CLINICAL RESEARCH STUDY

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Antihistamine Therapy and Bone Mineral Density: Analysis in a Population-Based US Sample

Mitsuyo Kinjo, MD, MPH,[a] Soko Setoguchi, MD, DrPH,[b] Daniel H. Solomon, MD[c]

[a]Department of Medicine, Okinawa Chubu Hospital, Okinawa, Japan; [b]Division of Pharmacoepidemiology, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass; [c]Division of Rheumatology, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass.

ABSTRACT

BACKGROUND: Histamine may play an important role in bone turnover. The data regarding histamine 1 receptor antagonist (H1RA), histamine 2 receptor antagonist (H2RA), and bone mineral density in humans are sparse. We examined bone mineral density in subjects using histamine receptor antagonists in a representative US population-based sample from the Third National Health and Nutrition Examination Survey (1988-1994).

METHODS: Adult subjects aged 60 years and more using H1RA or H2RA who underwent dual energy x-ray absorptiometry scanning in the Third National Health and Nutrition Examination Survey were identified. We compared the femoral neck bone mineral density among users of these agents with nonusers in adjusted linear regression models that included known demographic, anthropometric, and medical risk factors for osteoporosis.

RESULTS: The mean age of the study subjects was 72.6 years; 52% were women and 59% were white. Among subjects with femoral neck bone mineral density measured, 199 used H1RAs, 297 used H2RAs, and 4162 were nonusers of histamine receptor antagonists. Femoral neck bone mineral density adjusting for age and gender and other covariates was slightly higher in H1RA users (0.74 g/cm^2) versus nonusers (0.72 g/cm^2; $P = .037$). H2RA users showed slightly lower adjusted bone mineral density compared with nonusers (0.69 g/cm^2 vs 0.72 g/cm^2; $P = .003$), but bone densities were similar between H2RA users and nonusers when daily calcium intake exceeded 800 mg per day.

CONCLUSION: Femoral neck bone mineral density may be higher in H1RA users than nonusers among older adults. H2RA users with reduced calcium intake had lower bone mineral density than nonusers.
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KEYWORDS: Bone mineral density; Calcium intake; Histamine receptor antagonists; NHANES III

A novel role of histamine for bone health has been suggested in mastocytosis and animal studies.[1] Excess histamine accelerated bone resorption, and osteoporosis has been observed in patients with systemic mastocytosis, in which proliferating mast cells release histamine.[2] In contrast, mast cell-deficient mice showed ineffective osteoclastic recruitment and retarded bone remodeling.[3] Blocking histamine uptake by histamine 1 receptor antagonist (H1RA) and histamine 2 receptor antagonist (H2RA) reduced bone resorption and decreased osteoclast activity in ovariectomized rats.[4,5] A mouse model of histamine deficiency increased osteoclast differentiation factor (ODF) and receptor activator of nuclear factor-kappaB ligand (RANKL) secretion but failed to develop effective osteoclastogenesis, in which histamine may be needed to co-stimulate RANKL.[6] These data suggest that histamine may modulate bone resorption through the osteoclastic pathway. The mechanism of H1RA and H2RA on bone remodeling in humans remains

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Requests for reprints should be addressed to Mitsuyo Kinjo, MD, MPH, Okinawa Chubu Hospital, 281 Miyasato, Uruma City, Okinawa 904-2293 Japan.

E-mail address: mitsuyos220@worldnet.att.net

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unclear, but blocking histamine receptors might retard osteoclastogenesis in humans.

Previous human studies show skeletal effects differ between H1RA and H2RA. H1RA is frequently used for nasal congestion and rhinorrhea,[7] and appears to counteract bone loss in subjects with allergy: H1RA users had less nontraumatic fractures compared with those allergic subjects not taking H1RA.[8] H2RA is a common acid suppressive therapy for peptic ulcer disease and gastroesophageal reflux disease (GERD). In contrast with H1RA, there may be a small increased risk of hip fracture in those using H2RA.[9] It is unclear whether calcium malabsorption causes bone loss in users of H2RA, similar to what is observed among users of proton pump inhibitors, which are associated with vertebral and nonvertebral fracture incidence.[9,10] Histamine receptor antagonists are widely used among older people at risk for osteoporosis, but human data on their medications and bone density are sparse. We thus examined the bone mineral density among subjects aged 60 years and older using H1RA and H2RA, and the bone density was compared with nonusers of these antihistamine products in a representative US population-based sample from the Third National Health and Nutrition Examination Survey (NHANES III: 1988-1994).

CLINICAL SIGNIFICANCE

- The use of histamine-1 receptor antagonists, such as diphenhydramine and loratadine, may increase bone mineral density.
- However, histamine-2 receptor antagonists, such as cimetidine and ranitidine, may reduce bone mineral density when calcium and vitamin D intake are inadequate.

MATERIALS AND METHODS

Data Source and Histamine Receptor Antagonist Use

NHANES III was conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention between 1988 and 1994. The sample represents the civilian, noninstitutionalized population of the United States.[11] Histamine receptor antagonists are widely used among an older population who tend to be vulnerable to fractures. We identified subjects aged 60 years and older who underwent femoral neck bone mineral density measurement and compared users of H1RA or H2RA with nonusers. This study includes subjects aged 60 years and older because NHANES performs bone density scans on this population. Subjects without a dual-energy x-ray absorptiometry measurement were excluded from the analysis.

Adult subjects exposed to H1RA, H2RA, and proton pump inhibitor in NHANES III were identified. H1RA included mepyramine (pyrilamine), antazoline, diphenhydramine, carbinoxamine, clemastine, dimenhydrinate , pheniramine, chlorphenamine (chlorpheniramine), dexchlorphenamine, brompheniramine, triprolidine, hydroxyzine, meclizine, promethazine, cyproheptadine, azatadine, loratadine, mizolastine, terfenadine, levocetirizine, desloratadine, and fexofenadine. H2RA included cimetidine, famotidine, nizatidine, and ranitidine. The only available proton pump inhibitor was omeprazole. Over-the-counter antacid use was determined, although some of these products currently available without a prescription (eg, ranitidine [Zantac, GlaxoSmithKline, Brentford, London, UK]) were available only by prescription at the time of data collection.

Relevant Medication Use

We also considered potentially relevant medications: Glucocorticoids (nasal or oral) may increase risk of osteoporosis, and thiazide diuretics or estrogen could retard bone loss. We did not include osteoporosis therapy such as calcitonin, bisphosphonate, or selective estrogen receptor modulators in the model because few subjects were taking these medications. Medication and supplement information was also collected by asking participants to bring in all currently used products. The identity of each medication was ascertained by asking, "Have you taken or used any medicines for which a doctor's or dentist's prescription is needed in the past month?" Each medication container was checked by the interviewers to record the product name. If the container was unavailable, the interviewer probed for the information. Participants were also asked to describe the health problem for which they took the medicine and how long they had been taking it. The generic name and product code were coded as "blank but applicable" when the name reported did not refer to a specific product or when the name could not be identified.

Covariates

Demographic risk factors (gender, age, and race) and potential covariates for reduced bone mineral density include body mass index (BMI) (kilograms/meter squared), smoking (current vs former or never), alcohol intake (number of drinks in the previous month), poor self-reported health, and history of hip or wrist fracture. Leisure-time physical activity (walking, jogging or running, bicycling or bicycling on an exercise-bike, swimming, aerobics or aerobic dancing, other dancing, calisthenics or exercises, gardening or yard work, and lifting weights) during the previous month was calculated as the metabolic equivalent of the task (MET) per month. History of relevant chronic medical conditions such as arthritis, diabetes, myocardial infarction, congestive heart failure, cerebrovascular accidents, chronic obstructive lung disease (COPD), allergic rhinitis, asthma, and peptic ulcer disease or GERD were based on patients' reports of doctors' diagnoses. Dietary calcium and vitamin D consumption was

calculated from a 24-hour recall of food intake on the previous day.[12] Supplemental calcium and vitamin D consumed in the previous 30 days was also reported.[13] Total calcium intake (milligrams/day) and total vitamin D intake (international units/day) were calculated by combining dietary and supplemental calcium or vitamin D. Serum levels of 25-hydroxy vitamin D (nanograms/milliliter) were also considered as potential confounders of the association between antihistamine use and bone density.[14] Variables that might retard or reverse bone loss were higher BMI, physical activity (MET), calcium and vitamin D intake, and use of thiazide or estrogens. Other covariates could independently be a risk for osteoporosis associated with the use of histamine receptor antagonists.

Bone Mineral Density

The bone density of femoral neck was measured by trained examiners using dual-energy x-ray absorptiometry (Hologic QDR 1000, Waltham, Mass). The left hip was scanned unless there was a history of fracture or surgery; scanning of the right femur was performed in only 1% of the study sample and inclusion did not alter estimates. Scans were reviewed by consultants at the Mayo Clinic, Rochester, Minn, for quality control. The intraobserver and interobserver coefficients of variation were 2.1% and 2.5%, respectively.[15] The bone mineral density of other anatomic sites are not available in NHANES III.

Statistical Analysis

Baseline characteristics of subjects exposed to medications of interest and nonusers were compared by Student *t* test for continuous variables and Pearson's chi-square test for categoric variables. The bone mineral density of proximal femoral neck was considered as the primary outcome in all analyses. We used a multivariable linear regression model to assess the relationship between the medication use and the bone density. All femoral neck bone densities were adjusted for age, gender, race, BMI, smoking, alcohol, METs per month, previous fractures, self-reported health, serum vitamin D, total calcium and vitamin D intake, glucocorticoids (nasal or oral), thiazide, estrogen, and comorbidity (arthritis, diabetes, myocardial infarction, congestive heart failure, cerebrovascular accident, chronic obstructive pulmonary disease, asthma, allergic rhinitis, GERD or peptic ulcer disease, cancer). For H2RA users, we compared femoral neck bone mineral density according to daily calcium intake. We also examined for each medication by duration of its use. Subjects receiving a proton pump inhibitor or more than 2 medications of interest (6 for proton pump inhibitor, 27 for H1RA + H2RA, 3 for H2RA + proton pump inhibitor, but none for H1RA + proton pump inhibitor or H1RA + H2RA + proton pump inhibitor) were excluded from analysis. Two-sided *P* values less than .05 were considered statistically significant. All analyses were conducted in SAS 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

Among 5724 eligible subjects aged 60 years and older, dual-energy x-ray absorptiometry measurements were available for 199 (3.5%) H1RA users, 297 (5.2%) H2RA users, and 4162 nonusers. The baseline characteristics of subjects are shown in Table 1. The users of H1RAs were more likely to be female than nonusers, and H2RA users were more often physically inactive than nonusers. Compared with nonusers, subjects using H1RA or H2RA reported poorer health and were more likely to include patients with a history of myocardial infarction, congestive heart failure, COPD, allergic rhinitis or asthma, and more GERD or peptic ulcer disease. Subjects with histamine receptor antagonists were more likely to be prescribed glucocorticoids (nasal or oral) (all *P* values $< .05$). When we repeated analysis for all subjects with and without dual-energy x-ray absorptiometry measurement, the distributions of baseline characteristics were similar.

Unadjusted femoral neck bone density was similar for H1RA users and nonusers (0.74 g/cm^2 vs 0.74 g/cm^2; $P = .7$). However, in fully adjusted analysis for other covariates, as well as age and gender, there was a trend for higher bone density in H1RA users than in nonusers (0.74 g/cm^2 vs 0.72 g/cm^2; $P = .037$). Adjusted femoral neck bone mineral density was slightly lower for H2RA users than nonusers ($P = .003$) (Table 2). When analysis was stratified by daily calcium intake, the relationship between H2RA use and lower bone density was not significant in the group taking more calcium (Table 3). The results were unchanged with different cutoff values of daily calcium intake of 1000 mg per day or 1200 mg per day. The difference between H1RA users and nonusers was not significant when their calcium intake cutoff points were similarly examined. In analyses restricted to patients with conditions requiring acid suppressive therapy (ie, GERD or peptic ulcer disease), no difference in bone mineral density was observed between H2RA users and non-H2RA antacid users when daily calcium intake exceeded 800 mg per day (0.71 g/cm^2 vs 0.72 g/cm^2; $P = .7$), but there was a trend for lower bone mineral density among H2RA users when daily calcium intake was less than 800 mg (0.67 g/cm^2 vs 0.70 g/cm^2; $P = .065$). Among patients with vitamin D intake less than 400 IU per day, H1RA users had higher bone density than nonusers (0.74 g/cm^2 vs 0.72 g/cm^2; $P = .016$). Among the same group of patients with vitamin D intake less than 400 IU per day, H2RA users showed lower bone density compared with nonusers (0.68 g/cm^2 vs 0.72 g/cm^2; $P = .002$). There was no difference between medication users and nonusers when vitamin D intake was more than 400 IU per day. We observed no effect of duration of use on bone density for any of the medications studied (data not shown).

DISCUSSION

We found a trend for higher femoral neck bone mineral density in H1RA users among older adult subjects in this

Table 1 Baseline Characteristics of Subjects Comparing Medication Users and Nonusers (n = 4658)

	H1RA (n = 199) N (%) or mean (SD)	H2RA (n = 297)	Nonuser (n = 4162)
Age	72.6 (8.4)	72.1 (7.8)	71.7 (8.1)
Female	120 (60.3)†	157 (52.9)	2090 (50.2)
White	125 (62.8)	179 (60.3)	2430 (58.4)
BMI (kg/m^2)	27.4 (5.2)	27.3 (5.2)	26.9 (5.0)
Current smoker	21 (10.5)	39 (13.1)	639 (15.4)
Alcohol (drinks/mo)	8.8 (22.7)	7.1 (34.8)	9.3 (31.7)
Physical activity (METs/mo)	66.0 (98.5)	61.7 (97.3)†	78.9 (104.8)
Hip or wrist fracture*	25 (12.6)	34 (11.5)	445 (10.7)
Self-reported health (poor)	19 (9.6)†	54 (18.2)†	318 (7.6)
Serum 25(OH) vitamin D (ng/mL)	26.6 (10.4)	26.5 (11.2)	26.4 (10.5)
Total calcium intake (mg/d)*	713.2 (456.2)	719.4 (467.0)	713.1 (463.6)
Total vitamin D intake (IU/d)	240.1 (237)†	187.6 (137.6)	191.3 (181.2)
Intranasal glucocorticoid use‡	19 (9.5)†	7 (2.4)†	25 (0.6)
Oral glucocorticoid use‡	12 (6.0)†	18 (6.1)†	67 (1.6)
Use of thiazide‡	37 (18.6)	44 (14.8)	596 (14.3)
Use of estrogen‡**	7 (5.8)	12 (7.6)	117 (5.6)
Arthritis*	127 (63.8)†	169 (56.9)†	1766 (42.4)
Diabetes*	41 (18.1)	53 (16.2)	630 (15.1)
Myocardial infarction*	28 (14.1)	52 (17.5)†	437 (10.5)
Congestive heart failure*	24 (12.1)†	46 (15.5)†	321 (7.7)
Cerebrovascular accident*	12 (6.1)	25 (8.4)	296 (7.1)
COPD*	54 (27.1)†	62 (20.9)†	576 (13.8)
Asthma*	25 (12.6)†	30 (10.1)†	267 (6.4)
Allergic rhinitis*	89 (44.7)†	84 (28.3)†	846 (20.3)
GERD or PUD*	3 (1.5)†	122 (41.1)†	11 (0.3)
Non-skin cancer*	18 (9.1)	28 (9.4)	339 (8.2)

MET = metabolic equivalent of the task; IU = international unit; H1RA = histamine 1 receptor antagonist; H2RA = histamine 2 receptor antagonist; COPD = chronic obstructive pulmonary disease; GERD = gastroesophageal reflux disease; PUD = peptic ulcer disease; BMI = body mass index.

*Medical history.

†$P \leq .05$ compared with nonuser.

‡Current use.

**Used by females.

study of a representative US population. H2RA users with reduced calcium intake had lower bone density compared with nonusers.

Histamine 1 Receptor Antagonists and Bone Density

Our findings corroborate other studies in which H1RAs have been shown to protect against bone loss. To our knowledge, there have been only 2 human studies evaluating H1RA and bone mineral density. Tyan[16] reported higher bone density with the use of H1RA in 54 ambulatory postmenopausal subjects with osteoporosis who were randomly assigned to calcium plus promethazine (H1RA) versus calcium alone for up to 30 months. Baseline characteristics of subjects in each group were similar in age, weight and height, ethnicity, smoking, and relevant medications use. Lumbar bone mineral content was

Table 2 Femoral Neck Bone Mineral Density* Among Medication Users and Nonusers

	H1RA	*P* Value†	H2RA	*P* Value†	Nonuser
N	199		297		4162
Unadjusted	0.72 (0.72-0.72)	.7	0.69 (0.69-0.70)	.007	0.72 (0.72-0.72)
Fully adjusted	0.74 (0.73-0.75)	.037	0.69 (0.68-0.70)	.003	0.72 (0.71-0.72)

H1RA = histamine 1 receptor antagonist; H2RA = histamine 2 receptor antagonist. All femoral neck bone mineral densities were adjusted for age, gender, race, BMI, smoking, alcohol, METs/month, fracture, self-reported health, serum vitamin D, total calcium and vitamin D intake, glucocorticoids (nasal or oral), thiazide, estrogen, and comorbidity (arthritis, diabetes, myocardial infarction, congestive heart failure, cerebrovascular accident, COPD, asthma, allergic rhinitis, GERD or peptic ulcer disease, cancer).

*Least square mean (95% confidence interval) (g/cm^2).

†*P* value compared with nonuser.

Table 3 Femoral Neck Bone Mineral Density* between Histamine 2 Receptor Antagonist Users and Nonusers Stratified by Daily Calcium Intake with Different Cutoff Value

Daily Calcium Intake	H2RA User (n = 297)	*P* Value†	Nonuser (n = 4162)
≥800 mg (n = 1461)	0.70 (0.69-0.71)	.19	0.73 (0.73-0.73)
≤799 mg (n = 2998)	0.68 (0.67-0.69)	.006	0.72 (0.72-0.72)
≥1000 mg (n = 934)	0.69 (0.67-0.71)	.16	0.72 (0.72-0.72)
≤999 mg (n = 3525)	0.68 (0.67-0.69)	.007	0.72 (0.72-0.72)
≥1200 mg (n = 571)	0.71 (0.68-0.74)	.5	0.74 (0.73-0.74)
≤1199 mg (n = 3888)	0.68 (0.67-0.69)	.002	0.72 (0.71-0.72)

H2RA = histamine 2 receptor antagonist. All femoral neck bone mineral densities were adjusted for age, gender, race, BMI, smoking, alcohol, METs/month, fracture, self-reported health, serum vitamin D, total calcium and vitamin D intake, glucocorticoids (nasal or oral), thiazide, estrogen, and comorbidity (arthritis, diabetes, myocardial infarction, congestive heart failure, cerebrovascular accident, COPD, asthma, allergic rhinitis, GERD or peptic ulcer disease, cancer).

*Least square mean (95% confidence interval) (g/cm^2).

†*P* value compared with nonuser.

increased by 3.2% per year in subjects who used both promethazine and calcium, compared with its reduction by 1.5% in subjects who used only calcium without hormone replacement therapy. With estrogen replacement therapy, H1RA users increased bone mass even greater compared with subjects only being treated with calcium. Ferencz et al[8] demonstrated that H1RA may counteract bone loss or fracture. This was a cross-sectional study that assessed 125 postmenopausal women who had pollen allergy for at least 5 years. Compared with patients without allergy matched for age, BMI, and age at menopause, allergic women untreated with H1RA showed lower bone density and increased fracture risk by 3-fold, probably because of enhanced histamine production or use of nasal steroid inhalers. Among patients with allergy, H1RA-treated subjects showed higher bone density than those without H1RA treatment, and neither hip nor vertebral fracture was observed in patients receiving H1RA.

Impaired histamine production and histamine receptor antagonists also prevented bone loss in ovariectomized rats.[17] Histamine seems to mediate the osteoclastic pathway by expression of RANKL in osteoblasts and bone marrow stromal cells.[18] Histamine deficiency increased serum calcitriol and directly enhanced bone formation by stimulating calcitriol synthesizing enzyme in the kidney. Calcitriol also stimulated RANKL expression, but osteoclastogenesis was blunted because of histamine depletion, resulting in increasing bone mineral density and cortical bone thickness in histamine-deficient mice.[6]

Logically, the skeletal effects of excess histamine may mirror those of histamine depletion. Bone loss is known to be associated with mastocytosis, in which excess release of histamine enhances bone remodeling.[19] Estrogen's effect on bone health may be partly related to histamine; estrogen depletion directly stimulates histamine release from mast cells and increases bone resorption through osteoclastogenesis.[17,20] Our observation of an increase in bone density in H1RA users suggests that histamine blockade by H1RA may protect against osteoporosis.

Histamine 2 Receptor Antagonists and Bone Health

H2RA users had lower femoral neck bone density compared with nonusers, but the bone density was not significantly different among subjects with increased daily calcium intake. We also observed lower bone density when vitamin D intake was insufficient. Few data on bone density among H2RA users have been reported. Adachi et al[21] reported bone density of 33 gastrectomized Japanese subjects treated with H2RA for more than 2 years. There was no difference in lumbar bone density compared with that of age- and sex-matched healthy controls. The researchers concluded that H2RA had little effect on bone density, but their results are difficult to interpret because of small sample size with H2RA use limited only to postgastrectomy cases, lack of adjustment for potential confounders, and no information on study controls.

Studies of H2RA on fracture risk are conflicting. Grisso et al[22] examined 356 cases of hip fracture and 402 controls at 34 hospitals in the United States between 1991 and 1993. They found a 2.5-fold increased risk of hip fracture in male patients treated with cimetidine. In contrast, a larger-scale Danish study reported by Vestergaard et al[10] showed a two-thirds lower risk of hip fracture in H2RA users among 500,000 subjects. The Danish study adjusted for many important covariates but failed to control for several confounders, such as weight, physical activity, smoking, or use of calcium/vitamin D supplements. Another large case-control study in the United Kingdom demonstrated H2RA users had a 20% to 30% increased risk of hip fracture, but the association became insignificant with little change in point estimate when the analyses were restricted to patients with documented GERD. They did not observe a dose-response effect associated with H2RA.[9] Our findings support the hypothesis that H2RA could negatively impact bone mass under circumstances of inadequate calcium intake. Theoretically, the H2RA-induced reduction of gastric acidity could impair calcium solubility and absorption of calcium, but the contribution of this mechanism to bone loss remains unclear.[23,24]

Difference between Histamine Receptor Antagonists

Inconsistent bone density changes between H1RA and H2RA users may derive from confounding by indication. Older subjects using H2RAs may have lower bone density if peptic ulcer disease or GERD independently increases the risk of osteoporosis.[25] We limited our analysis to subjects using antacids for conditions requiring acid suppressive therapy and still found no association between H2RA and lower bone density among subjects with adequate calcium intake. Several medical conditions that may be linked with increased prescribing of acid suppressive therapy could be related to osteoporosis, and thus we considered that important comorbidity in the model. Another reason for the difference between H1RA and H2RA may arise from histamine receptor class. In vitro, fexofenadine (H1RA) inhibits macrophage activation induced by histamine, but ranitidine (H2RA) does not.[26] H1RA also exhibits anti-inflammatory effects independently of the H1 receptor.[27] Further research is needed to assess the class effect of a histamine receptor in bone.

The duration of use of H1RA or H2RA did not influence bone mineral density in our study. Animal studies suggested that histamine is involved in the early phase of bone destruction,[18,20] and that decreased osteoclastic activation by H1RA may not last long.[28] Along with the fact that the protective effect of histamine antagonists against femoral bone loss did not last more than 6 months after the beginning of the treatment,[20] our observation also suggests that the inhibitory effects of these medications on bone loss may not persist over time.

STUDY STRENGTHS AND LIMITATIONS

To our knowledge, there has been no population-based study that evaluated histamine receptor antagonists and bone density. We analyzed many important covariates, including comorbidities and prescription and over-the-counter medications.

Several limitations of our study merit discussion. First, the cross-sectional nature of this study limits our ability to assess the temporal association between histamine receptor antagonists and bone mineral density. All the H1RA and H2RA users were current users at the time of interview and bone mineral density measurement. Those patients who stopped using histamine antagonists before the interview were considered nonusers. For example, H1RA users with seasonal allergies may be classified as nonusers. However, differential misclassification of H1RA and H2RA users to nonusers would likely reduce the difference between medication users and nonusers, and thus the observed positive association is unlikely to change. Second, the lack of a duration effect may derive from intermittent medication use or self-report to determine duration of their use. Third, we did not have dosage information for the medications of interest and thus cannot examine possible dose effects. Fourth, we observed significant differences between medication users and nonusers in glucocorticoid use, prevalence of arthritis, myocardial infarction, congestive heart failure, COPD, and GERD/peptic ulcer disease, any of which might negatively affect bone mineral density. Controlling for these covariates resulted in increased bone density in H1RA but bone mass reduction in H2RA, and thus confounding by indication cannot account for bone density difference between H1RA and H2RA. Finally, we had no bone mineral density data on anatomic sites other than the femur. The effect of these medications may be different in other bones.

CONCLUSIONS

We found slightly higher femoral neck bone mineral density among elderly subjects using H1RA. Femoral neck bone density was lower in H2RA users, especially when calcium intake was reduced. Risk estimates of the bone density changes associated with H1RA and H2RA do not seem to be large; thus, clinical consequences in this regard are uncertain and future study is warranted. Further in vitro and animal studies would help to clarify the relationships between histamine receptor antagonists and bone density, as would longitudinal studies with bone mineral density and markers of bone metabolism.

References

1. Chiappetta N, Gruber B. The role of mast cells in osteoporosis. *Semin Arthritis Rheum*. 2006;36:32-36.
2. Johansson C, Roupe G, Lindstedt G, Mellstrom D. Bone density, bone markers and bone radiological features in mastocytosis. *Age Ageing*. 1996;25:1-7.
3. Silberstein R, Melnick M, Greenberg G, Minkin C. Bone remodeling in W/Wv mast cell deficient mice. *Bone*. 1991;12:227-236.
4. Rico H, Gomez M, Revilla M, et al. Effects of promethazine on bone mass and on bone remodeling in ovariectomized rats: a morphometric, densitometric, and histomorphometric experimental study. *Calcif Tissue Int*. 1999;65:272-275.
5. Lesclous P, Guez D, Saffar JL. Short-term prevention of osteoclastic resorption and osteopenia in ovariectomized rats treated with the H2 receptor antagonist cimetidine. *Bone*. 2002;30:131-136.
6. Fitzpatrick LA, Buzas E, Gagne TJ, et al. Targeted deletion of histidine decarboxylase gene in mice increases bone formation and protects against ovariectomy-induced bone loss. *Proc Natl Acad Sci*. 2003;100:6027-6032.
7. Simasek M, Blandino DA. Treatment of the common cold. *Am Fam Physician*. 2007;75:515-520.
8. Ferencz V, Meszaros S, Csupor E, et al. Increased bone fracture prevalence in postmenopausal women suffering from pollen-allergy. *Osteoporos Int*. 2006;17:484-491.
9. Yang Y-X, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA*. 2006;296:2947-2953.
10. Vestergaard P, Rejnmark L, Mosekilde L. Proton pump inhibitors, histamine H2 receptor antagonists, and other antacid medications and the risk of fracture. *Calcif Tissue Int*. 2006;79:76-83.
11. Plan and operation of the Third National Health and Nutrition Examination Survey, 1988-94. Series 1: programs and collection procedures. *Vital Health Stat 1*. 1994:1-407.
12. NHANES III. *Total Nutrient Intakes File Documentation*. Hyattsville, MD: Centers for Disease Control and Prevention; 1998.
13. U.S. Department of Health and Human Services (DHHS) NCfHS. *Third National Health and Nutrition Examination Survey: 1988-94: NHANES III Dietary Supplement Data File (CD-ROM Series 11, No. 2A)*. Hyattsville, MD; Centers for Disease Control and Prevention; 1998.

14. *Third National Health and Nutrition Examination Survey, 1988-1994: NHANES III Reference Manuals and Reports: Laboratory Manual (CD-ROM)*. Vol. Public use data file documentation no. 76200. Hyattsville, MD: Centers for Disease Control and Prevention; US Department of Health and Human Services (DHHS); National Center for Health Statistics; 1996.
15. Wahner HW, Looker A, Dunn WL, et al. Quality control of bone densitometry in a national health survey (NHANES III) using three mobile examination centers. *J Bone Miner Res*. 1994;9:951-960.
16. Tyan ML. Effect of promethazine on lumbar vertebral bone mass in postmenopausal women. *J Intern Med*. 1993;234:143-148.
17. Lesclous, Guez D, Baroukh B, et al. Histamine participates in the early phase of trabecular bone loss in ovariectomized rats. *Bone*. 2004; 34:91-99.
18. Deyama Y, Kikuiri T, Ohnishi G, et al. Histamine stimulates production of osteoclast differentiation factor/receptor activator of nuclear factor-kappaB ligand by osteoblasts. *Biochem Biophys Res Commun*. 2002;298:240-246.
19. Lidor C, Frisch B, Gazit D, et al. Osteoporosis as the sole presentation of bone marrow mastocytosis. *J Bone Miner Res*. 1990;5:871-876.
20. Lesclous P, Schramm F, Gallina S, et al. Histamine mediates osteoclastic resorption only during the acute phase of bone loss in ovariectomized rats. *Exp Physiol*. 2006;91:561-570.
21. Adachi Y, Shiota E, Matsumata T, et al. Bone mineral density in patients taking H2-receptor antagonist. *Calcif Tissue Int*. 1998;62: 283-285.
22. Grisso JA, Kelsey JL, O'Brien LA, et al. Risk factors for hip fracture in men. Hip Fracture Study Group. *Am J Epidemiol*. 1997;145: 786-793.
23. Bo-Linn GW, Davis GR, Buddrus DJ, et al. An evaluation of the importance of gastric acid secretion in the absorption of dietary calcium. *J Clin Invest*. 1984;73:640-647.
24. O'Connell MB, Madden DM, Murray AM, et al. Effects of proton pump inhibitors on calcium carbonate absorption in women: a randomized crossover trial. *Am J Med*. 2005;118:778-781.
25. Sawicki A, Regula A, Godwod K, Debinski A. Peptic ulcer disease and calcium intake as risk factors of osteoporosis in women. *Osteoporos Int*. 2003;14:983-986.
26. Marone G, Granata F, Spadaro G, Genovese A, Triggiani M. The histamine-cytokine network in allergic inflammation. *J Allergy Clin Immunol*. 2003;112(4, Suppl 1):S83-S88.
27. MacGlashan D. Histamine: a mediator of inflammation. *J Allergy Clin Immunol*. 2003;112(4, Suppl 1):S53-S59.
28. Christine Dobigny J-LS. H1 and H2 histamine receptors modulate osteoclastic resorption by different pathways: evidence obtained by using receptor antagonists in a rat synchronized resorption model. *J Cell Physiol*. 1997;173:10-18.