD, respectively), and least reduced in recovered women (−0.6 and 0.5 SD, respectively; Fig. 1). The 32 women treated with ERT for 6.6 yr (range, 2.1–16) had half the deficit in vBMD compared with 26 women treated with ERT for 1.4 yr (range, 1–2; vertebra: −0.8 ± 0.2 *vs.* −1.6 ± 0.2 SD; $P < 0.05$, respectively; femoral neck: −0.4 ± 0.2 *vs.* −0.9 ± 0.2 SD; $P = 0.1$, respectively).

Effect of fat mass and lean mass

As shown in Table 2, after adjusting for differences in fat and lean mass, vertebral body and femoral neck width were no longer reduced in untreated, ERT-treated, and recovered women relative to those in controls (except for a remaining deficit in femoral neck width in ERT-treated women; $P < 0.05$), whereas vertebral body and femoral neck width were no longer reduced in ERT-treated women relative to those in recovered women. Adjustment for body composition had little effect on group differences in vBMD relative to control values. Nevertheless, vertebral and femoral neck vBMD were no longer reduced in ERT-treated women relative to recovered women after adjustment for differences in body composition.

Discussion

We report that 1) a substantial proportion of the deficit in bone mass in women with anorexia nervosa relative to controls is due to their smaller bone size; 2) ERT is associated with higher vBMD and bone size relative to those in untreated women; 3) recovery from illness is associated with a near-normal bone size and vBMD; and 4) incomplete recov-

TABLE 1. Age, height, weight, body mass index (BMI), body composition, age of onset, duration of disease, bone size, bone mineral content (BMC), areal bone mineral density (BMD), and volumetric BMD at the third lumbar vertebra (L3) and femoral neck in women with untreated anorexia nervosa, women with anorexia nervosa treated with estrogen replacement therapy (ERT), women recovered from anorexia nervosa and healthy age-matched controls

Variables	Women with anorexia nervosa		Women recovered from anorexia nervosa (n = 26)	Healthy age-matched controls (n = 205)
	Untreated (n = 77)	ERT treated (n = 58)		
Age (yr)	25.9 ± 0.8	28.4 ± 1.0	27.3 ± 1.3	27.3 ± 0.4
Ht (cm)	164.6 ± 0.7	165.5 ± 0.9	163.7 ± 1.1	165.5 ± 0.4
Wt (kg)	42.2 ± 0.6[a]	42.3 ± 0.8[a]	54.4 ± 1.3[a,b,c]	63.1 ± 0.8
BMI (kg/m^2)	15.6 ± 0.2[a]	15.4 ± 0.2[a]	20.3 ± 0.4[a,b,c]	23.1 ± 0.3
Total body fat (kg)	6.2 ± 0.3[a]	4.6 ± 0.4[a,d]	15.4 ± 1.3[a,b,c]	21.7 ± 0.7
Total lean body mass (kg)	33.8 ± 0.5[a]	35.3 ± 0.7[a]	38.5 ± 0.7[e,f]	39.3 ± 0.3
Lowest BMI (kg/m^2)	13.0 ± 0.4	12.2 ± 0.3	14.4 ± 0.3[e,g]	
Age of onset (yr)	19.9 ± 0.6	21.8 ± 0.9	19.1 ± 1.1	
Duration of disease (yr)	5.4 ± 0.6	4.5 ± 0.7	3.5 ± 0.6	
Bone size (cm)				
Vertebral body width	3.69 ± 0.04[a]	3.81 ± 0.05[a,h]	3.90 ± 0.05[i]	4.02 ± 0.03
z-Scores	−1.0 ± 0.1[a]	−0.6 ± 0.1[a,j]	−0.3 ± 0.2[i]	
Vertebral body ht	3.48 ± 0.03	3.53 ± 0.06	3.44 ± 0.04	3.48 ± 0.02
z-Scores	0.1 ± 0.1	0.2 ± 0.2	−0.1 ± 0.1	
Femoral neck width	3.05 ± 0.03[k]	3.04 ± 0.04[k]	3.05 ± 0.04	3.13 ± 0.02
z-Scores	−0.3 ± 0.1[k]	−0.4 ± 0.2[k]	−0.3 ± 0.2	
BMC (g)				
L3 vertebra	13.05 ± 0.34[a]	14.54 ± 0.47[a,d]	15.72 ± 0.41[b,l]	17.66 ± 0.20
z-Scores	−1.6 ± 0.1[a]	−1.1 ± 0.2[a]	−0.7 ± 0.2[b,l]	
Femoral neck	3.84 ± 0.10[a]	4.14 ± 0.14[a,j]	4.31 ± 0.15[a,i]	4.87 ± 0.05
z-Scores	−1.6 ± 0.1[a]	−1.1 ± 0.2[a]	−0.9 ± 0.2[a,i]	
Areal BMD (g/cm^2)				
L3 Vertebra	1.01 ± 0.02[a]	1.08 ± 0.02[a,h]	1.17 ± 0.02[a,b,g]	1.26 ± 0.01
z-Scores	−2.0 ± 0.1[a]	−1.4 ± 0.2[a,h]	−0.7 ± 0.1[a,b,g]	
Femoral neck	0.85 ± 0.02[a]	0.91 ± 0.03[a,j]	0.93 ± 0.03[a,i]	1.04 ± 0.01
z-Scores	−1.6 ± 0.1[a]	−1.0 ± 0.2[a,j]	−0.9 ± 0.2[a,i]	
Volumetric BMD (g/cm^3)				
L3 Vertebra	0.29 ± 0.01[a]	0.30 ± 0.01[a,h]	0.31 ± 0.01[b,g,l]	0.34 ± 0.01
z-Scores	−1.6 ± 0.1[a]	−1.2 ± 0.2[a,j]	−0.6 ± 0.1[b,g,l]	
Femoral neck	0.36 ± 0.01[a]	0.38 ± 0.01[a,j]	0.39 ± 0.01[i,k]	0.43 ± 0.01
z-Scores	−1.1 ± 0.1[a]	−0.6 ± 0.2[a]	−0.5 ± 0.2[i,k]	

Results were expressed as the mean ± SEM.
[a] $P < 0.001$ *vs.* age-matched controls.
[b] $P < 0.001$ *vs.* untreated women.
[c] $P < 0.001$ *vs.* ERT-treated women.
[d] $P < 0.01$ *vs.* untreated women.
[e] $P < 0.01$ *vs.* untreated women.
[f] $P < 0.01$ *vs.* ERT-treated women.
[g] $P < 0.05$ *vs.* ERT-treated women.
[h] $P < 0.05$ *vs.* untreated women.
[i] $P < 0.05$ *vs.* untreated women.
[j] $P = 0.06$ *vs.* untreated women.
[k] $P < 0.05$ *vs.* age-matched controls.
[l] $P < 0.01$ *vs.* age-matched controls.

ery of lean and fat mass may account for part of the remaining deficits in bone size, not vBMD.

The deficit in BMC in anorexia nervosa relative to that in controls is attributed to excessive bone loss, reduced peak mineral accrual, or both. These data suggest that 1) about 50% of the deficit in vertebral BMC in untreated and ERT-treated women (relative to controls) was due to reduced vertebral body width; 2) as femoral neck width was less reduced than vertebral body width, a smaller proportion of the deficit in femoral neck BMC (relative to that in healthy controls) was due to the reduced femoral neck width; and 3) about 50% of the higher vertebral BMC in ERT-treated and recovered women (relative to that in women with untreated anorexia nervosa) was due to their larger bone size. As aBMD (the most common expression of bone mass or density) is partly corrected for bone size, a smaller proportion of the deficit in aBMD at these sites (<30%) was explained by reduced bone size. The relevance of the observation resides in understanding its pathogenesis, not necessarily in fracture risk prediction, as there is little, if any, compelling evidence that any of the expressions of bone mass (BMC, aBMD, and vBMD) are better predictors of fracture (*i.e.* more sensitive or specific) than any other (13, 20, 21).

The effect of anorexia nervosa on bone size and the contribution of reduced bone size to the deficit at the spine have not been reported previously. The failure to recognize the confounding effect of bone size on the expressions of bone mass or density will lead to erroneous inferences regarding the pathogenesis of bone fragility and its restoration after treatment or remission from illness. For example, the deficit

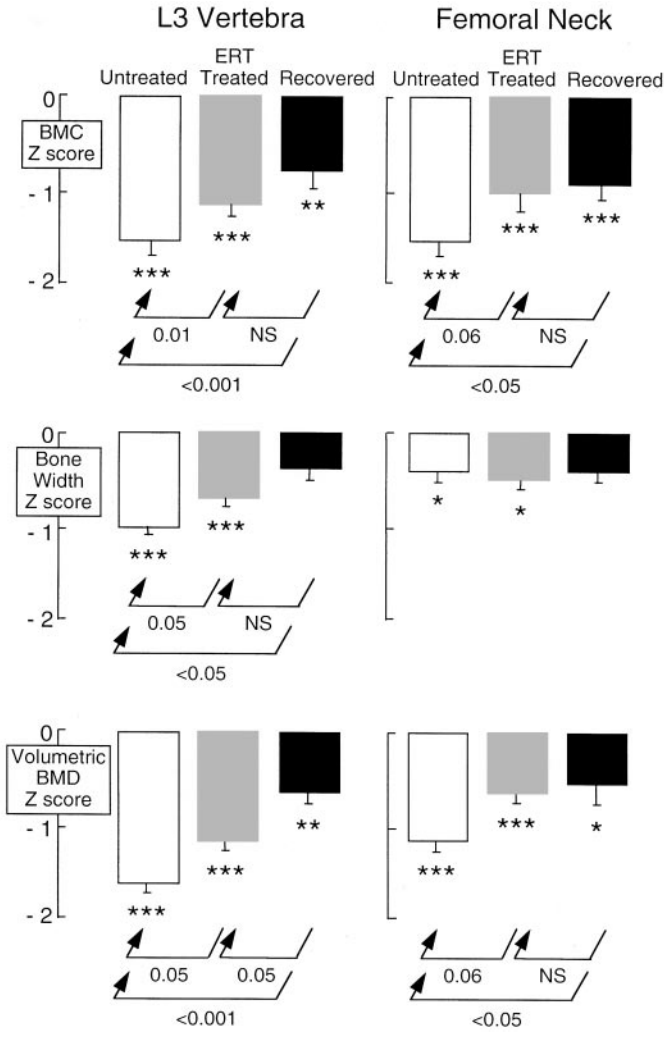

FIG. 1. BMC, bone width, and vBMD at the third lumbar vertebra (L3) and femoral neck (expressed as z-scores) in women with untreated anorexia nervosa (n = 77), women with anorexia nervosa receiving ERT (n = 58), and women recovered from anorexia nervosa (n = 26). *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$ (comparing women with untreated anorexia nervosa, women with anorexia nervosa receiving ERT, and women recovered from anorexia nervosa with healthy age-matched women).

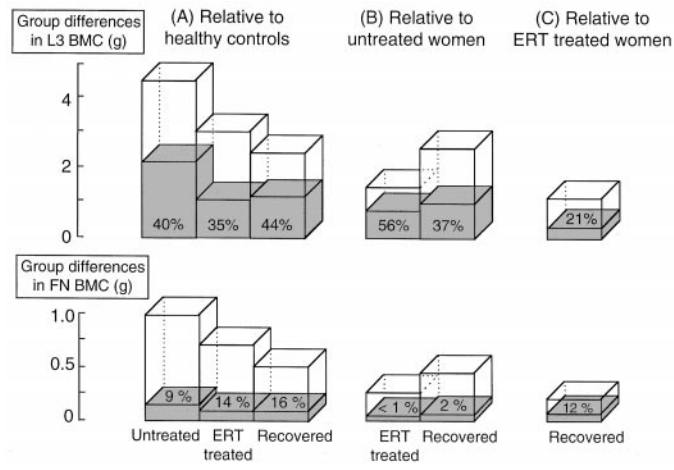

FIG. 2. *Columns* depict the total group differences in BMC at the third lumbar vertebra (L3) and femoral neck (FN) in women with untreated anorexia nervosa (A; n = 77), women with anorexia nervosa receiving ERT (A; n = 58), and women recovered from anorexia nervosa (A; n = 26) relative to healthy controls, ERT-treated and recovered women relative to untreated women (B), and recovered women relative to ERT-treated women (C). *Shaded regions* represent the proportion of the total group differences in BMC explained by the group differences in bone size.

in BMC relative to that in controls (with larger bones) will be exaggerated and attributed to excessive bone loss or reduced peak bone mass accrual. Similarly, partial or complete reversal of the deficit with recovery from anorexia nervosa will be erroneously attributed to recommencement of mineral accrual or restoration of the lost bone, rather than being also due to periosteal bone growth. In addition, the greater deficit in aBMD at the vertebra than at the femoral neck is probably due to the greater deficit in vertebral body size.

The deficit in vertebral vBMD is probably largely the result of estrogen deficiency, as vertebral vBMD in women treated with ERT for over 2 yr was greater than that in women treated for 1–2 yr, similar to vBMD in recovered women. Nevertheless, vertebral vBMD was not normal in the recovered women and those treated with ERT for over 2 yr, perhaps due to the short duration of recovery, the failure to administer ERT at diagnosis, or poor compliance. Whether BMD may be normal if ERT is given at diagnosis and throughout the illness or when recovery is more prolonged will require randomized controlled trials.

By contrast, the deficits in vertebral body width may be the result of both estrogen- and nonestrogen-dependent mechanisms, as no difference was found between women with ERT treatment for less than 2 yr and women with ERT treatment for more than 2 yr. Malnutrition may have contributed to the deficit in bone size, because the recovered women had minimal deficits in vertebral body size, whereas any remaining differences in bone size in recovered patients (relative to controls) disappeared after adjustment for their lower fat mass. Similarly, adjusting for fat and lean mass reduced the deficit in bone size in untreated patients relative to that in controls and ERT-treated women as well as between ERT-treated and recovered women. By contrast, adjustment for fat and lean mass had little or no effect on group differences in vBMD.

There have been several retrospective and prospective studies reporting the effect of recovery from anorexia nervosa on aBMD. Investigators report increased aBMD in subjects who increased their body weight, had persistent deficits in aBMD, or continued bone loss despite recovery (4, 22–27). Hay *et al.* reported a 14% higher spine aBMD in 21 women recovered from anorexia nervosa compared to those with ongoing anorexia nervosa (28); aBMD was 7% lower than that in healthy controls. These disparate reports may be the result of methodological problems such as small sample sizes, variable definitions of recovery, differences in disease severity before recovery, differences in the duration of disease and recovery, and, failure to account for differences in bone size.

As this study was cross-sectional, we cannot exclude the possibility that women receiving ERT or women recovered

TABLE 2. Differences in bone width and volumetric bone mineral density (vBMD) before and after adjustment for fat and lean mass in women with untreated anorexia nervosa *vs.* controls (A), estrogen replacement therapy (ERT)-treated women with anorexia nervosa *vs.* controls (B), women recovered from anorexia nervosa *vs.* controls (C), and women recovered from anorexia nervosa *vs.* ERT-treated women with anorexia nervosa (D)

Variables	Group A		Group B		Group C		Group D	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Bone width difference (mm)								
L3 vertebral body width	−3.31[a]	−0.65	−2.03[a]	0.05	−1.15	−0.28	0.98	−0.27
Femoral neck width	−0.73[b]	0.13	−0.91[b]	0.32[b]	−0.71	−0.19	0.20	−0.13
vBMD difference (mg/cm^3)								
L3 vertebra	−54[a]	−58[a]	−40[a]	−40[a]	−19[c]	−22[c]	21[b]	13
Femoral neck	−73[a]	−75[c]	−46[a]	−41[a]	−34[b]	−36[b]	11	−4

Significance is indicated for comparisons of untreated, ERT-treated, and recovered women with healthy controls and of recovered women with ERT-treated women.

[a] $P < 0.001$.
[b] $P < 0.05$.
[c] $P < 0.01$.

from anorexia nervosa had milder disease and more modest deficits in bone size and vBMD than the untreated patients. However, deficits in femoral neck width, aBMD, and minimum body weight were similar in the three groups; women treated with ERT for less than 2 yr had similar deficits in bone size and vBMD as untreated women, whereas the greater bone size and vBMD in recovered women was not due to shorter disease than that in untreated anorexia nervosa women, as matching recovered patients with women with untreated anorexia nervosa by duration of illness did not alter the findings (data not shown).

In summary, the increased risk for fracture associated with anorexia nervosa is conferred by reduced bone size and reduced vBMD. Malnutrition may account for reduced bone size, whereas estrogen deficiency may account for reduced vBMD. ERT and remission are associated with more modest deficits in these traits. Randomized, double blind, placebo-controlled trials are needed to establish whether the more modest deficits associated with ERT are causally related to ERT. Prospective studies are needed to establish whether there is a causal relationship between the more modest deficits in recovered patients. However, these trials are difficult to execute successfully, and recovery is very uncommon. The work presented here is at least consistent with the view that improvement in deficits in vBMD may be achieved using ERT. Given that restoration of normal body weight and normal menstrual cycles occurs in only 50% of patients, and fractures occur frequently (4, 5, 7, 9, 22, 28, 29), ERT should be considered soon after diagnosis. Understanding the bone fragility in anorexia nervosa requires study of the growth of axial and appendicular bone size, mineral accrual, as well as subsequent loss of bone during adulthood.

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References

1. **American Psychiatric Association.** 1994 Diagnostic and statistical manual of mental disorders (DSM-IV), 4th Ed. Washington DC; American Psychiatric Association; 539–545.
2. **Sullivan PF.** 1995 Mortality in anorexia nervosa. Am J Psychiatry. 152:1073–1074.
3. **Ayers JW, Gidwani GP, Schmidt IM, Gross M.** 1984 Osteopenia in hypoestrogenic young women with anorexia nervosa. Fertil Steril. 41:224–228.
4. **Rigotti NA, Nussbaum SR, Herzog DB, Neer RM.** 1984 Osteoporosis in women with anorexia nervosa. N Engl J Med. 311:1601–1606.
5. **Szmukler GI, Brown SW, Parsons V, Darby A.** 1985 Premature loss of bone in chronic anorexia nervosa. Br Med J (Clin Res Ed). 290:26–27.
6. **Biller BM, Saxe V, Herzog DB, Rosenthal DI, Holzman S, Klibanski A.** 1989 Mechanisms of osteoporosis in adult and adolescent women with anorexia nervosa. J Clin Endocrinol Metab. 68:548–554.
7. **Bachrach LK, Guido D, Katzman D, Litt IF, Marcus R.** 1990 Decreased bone density in adolescent girls with anorexia nervosa. Pediatrics. 86:440–447.
8. **Joyce JM, Warren DL, Humphries LL, Smith AJ, Coon JS.** 1990 Osteoporosis in women with eating disorders: comparison of physical parameters, exercise, and menstrual status with SPA and DPA evaluation. J Nucl Med. 31:325–331.
9. **Seeman E, Szmukler GI, Formica C, Tsalamandris C, Mestrovic R.** 1992 Osteoporosis in anorexia nervosa: the influence of peak bone density, bone loss, oral contraceptive use, and exercise. J Bone Miner Res. 7:1467–1474.
10. **Cornish J, Callon KE, Cooper GJ, Reid IR.** 1995 Amylin stimulates osteoblast proliferation and increases mineralized bone volume in adult mice. Biochem Biophys Res Commun. 207:133–139.
11. **Bonjour JP, Theintz G, Buchs B, Slosman D, Rizzoli R.** 1991 Critical years and stages of puberty for spinal and femoral bone mass accumulation during adolescence. J Clin Endocrinol Metab. 73:555–563.
12. **Gilsanz V, Gibbens DT, Roe TF, et al.** 1988 Vertebral bone density in children: effect of puberty. Radiology. 166:847–850.
13. **Duan Y, Parfitt A, Seeman E.** 1999 Vertebral bone mass, size, and volumetric density in women with spinal fractures. J Bone Miner Res. 14:1796–1802.
14. **WHO, ICD-10.** 1992 Classification of mental and behaviour disorders: clinical description and diagnostic guidelines, 10th Ed. WHO: Geneva; 176–179.
15. **Mazess RB, Wahner HM.** 1988 Nuclear medicine and densitometry. In: Riggs BL, Melton III LJ, eds. Osteoporosis: aetiology, diagnosis and management. New York: Raven Press; 251–295.
16. **Carter DR, Bouxsein ML, Marcus R.** 1992 New approaches for interpreting projected bone densitometry data. J Bone Miner Res. 7:137–145.
17. **Lu PW, Cowell CT, Lloyd-Jones SA, Briody JN, Howman-Giles R.** 1996 Volumetric bone mineral density in normal subjects, aged 5–27 years. J Clin Endocrinol Metab. 81:1586–1590.
18. **Smith DM, Johnston Jr CC, Yu PL.** 1972 *In vivo* measurement of bone mass. Its use in demineralized states such as osteoporosis. JAMA. 219:325–329.
19. **Smith DM, Khairi MR, Johnston Jr CC.** 1975 The loss of bone mineral with aging, and its relationship to risk of fracture. J Clin Invest. 56:311–318.
20. **Cummings SR, Marcus R, Palermo L, Ensrud KE, Genant HK, Study of Osteoporotic Fractures Research Group.** 1994 Does estimating volumetric bone density of the femoral neck improve the prediction of hip fracture? A prospective study. J Bone Miner Res. 9:1429–1432.
21. **Tabensky AD, Williams J, Deluca V, Brigant E, Seeman E.** 1996 Bone mass,

areal and volumetric bone density are equally accurate, sensitive, and specific surrogates of the breaking strength of the vertebral body: an *in vitro* study. J Bone Miner Res. 11:1981–1988.
22. **Bachrach LK, Katzman DK, Litt IF, Guido D, Marcus R.** 1991 Recovery from osteopenia in adolescent girls with anorexia nervosa. J Clin Endocrinol Metab. 72:602- 606.
23. **Brooks ER, Ogden BW, Cavalier DS.** 1998 Compromised bone density 11.4 years after diagnosis of anorexia nervosa. J Womens Health. 7:567–574.
24. **Herzog W, Minne H, Deter C, Leidig G, Schellberg D, WÜster C, et al.** 1993 Outcome of bone mineral density in anorexia nervosa patients 11.7 years after first admission. J Bone Miner Res. 8:597–605.
25. **Rigotti NA, Neer RM, Skates SJ, Herzog DB, Nussbaum SR.** 1991 The clinical course of osteoporosis in anorexia nervosa. A longitudinal study of cortical bone mass. JAMA. 265:1133–1138.
26. **Kooh SW, Noriega E, Leslie K, Muller C, Harrison JE.** 1996 Bone mass and soft tissue composition in adolescents with anorexia nervosa. Bone. 19:181–188.
27. **Ward A, Brown N, Treasure J.** 1997 Persistent osteopenia after recovery from anorexia nervosa. Int J Eat Disord. 22:71–75.
28. **Hay PJ, Hall A, Delahunt JW, Harper G, Mitchell AW, Salmond C.** 1989 Investigation of osteopaenia in anorexia nervosa. Aust NZ J Psychiatry. 23:261–268.
29. **Lucas AR, Melton III LJ, Crowson CS, O'Fallon WM.** 1999 Longterm fracture risk among women with anorexia nervosa: a population-based cohort study. Mayo Clinic Proc. 74:972–977.