

## BONE MINERAL DENSITY IN WOMEN WITH DEPRESSION

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## ABSTRACT

**Background** Depression is associated with alterations in behavior and neuroendocrine systems that are risk factors for decreased bone mineral density. This study was undertaken to determine whether women with past or current major depression have demonstrable decreases in bone density.

**Methods** We measured bone mineral density at the hip, spine, and radius in 24 women with past or current major depression and 24 normal women matched for age, body-mass index, menopausal status, and race, using dual-energy x-ray absorptiometry. We also evaluated cortisol and growth hormone secretion, bone metabolism, and vitamin D-receptor alleles.

**Results** As compared with the normal women, the mean ( $\pm$ SD) bone density in the women with past or current depression was 6.5 percent lower at the spine ( $1.00 \pm 0.15$  vs.  $1.07 \pm 0.09$  g per square centimeter,  $P=0.02$ ), 13.6 percent lower at the femoral neck ( $0.76 \pm 0.11$  vs.  $0.88 \pm 0.11$  g per square centimeter,  $P<0.001$ ), 13.6 percent lower at Ward's triangle ( $0.70 \pm 0.14$  vs.  $0.81 \pm 0.13$  g per square centimeter,  $P<0.001$ ), and 10.8 percent lower at the trochanter ( $0.66 \pm 0.11$  vs.  $0.74 \pm 0.08$  g per square centimeter,  $P<0.001$ ). In addition, women with past or current depression had higher urinary cortisol excretion ( $71 \pm 29$  vs.  $51 \pm 19$   $\mu$ g per day [ $196 \pm 80$  vs.  $141 \pm 52$  nmol per day],  $P=0.006$ ), lower serum osteocalcin concentrations ( $P=0.04$ ), and lower urinary excretion of deoxyriodinoline ( $P=0.02$ ).

**Conclusions** Past or current depression in women is associated with decreased bone mineral density. (N Engl J Med 1996;335:1176-81.)

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**M**AJOR depression is a complex disorder reflecting genetic, developmental, and environmental factors. Although its pathophysiology is not clearly understood, depression is associated with hypothalamic dysfunction — specifically, hypercortisolism, the diminished secretion of growth hormone, hypothalamic hypogonadism, and anorexia.<sup>1</sup> Depressive illness is characterized by remissions and exacerbations, and the cumulative effects of the exacerbations and accompanying hormonal and nutritional abnormalities can lead to lasting changes in peripheral tissues, such as bone. Once lost, bone density is difficult to regain, and intermittent, gradual changes are therefore likely to be additive.

Because major depression affects 5 to 9 percent of

women<sup>2</sup> and decreases in bone mineral density of 10 percent are associated with increases in rates of hip fracture of more than 40 percent over a period of 10 years,<sup>3</sup> the status of bone mineral density in women with depression is of interest not only from a theoretical perspective, with regard to somatic changes in a psychiatric disorder, but from a public health perspective as well. This study was designed to determine whether women with past or current depression have decreased bone mineral density or abnormalities of bone metabolism, function of the hypothalamic-pituitary-adrenal axis, or secretion of growth hormone.

## METHODS

## Study Subjects

We studied 24 women with past or current major depression and 24 normal women. The women were individually matched for age ( $\pm 5$  years), body-mass index ( $\pm 2.5$  [with the index calculated as the weight in kilograms divided by the square of the height in meters]), menopausal status, and self-described race (Table 1). The women with depression were recruited by advertisement and through referrals from health care providers, and the normal women were recruited through the normal-volunteer office of the National Institutes of Health. All the women were aware that the study concerned bone density. None had had their bone mineral density measured. The study was approved by the institutional review board of the National Institute of Mental Health, and all the women gave informed consent.

Each woman with depressive illness met the criteria of the *Diagnostic and Statistical Manual of Mental Disorders* (third edition, revised) (DSM-III-R) for one or more major depressive episodes lasting at least three months, as assessed by clinical interview with a psychiatrist and confirmed by the administration of the structured clinical interview for DSM-III-R. Each normal woman gave a psychiatric history and also underwent the structured clinical interview for DSM-III-R. All the women gave medical, dietary, and current exercise histories and underwent physical examination and screening laboratory examinations, including tests of hematologic, thyroid, liver, and renal function and measurements of serum calcium, magnesium, and phosphate. Women were excluded if they had known risk factors for decreased bone density, including a history of an eating disorder, more than one year of treatment with an anticonvulsant drug (one depressed woman had taken valproate for seven months), amenorrhea associated with depressive episodes, or a history of menstrual disorders; also exclud-

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**TABLE 1.** CLINICAL CHARACTERISTICS OF 24 DEPRESSED AND 24 NORMAL WOMEN.\*

| CHARACTERISTIC                          | DEPRESSED WOMEN | NORMAL WOMEN |
|---|-----------------|--------------|
| Age (yr)                                | 41±8            | 41±7         |
| Body-mass index†                        | 23.7±2.6        | 23.6±2.9     |
| Height (cm)                             | 165±7           | 164±4        |
| Weight (kg)                             | 65.0±10.7       | 63.3±7.6     |
| Race (no. of women)                     |                 |              |
| White                                   | 22              | 19           |
| Black                                   | 2               | 2            |
| Asian                                   | 0               | 3            |
| Postmenopausal status (no. of women)    | 2‡              | 2§           |
| Cigarette use (no. of women)            | 1¶              | 2            |
| Calcium supplementation (no. of women)  | 0               | 2            |
| Vegetarian diet (no. of women)          | 1               | 3            |
| Current regular exercise (no. of women) | 4               | 4            |

\*Plus-minus values are means ±SD.

†The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡One woman had been postmenopausal for six years, and the other woman for less than one year.

§One woman had been postmenopausal for three years, and the other woman for less than one year.

¶This woman had smoked for six pack-years.

||One woman had smoked for three pack-years, and the other woman for four pack-years.

ed were women with abnormal results on any of the laboratory tests listed above. Only three women smoked (two normal women and one woman with depressive illness), and none had smoked for more than six pack-years (the number of packs per day multiplied by the number of years of smoking). No woman was taking more than two alcoholic drinks per day at the time of the study, but three of the women with depressive illness met DSM-III-R criteria for past alcohol abuse. The data on the risks for decreased bone mineral density are shown in Table 1.

At the time of the study, 14 women were actively depressed or had been free of depression for less than six months, and 10 had been free of symptoms for at least six months. The details of antidepressant-drug therapy, hospitalizations, and weight loss in these women are shown in Table 2.

## Analytic Methods

### Measurements of Bone Mineral Density

We measured bone mineral density with a Hologic QDR-2000 dual-energy x-ray absorptiometer (Hologic, Waltham, Mass.), using a fan beam and an array of detectors for the anteroposterior and lateral lumbar-spine and hip determinations (only 23 women with depressive illness and 23 normal women had the lateral lumbar-spine measurements). Pencil-beam scans were used to measure radial bone density. Both the anteroposterior and lateral lumbar-spine scans were done with the women in the supine position. Area density measurements, in grams per square centimeter, were obtained for the anteroposterior lumbar spine (vertebrae L1 to L4), the lateral lumbar-spine vertebral bodies (L2 to L4), the femoral neck, Ward's area of the femoral neck, the trochanter area

of the upper femur, and the junction of the middle and distal thirds of the radius. Lateral lumbar-spine measurements were converted to grams per cubic centimeter by dividing by the average vertebral-body width obtained from the anteroposterior scan. Each measurement was expressed as absolute bone mineral density and as a normalized deviate (standard deviations from the predicted peak bone density) derived from a population-based study of 747 normal white women.<sup>4</sup>

Daily scans of a phantom equivalent to lumbar-spine tissue for five months gave a coefficient of variation of 0.49 percent for the anteroposterior measurement and of 0.67 percent for the lateral measurement. All scans were reviewed by a physician in nuclear medicine to ensure that the measurements did not include areas of vascular calcification or degenerative arthritis and did not overlap with the iliac crest or ribs.

### Laboratory Measures of Bone Metabolism

Serum osteocalcin and serum parathyroid hormone were measured by immunoradiometric assay (SmithKline Beecham, Van Nuys, Calif.), serum 25-hydroxyvitamin D by competitive protein-binding analysis, and serum 1,25-dihydroxyvitamin D by column chromatography. In 19 women with past or current depression and 19 normal women, one 24-hour urine sample was analyzed for the ratios of deoxypyridinoline cross-links to creatinine and of *N*-telopeptides to creatinine by enzyme-linked immunosorbent assay (Endocrine Science, Calabasas Hills, Calif.).

### Vitamin D-Receptor Genotype

We tested for three vitamin D-receptor polymorphisms (Aa, Bb, and Tt) by restriction-fragment-length polymorphism analysis at the restriction-enzyme sites *BsmI* (13 pairs of women with depressive illness and normal women), *ApaI* (12 pairs), and *TaqI* (10 pairs). After the extraction of full-length DNA with the use of a commercially available kit (Scottlab, Shelton, Conn.), 100 µg of DNA was amplified in separate polymerase chain reactions with the use of previously described primers flanking the *BsmI*,<sup>5</sup> *ApaI*, and *TaqI* polymorphic sites.<sup>6</sup> The digestions were carried out with the respective enzymes (Boehringer Mannheim, Indianapolis), after which the products were fractionated by electrophoresis and analyzed in a masked fashion by one of us.

### Assessment of the Hypothalamic-Pituitary-Adrenal and Growth Hormone Axes

Urinary cortisol was measured by radioimmunoassay in all the women (SmithKline Beecham, Norristown, Pa.). Urinary cortisol was also measured in a separate subgroup of 14 women who were actively depressed and had been medication-free for at least two

**TABLE 2.** ILLNESS AND MEDICATION-EXPOSURE PROFILES OF 24 DEPRESSED WOMEN.

| VARIABLE                               | MEAN ±SD | NO. OF WOMEN |
|--|----------|--------------|
| Years since onset of illness           | 15±12    | 24           |
| No. of hospitalizations                | 0.6±1.2  | 7            |
| Weight loss with depression (kg)       | 5.0±1.1  | 6            |
| Duration of drug therapy (yr)          |          |              |
| Tricyclic antidepressant               | 2.3±2.7  | 11           |
| Selective serotonin-reuptake inhibitor | 1.5±1.0  | 15           |
| Heterocyclic antidepressant            | 0.6±0.6  | 4            |
| Bupropion                              | 1.1±0.7  | 4            |
| Monoamine oxidase inhibitor            | 1.3±1.1  | 2            |
| Lithium                                | 0.8±0.8  | 4            |
| Valproate                              | 0.5      | 1            |

**TABLE 3. BONE MINERAL DENSITY IN 24 DEPRESSED AND 24 NORMAL WOMEN.\***

| BONE MEASURED†                 | DEPRESSED WOMEN | NORMAL WOMEN | MEAN DIFFERENCE (95% CI) | P VALUE |
|--------------------------------|-----------------|--------------|--------------------------|---------|
| Lumbar spine (anteroposterior) |                 |              |                          |         |
| Density (g/cm <sup>2</sup> )   | 1.00±0.15       | 1.07±0.09    | 0.08 (0.02 to 0.14)      | 0.02    |
| SD from expected peak          | -0.42±1.28      | 0.26±0.82    | 0.68 (0.13 to 1.23)      |         |
| Lumbar spine (lateral)‡        |                 |              |                          |         |
| Density (g/cm <sup>2</sup> )   | 0.74±0.09       | 0.79±0.07    | 0.05 (0.00 to 0.09)      | 0.03    |
| SD from expected peak          | -0.88±1.07      | -0.36±0.80   | 0.50 (0.04 to 1.03)      |         |
| Femoral neck                   |                 |              |                          |         |
| Density (g/cm <sup>2</sup> )   | 0.76±0.11       | 0.88±0.11    | 0.11 (0.06 to 0.17)      | <0.001  |
| SD from expected peak          | -1.30±1.07      | -0.22±0.99   | 1.08 (0.55 to 1.61)      |         |
| Ward's triangle                |                 |              |                          |         |
| Density (g/cm <sup>2</sup> )   | 0.70±0.14       | 0.81±0.13    | 0.11 (0.06 to 0.17)      | <0.001  |
| SD from expected peak          | -0.93±1.24      | 0.18±1.22    | 1.11 (0.60 to 1.62)      |         |
| Trochanter                     |                 |              |                          |         |
| Density (g/cm <sup>2</sup> )   | 0.66±0.11       | 0.74±0.08    | 0.08 (0.04 to 0.13)      | <0.001  |
| SD from expected peak          | -0.70±1.22      | 0.26±0.91    | 0.97 (0.46 to 1.47)      |         |
| Radius                         |                 |              |                          |         |
| Density (g/cm <sup>2</sup> )   | 0.68±0.04       | 0.70±0.04    | 0.01 (-0.01 to 0.04)     | 0.25    |
| SD from expected peak          | -0.19±0.67      | 0.03±0.67    | 0.21 (-0.21 to 0.64)     |         |

\*Plus-minus values are means ±SD. CI denotes confidence interval.

†Values for "SD from expected peak" are the numbers of standard deviations from the expected peak density derived from a population-based study of normal white women.<sup>3</sup>

‡This measurement was made in 23 depressed women and 23 normal women.

weeks. Urinary creatinine was measured to assess the completeness of collection. Serum insulin-like growth factor I was measured by radioimmunoassay (Endocrine Science) in 10 actively depressed women who had been medication-free for at least two weeks and in 10 matched normal women.

### Statistical Analysis

Bone mineral density and laboratory values were compared in the groups with the use of paired Student's *t*-tests. The distribution of vitamin D-receptor alleles among the groups at each restriction-enzyme site was compared with the use of the Maxwell-Stuart three-by-three McNemar comparison.<sup>7</sup> The relation between bone mineral density and lifetime antidepressant-drug therapy was assessed with the use of an analysis of covariance in which the covariates were age and body-mass index.

## RESULTS

### Measurements of Bone Mineral Density

As compared with the normal women, the women with past or current depression had decreased bone mineral density at each trabecular-bone site studied, both in absolute values and in deviations from expected peak bone density (Table 3 and Fig. 1). Radial bone mineral density (cortical bone) was similar in both groups. The results were similar when the values in postmenopausal women were excluded from the analysis. Ten of the 24 women with past or current depression had bone mineral densities  $\geq 2$  SD below the expected peak density at one or more sites, and 8 of these women were 44 years old or younger. No normal woman had a deficit of similar magnitude. After control for age and body-mass index, bone mineral density did not correlate with the duration of antidepressant-drug therapy, which was categorized

as none (3 women), brief (one year or less, 6 women), moderate (from more than one to three years, 10 women), or long (more than three years, 5 women).

### Laboratory Evaluation of Bone Metabolism

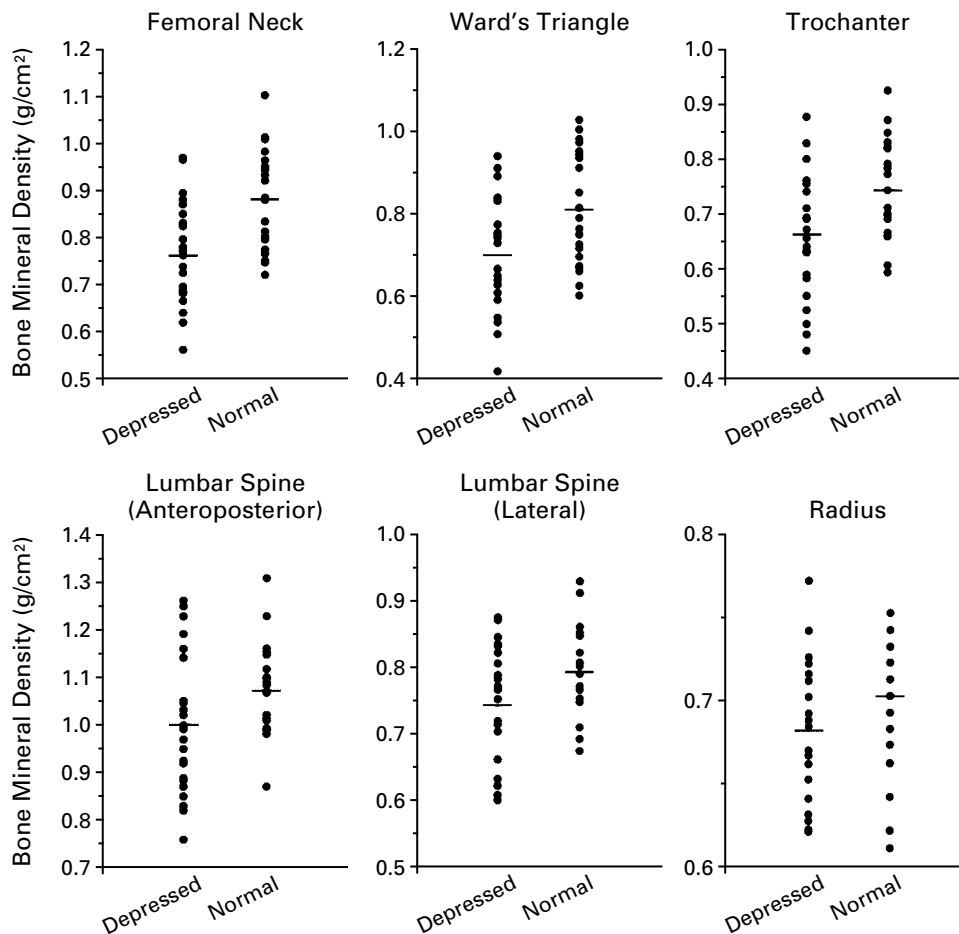
The mean serum concentration of osteocalcin was lower in the women with past or current depression than in the normal women (Table 4). Serum concentrations of 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and parathyroid hormone were similar in both groups. The mean ratio of urinary deoxypyridinoline cross-links to creatinine was lower in the women with depressive illness than in the normal women. Urinary *N*-telopeptide excretion was similar in both groups, as was the distribution of each of the three sets of vitamin D-receptor alleles (Aa, Bb, and Tt).

### Hypothalamic-Pituitary-Adrenal Function

Mean ( $\pm$ SD) urinary cortisol excretion was higher in the women with past or current depression than in the normal women (Table 4). The mean value was also higher in the 14 depressed women who collected samples while actively depressed and medication-free than in the matched normal women ( $82 \pm 31$  vs.  $55 \pm 21$   $\mu$ g per day [ $226 \pm 86$  vs.  $152 \pm 58$  nmol per day],  $P = 0.02$ ).

### Secretion of Growth Hormone

The mean serum concentrations of insulin-like growth factor I in the 10 women studied while actively depressed and in the matched normal women were similar (Table 4).



**Figure 1.** Bone Mineral Density in Depressed Women and Normal Women.

Some graphs appear to show fewer measurements because values were similar in several women. The horizontal lines indicate the mean values. Each measurement was made in 24 women with depressive illness and 24 normal women, except those of the lateral lumbar spine, which were made in 23 women in each group.

## DISCUSSION

We found that women with current or past depression had a lower density of trabecular but not cortical bone, slightly lower serum osteocalcin concentrations and urinary excretion of deoxypyridinoline cross-links, and greater urinary cortisol excretion than normal women. In one previous study, lumbar-spine bone density was reduced in depressed women, as measured by computed tomography.<sup>8</sup> Our study differs in that the women with depressive illness were younger (mean, 41 vs. 62 years); the women with depressive illness and the normal women were individually matched for age, body-mass index, and menstrual status; women with many of the risk factors associated with decreased bone mineral density were excluded; dual-energy x-ray absorptiometry was used to measure bone density at the spine, hip, and radius; and bone metabolic activity and hormonal measures related to depression were assessed.

The specificity of our findings and their underlying pathophysiology are uncertain. Decreased bone density has been found in patients with anorexia nervosa,<sup>9</sup> schizophrenia,<sup>10</sup> and other psychiatric disorders.<sup>11</sup> The increases in cortisol secretion in women with depressive illness, though small, are in the range reported to lead to decreased bone mineral density.<sup>12,13</sup> Because the recovery of bone density in patients with Cushing's syndrome can take up to 10 years,<sup>14,15</sup> the mild-to-moderate hypercortisolism typical of depression could contribute to bone loss that, because of recurrent episodic illness, never returns to normal.

Hypogestrogenism is associated with decreased bone density, but none of the women with past or current depression reported menstrual disorders or amenorrhea (other than menopause). Although small decreases in estrogen secretion could have occurred, subtle ovulatory abnormalities do not affect bone

**TABLE 4.** BIOCHEMICAL PROFILE OF 24 DEPRESSED AND 24 NORMAL WOMEN.\*

| VARIABLE  | DEPRESSED WOMEN | NORMAL WOMEN    | P VALUE |
|---|-----------------|-----------------|---------|
| Urinary cortisol ( $\mu\text{g}/\text{day}$ )†                      | 71 $\pm$ 29     | 51 $\pm$ 19     | 0.006   |
| Serum osteocalcin ( $\text{ng}/\text{ml}$ )‡                        | 7.0 $\pm$ 2.9   | 8.8 $\pm$ 2.4   | 0.04    |
| Urinary deoxypyridinoline:creatinine ( $\text{nmol}:\text{mmol}$ )§ | 2.8 $\pm$ 1.1   | 3.8 $\pm$ 1.7   | 0.02    |
| Urinary N-telopeptide:creatinine ( $\text{pmol}:\mu\text{mol}$ )§   | 38.5 $\pm$ 19.8 | 44.6 $\pm$ 44.7 | 0.53    |
| Serum parathyroid hormone ( $\text{pg}/\text{ml}$ )                 | 40 $\pm$ 16     | 34 $\pm$ 20     | 0.24    |
| Serum 25-hydroxyvitamin D ( $\text{ng}/\text{ml}$ )¶                | 39 $\pm$ 18     | 35 $\pm$ 16     | 0.44    |
| Serum 1,25-dihydroxyvitamin D ( $\text{pg}/\text{ml}$ )             | 50 $\pm$ 20     | 44 $\pm$ 19     | 0.25    |
| Serum insulin-like growth factor I ( $\text{ng}/\text{ml}$ )**      | 189 $\pm$ 86    | 189 $\pm$ 37    | 0.98    |

\*Plus-minus values are means  $\pm$ SD.

†To convert values for urinary cortisol to nanomoles per day, multiply by 2.76.

‡To convert values for osteocalcin to nanomoles per liter, multiply by 0.1538.

§This variable was measured in 19 depressed women and 19 normal women.

¶To convert values for 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.4.

||To convert values for 1,25-dihydroxyvitamin D to nanomoles per liter, multiply by 2.496.

\*\*This variable was measured in 10 depressed women and 10 normal women. To convert values for insulin-like growth factor I to nanomoles per liter, multiply by 0.1307.

mass.<sup>16</sup> A deficiency in growth hormone can result in the loss of bone density, but the secretion of insulin-like growth factor I in a subgroup of actively depressed women was normal. Vitamin D-receptor genotype, which has been reported to be an important determinant of bone density by some though not all investigators,<sup>5,6,17,18</sup> was similar in the two groups of women.

Depression is associated with both decreased physical activity (psychomotor retardation) and increased activity (agitated depression), and physical activity affects bone density. These skeletal effects are most evident in patients with extreme inactivity<sup>19</sup> or regular exercise,<sup>20</sup> however, and the effects of small changes in daily activity are not known. Furthermore, quantifying levels of activity retrospectively is difficult. Thus, because self-reports of current exercise patterns in the depressed and normal women were similar, the contribution of physical activity to the measured decreases in bone density was probably small. Anorexia and weight loss can also lead to decreased bone mineral density. Of the six depressed women who reported weight loss while depressed, however, only one had very low bone mineral density.

The decreases in serum osteocalcin (a marker of

osteoblastic activity) and urinary deoxypyridinoline excretion (a marker of bone resorption) suggest decreased bone turnover and are consistent with the alterations in these measures found in patients with Cushing's syndrome.<sup>15,21,22</sup> Urinary N-telopeptide excretion (another index of bone resorption) was not decreased, however, suggesting that if bone turnover is decreased in women with past or current depression, the decrease is small.

A majority of the women with depressive illness had been treated with antidepressant drugs, raising the possibility that these drugs contributed to the decreased bone density. Although we found no association between lifetime antidepressant-drug treatment and bone density, anticonvulsant drugs such as carbamazepine and valproic acid that are sometimes used in the treatment of depression can lower bone density,<sup>23</sup> and some women may have inaccurately estimated their previous therapy. Administering antidepressant drugs to laboratory animals<sup>24,25</sup> and imipramine to normal humans<sup>26</sup> decreases the secretion of hypothalamic corticotropin-releasing hormone, and in depressed patients, cortisol secretion declines after successful treatment with antidepressant drugs.<sup>27</sup> We would therefore expect antidepressant-drug treatment to counter glucocorticoid-induced loss of bone density and, by resolving depressive symptoms, to restore more-normal appetite and activity patterns.

The decreased bone mineral density in women with past or current depression may be clinically important. Among the women who were premenopausal, more than a third had bone mineral density  $\geq 2$  SD below the expected peak — a degree of loss similar to that of postmenopausal women.<sup>28</sup> The bone mineral density in the women with depression was on average 6 percent lower in the spine and 10 to 14 percent lower in the hip than in the normal women. The prominence of the deficits seen in these relatively young patients suggests that the lifetime risk of fracture related to depression is substantial.

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