Low Bone Mass in Premenopausal Women With Depression

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Background: An increased prevalence of low bone mineral density (BMD) has been reported in patients with major depressive disorder (MDD), mostly women.

Methods: Study recruitment was conducted from July 1, 2001, to February 29, 2003. We report baseline BMD measurements in 89 premenopausal women with MDD and 44 healthy control women enrolled in a prospective study of bone turnover. The BMD was measured by dual-energy x-ray absorptiometry at the spine, hip, and forearm. Mean hourly levels of plasma 24-hour cytokines, 24-hour urinary free cortisol, and catecholamine excretion were measured in a subset of women. We defined MDD according to the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition).

Results: The prevalence of low BMD, defined as a T score of less than −1, was greater in women with MDD vs controls at the femoral neck (17% vs 2%; P = .02) and total hip (15% vs 2%; P = .03) and tended to be greater at the lumbar spine (20% vs 9%; P = .14). The mean ± SD BMD, expressed as grams per square centimeters, was lower in women with MDD at the femoral neck (0.849 ± 0.121 vs 0.866 ± 0.094; P = .05) and at the lumbar spine (1.024 ± 0.117 vs 1.043 ± 0.092; P = .05) and tended to be lower at the radius (0.696 ± 0.049 vs 0.710 ± 0.055; P = .07). Women with MDD had increased mean levels of 24-hour proinflammatory cytokines and decreased levels of anti-inflammatory cytokines.

Conclusions: Low BMD is more prevalent in premenopausal women with MDD. The BMD deficits are of clinical significance and comparable in magnitude to those resulting from established risk factors for osteoporosis, such as smoking and reduced calcium intake. The possible contribution of immune or inflammatory imbalance to low BMD in premenopausal women with MDD remains to be clarified.

Trial Registration: clinicaltrials.gov Identifier: NCT00006180

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Major Depressive Disorder (MDD) is a common condition and a major cause of disability. Besides mood changes, MDD is associated with increased morbidity and non-suicide-related mortality. In addition to poor medical compliance and lifestyle factors, endocrine, immune, and autonomic dysregulation may play a causative role in producing medical illnesses in patients with MDD.

Ten million Americans older than 50 years have documented osteoporosis, and an additional 34 million have osteopenia at the level of the hip, which may put them at risk for osteoporotic fractures later in life. An estimated 1.5 million Americans have osteoporosis-related fractures annually, with costs of $17 billion in the year 2001. Osteoporosis remains mostly asymptomatic and goes undiagnosed until a pathologic fracture ensues. Because it is undiagnosed, silent osteoporosis is unlikely to induce depression and serves as a good model of a physical illness associated with MDD.

In young women, MDD has been associated with low BMD in several small studies. A decade after the first of these reports and despite multiple studies linking depression and osteoporosis in hundreds of patients, MDD still is not recognized as a risk factor for osteoporosis, as evidenced by official statements. A role for depression in causing low BMD is biologically plausible because several endocrine mechanisms may account for bone loss, including hypercortisolemia and a hyperadrenergic state. Alterations of the im-

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Group Information: The POWER Study Group investigators are listed at the end of this article.
immune system, such as an increase in interleukin 6 (IL-6)—one of the most potent bone resorption factors—may also contribute to bone loss.

Recently, a study conducted in mice indicated that chronic stress may induce bone loss via activation of the sympathetic nervous system, a process that is partly prevented by antidepressants.

We investigated the association of MDD and BMD in a prospective study of bone turnover in which immune, pituitary-adrenal, and sympathetic biomarkers were measured. We sought to determine whether premenopausal women with MDD had a higher prevalence of osteopenia and osteoporosis and of lower BMD than did healthy women. In this article, we report the baseline cross-sectional findings.

**METHODS**

**PARTICIPANTS**

Study participants were community-dwelling 21- to 45-year-old premenopausal women with current or recent MDD and healthy control women participating in the Premenopausal Osteoporosis Women, Alendronate, Depression (POWER) Study, a prospective investigation of bone turnover conducted at the National Institutes of Health Clinical Center. Recruitment was conducted from July 1, 2001, to February 29, 2003, in the Washington, DC, metropolitan area by newspaper, radio, Internet, and flyer advertisement. Women were enrolled if they met Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) (DSM-IV) criteria for MDD and had experienced a depressive episode in the preceding 3 years, a limit chosen to minimize recall problems associated with more remote depressive episodes.

Exclusion criteria were depression with suicidal risk, schizophrenia, schizoaffective disorders, eating disorders, bipolar illness, hyperthyroidism, vitamin D deficiency or other conditions or treatments that might affect bone turnover, and menopause, defined as the absence of spontaneous menses during the preceding 6 months. Women whose last menstrual period occurred 3 to 6 months before the start of the study were also excluded if their serum estradiol level was lower than 20 pg/mL (to convert to picomoles per liter, multiply by 3.671) and their serum follicle-stimulating hormone level was above 20 mIU/mL (to convert to international units per liter, multiply by 1.0). Patients treated for depression were allowed to continue their usual treatment. Patients with anxiety disorders or a history of alcohol or drug dependence in remission for 5 years were eligible. Controls were also excluded if they had a history of any DSM-IV diagnosis other than past alcohol abuse. Forty-four control women were individually matched with a subset of 44 patients with MDD based on age (±3 years) and height (±2.0). Except for 2 pairs, all other pairs were also matched by self-defined race. The institutional review board of the National Institute of Mental Health approved this study. Written informed consent was obtained from each participant.

**PROCEDURES**

Screening evaluation included a serum pregnancy test; complete blood cell count; chemistry panel; measurement of levels of thyrotropin, free thyroxine, intact parathyroid hormone (iPTH), and 25-hydroxyvitamin D; urinalysis; and urine toxicology screening. Weight and height were measured to the nearest 0.1 kg and the nearest 0.1 cm, respectively.

**Psychiatric Assessment**

The MDD was diagnosed by 2 of the authors (P.E.M. and S.T.) according to the DSM-IV criteria, using the Structured Clinical Interview for DSM-IV. The Global Assessment of Functioning Scale of the Structured Clinical Interview for DSM-IV was used as a measure of the level of functioning. Current severity of depression and anxiety were assessed using the Hamilton Depression Scale (24 questions) and the Hamilton Anxiety Scale (14 questions).

**Bone Mineral Density**

The BMD was measured by dual-energy x-ray absorptiometry (DEXA QDR 4500 machine; Hologic Inc, Bedford, Massachusetts) at the anteroposterior lumbar (L1-L4) spine, femoral neck, total hip, and middistal radius. The coefficient of variation was 0.4% or less at each site.

**Miscellaneous Assessments**

Intake of calcium from food and supplements, caffeine, and alcohol was assessed with a self-reported food frequency questionnaire. We also queried participants about cigarette smoking and previous nontraumatic fractures. The distance a person is able to cover during 12 minutes by running or walking as fast as possible was used as an indirect index of physical fitness (Cooper test).

**Blood and Urine Tests**

Assays were performed at the National Institutes of Health Clinical Center and exhibited interassay coefficients of variation ranging from 10% to 15%. Serum iPTH, osteocalcin, and urinary-free cortisol were measured by chemiluminescent immunoassays with the Nichols Advantage apparatus (Nichols Institute Diagnostics, San Clemente, California). 25-Hydroxyvitamin D was also assessed (Nichols Advantage Chemiluminescence System; Nichols Institute Diagnostics, San Clemente, California).

Serum bone-specific alkaline phosphatase was measured by immunoenzymatic assay. Urinary N-telopeptide was measured by the Vitros ECI competitive assay and urinary creatinine by the Jaffe reaction (Mayo Medical Laboratory, Mayo Clinic, Rochester, Minnesota) at the Mayo Medical Laboratory. Urinary catecholamines were measured by high-performance liquid chromatography with electrochemical detection. Levels of IL-1β, IL-2, IL-6, tumor necrosis factor α, IL-10, and IL-13 were measured in plasma (T.M.P.) without knowledge of group allocation, using recycling immunoaffinity chromatography, with recovered analyte quality control by time-of-flight mass spectrometry, using specific anticytokine antibodies obtained from R & D Systems (Minneapolis, Minnesota), as previously described.

**STATISTICAL ANALYSES**

All data are reported as mean ± SD or percentages. For most statistical analyses, data from the entire group of 89 women with MDD were compared with those from the 44 controls. We also compared the subgroup of 44 women with MDD with their individually matched controls. We assessed differences in the overall group by the t test and Fisher exact test and differences between matched pairs by the paired t test and McNemar test.
The analyses that compared BMD between controls and women with MDD depict analysis of covariance \( P \) values adjusted for BMI. Associations between BMD and clinical features of depression were evaluated using Pearson correlations. We performed analyses of covariance comparing BMD between women who were taking a selective serotonin reuptake inhibitor vs the ones who were not taking a selective serotonin reuptake inhibitor, accounting for the differences in BMI.

All tests were 2-sided with a significance level of .05. According to an a priori power calculation based on published findings by Michelson et al,\(^1\) we estimated that 40 women per group would be needed to detect a 6% BMD difference at the anteroposterior spine with 85% statistical power. We chose a 2:1 allocation of patients vs controls to collect more information on women with MDD.

**RESULTS**

**DEMOGRAPHIC CHARACTERISTICS, RISK FACTORS FOR OSTEOPOROSIS, AND CLINICAL FEATURES OF DEPRESSION**

The Figure depicts the number of individuals screened, reasons for exclusion, and enrolled patients. Our sample was composed of mostly white, college-educated women (Table 1). Demographic characteristics were similar between women with MDD and controls, with the exception of BMI, which was higher in women with MDD. Smoking; intake of calcium, caffeine, and alcohol; and distance covered on the Cooper test were similar between the 89 women with MDD and the 44 controls and in the 2 matched subgroups.

Table 2 lists the clinical features of the participants. Seventeen percent of women with MDD were currently depressed (defined as a depressive episode during the preceding 4 weeks). On average, women with MDD exhibited mild symptoms of depression and anxiety. An average score of 63 on the Global Assessment of Functioning Scale indicated a good level of functioning. However, patients with MDD had a cumulative history of depression of approximately 5 years and 4 episodes of depression. Age at onset of depression was in the late teens, and approximately half the women with MDD also currently or previously had anxiety disorders. Eighty-two percent of the women with MDD were taking antidepressants.

**BONE MINERAL DENSITY**

We analyzed differences in BMD between patients with MDD and controls as a continuous variable (grams per square centimeter and T score; Table 3) and as a categorical variable (presence or absence of low BMD), defined as a T score of less than −1 at the hip and/or spine (Table 3). After adjusting for BMI, bone density was significantly lower (by approximately 2%) in patients with MDD vs controls at the anteroposterior spine and the femoral neck and tended to be lower at the radius; the T score was significantly lower at the femoral neck and the radius (Table 3). The matched subgroup of women with MDD had a lower BMD than controls, but the difference was significant only at the radius. The prevalence of low BMD was greater in women with MDD vs controls (28% vs 11%; \( \text{P} = .046 \)), greater at the femoral neck (17% vs 2%; \( \text{P} = .02 \)) and total hip (15% vs 2%; \( \text{P} = .03 \)), and tended to be greater at the lumbar spine (20% vs 9%; \( \text{P} = .14 \)). Findings were similar in the matched subgroups (low BMD: overall: 32% vs 11%, \( \text{P} = .02 \); femoral neck: 20% vs 2%, \( \text{P} = .02 \); total hip: 16% vs 2%, \( \text{P} = .03 \)).

Among the 89 women with MDD, no significant relationships were found between T score and the duration or severity of depression or anxiety, as measured by the age at onset of depression, the number of depressive episodes, the cumulative months of depression, or the Global Assessment of Functioning Scale, the Hamilton Depression Scale, or the Hamilton Anxiety Scale scores (data not shown). None of the study participants had atraumatic fractures.

Twenty-five women with MDD had a T score lower than −1 SD at the spine or hip, and 2 of these women had osteoporosis, defined as a T score at the anteroposterior spine or hip lower than −2.5 SDs. These 25 women had significantly lower BMI (\( \text{P} = .01 \)) and weight (\( \text{P} < .001 \)) and traversed a greater distance during the Cooper test (\( \text{P} < .001 \)) than did women with MDD, normal BMD, and higher T scores. No differences were observed in age, age

\[ \text{Figure. Study flow diagram. The number of individuals} \]
\[ \text{screened, reasons for exclusion, and number of individuals} \]
\[ \text{enrolled in the study are listed. MDD indicates} \]
\[ \text{major depressive disorder; PTSD, posttraumatic stress} \]
\[ \text{disorder.} \]
at menarche, smoking, or calcium, caffeine, or alcohol intake between these 25 patients and the remaining women with MDD. Except for the more frequent history of drug abuse or dependence in the low-BMD group (28% vs 9%; *P* = .04), the numbers of depressive episodes, cumulative duration of depression, and presence of other psychiatric conditions were similar between the groups. Of 73 women with MDD who were taking an antidepressant medication at the time of enrollment, 54 were taking 1 form of selective serotonin reuptake inhibitor. Use of a selective serotonin reuptake inhibitor did not contribute to low BMD after accounting for BMI: lumbar spine (*P* = .95), femoral neck (*P* = .99), total hip (*P* = .11), and radius (*P* = .93).

**Table 1. Demographic Characteristics and Risk Factors for Osteoporosis in Study Participants**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Subjects (n=44)</th>
<th>Subgroup of Matched Women With MDD (n=44)</th>
<th>All Women With MDD (n=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>35±6.8</td>
<td>35±6.8</td>
<td>35±6.9</td>
</tr>
<tr>
<td>BMI</td>
<td>24.2±3.7</td>
<td>24.1±4.1</td>
<td>26.7±6.3</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>68.0±11.0</td>
<td>66.1±12.5</td>
<td>73.1±18.6</td>
</tr>
<tr>
<td>Race (white), No. (%)</td>
<td>39 (89)</td>
<td>42 (95)</td>
<td>82 (92)</td>
</tr>
<tr>
<td>Educational level, y</td>
<td>16±2.1</td>
<td>17±1.9</td>
<td>16±2.0</td>
</tr>
<tr>
<td>Married, No. (%)</td>
<td>22 (50)</td>
<td>16 (36)</td>
<td>31 (35)</td>
</tr>
<tr>
<td>Age at menarche, y</td>
<td>13±1.6 (n=43)</td>
<td>13±1.5 (n=42)</td>
<td>12±1.6 (n=82)</td>
</tr>
<tr>
<td>No. of pregnancies</td>
<td>1±1.4</td>
<td>1±1.4</td>
<td>1±1.6</td>
</tr>
<tr>
<td>Use of oral contraceptives, No. %</td>
<td>16 (36)</td>
<td>14 (32)</td>
<td>27 (30)</td>
</tr>
<tr>
<td>Smokers, No. (%)</td>
<td>14 (2)</td>
<td>13 (30)</td>
<td>29 (33)</td>
</tr>
<tr>
<td>Cigarette smoking, No. of pack-years</td>
<td>4.0±12.8</td>
<td>3±5.8</td>
<td>2.4±5.4 (n=87)</td>
</tr>
<tr>
<td>Total calcium intake, mg/d</td>
<td>1408±755 (n=41)</td>
<td>1307±664 (n=42)</td>
<td>1381±663 (n=77)</td>
</tr>
<tr>
<td>Caffeine intake, mg/d</td>
<td>201±164 (n=37)</td>
<td>198±248 (n=40)</td>
<td>203±244 (n=71)</td>
</tr>
<tr>
<td>Alcohol consumption, g/d</td>
<td>7±11.6 (n=41)</td>
<td>6±7.0</td>
<td>4±5.8</td>
</tr>
<tr>
<td>Cooper test (distance covered in 12 min), m</td>
<td>1411±272 (n=21)</td>
<td>1368±372 (n=22)</td>
<td>1306±328 (n=37)</td>
</tr>
</tbody>
</table>

**Table 2. Characteristics of Study Participants**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control Subjects (n=44)</th>
<th>Subgroup of Matched Women With MDD (n=44)</th>
<th>All Women With MDD (n=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current depression, No. (%)</td>
<td>NA</td>
<td>10 (23)</td>
<td>15 (17)</td>
</tr>
<tr>
<td>Hamilton Depression Scale score</td>
<td>2±2.0 (n=39)</td>
<td>10±7.1 (n=43)</td>
<td>9±6.7 (n=78)</td>
</tr>
<tr>
<td>Hamilton Anxiety Scale score</td>
<td>1±1.8 (n=39)</td>
<td>8±5.5 (n=43)</td>
<td>7±4.8 (n=78)</td>
</tr>
<tr>
<td>Global Assessment of Functioning Scale score</td>
<td>81±4.3</td>
<td>63±10.5</td>
<td>63±9.4</td>
</tr>
<tr>
<td>No. of depressive episodes</td>
<td>NA</td>
<td>4±2.2 (n=35)</td>
<td>4±2.6 (n=65)</td>
</tr>
<tr>
<td>Cumulative depression, mo</td>
<td>64±67.1 (n=35)</td>
<td>63±69.4 (n=65)</td>
<td></td>
</tr>
<tr>
<td>Age at the onset of depression, y</td>
<td>NA</td>
<td>18±5.6 (n=35)</td>
<td>19±9.0 (n=65)</td>
</tr>
<tr>
<td>Other Axis I diagnoses, No. (%)</td>
<td>7 (16)</td>
<td>24 (55)</td>
<td>47 (53)</td>
</tr>
<tr>
<td>Anxiety disorders, No. (%)</td>
<td>NA</td>
<td>19 (43)</td>
<td>38 (43)</td>
</tr>
<tr>
<td>Posttraumatic stress disorder, No. (%)</td>
<td>NA</td>
<td>5 (11)</td>
<td>12 (13)</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder, No. (%)</td>
<td>NA</td>
<td>3 (7)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Other anxiety disorders, No. (%)</td>
<td>NA</td>
<td>18 (41)</td>
<td>31 (35)</td>
</tr>
<tr>
<td>History of eating disorders, No. (%)</td>
<td>NA</td>
<td>1 (2)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>History of substance abuse or dependence, No. (%)</td>
<td>7 (16)</td>
<td>16 (36)</td>
<td>26 (29)</td>
</tr>
<tr>
<td>Antidepressant medications, No. (%)</td>
<td>NA</td>
<td>25 (57)</td>
<td>54 (61)</td>
</tr>
<tr>
<td>Tricyclics</td>
<td>NA</td>
<td>1 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>NA</td>
<td>20 (45)</td>
<td>41 (46)</td>
</tr>
<tr>
<td>Anxiolytic medications</td>
<td>1 (2)</td>
<td>9 (20)</td>
<td>13 (15)</td>
</tr>
<tr>
<td>Other psychotropics</td>
<td>0</td>
<td>8 (18)</td>
<td>14 (16)</td>
</tr>
</tbody>
</table>

**Abbreviations:** BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); MDD, major depressive disorder.

*All values are reported as mean±SD unless otherwise indicated.
Subgroup of women with MDD individually matched with control subjects based on age and BMI.
*P* < .05 based on *t* test or Fisher exact test comparing the MDD group with controls.

*Current depression is defined as depression during the preceding 4 weeks.*
HORMONES, BIOCHEMICAL MARKERS OF BONE TURNOVER, AND CYTOKINES

Table 4 presents the findings for the bone biochemical markers, calcium metabolism parameters, and urinary-free cortisol and catecholamine excretion in patients with MDD and control subjects. Overall, bone biochemical markers were within the reference range in both women with MDD and controls. In the MDD group, levels of serum bone-specific alkaline phosphatase, a bone formation marker, were slightly higher ($P = .03$), whereas those of urinary N-telopeptide, a bone resorption marker, were nonsignificantly lower ($P = .07$). No differences were observed in serum osteocalcin levels, another bone formation marker. In addition, within the MDD group, no differences were seen in levels of serum osteocalcin, bone-specific alkaline phosphatase, and urinary N-telopeptide between women with MDD and normal BMD and women with MDD and low BMD (data not shown). The iPTH level was slightly higher, whereas serum ionized calcium and plasma 25-hydroxyvitamin D concentrations were lower, although within normal limits, in the MDD group compared with controls. Urinary-free cortisol and urine catecholamine concentrations were within the reference ranges and similar between women with MDD and controls. Furthermore, no differences were found in the levels of urinary cortisol and urinary catecholamines between women with MDD and normal vs low BMD (data not shown). Urinary concentrations of epinephrine, norepinephrine, and dopamine were similar between women with MDD and controls.

Table 5. Mean Hourly Plasma Concentrations of Proinflammatory and Anti-inflammatory Cytokines, Measured for 25 Hours, in a Subgroup of Study Participants

Table 3. BMD of Study Participants

Table 4. Biochemical Markers of Bone Turnover and Calcium Metabolism and Plasma Cortisol Levels in Study Participants

The plasma cytokine concentration was measured hourly for 25 hours in 17 women with MDD and 14 controls (Table 5). Demographic, endocrine, and metabolic characteristics in these subgroups were similar to those in the overall study sample (data not shown). Women with MDD had much higher concentrations of the proinflammatory cytokines IL-1β, IL-2, IL-6, and tu-
mor necrosis factor α, similar levels of the anti-inflammatory cytokine IL-10, and lower levels of anti-inflammatory IL-13.

**COMMENT**

One in 5 premenopausal women with MDD exhibited low BMD. Decreased bone mass was especially common at the hip, which is important because hip fractures are the most serious consequence of osteoporosis. The bone mass deficits observed are of clinical significance. The 2% difference observed at the hip is similar to or greater in magnitude than that of recognized osteoporosis risk factors, such as cigarette smoking, lack of exercise, and absence of calcium supplementation. In premenopausal women, annual bone reduction rates of 0.3% and 0.5% are observed at the femoral neck and spine, respectively, rates less pronounced than those in early menopause. Therefore, women with depression are at increased risk for osteoporotic fractures after menopause. Because the relationship between BMD and fracture risk is exponential, small deficits in BMD translate into larger increases in fracture rates. Given a prevalence of MDD in the 13.4 million US women between the ages of 21 and 45 years of approximately 16%, we estimate that nearly 4 million women with MDD may have undetected deficits in BMD.

We confirmed the existence of low bone mass originally reported by Michelson et al in a smaller sample of premenopausal women with MDD. In that report, bone loss was also more accentuated at the femoral neck than at the anteroposterior spine. In that study, the magnitude of bone loss was greater than what we observed probably because their patients were more severely depressed. In addition, women with MDD in our cohort were approximately 5 kg heavier than controls, which is consistent with prior epidemiologic data. Because thinness negatively affects BMD, the greater weight of our MDD group may have mitigated bone loss. We found no significant relationships between BMD and chronicity or severity of depression. This finding is consistent with reports that show no relationships between BMD and the number of depressive episodes, antidepressant use, or bone resorptive properties. Limitations in these studies attributable to the recollection of depressive episodes may have played a role. Moreover, they may also have been inadequately powered to detect a relationship between MDD and bone loss.

We observed a striking difference in plasma cytokine concentrations between the MDD group and controls. Pro-inflammatory cytokine levels were substantially higher and anti-inflammatory cytokine levels were lower in our MDD group. Several of these cytokines, including IL-6, have bone resorptive properties. Measurement of cytokines at a single time point may have biased findings in prior studies of depression by not accounting for circadian variability. By measuring cytokines every hour for 25 hours, we detected increased mean hourly concentrations of proinflammatory cytokines and decreased concentrations of anti-inflammatory cytokines, which is consistent with a systemic proinflammatory state.

Such shifts in immune or inflammatory imbalance have previously been associated with other medical illnesses, including coronary heart disease and insulin resistance. Thus, such an immune imbalance could have contributed to the development of osteoporosis in women with depression. Although increased cytokine concentrations have previously been noted in severe depression, to our knowledge this is the first report of elevated plasma cytokine levels in mildly depressed women. Of note, cytokine concentrations are known to increase in women after menopause, whereas we observed elevations before menopause. In addition, we used a highly sensitive method to measure a large number of cytokines that were functionally related, including the less well-described anti-inflammatory cytokines. Our analytical determinations were confirmed by mass spectrometry, adding validity to our findings.

No increases in plasma cortisol, urinary-free cortisol, or catecholamine concentrations were seen, most likely because these patients were treated and in clinical remission. We previously reported that patients with active depression exhibit both sustained activation of the sympathetic nervous system and augmented IL-6 secretion. Of the studies on depression and osteoporosis with cortisol measurements, only 1 study observed greater urinary-free cortisol levels in the MDD group. Recently, a direct cause-effect relationship between stress and bone loss was demonstrated in mice. Therefore, the relative importance of hypercortisolism in depression-induced bone loss, compared with alterations in catecholamines and proinflammatory cytokines, deserves reevaluation.

Levels of serum bone-specific alkaline phosphatase, a bone formation marker, were higher in the MDD group, whereas levels of urinary N-telopeptide, a bone resorption marker, tended to be lower. Bone formation may have been activated as an attempt to recover from previous periods of loss. Women with MDD exhibited slightly but nonsignificantly higher intact PTH concentrations and lower 25-hydroxyvitamin D and ionized calcium levels compared with controls. These variations were within the reference range.

One contributory factor to low BMD may have been failure to achieve optimal peak bone mass. Because in our study the first depressive episode occurred in the late teens, it is possible that early depression may have interfered with achievement of full bone mass. The role that traditional osteoporosis risk factors play in premenopausal women is not well established. Insufficient calcium intake, smoking, and inadequate physical activity were not related to bone loss in a large prospective study of premenopausal women. In our sample, age at menarche; calcium, caffeine, and alcohol intake; smoking; and physical fitness were similar in the MDD group and controls. Episodes of amenorrhea were not reported, and use of oral contraceptives, which has been associated with increased bone mass, was similar between groups. In a recent prospective cohort study, use of selective serotonin reuptake inhibitors was found to be associated with a 2-fold increase in risk of clinical fragility fracture. In the current study, use of selective serotonin reuptake inhibitors was not associated with low BMD.
This study had several strengths. It was well controlled, and depression was diagnosed by DSM-IV criteria. To minimize recall bias, only individuals with a current or recent history of depression were enrolled. Our study cohort was prospectively assembled, relatively homogeneous, well characterized, and relatively large compared with those of previous reports. Participants were predominantly white and drawn from a community sample and consisted of women with MDD mostly in remission. Few data points were missing in this large data set, limiting the possibility of a nondirectional bias.

This study had several limitations, including racial homogeneity of the study participants and use of medications for their depression by most participants, most of whom were in remission. The latter factor may have been associated with correction of hypothalamic-pituitary-adrenal axis disturbances described in patients with active depression. In addition, the effect of antidepressants on BMD may have confounded the results of the study. Known risk factors for osteoporosis, such as exercise, smoking, and calcium intake, were assessed cross-sectionally and relied on recollection. Finally, cytokine measurements were performed in only a subset of participants, preventing us from establishing a statistically meaningful association between cytokine levels and BMD.

The usefulness of antidepressants for bone loss in MDD should be evaluated. Prospective studies should establish whether women with MDD experience a more sustained bone loss during the perimenopausal or postmenopausal period than women without depression. Exploratory studies of bone mass should be conducted in conditions associated with an activation of the sympathetic nervous system, such as posttraumatic stress disorders. The possibility that patients with depression may fail to reach peak bone mass should be investigated.

In summary, we observed lower BMD, increased prevalence of low BMD, and an increase in proinflammatory cytokines in premenopausal women with MDD. Fracture risk may be increased in women with MDD, especially after the onset of menopause. Given that MDD is a common chronic condition and that osteopenia is often clinically silent, our sample may be representative of a large population with undiagnosed conditions until the time of fracture. Therefore, MDD should be formally recognized as a risk factor for low BMD in premenopausal women.

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