Statin Use, Bone Mineral Density, and Fracture Risk

Geelong Osteoporosis Study

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Background: Recent data suggest that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) decrease fracture risk and increase bone mineral density (BMD).

Methods: This cross-sectional study is set in southeastern Australia. We evaluated the association between statin use, fracture risk, and BMD in 1375 women (573 with incident fractures and 802 without incident fracture, all drawn from the same community). Fractures were identified radiologically. Medication use and lifestyle factors were documented by questionnaire.

Results: Unadjusted odds ratio for fracture associated with statin use was 0.40 (95% confidence interval [CI], 0.23-0.71). Adjusting for BMD at the femoral neck, spine, and whole body increased the odds ratio to 0.45 (95% CI, 0.25-0.80), 0.42 (95% CI, 0.24-0.75), and 0.43 (95% CI, 0.24-0.78), respectively. Adjusting for age, weight, concurrent medications, and lifestyle factors had no substantial effect on the odds ratio for fracture. Statin use was associated with a 3% greater adjusted BMD at the femoral neck (P=.08), and BMD tended to be greater at the spine and whole body but did not achieve statistical significance.

Conclusion: The substantial 60% reduction in fracture risk associated with statin use is greater than would be expected from increases in BMD alone.

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SUBJECTS AND METHODS

Subjects in this case-control study were drawn from the Barwon Statistical Division in southeastern Australia for participation in the Geelong Osteoporosis Study; details about participants have been described elsewhere. Of 1443 women aged between 50 and 95 years, 68 were excluded because of incomplete medication histories. Current statin use was evaluated in 573 women with nonpathological incident fractures (all causes) during the 2-year period from February 1994 through February 1996 and in an age-stratified random sample of 802 women without incident fractures. All fracture cases were identified from radiological reports of the 2 radiological practices that service the region. This method of fracture case ascertainment has been validated.9

Self-reported use of statins and other medications, together with details about diet and lifestyle, were documented by questionnaire. Statin use was classified as current if the subjects were using statins at the time of assessment. Duration of statin use was documented in years, but the dosage remained unspecified. Calcium intake was estimated for 1370 subjects using a validated food frequency questionnaire.10 Subjectsm were classified as alcohol consumers if they regularly consumed more than 2 standard drinks per week (1 standard drink is equivalent to approximately 10 g of alcohol); regular cigarette smoking was classified as current/not current and ever/never; current exercise levels were classified as active if exercise was performed regularly, otherwise they were designated as sedentary. Bone mineral density was measured at the femoral neck (n=1354), spine (L2–4, anterior-posterior projection; n=1373), and whole body (n=1311) (Lunar DPX-L, software version 1.31; LUNAR Corporation, Madison, Wis). Short-term precision in vivo at these sites was 1.6%, 0.6%, and 0.4%, respectively. The median time between the fracture event and assessment was 59 days. Questionnaire data collection and BMD assessments were performed concurrently. Written informed consent was obtained from all participants. The study was approved by the Barwon Health Research and Ethics Advisory Committee.

Between statin users and nonusers or between fracture and nonfracture groups, differences in exposure to other medications, consumption of alcohol, cigarette smoking, activity levels, or fracture site were determined with the χ² test (and Yates adjustment when applicable), whereas differences in BMD, age, weight, height, and dietary calcium intake were determined with 2-sample t tests. Differences in duration of exposure among statin users with and without fracture were determined using a Mann-Whitney test. Odds ratios for fracture associated with statin use have been expressed with 95% confidence intervals before and after adjusting for BMD, age, weight, dietary calcium, alcohol use, smoking (current and ever), activity levels, and exposure to hormone replacement therapy, glucocorticoids, and calcium and/or vitamin D supplements. Differences in BMD adjusted for age, weight, fracture/nonfracture status, and confounders were assessed using analysis of covariance. In validating the models, interaction terms were tested for significance. All statistical analyses were performed using Minitab software (release 12; Minitab, State College, Pa).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Statin Users</th>
<th>Nonusers</th>
<th>P Value</th>
<th>Fracture</th>
<th>Nonfracture</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70.3 ± 8.9</td>
<td>69.4 ± 10.5</td>
<td>.4</td>
<td>69.6 ± 9.5</td>
<td>69.3 ± 11.1</td>
<td>.5</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>68.1 ± 12.0</td>
<td>67.0 ± 13.3</td>
<td>.5</td>
<td>66.6 ± 13.2</td>
<td>67.5 ± 13.3</td>
<td>.2</td>
</tr>
<tr>
<td>Height, cm</td>
<td>158.1 ± 6.1</td>
<td>158.2 ± 6.6</td>
<td>.9</td>
<td>158.3 ± 6.7</td>
<td>158.1 ± 6.5</td>
<td>.5</td>
</tr>
<tr>
<td>Dietary calcium intake, mg/d</td>
<td>682 ± 424</td>
<td>699 ± 434</td>
<td>.8</td>
<td>723 ± 494</td>
<td>681 ± 384</td>
<td>.1</td>
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<tr>
<td>Alcohol consumption (&gt;2 standard drinks/wk)</td>
<td>18 (26)</td>
<td>364 (39)</td>
<td>.7</td>
<td>200 (35)</td>
<td>297 (37)</td>
<td>.4</td>
</tr>
<tr>
<td>Cigarette smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>7 (11)</td>
<td>121 (10)</td>
<td>.8</td>
<td>56 (10)</td>
<td>72 (9)</td>
<td>.6</td>
</tr>
<tr>
<td>Ever</td>
<td>26 (38)</td>
<td>457 (54)</td>
<td>.6</td>
<td>210 (37)</td>
<td>273 (34)</td>
<td>.3</td>
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<tr>
<td>Physically active</td>
<td>34 (49)</td>
<td>640 (49)</td>
<td>.97</td>
<td>267 (47)</td>
<td>407 (51)</td>
<td>.1</td>
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<tr>
<td>HRT exposure</td>
<td>9 (13)</td>
<td>174 (13)</td>
<td>.9</td>
<td>59 (10)</td>
<td>124 (15)</td>
<td>.005</td>
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<tr>
<td>Glucocorticoid exposure</td>
<td>5 (7)</td>
<td>67 (5)</td>
<td>.6</td>
<td>44 (8)</td>
<td>28 (3)</td>
<td>.001</td>
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<tr>
<td>Calcium/vitamin D supplement use</td>
<td>15 (22)</td>
<td>249 (19)</td>
<td>.6</td>
<td>129 (23)</td>
<td>135 (17)</td>
<td>.008</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD or number (percentage) of subjects. HRT indicates hormone replacement therapy.

not entirely explained by BMD, and adjusting for individual potential confounders had little effect on the odds ratio for fracture (Table 2).

After adjusting for age, weight, and fracture status, statin use was associated with a 3% greater BMD at the femoral neck (P=.08) (Table 3). Statin use remained in the model with only minor changes to the coefficient after the addition of potential confounders including smoking (current and ever), use of hormone replacement therapy, use of calcium and/or vitamin D supplements, and activity levels to the regression model. There was a pattern of greater BMD at the other sites among statin users; however, adjusted differences did not achieve significance (Table 3). At α=.05, we had 80% power for detecting differences in BMD equal to or greater than 19%, 20%, and 12% at the femoral neck, spine, and whole body, respectively. Thus, the small number of statin users may have limited the power to detect differences in BMD at the spine and whole body. No effect of duration of exposure on BMD was detected.
We confirm observations that statin use is associated with a reduction in fracture risk. This risk reduction is not explained by the effects of BMD as indicated by the small change in odds ratio after adjustment for BMD. Although there were differences in exposures to other medication and lifestyle factors, these potential confounders had no impact on the odds ratio for fracture.

In addition to statin use, BMD measurements were obtained for fracture and nonfracture cases, making this study unique. The effect of statin use on BMD was small after adjusting for age and weight. Statin users tended to be younger and heavier within the fracture cohort, whereas a reverse pattern occurred for age in the nonfracture group. The apparent 13% and 10% differences in unadjusted BMD between statin users and nonusers at the femoral neck and spine in the fracture group were likely affected by differences in distribution of age and weight.

The 60% reduction in fracture risk associated with statin use is consistent with other case-control studies in different populations. An exception to this finding reports no effect of pravastatin use on fracture frequency. In contrast to other statins, pravastatin does not induce bone morphogenetic protein-2 in human osteosarcoma cells, which may explain the negative finding. The apparent, substantial statin-related differences in BMD reported recently suggest that reductions in fracture risk could operate entirely through increased BMD. However, results from our study suggest that increases in BMD associated with statin use may be too small to account for the observed reduction in fracture risk. Furthermore, the fracture risk reduction conferred by adjusting the odds ratio for BMD supports this notion. Unless confounded by unrecognized factors, statin use is associated with substantial protection against fracture, but the mechanisms of action remain unclear. Even with increased power to detect smaller changes in BMD, the bone densitometry technology is limited in its ability to detect changes on bone surfaces that might protect against fracture. Studies focused on the effects of statins on bone architecture by histomorphometry or noninvasive techniques are needed to clarify the mechanism of action.

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REFERENCES