Association of Low Bone Mineral Density With Selective Serotonin Reuptake Inhibitor Use by Older Men

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Background: Selective serotonin reuptake inhibitors (SSRIs) are a widely used class of antidepressants that block the serotonin transporter. Osteoblasts and osteocytes express functional serotonin transporters; serotonin transporter gene disruption in mice results in osteopenia; and SSRI use has been associated with increased risk of hip fracture.

Methods: To determine whether SSRI use is associated with lower bone mineral density (BMD) in older men and to compare the results for SSRIs with those of other antidepressants, we performed a cross-sectional analysis of data from 5995 men 65 years and older participating in the prospective cohort Osteoporotic Fractures in Men Study. Main outcome measures included medication use; BMD at the femoral neck, greater trochanter, and lumbar spine measured by dual-energy x-ray absorptiometry; and potential covariates.

Results: In adjusted analyses, mean BMD among SSRI users (n=160) was 3.9% lower at the total hip and 5.9% lower at the lumbar spine compared with BMD in men reporting no antidepressant use (n=5708 [P=.002 for total hip; P<.001 for lumbar spine]). There was no significant difference among users of trazodone hydrochloride (n=52) or tricyclic antidepressants (n=99) compared with nonusers. Adjusting for variables that could be associated with BMD and/or SSRI use did not significantly alter these results. The observed difference in BMD for SSRIs is similar to that seen with glucocorticoids.

Conclusions: In this population of men, BMD was lower among those reporting current SSRI use, but not among users of other antidepressants. Further research is needed to confirm this finding in light of widespread SSRI use and potentially important clinical implications.

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See also pages 1231 and 1240

Functional serotonin transporters have been identified in osteoblasts, osteocytes, and osteoclasts. The functionality of these bone serotonin transporters is suggested by studies in a mouse model of long-term selective serotonin reuptake inhibitor (SSRI) use. In this model, mice with genetic disruption of the serotonin transporter gene have lower bone mineral density (BMD) when compared with wild-type mice.

Selective serotonin reuptake inhibitors are first-line therapy for depression and account for approximately 62% of all antidepressant prescribing in the United States. They function by inhibiting the serotonin transporter. In addition to the cited studies suggesting an association between disruption of the serotonin transporter function and lower BMD in mice, data in humans show that SSRIs are associated with hip fracture independent of falls or fall risk. Indeed, depression itself has been shown to be associated with hip fracture in older women, a finding not entirely explained by falls. In studies of antidepressants, adjusted odds ratio point estimates for hip fracture are higher among SSRI users compared with users of tricyclic antidepressants (TCAs) or other antidepressants. It remains unclear whether it is the disease process, the treatment of depression, or the effects of depression on activity, mobility, and weight change that leads to decreased BMD among depressed people.

A large analysis of variables contributing to BMD in the Osteoporotic Fractures in Men (MrOS) Study suggested that SSRI use is a determinant of BMD among men. However, that study did not examine how adjustment for potential confounders affected the association between SSRIs and BMD, and it did not examine the association between use of other antidepressants and BMD. We planned the present study to more fully characterize the effect of SSRI use on BMD...
in men. First, we hypothesized that those taking SSRIs would have lower BMD than those not using SSRIs and that this association would not be fully explained by major confounding variables. Second, we compared the SSRI-BMD association with that of other antidepressants, including trazodone hydrochloride and TCAs, in an attempt to distinguish treatment from disease effects.

STUDY DESIGN AND PARTICIPANTS

We performed a cross-sectional analysis using data from participants in the MrOS Study. The MrOS Study includes 5995 men 65 years or older who were recruited from 6 regions of the United States (Birmingham, Ala; Minneapolis, Minn; Monongahela Valley near Pittsburgh, Pa; Palo Alto, Calif; Portland, Ore; and San Diego, Calif) between March 1, 2000, and April 30, 2002. The institutional review boards at each site approved the study. Written informed consent was obtained from all participants.14,15

BONE MINERAL DENSITY

The main outcome variables were BMD for the total hip (and subregions: the greater trochanter and femoral neck) and lumbar spine. Bone mineral density at baseline was measured using fan-beam dual-energy x-ray absorptiometry (QDR-4500W; Hologic Inc, Bedford, Mass). All measurements at the hip were performed on the right hip unless a participant reported a right hip replacement or metal objects in the right leg, in which case the measurement was performed on the left hip. Standardized procedures for participant positioning and scan analysis were executed for all scans. Spine and hip phantom scan results were assessed for longitudinal and cross-sectional quality control. The intrainclinic coefficients of variation for spine phantoms (0.34% to 0.42%) and hip phantoms (0.37% to 0.58%) were within acceptable limits. The interclinic coefficients of variation were 0.6% (spine) and 0.9% (hip), and the maximum difference between means was 1.4% (spine) and 2.2% (hip).14,16

All dual-energy x-ray absorptiometry operators at the different clinic sites were centrally certified on the basis of an evaluation of scanning and analysis techniques. To adjust for interclinic differences, statistical models included a variable for clinic site. Body size measurements, including total lean and fat mass, were also obtained from dual-energy x-ray absorptiometry.

MEDICATION USE

Participants brought all medications to their baseline clinic visit, where interviewers recorded all prescription medications used daily or almost daily for at least the past month. Medications were coded by class according to a standardized computerized study-specific medication dictionary, based on product brand or generic names from the containers. Antidepressant information was used to sort the participants into the following categories: SSRI users, trazodone users, TCA users, combination users (any 2 categories of antidepressant), and nonusers (no use of any antidepressant).

POTENTIAL COVARIATE MEASURES

Potential covariate measures for BMD were obtained from the baseline questionnaire, interview, and examination. These included demographic characteristics such as age, race/ethnicity, and clinic site; anthropometric measurements, including height, weight, body mass index, lean and fat mass, and self-reported height and weight change since age 25 years; medical conditions, including hypertension, Parkinson disease, hypothyroidism, diabetes, and stroke; lifestyle factors such as physical activity, history of heavy alcohol use, current smoking, and marital status; family history of fracture; and any history of falls. Race and/or ethnicity was ascertained by self-declaration as white, black or African American, Asian, Hispanic or Latino, and other. Any participant who indicated Hispanic background, regardless of the race category, was classified as Hispanic; those not meeting any of the descriptors listed were classified as other.

Physical activity was assessed using the Physical Activity Scale for the Elderly.17 Perceived health status was obtained from the Medical Outcomes Study 12-Item Short-Form Health Survey (SF-12)18 scored for physical and mental well-being. The mental component summary (MCS) scale of the SF-12 is a reliable measure that has been shown to distinguish between major depressive disorder, depressive symptoms, and no depression.19,20 In addition, the individual questions, as surrogates for depressed mood, were tested for correlation with BMD and use of SSRIs. Accomplishment of independent activities of daily living was self-reported. Dietary calcium and vitamin D intake was calculated using a modified food frequency questionnaire developed specifically for the MrOS Study by Block Dietary Data Systems, Berkeley, Calif (http://www.nutritionquest.com). As part of the clinic visit, participants completed tests of neuromuscular function, including walking speed, grip strength, and completion of 5 chair stands (rising from a seated position without using the chair’s arms).

STATISTICAL ANALYSIS

We compared the characteristics of men using SSRIs with those of men not using any antidepressant, using unpaired, 2-tailed t tests for continuous variables and contingency tables for categorical variables. We conducted descriptive analyses to understand the associations between medication use and all other potential covariates.

MULTIVARIABLE MODELS

To test the hypothesis that SSRI use was associated with decreased BMD, we used age-adjusted linear regression models. We included clinic site and race in all models to account for sampling method. Because of the large effect of body weight on BMD,21 we also added body weight to the models. We then systematically assessed potential confounding variables using a list of variables that have been found to be significant predictors of BMD in this population22 or that might be associated with both BMD and use of SSRIs. For the most parsimonious model, we retained only the variables that influenced the parameter estimate for SSRI use (P <.05). All final models included clinic site, age, race, and body weight. Because none of the other variables confounded the association between SSRI use and BMD, we did not retain them in the models. We estimated the mean BMD according to medication use from the linear models (PROC GLM in SAS; SAS Institute Inc, Cary, NC).

Our analyses also included an assessment of whether the association between BMD and use of SSRIs could be explained by mood. The baseline MrOS data do not contain a rigorous measure of depression or depressive symptoms but do contain the SF-12 findings, from which an MCS score can be calculated. Also, there are specific SF-12 questions about feeling “downhearted and blue,” having “accomplished less than you would like because of emotional problems (being depressed or anxious),” or not doing “work or activities as carefully as usual because of emotional problems.” Thus, to evaluate the influ-
ence of mood on the association between SSRI use and BMD, we compared these models with those including the SF-12 MCS score and individual mental health questions from the SF-12.

We next evaluated whether the BMD-SSRI association was common to other antidepressants (trazodone, TCAs, or combined antidepressants). We compared the mean BMDs for each of the antidepressant user groups with the nonuser group. Finally, to understand the relative effect of SSRIs on BMD, we compared these models with those including the SF-12 MCS and individual mental health questions from the SF-12. This did not significantly change the parameter estimate for SSRIs.

**RESULTS**

**CHARACTERISTICS OF THE STUDY POPULATION**

At baseline, the mean age of the 5995 study participants was 73.7 (SD, 5.9) years; 89.4% were white; and 39.4% had a college education. Overall, 160 men (2.7%) reported current SSRI use; 99 (1.7%) reported TCA use; and 52 (0.9%) reported trazodone use. Table 1 shows the demographic characteristics for SSRI users compared with the users of other antidepressants and those who used no antidepressants (nonusers). There were no significant differences among the groups in terms of education (college degree or higher), height, height loss since age 25 years, current tobacco use, glucocorticoid use, total daily calcium intake, and history of nontraumatic fracture after age 50 years. The group that reported using more than 1 type of antidepressant consisted mainly of SSRI users who were also taking trazodone or a TCA (95.8%). Overall, those reporting any SSRI use (alone or in combination with other antidepressants) did not differ significantly from SSRI nonusers by age, race/ethnicity, height, weight, body mass index, reported weight change, or current tobacco or glucocorticoid use. The SSRI users were more likely to have been heavy drinkers at some time in their lives (P < .001). All antidepressant users had lower physical activity scores compared with nonusers (P < .001).

Table 2 shows the estimated least square mean BMD at the total hip, femoral neck, trochanter, and lumbar spine for users of the 3 antidepressants (SSRIs, TCAs, and trazodone), users of multiple antidepressants, and nonusers. Total hip BMD was 3.9% lower among SSRI users compared with nonusers (0.92 vs 0.96 g/cm² [P = .002]). There were no significant differences in BMD among TCA and trazodone users compared with nonusers. Adjusted spine BMD was 5.9% lower among SSRI users compared with nonusers of antidepressants (1.01 vs 1.07 g/cm² [P < .001]). There were no significant differences at the spine among TCA and trazodone users compared with nonusers of antidepressants. Results for the femoral neck and greater trochanter were similar, ie, adjusted BMDs were lower by 4.7% (P < .001) and 3.6% (P = .01), respectively.

We conducted additional analyses including different variables in the model. The associations between SSRI use and BMD were not significantly altered by educational or marital status, weight change, height or height loss, body mass index, lean or fat mass, pack-years of tobacco history, current smoking, SF-12 physical score or Physical Activity Scale for the Elderly, SF-12, 12-Item Short-Form Health Survey; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

**Table 1. Demographics of the MrOS Cohort by Antidepressant Use**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SSRIs Only (n = 137)</th>
<th>TCAs Only (n = 91)</th>
<th>Trazodone Hydrochloride Only (n = 35)</th>
<th>Nonusers (n = 5708)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>73.2 (5.5)</td>
<td>74.1 (5.1)</td>
<td>76.5 (5.9)</td>
<td>73.6 (5.9)</td>
<td>.02</td>
</tr>
<tr>
<td>African American, No. (%)</td>
<td>6 (4.4)</td>
<td>9 (9.9)</td>
<td>0</td>
<td>229 (4.0)</td>
<td>.02</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>23.6 (8.0)</td>
<td>22.4 (6.6)</td>
<td>22.6 (9.3)</td>
<td>21.6 (7.0)</td>
<td>.007</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>85.9 (15.8)</td>
<td>83.8 (12.4)</td>
<td>83.4 (15.4)</td>
<td>83.1 (13.2)</td>
<td>.09</td>
</tr>
<tr>
<td>Weight change since age 25 years, kg</td>
<td>14.5 (13.5)</td>
<td>10.0 (12.2)</td>
<td>13.0 (15.4)</td>
<td>10.2 (11.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Heavy alcohol use, ever had ≥5 drinks/d, No. (%)</td>
<td>36 (26.3)</td>
<td>20 (22.0)</td>
<td>8 (22.9)</td>
<td>861 (15.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI</td>
<td>28.3 (4.4)</td>
<td>27.4 (3.6)</td>
<td>27.4 (4.3)</td>
<td>27.4 (3.8)</td>
<td>.05</td>
</tr>
<tr>
<td>SF-12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental component score</td>
<td>49.4 (10.0)</td>
<td>54.6 (8.1)</td>
<td>52.3 (9.1)</td>
<td>55.8 (6.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Physical component score</td>
<td>43.9 (12.9)</td>
<td>40.8 (12.6)</td>
<td>41.8 (12.0)</td>
<td>49.1 (10.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PASE score</td>
<td>129.2 (70.2)</td>
<td>123.9 (66.2)</td>
<td>123.4 (64.2)</td>
<td>147.6 (68.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Grip strength, kg</td>
<td>39.3 (7.7)</td>
<td>40.7 (8.2)</td>
<td>36.7 (7.3)</td>
<td>41.9 (8.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Able to rise from chair 5 times, No. (%)</td>
<td>129 (94.2)</td>
<td>85 (93.4)</td>
<td>34 (97.1)</td>
<td>5558 (97.4%)</td>
<td>.04</td>
</tr>
<tr>
<td>No. of medical problems</td>
<td>2.2 (1.3)</td>
<td>2.4 (1.3)</td>
<td>1.8 (1.1)</td>
<td>1.6 (1.1)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); MrOS, Osteoporotic Fractures in Men; PASE, Physical Activity Scale for the Elderly; SF-12, 12-Item Short-Form Health Survey; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant. *Users of multiple antidepressant medications were excluded. Continuous variables are reported as mean (SD); categorical variables, as number (percentage). Unless otherwise indicated, data are expressed as mean (SD).
The SSRI-BMD association reported herein is consistently associated with lower BMD at the hip (3.9% lower) and spine (5.6% lower). This association remained consistent in several separate models when adjusted for major potential confounding variables and was unique to SSRI users among the antidepressants studied. In this population, a decrease of 0.1 g/cm² in age-adjusted total hip BMD results in a 3.2% increase in fracture risk. Measured BMD of 0.897 g/cm² corresponds to a T score of −1.22.

Lower BMD among men using SSRIs is supported by in vitro and animal data. Osteoblastic and osteocytic cells express a functional serotonin transporter system, with mechanisms for responding to and regulating uptake of serotonin. Serotonin regulates prostaglandin E₂ activity in osteocytic cells. Serotonin induces murine osteoblast proliferation and human osteoclast differentiation in vitro. In cultured cells, the serotonin receptor (5-HT₁₅) contributes in an autocrine manner to osteogenic differentiation. Mice with disruption of the serotonin transporter gene have reduced bone mass, altered bone geometry, and reduced mechanical strength. Wild-type mice treated with fluoxetine hydrochloride (an SSRI) have reduced bone mineral content and reduced bone formation rates. These studies support the hypothesis that serotonin transporters expressed in bone cells have a functional role in determining bone mass, architecture, and strength. Imaging findings are similar to results from another clinical study wherein SSRI use was associated with increased rates of bone loss among elderly women.

Neurohormonal signaling in bone is an area of growing interest and investigation, but the effects of serotonin transporters in bone are not yet well understood. One potential mechanism to explain our findings is a reduction in osteoblast activity as a result of serotonin transporter inhibition leading to lower BMD, as documented in the mice with disruption of the serotonin transporter gene. We did not measure bone formation rates in our population and cannot be certain that this is the explanation for the observed associations. Alternatively, a reduction in overall remodeling (coupled osteoclast/osteoblast activity) leading to a decrease in osteoblast bone formation is possible given the negative effects of SSRIs on osteoclast differentiation in vitro.

An alternative mechanism to explain lower BMD among SSRI users is an association between BMD and depression per se or a depression-associated comorbidity such as tobacco use, alcohol excess, weight loss, or low physical activity. Depression has been associated with lower BMD in some studies but not all. Many of these studies used select psychiatric populations or failed to adjust for medication use. Indirect effects on bone such as changes in cortisol metabolism or physical activity among depressed individuals are other possible mechanisms for an association. Neither of these proposed mechanisms has consistently explained associations with lower BMD in depressed people.

The SSRI-BMD association reported herein is consistent with other literature, not explained by major covariates, and likely to be clinically important because of the percent difference in BMD. The observed effect size is similar to the well-known detrimental effect of corticoste-
roids on bone loss. However, we did not have information on the dose and duration of glucocorticoid therapy, and the degree of change we observed for SSRIs, although similar to that for glucocorticoids in this population, may be somewhat lower than other observational studies of glucocorticoids have reported and may not correspond to the same fracture risk.

The strengths of this study include its size, the population-based recruitment of a multicer terized cohort of men, the reliability of our BMD measurements, and the many covariates and potential confounders evaluated.

There are several important limitations to this study. One limitation is the relatively small number of men using antidepressants (which was less than the rate expected on the basis of data from the general population) compatible with a healthy volunteer effect in observational studies. Cross-sectional studies do not demonstrate a cause-and-effect association, although it is hard to imagine how a low BMD could lead to SSRI use. Furthermore, the consistency of the observed association with published results in women, who have a much higher SSRI use, supports a true association. Unfortunately, data were not collected on the dose or the duration of SSRI use, and therefore we were unable to assess for a dose effect. Trazodone and TCAs are used in low doses to treat insomnia and neuropathic pain, at lower doses than those used for antidepressant effect. Diagnosed depression may have been less common among participants using trazodone or TCAs. Most TCAs and trazodone have some blocking effect at the serotonin transporter, but this effect is much weaker than that of SSRIs.

Because no standard instrument for depression or depressed mood was obtained, we could not adjust for depression or depressive symptoms. However, results were not altered by adjustment for the SF-12 MCS score, which captures depressed mood with several items. These analyses do not take into consideration cortisol or sex steroid levels, which also have a potential effect on depression and bone mass. A final caveat is the possibility of residual confounding, based on the inability to correct for etiologic variables that were not considered or not measured well. Reported diet and physical activity are examples of such variables considered herein but with well-known limitations in self-report and a potential to be associated with BMD, depression, and SSRI use.

These findings need confirmation in prospective studies. Additional clinical studies should include longitudinal studies of antidepressants, BMD, bone turnover markers, and fracture outcomes. More rigorous evaluation of the influence of SSRI use on BMD adjusting for depressive symptoms, diagnoses of major depression, and other variables that could explain this association is warranted. Studies of bone quality using metrics other than BMD will also be important. Although the effect of SSRIs on BMD observed herein would contribute to fracture risk, the effects of SSRIs on measures of bone quality, rather than density, have been investigated only in a study of fluoxetine-treated growing rats. Fluoxetine significantly reduced trabecular thickness, ultimate stress, and Young's modulus, indicating that less force per area is needed to deform and subsequently break the bone. For further understanding of the mechanism, it will be important to investigate the neurohormonal signaling pathways in bone, with particular attention to the serotonin transporter.

In conclusion, in this cohort of community-dwelling older men, femoral neck and lumbar spine BMD measurements were significantly lower among men using SSRIs compared with men not using any antidepressant or using a non-SSRI antidepressant; these associations were independent of multiple covariates. These associations are biologically plausible and clinically important. Because SSRI use is prevalent in the general population, our findings have a potentially important public health impact. If confirmed, people using SSRIs might be targeted for osteoporosis screening and preventive intervention.

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Author Contributions: Dr Haney had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Haney, Cauley, and Orwoll. Acquisition of data: Ensrud, Cauley, Barrett-Connor, and Orwoll. Analysis and interpretation of data: Haney, Chan, Diem, Ensrud, Barrett-Connor, and Bliziotes. Drafting of the manuscript: Haney and Chan. Critical revision of the manuscript for important intellectual content: Haney, Diem, Ensrud, Cauley, Barrett-Connor, and Bliziotes. Statistical analysis: Chan and Barrett-Connor. Obtained funding: Ensrud, Cauley, Barrett-Connor, and Orwoll. Administrative, technical, and material support: Cauley and Orwoll. Study supervision: Orwoll.

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### REFERENCES


