Loop Diuretic Use and Increased Rates of Hip Bone Loss in Older Men

The Osteoporotic Fractures in Men Study

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Background: Older adults commonly use loop diuretics, which can increase urinary calcium excretion, leading to potential bone loss. Studies examining the association between loop diuretics and bone mineral density (BMD) are lacking, particularly those involving men.

Methods: In this cohort study, we ascertained medication use (interviewer-administered questionnaire verified with inspection of medication containers) and measured the BMD of the total hip and 2 subregions (by dual-energy x-ray absorptiometry) at baseline and at a second visit an average of 4.6 years later among 3269 men aged 65 years and older.

Results: Eighty-four men were categorized as continuous users of loop diuretics, 181 as intermittent users of loop diuretics, and 3004 men as nonusers of loop diuretics. After adjustment for age, baseline BMD, body mass index, weight change from baseline, physical activity, clinic site, perceived health status, cigarette smoking status, diabetes mellitus, chronic obstructive pulmonary disease, congestive heart failure, hypertension, and statin use, the average annual rate of decline in total hip BMD steadily increased from –0.33% (95% confidence interval [CI], –0.36% to –0.31%) for nonusers, to –0.58% (95% CI, –0.69% to –0.47%) for intermittent users, and to –0.78% (95% CI, –0.96% to –0.60%) for continuous users. Findings were similar for change in BMD at the femoral neck and trochanter.

Conclusions: We conclude that loop diuretic use in older men is associated with increased rates of hip bone loss. These results suggest that the potential for bone loss should be considered when loop diuretics are prescribed to older patients in clinical practice.

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Osteoporosis is characterized by reduced bone mass, increased skeletal fragility, and increased risk of fractures. Although osteoporosis is traditionally considered a disease of women, 20% of persons with osteoporosis are men.1 In the United States, 1 to 2 million men have osteoporosis and another 8 to 13 million men have osteopenia or low bone mass.2 Osteoporosis in men results in approximately 90,000 hip and 140,000 vertebral fractures annually.3,4

Loop diuretics are one of the most commonly prescribed medications among older adults. More than 34 million prescriptions were written for furosemide in 2005, making it the sixth most commonly prescribed generic medication in the United States.5 It is also the most commonly prescribed medication among community-dwelling men aged 65 years and older, with an estimated 12% prevalence of use.6 Loop diuretics are typically prescribed to induce diuresis in fluid overload states (eg, congestive heart failure [CHF]) and to treat hypertension, especially when it is associated with renal impairment. Loop diuretics inhibit the sodium-potassium-chloride cotransporter in the loop of Henle of the kidney, which increases urinary calcium excretion, potentially leading to bone loss if the diuretics are used on a long-term basis.7,8 In contrast, thiazide diuretics, which exert a hypocalciuric effect, have been shown to increase bone mineral density (BMD)9-11 in randomized trials.

Loop diuretic use has been associated with an increased risk of hip and other osteoporotic fractures in several observational studies.12-15 However, there is uncertainty as to whether this increased fracture risk is attributable to negative effects on BMD, fall-related mechanisms (eg, dizziness and orthostasis), or associated comorbidities. Previously, we examined the cross-sectional association of various diuretics, including loop diuretics, on BMD in the Osteoporotic Fractures in Men (MrOS) study cohort.16 We determined that loop diuretics, despite their use in patients with osteoporosis, were associated with increased rates of hip bone loss.
uretic users had a higher age-adjusted BMD at the hip (3.1% [95% confidence interval (CI), 1.3% to 5.0%]) and femoral neck (4.6% [95% CI, 2.6% to 6.7%]) than nonusers. However, after multivariable adjustment, the differences in BMD were diminished and were no longer significant (−0.3% [95% CI, −2.1% to 1.6%]) at the total hip and 0.9% [95% CI, −1.2% to 3.0%] at the femoral neck). In large part, the association between loop diuretic use and higher hip BMD was primarily explained by a higher body mass index (BMI) and a higher prevalence of diabetes mellitus among loop diuretic users.

However, potential biases, residual confounding, and other methodological issues in our cross-sectional data also might have substantially underestimated or overestimated the actual association. Other cross-sectional studies that have examined the association between loop diuretic use and bone density have reported inconsistent results. However, in a small randomized controlled trial, postmenopausal women treated with the loop diuretic bumetanide experienced a 2% decrease in total hip BMD compared with those treated with placebo. To our knowledge, no previous large prospective studies have examined the association between loop diuretic use and rates of change in BMD in older individuals. We hypothesized that loop diuretic use in older men is associated with increased rates of bone loss at the hip. To test our hypothesis, we ascertained medication use and measured hip BMD at baseline and at the second visit among 3269 men aged 65 years and older enrolled in the MrOS study.

METHODS

PARTICIPANTS

The MrOS study is a prospective cohort study that was designed to examine how fracture risk in older men is influenced by bone mass, geometry, lifestyle, anthropometric and neuromuscular measures, and fall propensity as well as how fractures affect quality of life. The MrOS cohort includes 5995 community-dwelling men aged 65 years and older who were recruited primarily from population-based sources between March 2000 and April 2002 in 6 regions of the United States: Birmingham, Alabama; Minneapolis, Minnesota; Palo Alto, California; Pittsburgh, Pennsylvania; Portland, Oregon; and San Diego, California. Men eligible to participate in the MrOS study were aged 65 years or older at the baseline visit, had no history of bilateral hip replacements, and were able to walk without the assistance of another person. Further details of the MrOS study and recruitment protocol have been previously described.

The MrOS participants returned for a second study visit between March 2005 and April 2006. A total of 637 participants died (n=571) or dropped out of the study (n=86) before being contacted for visit 2. Of the remaining 5338 participants, all were contacted for participation in the second visit: 5229 (98.0%) completed a second examination or an associated questionnaire and 109 (2.0%) refused. Of the 5229 men who participated in the second visit, 699 provided only questionnaire data and therefore did not undergo dual-energy x-ray absorptiometry (DXA) hip BMD measurement at the second visit. Of the 4530 men with visit 2 BMD measurements, 4474 had technically adequate DXA measures available for hip BMD. Change in hip BMD could not be calculated for 57 of the 4474 men because the same hip was not scanned at both visits. Of the 4417 men with change in hip BMD data, 1148 were excluded from the present analysis because of missing medica-

tion data at the second visit (n=5) or because they used a non-loop diuretic at either the baseline or the second visit (n=1143). The remaining 3269 men with BMD measurements and verification of loop diuretic use or nonuse at both visits were included in our analyses. The mean (SD) follow-up time between the 2 visits was 4.6 (0.4) years. Written informed consent was obtained from the participants, and the institutional review board at each site approved the study protocol.

ASCERTAINMENT OF LOOP DIURETIC USE

Current loop diuretic use was ascertained with an interviewer-administered questionnaire at baseline and at the second visit. Participants were asked to bring all medications taken within the last 30 days to the study visits for verification of use. Medication type was classified from product brand or generic names obtained from their medication containers. At the second visit, all prescription medications recorded by the clinics were stored in the electronic Medication Inventory Form (Version 6.15; San Francisco Coordinating Center, San Francisco, California). Each medication was matched to its ingredient(s). Ingredients were based on the Iowa Drug Information Service Drug Vocabulary (College of Pharmacy, University of Iowa, Iowa City). Participants were considered users of loop diuretics if they were taking an ingredient that was categorized by the Iowa Drug Information Service as “Diuretics—loop.” Loop diuretics included furosemide, bumetanide, and torsemide. After the exclusion of participants who used any non–loop diuretics at either visit, whether alone or in combination with loop diuretics, the men were categorized into the following 3 groups according to their reported loop diuretic use: (1) continuous users (n=84), who used loop diuretics at both the baseline and the second visit; (2) intermittent users (n=181), those who used loop diuretics at either the baseline or the second visit; and (3) nonusers (n=3004), those who did not use loop diuretics at either the baseline or the second visit.

MEASUREMENT OF BMD

Participants underwent measurement of hip BMD at the baseline and second visits. Hip BMD measurements were obtained on the right hip unless the participant reported a right hip replacement or metal object in the right hip, in which case the measurement was performed in the left hip. The BMD measurements were obtained at the total hip and at 2 subregions (femoral neck and trochanter) using DXA with bone densitometry scanners (Hologic QDR 4500W; Hologic Inc, Bedford, Massachusetts). A central quality control laboratory, certification of DXA operators, and standardized procedures for scanning were used to ensure the reproducibility of the DXA measurements. At baseline, a hip phantom was circulated and measured at the 6 clinical sites. The variability across clinics was within acceptable limits, and cross-calibration correction factors were not required. To adjust for interclinic differences, statistical models included an indicator variable for the individual scanners. Each clinic scanned a hip phantom throughout the study to monitor longitudinal changes, and correction factors were applied to participant data as appropriate. The precision of DXA scans of the spine and hip is 1% to 2%. The intracleratic coefficients of variation at the 6 study sites were about 0.5%.

OTHER MEASUREMENTS

At study baseline, a self-administered questionnaire was used to obtain information on demographic characteristics (age and race), lifestyle factors (physical activity, tobacco use, and diet), perceived health status, and medical history. Physical activity was measured with the Physical Activity Scale for the Elderly,
which contains items regarding household, leisure, and occupational activities over the past 7 days. With respect to tobacco use, participants were categorized into past, current, and never smokers. Dietary information was acquired using a modified version of the Block Food Frequency Questionnaire. Intakes of calcium and vitamin D were estimated by summing the average daily consumption of each from diet and from supplements. Perceived health status was obtained with the following question: “Compared to other people your own age, how would you rate your overall health?” Respondents were dichotomized into 2 groups: those who rated their health as excellent or good and those who rated their health as fair, poor, or very poor. Participants were questioned regarding whether they had ever been diagnosed by a physician or other health care provider as having diabetes mellitus, hypertension, CHF, or chronic obstructive pulmonary disease (COPD). The use of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-Co-A) reductase inhibitors (statins) was also assessed at baseline. Serum potassium (n=3010) and creatinine (n=3013) levels were obtained from a subset of participants who had blood samples drawn at baseline (92% of analysis cohort). Participants’ renal function was assessed by estimating the glomerular filtration rate (GFR) based on the Modified Diet in Renal Disease equation: GFR=175 × SCr⁻¹.¹⁹ × age⁻².⁰³ × L.²¹² (if black race), where SCr is serum creatinine. Participants had their current weight and height determined using a balanced beam or digital scale and stadiometer, respectively, from which the BMI was calculated as weight in kilograms divided by height in meters squared. The weight difference between the baseline and the second visit was calculated as a percentage of the baseline weight.

SELECTION OF COVARIATES AND STATISTICAL ANALYSIS

Differences in baseline characteristics between participants in the different loop diuretic user groups were assessed using analysis of variance for continuous variables and χ² analyses for categori- cal variables. The adjusted least squares means procedure was used to estimate the association between the category of loop diuretic use and the rate of change in hip BMD, expressed as the annualized percentage change from the baseline BMD value and the associated 95% CIs. Initially, we used analysis of covariance to assess the bivariate (age and baseline BMD) change in hip BMD. Subsequently, additional risk factors for bone loss and factors related to loop diuretic use were considered as confounders for potential inclusion in our multivariable models. They included self-reported COPD, CHF, hypertension, and diabetes mellitus, to address confounding by indication. From among baseline vari- ables with differences (P < .10) between diuretic groups, we selected a final set of additional variables to include in the multi- variable models. As above, we used analysis of covariance to assess the multivariable-adjusted associations between the loop diuretic group and the annualized percentage change in hip BMD. Any overall difference in hip BMD change between categories of diuretic users was tested using the F test, with statistical signifi- cance established at P < .05. Differences between pairs of diuretic categories were then tested using the 2-tailed tests of the adjusted least squares means. Pairwise comparisons were ad- justed using the Bonferroni method. We presented results from analyses adjusted for age and baseline BMD alongside results from multivariable models. To examine whether the association between loop diuretic use and higher rates of bone loss was explained by poorer renal function or differences in serum potassium levels, we performed a secondary analysis further adjusting for serum potassium and renal function using the 4-variable version of the Modified Diet in Renal Disease equation, as described above. We also looked for evidence of bias from missing data at visit 2 owing to participant death or to defaulting on fol- low-up BMD measurements.

RESULTS

CHARACTERISTICS OF THE STUDY POPULATION

The mean (SD) age of the study participants was 72.7 (5.4) years, and 2983 (91%) of the participants were white. Of the 265 continuous or intermittent users of loop diuretics, 231 (87%) took furosemide at the second visit. Characteristics of the 3269 participants at baseline according to category of loop diuretic use are shown in Table 1. Loop diuretic users (intermittent and continuous) were older and heavier on average than nonusers. Continuous loop diuretic users experienced almost twice the percentage weight loss between baseline and second visits as did nonusers. There were also differences in perceived health status across the 3 groups. Compared with nonusers, users of loop diuretics less frequently perceived their health as excellent or good, they were less physically active, and they were more likely to have diabetes mellitus, COPD, CHF, and hypertension. Loop diuretic users also used statin medications more frequently than nonusers did. Vitamin D and calcium intake were similar in all 3 groups. Loop diuretic users also had slightly higher baseline serum po- tassium levels than nonusers. There were significant differences in renal function between all 3 groups, with continuous loop diuretic users having the lowest estimated GFR (P < .001). The 1521 participants who did not return for the second clinic visit because of death (n=571), study termination (n=86), refusal to participate in the sec- ond visit (n=109), unwillingness to undergo an exami- nation at the visit (n=699), or missing BMD data at the second visit (n=56) were more likely to have used loop diuretics at baseline than those in our analytic cohort (9.7% vs 3.2%, P < .05). They also had an average total hip BMD that was 2% lower than that of our cohort at baseline (0.940 g/cm² vs 0.960 g/cm², P < .05).

LOOP DIURETIC USE AND RATE OF HIP BONE LOSS

Men who were continuous loop diuretics users had the greatest average rate of bone loss at the total hip compared with intermittent users and nonusers of loop diuretics (Figure). Their rate of bone loss was almost 3-fold greater than that of nonusers and 1.5-fold greater than that of intermittent users after adjustment for age and base- line BMD. Multivariable adjustment for age, baseline BMD, BMI, percentage weight change from baseline, Physical Activity Scale for the Elderly score, clinic site, health sta- tus, cigarette smoking status, diabetes mellitus, COPD, CHF, hypertension, and statin use attenuated the estimated mean annualized percentage bone loss among loop diuretic users, but the group differences between inter- mittent and continuous users vs nonusers remained sig- nificant (P < .01). The rate of bone loss at the total hip among intermittent loop diuretic users was intermediate between that among nonusers of diuretics and that...
among continuous loop diuretic users. Results for differences in rate of bone loss between loop diuretic user groups at the femoral neck and trochanter were similar to those observed at the total hip (Table 2).

In an analysis limited to the 3010 men for whom measurements of serum potassium levels and renal function were available, we further examined whether the association between loop diuretic use and higher rates of bone loss was explained by poorer renal function or differences in serum potassium levels. Adding these variables to the multivariable model did not alter the intergroup differences at the total hip, femoral neck, and trochanter (data not shown).

### Table 1. Baseline Characteristics of 3269 Study Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nonuser (n=3004)</th>
<th>Intermittent User (n=181)</th>
<th>Continuous User (n=84)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loop diuretic</td>
<td>NA</td>
<td>Baseline</td>
<td>Visit 2</td>
<td>NA</td>
</tr>
<tr>
<td>Furosemide</td>
<td>NA</td>
<td>25 (13.8)</td>
<td>157 (86.7)</td>
<td>74 (88.1)</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>NA</td>
<td>1 (0.6)</td>
<td>2 (1.1)</td>
<td>7 (8.3)</td>
</tr>
<tr>
<td>Torsemide</td>
<td>NA</td>
<td>0</td>
<td>0</td>
<td>3 (3.6)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>72.5 (5.3)</td>
<td>75.4 (5.8)</td>
<td>75.4 (5.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>26.9 (3.4)</td>
<td>29.1 (4.7)</td>
<td>29.7 (4.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>% Weight change from baseline, mean (SD)</td>
<td>–1.4 (5.2)</td>
<td>–2.3 (6.4)</td>
<td>–2.7 (6.9)</td>
<td>.02</td>
</tr>
<tr>
<td>PASE score, mean (SD)</td>
<td>156 (67)</td>
<td>129 (63)</td>
<td>134 (77)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Site</td>
<td>Birmingham, Alabama</td>
<td>451 (15.0)</td>
<td>30 (16.6)</td>
<td>22 (26.2)</td>
</tr>
<tr>
<td></td>
<td>Minneapolis, Minnesota</td>
<td>517 (17.0)</td>
<td>38 (21.0)</td>
<td>14 (16.7)</td>
</tr>
<tr>
<td></td>
<td>Palo Alto, California</td>
<td>514 (17.1)</td>
<td>14 (7.7)</td>
<td>8 (9.5)</td>
</tr>
<tr>
<td></td>
<td>Pittsburgh, Pennsylvania</td>
<td>492 (16.4)</td>
<td>42 (23.2)</td>
<td>22 (26.2)</td>
</tr>
<tr>
<td></td>
<td>Portland, Oregon</td>
<td>503 (16.7)</td>
<td>33 (18.2)</td>
<td>9 (10.7)</td>
</tr>
<tr>
<td></td>
<td>San Diego, California</td>
<td>532 (17.7)</td>
<td>24 (13.3)</td>
<td>9 (10.7)</td>
</tr>
<tr>
<td>Perceived health status as excellent or good</td>
<td>2733 (91.0)</td>
<td>143 (79.0)</td>
<td>52 (61.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cigarette smoking status</td>
<td>Never</td>
<td>1237 (41.2)</td>
<td>54 (29.8)</td>
<td>32 (38.1)</td>
</tr>
<tr>
<td></td>
<td>Past</td>
<td>1674 (55.7)</td>
<td>122 (67.4)</td>
<td>50 (59.5)</td>
</tr>
<tr>
<td></td>
<td>Current</td>
<td>93 (3.1)</td>
<td>5 (2.8)</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>219 (7.3)</td>
<td>37 (20.4)</td>
<td>20 (23.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>COPD</td>
<td>286 (9.5)</td>
<td>35 (19.3)</td>
<td>19 (22.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CHF</td>
<td>62 (2.1)</td>
<td>24 (13.3)</td>
<td>37 (44.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>789 (26.3)</td>
<td>94 (51.9)</td>
<td>59 (70.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Statin use</td>
<td>716 (23.8)</td>
<td>64 (35.4)</td>
<td>32 (38.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Vitamin D, IU/d, mean (SD)</td>
<td>400 (246)</td>
<td>362 (227)</td>
<td>387 (248)</td>
<td>.12</td>
</tr>
<tr>
<td>Calcium intake, mg/d, mean (SD)</td>
<td>1154 (589)</td>
<td>1082 (522)</td>
<td>1159 (611)</td>
<td>.12</td>
</tr>
<tr>
<td>Baseline serum potassium, mEq/L, mean (SD)</td>
<td>4.28 (0.31)</td>
<td>4.35 (0.33)</td>
<td>4.33 (0.43)</td>
<td>.02</td>
</tr>
<tr>
<td>Estimated GFR by MDRD, mL/min/1.73m², mean (SD)</td>
<td>78.9 (16.6)</td>
<td>75.2 (19.0)</td>
<td>66.8 (21.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>GFR ≥ 60 mL/min/1.73m², mean (%)</td>
<td>332 (12.0)</td>
<td>35 (21.1)</td>
<td>34 (43.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Total hip</td>
<td>0.959 (0.135)</td>
<td>0.965 (0.142)</td>
<td>0.984 (0.169)</td>
<td>.23</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>0.784 (0.124)</td>
<td>0.796 (0.129)</td>
<td>0.808 (0.158)</td>
<td>.12</td>
</tr>
<tr>
<td>Trochanter</td>
<td>0.768 (0.124)</td>
<td>0.770 (0.130)</td>
<td>0.777 (0.140)</td>
<td>.81</td>
</tr>
</tbody>
</table>

Abbreviations: BMD, bone mineral density; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; MDRD, Modified Diet in Renal Disease; NA, not applicable; PASE, Physical Activity Scale for the Elderly.

*Conversion factors: To convert potassium to millimoles per liter, multiply by 1.0.

*Values are given as number (percentage) unless otherwise indicated.

bPerceived health status as excellent or good vs fair, poor, or very poor.

cFrom diet and supplements assessed with the Block Food Frequency Questionnaire.

dDenominator differs from study cohort owing to limited number of participants with available blood samples.

Our study suggests that older community-dwelling men taking loop diuretics have increased rates of hip bone loss. Compared with rates of hip bone loss among nonusers of diuretics, adjusted rates of loss were about 2-fold greater among intermittent loop diuretic users and about 2.5-fold greater among continuous loop diuretic users. In our previously published cross-sectional study, we found no significant differences in BMD at the hip between nonusers of diuretics and various groups of diuretic users, including those using loop diuretics. Because loop diuretics are known to exert a calciuric effect, we hypothesized that use of loop diuretics would be associated with lower BMD. However, much of the association between loop diuretic use and higher BMD was explained by confounding owing to comorbid conditions and other factors. More importantly, the earlier study highlighted the limitations of attempting to infer causality from cross-sectional analyses. Other cross-sectional studies have reported inconsistent results. One study involving 1405 subjects (45% men) aged 55 years and older showed no association be-
tween the use of loop diuretics and ultrasound measurements of the calcaneus after adjustment for age and BMI. However, a major limitation of that study was the small sample size (only 23 men using loop diuretics). Furthermore, ultrasound measurements of the calcaneus showed only modest correlations with BMD at the hip (r = 0.34-0.43) and are not necessarily predictive of low BMD. Another cross-sectional study examining the association between loop diuretic use and BMD measured by DXA was performed in 348 women older than 70 years. That study showed that users of loop diuretics (n = 41) had a lower BMD (-5%) at the femoral neck and trochanter than non-users after adjustment for age, years since menopause, and body weight. However, potential biases in cross-sectional data could also have substantially underestimated or overestimated the actual association.

In a recently published randomized control trial involving 87 postmenopausal women randomized to treatment with bumetanide (n = 46) or placebo for 1 year, the BMD in the bumetanide group compared with the placebo group was significantly decreased by 2%. At the end of the study period, the authors noted that serum parathyroid hormone (PTH) levels had increased in the bumetanide group but had decreased in the placebo group. Bone resorption and formation markers (serum CTX [carboxy-terminal collagen cross-links] and osteocalcin) differed at 3 and 12 weeks, respectively, and persisted throughout the treatment period. Serum CTX and osteocalcin levels were higher in the bumetanide group than in the placebo group. Substudy analysis revealed marked differences in the diurnal variation of urinary calcium and plasma PTH levels between the 2 groups. In the first 4 to 6 hours after the administration of bumetanide, there was an increase in urinary calcium excretion and an increase in plasma PTH levels in the treatment group. At 1 year, there were greater increases in 24-hour urinary calcium excretion among women receiving bumetanide than among those allocated to treatment with placebo. These findings suggest that in postmenopausal women long-term use of loop diuretics may decrease bone density at least in part by increasing urinary calcium excretion, as well as by a PTH-driven imbalance in bone turnover suggested by the lag between bone resorption and formation markers. A similar mechanism might at least partially account for the increased hip bone loss observed with loop diuretics in older men in the present study.

Our study has several strengths. It is one of the first longitudinal studies examining the association of loop diuretics and BMD in a large cohort of older men. Diuretic use was verified with visual confirmation of the prescription container by trained interviewers at baseline and recorded on the Medication Inventory Form at the second visit, which minimized the potential for misclassification based on self-report. The BMD measurements were obtained with high precision at skeletal hip sites that are widely used in clinical practice, and adjustments were made for the presence of multiple potentially confounding fac-
 tors, including renal function. There are also several limitations in our study. The proportion of loop diuretic users was slightly smaller (8%) in our study than in a recent sampling of older community-dwelling men (12%). Also, our analyses were limited to generally healthy, mostly white community-dwelling older men who attended baseline and follow-up visits, and study findings may therefore not be representative of loop diuretic users in general. We found that participants who did not return for the second clinic visit because of death or missing BMD data had a slightly lower average hip bone density and were more likely to have used loop diuretics at baseline. We were unable to obtain complete information on diuretic dose, which inhibited our ability to assess a dose-response relationship. Unmeasured changes in use of loop diuretics may have occurred between examinations. However, this limitation would tend to bias the estimates of the relationship between loop diuretic use and bone loss toward the null hypothesis of no association. Finally, analyses were adjusted for several factors to minimize confounding by indication and contraindication, but the possibilities of these biases cannot be eliminated without the use of a randomized, controlled trial design.

We conclude that loop diuretic use in older men is associated with increased rates of hip bone loss. Future research should further examine the biologic mechanisms, including urinary calcium loss and/or PTH-driven bone turnover, underlying this association. Our findings suggest that health care providers should take into account loop diuretic use when evaluating older men for risk factors for bone loss and fracture risk.

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Author Contributions: Dr Lim had full access to all of 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: Lim, Fink, and Ensrud. Acquisition of data: Ensrud. Analysis and interpretation of data: Lim, Fink, Kuskowski, Taylor, Schousboe, and Ensrud. Drafting of the manuscript: Lim. Critical revision of the manuscript for important intellectual content: Lim, Fink, Kuskowski, Taylor, Schousboe, and Ensrud. Statistical analysis: Fink and Kuskowski. Obtained funding: Ensrud. Administrative, technical, and material support: Taylor. Study supervision: Lim, Fink, and Schousboe.

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