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The Relationship of Antiresorptive Drug Use to Structural Findings and Symptoms of Knee Osteoarthritis

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Objective. **To examine the cross-sectional association between use of medications that have a bone antiresorptive effect (estrogen, raloxifene, and alendronate) and both the structural features of knee osteoarthritis (OA), assessed by magnetic resonance imaging (MRI) and radiography, and the symptoms of knee OA in elderly women.**

Methods. **Women in the Health, Aging and Body Composition Study underwent MRI and radiography of the knee if they reported symptoms of knee OA, and women without significant knee symptoms were selected as controls. MR images of the knee were assessed for multiple features of OA using the Whole-Organ MRI scoring method, and radiographs were read for Kellgren and Lawrence grade and individual features of OA. Concurrent medication use and knee symptoms were assessed by interview, and knee pain severity was evaluated using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).**

Results. **There were 818 postmenopausal women from whom we obtained MR images of the knee and data on medication use. Among these women, 214 (26.2%) were receiving antiresorptive drugs. We found no significant association between overall use of antiresorptive drugs and the presence of knee pain and radiographic changes of OA of the knee. Use of alendronate, but not estrogen, was associated with less severity of knee pain as assessed by WOMAC scores. Both alendronate use and estrogen use were associated with significantly less subchondral bone attrition and bone marrow edema–like abnormalities in the knee as assessed by MRI, as compared with women who had not received these medications.**

Conclusion. **Elderly women being treated with alendronate and estrogen had a significantly decreased prevalence of knee OA–related subchondral bone lesions compared with those reporting no use of these medications. Alendronate use was also associated with a reduction in knee pain according to the WOMAC scores.**

Osteoarthritis (OA) of the knee is a common condition in the United States and a leading cause of disability in elderly people (1–3). Nonoperative therapies are not curative, and a substantial number of affected people ultimately undergo total knee replacements (4).

The cartilage degradation that is central to OA is accompanied by important periarticular bone abnormalities, including subchondral bone thickening, deformation and cysts, and marginal osteophytosis. A higher rate of subchondral bone turnover, as indicated by increased uptake of scintigraphic tracer in subarticular bone, is associated with more rapid progression of knee OA (5). Markers of cartilage degradation, including crosslinked

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C-telopeptide fragments of type II collagen (CTX) (6), are elevated in synovial fluid of patients with primary knee OA (7), and elevated levels of both CTX and urinary N-terminal type I collagen telopeptide, a marker of bone resorption (8), have been reported in patients with progressive knee OA (9). Knee magnetic resonance imaging (MRI) findings that may be related to increased bone turnover, subchondral bone marrow edema–like lesions, and bone attrition are also very strong predictors of structural worsening of knee OA (10–12). Bone antiresorptive agents used to prevent or treat osteoporosis, including estrogen, bisphosphonates, calcitonin, and raloxifene, may influence the periarticular bone changes of OA and could, therefore, have an effect on the course of the disease, including the possibility of slowing its development and progression (6,13–14). Recent data also implicate inflammation as playing a pivotal role in OA disease progression, chronicity, and pain (11,15), and both estrogen (16) and bisphosphonates (17,18) may have antiinflammatory properties.

The results of epidemiologic studies of estrogen use as it relates to OA are conflicting. The majority of reports (19–23), although not all (24,25), suggest a beneficial effect of estrogen on OA. Studies evaluating structural changes of knee OA have found that radiographic changes are less frequent and less progressive in women taking estrogen compared with those not taking estrogen (20,26). Interestingly, a large effort is under way to test the efficacy of a currently available bisphosphonate as a treatment for knee OA (27,28).

MRI is one of the most sensitive techniques available to assess soft tissue and bone changes in the knee (29). Three studies have utilized knee MRI to examine the relationship between the use of estrogen and cartilage volume in the knee. One cross-sectional study demonstrated that estrogen use was associated with increased tibial cartilage volume (19); however, a more recent longitudinal study did not suggest that tibial cartilage volume was different in women receiving estrogen compared with those who had not taken estrogen (30). In addition, another study did not find that women receiving estrogen had greater patellar cartilage volume compared with those who had not received estrogen (31). However, no previous study has utilized MRI to examine the association of estrogen use with subchondral bone lesions. Due to the rather recent introduction of antiresorptive agents approved for the treatment of osteoporosis (including nitrogen-containing bisphosphonates and selective estrogen receptor modulators [SERMs]), little is known about their effects on any structural or clinical findings of knee OA.

The purpose of this cross-sectional study was to examine the association of use of antiresorptive therapy with the presence and severity of symptoms of knee pain, knee OA radiographic changes, and knee OA–related MRI changes in elderly women in the Health, Aging and Body Composition (Health ABC) Study cohort.

PATIENTS AND METHODS

Subjects. The Health ABC Study is a longitudinal study of the factors that contribute to disability in the elderly. The Study was approved by the Institutional Review Boards at The University of Tennessee and The University of Pittsburgh, which are the 2 clinical sites for the Study. To be eligible for participation in the Health ABC Study at baseline, participants had to report that they had no difficulty walking at least one-quarter mile and climbing 10 stairs without resting. A total of 3,075 male and female participants were enrolled in Memphis, Tennessee (n = 1,548) and in Pittsburgh, Pennsylvania (n = 1,527). Participants in the present analysis were women ages 69–81 years who had undergone the year 2 or year 3 examination of the Health ABC Study, which was conducted from July 1998 to July 2000, who underwent MRI or radiography of the knee, and who completed a medication use survey. Men were not included in this analysis because there were too few men in the antiresorptive user group in years 2 or 3 of the Health ABC Study (n = 9).

Participants were eligible to obtain bilateral knee radiographs and knee MR images at the year 2 or year 3 visits if they reported symptoms of OA (defined below) in at least 1 knee at that visit. In addition, a sample of participants who did not meet the study definition for knee OA symptoms were chosen at random to obtain knee MR images and radiographs.

Assessment and definition of knee symptoms. Study interviewers assessed knee symptoms at each visit by asking participants if they had "pain, aching or stiffness on most days for at least one month" at some time during the past year, and interviewers also administered a modified Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scale (32). The modified WOMAC pain subscale uses a 5-point Likert scale and asks subjects to rate any knee pain that occurs while walking on a flat surface, going up or down stairs, at night while in bed, standing upright, getting in or out of a chair, and getting in or out of a car. A knee was defined as having symptoms of OA if the participant reported pain, aching, or stiffness in that knee on most days for at least 1 month in the past 12 months or if they reported moderate or worse knee pain during the last 30 days in association with $\geq$1 activity listed in the WOMAC pain scale.

Medication use. As part of their yearly visits, participants were asked to bring in to the clinics all of their medications, including over-the-counter drugs and supplements that had been taken during the previous 2 weeks. Medications were recorded and matched to a dictionary of prescription and nonprescription drugs using the Iowa Drug Information System (33). This system identifies the ingredients of each drug in the dictionary and allows the identification of each individual pharmaceutical compound. In addition to the

name of the drug, participants were asked to indicate how long they had been treated with each drug. The date of the clinic visit at which the medication use was recorded was matched to the date of the radiograph and the MRI separately.

The women were included in the antiresorptive drug user group if they reported use of estrogen, raloxifene, or any bisphosphonate during the 2 weeks prior to the clinic visit. Calcitonin was not included in this analysis because only 1 participant reported its use. None of the participants reported use of pamidronate, etidronate, or risedronate in this study; therefore, alendronate was the only bisphosphonate included in the analysis. Use of calcium supplements, thiazide diuretics, and nonsteroidal antiinflammatory drugs (NSAIDs) was also ascertained as part of the drug identification process.

Knee imaging. Bilateral, standing, flexed views of the tibiofemoral compartment of the knee joint were obtained using the Fixed-Flexion technique (34), and axial (skyline) views were obtained of the patellofemoral joint. For the tibiofemoral compartment, both knees were assessed radiographically with a posteroanterior projection using a positioning frame (SynaFlexer; Synarc, San Francisco, CA) in order to fix knee flexion (between 20° and 30°) and external rotation of the feet at 10° for each subject. For the patellofemoral view, each knee was imaged separately with the participant in a standing position and the limb flexed at 30–40° during weightbearing (35).

Bilateral MR images of the knee were obtained at each clinical center using 1.5T whole-body scanners (General Electric Signa, Milwaukee, WI) and standard commercial, unilateral, circumferential knee coils. The short MRI protocol used in the Health ABC Study consisted of 3 sequences: 1) an axial T2-weighted fast spin echo (FSE) localizer encompassing the entire patella (30 seconds); 2) a sagittal T2-weighted FSE with frequency-selective fat suppression, spanning the entire synovial cavity (4 minutes, 30 seconds); and 3) a coronal T2-weighted FSE (4 minutes).

Assessment of knee images for OA. Radiographs and MR images were read centrally. Radiographs of the tibiofemoral joint were scored for Kellgren and Lawrence severity grade of knee OA, and the patellofemoral joint radiographs were scored for grade of individual radiographic features (e.g., joint space narrowing, osteophytes) based on the Osteoarthritis Research Society International Atlas (36). All knee radiographs obtained at the year 2 and year 3 visits were read at Boston University. The presence of tibiofemoral OA in a knee was defined as a Kellgren and Lawrence grade of ≥2. The presence of patellofemoral knee OA was defined as the presence of an osteophyte of grade ≥2 on a 0–3 scale or the presence of moderate to severe joint space narrowing (grade ≥2 on a 0–3 scale) with co-occurrence of a bone feature in the compartment affected (37).

MR images were evaluated using the multifeature semiquantitative Whole-Organ MRI Score (WORMS) method (38), conducted by trained readers at the Osteoporosis and Arthritis Research Group at the University of California at San Francisco (UCSF). Knees were randomly selected for reading according to strata defined by the presence and absence of knee symptoms.

Using the WORMS method, 8 separate morphologic features of knee OA were evaluated. Five features were related to the articular surface: cartilage damage, marginal osteophytes, subchondral bone marrow abnormality, subchondral bone cysts, and subchondral bone attrition. Articular surface features were scored in up to 15 separate anatomic regions of the knee, and the scores were then summed to yield total scores for each feature by compartment and for the whole knee (38). Three additional articular features that are important to the functional integrity of the knee were also scored: meniscal damage (medial, lateral, and total knee), ligament damage (total knee), and synovial distention/effusion (total knee). All features were scored using ordinal scales that are specific to the feature, with higher scores corresponding to more severe abnormalities. The interreader reliability between 3 MRI readers in the Health ABC Study was calculated by individual MRI feature, both within compartment and for the total knee. Interreader agreement for the WORMS assessments performed by the Health ABC Study MRI readers on 30 knees was good to excellent, with intraclass correlation coefficients (ICCs) between 0.62 and 0.93. (ICC values between 0 and 0.40 are interpreted as poor agreement, 0.41 and 0.75 as fair to good agreement, and ≥0.76 as excellent agreement [39]).

For this study, we hypothesized that antiresorptive medications would affect cartilage and subchondral bone lesions throughout the knee. Therefore, we utilized the total knee scores for the features of interest: osteophytes (range 0–112), subchondral bone marrow abnormality (range 0–45), subchondral bone attrition (range 0–42), and cartilage damage (range 0–84).

Measurement of covariates. Bone mineral density (BMD) of the total hip was measured using a Hologic QDR Model 4500A fan-beam densitometer (Waltham, MA). The DXA Quality Assurance Manual for the Health ABC Study (UCSF Prevention Sciences Group) was used to standardize participant positioning and scan analysis.

An isokinetic quadriceps strength test was performed using a dynamometer (Kin-Com Dynamometer, Chattanooga, TN) at visit 2. The maximum torque (moving from 80° to 40°) was recorded from averaged curves, with results expressed in Nm. There were 151 participants with knee radiographic or MRI data who did not or were unable to perform the strength test (for example, those with severe knee pain during the test).

Height was assessed using a Harpenden stadiometer (Pembrokeshire, UK). Weight (without shoes) was determined using a calibrated balance scale. Body mass index (BMI) was calculated by dividing weight (in kg) by height (in m^2). Each participant's age, race, history of knee surgery, current smoking status, self-report of osteoporosis or fracture after the age of 45 years, and use of walking device were derived from interviewer-administered questionnaire.

Statistical analysis. We included in these analyses all women with data on medication use and either an evaluable knee radiograph (n = 668) or at least 1 knee MRI reading completed by October 2002 (n = 540). Not all of the women with an evaluable knee radiograph had a knee MRI reading available, nor did all of the women with a knee MRI reading have an evaluable knee radiograph available. Women reporting use of multiple antiresorptive agents were excluded, because it would not be possible to determine the effect of an individual drug on an outcome. There were 8 women taking multiple antiresorptive agents who were excluded from the radiographic analyses and 5 women taking multiple antiresorp-

tive agents who were excluded from the MRI analyses. One woman taking calcitonin was also excluded.

Contingency tables were used to assess the statistical significance of differences in categorical covariates by antiresorptive use, and analysis of variance was used to assess whether there were significant differences in the mean values of the continuous covariates by antiresorptive use. We classified all women who had knee radiographs by the presence of radiographic knee OA and knee symptoms, and compared the frequency of antiresorptive use among the resulting 4 subgroups: no knee symptoms and no radiographic OA, no knee symptoms with radiographic OA, knee symptoms without radiographic OA, and knee symptoms with radiographic OA. Logistic regression was used to evaluate the differences in antiresorptive drug use among these categories, using the group with neither knee symptoms nor radiographic OA as the reference group. We then used knees as the unit of analysis to compare the MRI feature scores and the WOMAC pain scores between groups of knees defined by a subject's use of antiresorptive drugs.

Analysis of continuous or near-continuous scores was performed using linear regression. We also dichotomized the MRI feature scores (0 = no abnormalities, 1 = summed feature score ≥ 1) and compared the prevalence of any abnormality by antiresorptive use status using logistic regression. For both logistic and linear regression in which knees were the unit of analysis, we used generalized estimating equations to adjust for interknee correlations. All regression analyses were adjusted for age, race, study site, BMI, use of NSAIDs, use of thiazide diuretics, calcium supplementation, BMD of the hip, current smoking status, knee extensor strength, self-report of history of osteoporosis, self-report of fracture since age 45 years, and use of a walking device. The latter was not included in logistic models of cartilage lesions due to missing data. We evaluated possible interactions between antiresorptive use and radiographic status, as well as interactions between antiresorptive use and knee symptoms status, by including interaction terms in multivariate models. There were no interactions between antiresorptive use and radiographic OA status in their association with knee symptoms status and WOMAC scores ($P > 0.21$ for all), nor between antiresorptive use and knee symptoms status in their association with MRI features of OA or WOMAC scores ($P > 0.32$ for all). Statistical analyses were performed using the SAS System for Windows (version 9.1; SAS Institute, Cary, NC).

All of our analyses involving specific drug usage were prespecified and preplanned, not post hoc. Our justification for this was based on the known different potencies of the various antiresorptive agents (SERMs, estrogen, and bisphosphonates) for bone. For example, in a recent head-to-head comparison of raloxifene with alendronate (Evista Alendronate Comparison Trial), it was reported that alendronate had a much greater effect on bone biomarkers than did raloxifene (40).

RESULTS

Of the 668 women with radiographs and medication use data who were considered eligible for this study, there were 504 nonusers (75.4%) and 164 antiresorptive users (24.6%). Of the antiresorptive users, 125 were receiving estrogen, 8 were receiving raloxifene, and 31 were receiving a bisphosphonate (alendronate only). Of the 540 study-eligible women with MRI and medication use data, there were 383 nonusers (70.9%) and 157 antiresorptive users (29.1%) (comprising 114 estrogen users, 9 raloxifene users, and 34 bisphosphonate [alendronate only] users).

Table 1 shows the selected baseline characteristics of the combined study population of women with knee radiographic and/or MRI reading data (n = 818) by use of antiresorptive drugs. Users of antiresorptive therapies, compared with nonusers, were more likely to be white, thinner, and reside in Memphis and to take calcium supplements. Although knee extensor strength was lower in the antiresorptive drug user group compared with the nonuser group ($P = 0.01$), this difference disappeared after adjustment for BMI (data not shown). There were no significant differences between nonusers and users of antiresorptive drugs with respect to age, current smoking status, NSAID or thiazide use, total hip BMD, frequency of a T score less than or equal to -2.5, self-report of osteoporosis, self-report of fracture after age 45 years, and use of a walking device. With respect to specific antiresorptive drug use, bisphosphonate users were older than all other groups ($P < 0.01$), had a lower BMI than nonusers and estrogen users ($P < 0.01$ and $P = 0.02$, respectively), and had lower BMD of the total hip than did nonusers and estrogen users ($P < 0.01$ for both) (data not shown). Bisphosphonate users also had lower knee extensor strength than did nonusers ($P = 0.02$); however, this difference was no longer statistically significant after adjustment for BMI. Bisphosphonate users were not statistically significantly more likely to have osteoporosis (a T score less than or equal to -2.5 at the total hip) than were estrogen or raloxifene users ($P > 0.06$ compared with both drug use groups).

Table 2 denotes the association of antiresorptive use with the combined presence or absence of knee pain and radiographic changes of knee OA. There were no significant differences in the proportion of overall antiresorptive use between women classified by the presence of knee symptoms and tibiofemoral radiographic OA and women classified by knee symptoms and patellofemoral radiographic OA, after adjustment for covariates. Results were similar when we classified women based on the presence of knee symptoms and radiographic OA in the tibiofemoral and patellofemoral compartments combined (whole-knee OA).

We also found no association between overall antiresorptive use and the presence or absence of knee

Table 1. Selected characteristics of study population by use of antiresorptive therapy*

Characteristic	Nonusers (n = 604)	Antiresorptive users (n = 214)	*P*
Age, mean ± SD years	74.78 ± 2.94	74.81 ± 2.90	0.90
Race, no. (%)			<0.01
White	253 (41.9)	158 (73.8)	
African American	351 (58.1)	56 (26.2)	
Study site, no. (%)			<0.01
Memphis	271 (44.9)	122 (57.0)	
Pittsburgh	333 (55.1)	92 (43.0)	
BMI, mean ± SD kg/m^2	28.78 ± 5.62	26.35 ± 4.73	<0.01
Current smoker, %	9.1	8.4	0.75
Knee extensor strength, mean ± SD maximum torque, Nm	80.35 ± 22.67	75.53 ± 21.34	0.01
NSAID use, %	48.8	55.6	0.09
Thiazide use, %	24.8	29.0	0.24
BMD of total hip, mean ± SD gm/cm^2	0.817 ± 0.147	0.788 ± 0.144	0.19
T score ≤ −2.5, %	78.5	74.8	0.26
Calcium supplementation, %	21.0	33.6	<0.01
Self-report of osteoporosis, %	8.9	5.6	0.13
Self-report of fracture after age 45 years, %	20.4	20.7	0.93
Use of walking device, %	7.4	4.2	0.11

* BMI = body mass index; NSAID = nonsteroidal antiinflammatory drug; BMD = bone mineral density.

symptoms ($P = 0.14$), nor between overall antiresorptive use and the presence or absence of radiographic OA in the tibiofemoral ($P = 0.60$) or patellofemoral ($P = 0.31$) compartments or whole knee ($P = 0.31$), after adjustment for covariates (data not shown).

There was no association between individual antiresorptive drug use (estrogen, raloxifene, or bisphosphonates) and the presence or absence of knee symptoms ($P \geq 0.22$ for all drugs), nor between individual antiresorptive drug use and the presence or absence of radiographic OA in the tibiofemoral ($P \geq 0.90$ for all drugs) or patellofemoral ($P \geq 0.12$ for all drugs) compartments or whole knee ($P \geq 0.43$ for all drugs), after adjustment for covariates. Models were also run following the exclusion of black women from the analyses; this did not change any of the radiographic findings (data not shown).

The score ranges for the knee OA features

Table 2. Association between antiresorptive use and the combination of knee pain and radiographic evidence of osteoarthritis (OA)

Radiographic OA and knee pain status	No.	% antiresorptive users	*P*, vs. reference*
Tibiofemoral OA			
No knee pain/no radiographic OA	128	32.0	Reference
No knee pain/radiographic OA	31	16.1	0.63
Knee pain/no radiographic OA	262	24.8	0.21
Knee pain/radiographic OA	245	21.6	0.29
Patellofemoral OA			
No knee pain/no radiographic OA	135	31.1	Reference
No knee pain/radiographic OA	23	13.0	0.61
Knee pain/no radiographic OA	311	25.1	0.21
Knee pain/radiographic OA	198	20.2	0.37
Whole knee OA			
No knee pain/no radiographic OA	113	33.6	Reference
No knee pain/radiographic OA	45	15.6	0.63
Knee pain/no radiographic OA	206	25.7	0.20
Knee pain/radiographic OA	302	21.5	0.31

* Adjusted for age, race, study site, body mass index, use of nonsteroidal antiinflammatory drugs, use of thiazides, calcium supplementation, bone mineral density of the total hip, current smoking status, knee extensor strength, self-report of osteoporosis, self-report of fracture after age 45 years, and use of walking device.

Table 3. Knee osteoarthritis (OA) magnetic resonance imaging features and WOMAC scores by use and type of antiresorptive therapy*

Knee OA feature (score range)	Nonusers (645 knees)	Antiresorptive users (253 knees)†	Antiresorptive agent		
			Estrogen (178 knees)	Bisphosphonate (57 knees)	Raloxifene (18 knees)
Bone attrition (0–23)	2.0 ± 3.0	1.4 ± 2.9	1.4 ± 2.7	0.6 ± 1.3‡	3.9 ± 6.2
Osteophytes (0–85)	13.5 ± 14.4	9.8 ± 14.3	9.4 ± 13.2	6.9 ± 8.8	23.4 ± 26.9
Bone marrow abnormality (0–20)	2.6 ± 3.3	1.5 ± 2.6	1.5 ± 2.4	1.0 ± 1.7	3.8 ± 5.1
Cartilage lesions (0–78)	17.5 ± 16.0	13.6 ± 14.1	12.9 ± 13.7	14.1 ± 13.6	18.6 ± 18.6
WOMAC (0–18)	3.3 ± 4.5	3.0 ± 4.4	2.9 ± 4.4	2.9 ± 4.2‡	4.5 ± 4.8

* Values are the mean ± SD score. WOMAC = Western Ontario and McMaster Universities Osteoarthritis (Index).
† Estrogen, bisphosphonates, and raloxifene combined.
‡ $P < 0.05$ for linear regression coefficient for bisphosphonate users compared with nonusers, adjusted for age, race, study site, body mass index, use of nonsteroidal antiinflammatory drugs, use of thiazides, calcium supplementation, bone mineral density of the total hip, current smoking status, knee extensor strength, self-report of osteoporosis, self-report of fracture after age 45 years, and use of walking device.

assessed in our population are shown in Table 3. There were no significant differences in WORMS values for bone attrition, osteophytes, bone marrow abnormality, and cartilage lesions between users of all antiresorptive drugs combined compared with nonusers, after adjustment for covariates (Table 3). When the evaluation was focused on specific types of antiresorptive drugs, bisphosphonate use was associated with lower WORMS values for bone attrition as compared with that in the nonuse group (Table 3). There were no differences in total cartilage lesions by use of individual antiresorptive drugs as compared with nonusers. Among the African American group of bisphosphonate users, there were no significant differences compared with white bisphosphonate users in any MRI severity score ($P > 0.33$ for all parameters) (data not shown). WOMAC pain scores also did not differ by overall antiresorptive drug use (Table 3). However, after adjustment for covariates, bisphosphonate use was associated with significantly lower WOMAC pain scores compared with nonuse ($P = 0.02$) (Table 3).

When MRI feature scores were dichotomized by the presence of any knee OA feature abnormality, overall antiresorptive use, compared with nonuse, was associated with a significantly decreased likelihood (after adjustment for covariates) of having subchondral bone attrition and subchondral bone marrow abnormalities (Table 4). When comparing users of specific antiresorptive agents with nonusers of antiresorptives (Table 4), there was also a significantly decreased likelihood (after adjustment for covariates) of having bone attrition and bone marrow abnormalities in the estrogen users and bone marrow abnormalities in the bisphosphonate users. After adjustment for covariates, raloxifene use was not significantly associated with any MRI feature. Models were also run after exclusion of African American women from the analyses; bisphosphonate use remained significantly associated with fewer bone marrow abnormalities ($P < 0.01$), and a trend toward significance was observed in estrogen users ($P = 0.06$).

The mean duration of estrogen use was 13.8 years (range <1–45 years), and the mean duration of alendronate and raloxifene use was 1.8 years (range <1–4 years) and 0.3 years (range <1–1 years), respectively. To

Table 4. Adjusted odds ratios (95% confidence intervals) for the presence of knee osteoarthritis (OA) magnetic resonance imaging features by use and type of antiresorptive therapy*

Knee OA feature	Nonusers (645 knees)	Antiresorptive users (253 knees)	Antiresorptive agent		
			Estrogen (178 knees)	Bisphosphonate (57 knees)	Raloxifene (18 knees)
Bone attrition (46.5% of knees)	1.00	0.41 (0.21–0.84)†	0.36 (0.17–0.79)†	0.37 (0.08–1.71)	1.09 (0.19–6.19)
Osteophyte (80.3% of knees)	1.00	0.57 (0.37–2.44)	0.94 (0.33–2.63)	1.48 (0.19–11.76)	0.35 (0.07–1.77)
Bone marrow abnormality (59.9% of knees)	1.00	0.45 (0.22–0.89)†	0.48 (0.23–1.00)†	0.11 (0.01–0.89)†	0.87 (0.15–5.07)
Cartilage lesions (86.4% of knees)	1.00	1.32 (0.50–3.53)	1.50 (0.48–4.64)	0.97 (0.18–5.25)	0.70 (0.07–7.18)

* Adjusted for age, race, study site, body mass index, use of nonsteroidal antiinflammatory drugs, use of thiazides, calcium supplementation, bone mineral density of the total hip, current smoking status, knee extensor strength, self-report of osteoporosis, self-report of fracture after age 45 years, and use of walking device, compared with nonusers. (Cartilage models do not include use of walking device due to missing data.)
† $P \leq 0.05$ for logistic regression coefficient from adjusted models.

determine the effect of duration of use of antiresorptive drugs on MRI parameters and WOMAC pain scores, duration of use was dichotomized into short-term and long-term use, with the median duration of use of all antiresorptive drugs (6 years) as the cutoff. Among estrogen users, duration of use was not associated with the presence of any MRI lesions ($P > 0.14$, using logistic regression for all parameters) but did affect the severity of bone attrition and bone marrow abnormalities by MRI, with women whose duration of estrogen use was longer (≥6 years) having less bone attrition ($P = 0.05$, using linear regression) and less bone marrow abnormalities ($P < 0.01$, using linear regression). There was no effect of duration of estrogen use on WOMAC scores ($P = 0.15$). There was too little variability in duration of alendronate or raloxifene use to evaluate the effects of their long-term use on MRI and WOMAC parameters.

DISCUSSION

In this cross-sectional analysis of elderly African American and white female participants from the Health ABC Study, use of bone antiresorptive agents was associated with significantly fewer subchondral bone attrition and bone marrow abnormalities of the knee, as assessed by MRI, suggesting a potential beneficial effect on knee OA. These findings were consistent for the 2 most commonly used antiresorptive agents, estrogen and alendronate, despite adjustment for covariates related to the indication for antiresorptive treatment, including BMD and fracture history, that may alter the risk of knee OA or its progression. In addition, women reporting alendronate use had lower WOMAC knee pain scores compared with nonusers.

The biologic mechanisms by which antiresorptive agents, including estrogen, alendronate, and raloxifene, may theoretically have beneficial effects on OA are multifactorial, and may include decreasing subchondral bone resorption, one of the earliest changes of OA (13,14), as well as potential effects on inflammation (16–18). Subchondral bone in OA increases in material content but is mechanically weaker (13). Estrogen may also have direct effects on cartilage in OA by increasing production of insulin-like growth factor binding proteins and the synthesis of proteoglycans by chondrocytes (41–43). Tamoxifen, a SERM, also increases proteoglycan and prostaglandin production by cartilage (44).

In addition, inflammation may play a significant role in OA (15), since both knee effusions and synovial thickening are more frequent in patients with knee pain than in those without knee pain (45). Estrogen may have antiinflammatory properties and may prevent induction of inducible nitric oxide synthase and other components of inflammation (16), although some reports suggest that estrogen can also increase concentrations of C-reactive protein and increase inflammation (46,47). In another report, tamoxifen was shown to have effects on inflammatory markers by reducing C-reactive protein and fibrinogen levels in women (48). Bisphosphonates may have direct antiinflammatory effects (17,18). In particular, clodronate, a bisphosphonate, was shown to reduce synovial fluid levels of an inflammatory mediator, prostaglandin E_2 (49). However, we are not aware of evidence showing that alendronate has an antiinflammatory effect.

We found no effect of antiresorptive agent use on the presence of radiographic knee OA, including tibiofemoral, patellofemoral, and whole-knee OA, nor on the presence of knee symptoms of OA. Previous studies of the effects of estrogen use on knee OA have had conflicting results, with some studies suggesting a beneficial effect of estrogen use on radiographic changes of knee OA (19–22), while others have shown no benefit (24,25). To our knowledge, we are the first to explore the association of alendronate and raloxifene use with radiographic changes of OA. A recent report from a randomized controlled trial of 1 year's duration, comparing placebo, risedronate 5 mg once a day, and risedronate 15 mg once a day, suggests that this bisphosphonate may have beneficial effects on radiographic changes of OA of the knee as well as on symptoms measured by visual analog scale (28). However, the preliminary results, to date, from a larger, ongoing randomized controlled trial of risedronate and OA of the knee do not support a benefit of the use of risedronate on radiographic or WOMAC scores in patients with OA (27). Use of risedronate was not reported by any subjects in our study.

No previous study, to our knowledge, has examined the effect of antiresorptive drug use on radiographic changes of OA in the tibiofemoral and patellofemoral compartments separately. The importance of analyzing both patellofemoral and tibiofemoral OA has been underscored by several studies, which suggest that patellofemoral OA is common. Patellofemoral OA may occur in the absence of tibiofemoral disease (50), and the pathogenesis of tibiofemoral and patellofemoral OA may differ (51).

MRI may be superior to radiography in detecting OA pathology, because it provides direct multiplanar tomography with high spatial resolution and soft-tissue detail. In particular, MRI can identify areas of cartilage

loss in the knee (52,53). In our study, we found no association of any antiresorptive drug use with cartilage lesion scores assessed by the WORMS method (38). Although one cross-sectional study demonstrated that estrogen use was associated with greater tibial cartilage volume compared with nonuse (19), another, more recent longitudinal study did not make this observation (30). Moreover, in another study, estrogen users were not shown to have greater patellar volume than nonusers (31). We are not aware of other studies in which the effects of bisphosphonate use on cartilage volume by MRI are reported.

Our study is the first to demonstrate an association of alendronate and estrogen use with decreased subchondral bone attrition and bone marrow abnormalities of the knee as assessed by MRI. The importance of MRI bone marrow abnormality scores has recently been highlighted in studies that suggested that they are a strong predictor of progression of structural deterioration in knee OA (54,55). In addition, another report has suggested that bone marrow abnormalities on MRI are strongly associated with the presence of pain in knee OA (11). Although we found no significant association of use of alendronate or any antiresorptive agent with osteophyte scores, a recent study has suggested that in an animal model, osteophytes are significantly reduced with alendronate use (56).

The lack of a consistent association of joint pain with structural features of OA (57) makes it imperative to include measures of pain and its severity when studying the impact of drug therapy on OA. The WOMAC provides a reliable measure of the severity of activity-related pain in knee OA (58,59). We did not find an association of estrogen use with the presence or severity of knee pain, a finding consistent with the results of one randomized trial of estrogen replacement therapy (60). We found that alendronate use was associated with less severity of knee pain as assessed by WOMAC scores. In support of this, symptomatic relief of erosive OA of the hands (61) and OA of the knee with back or joint pain (62), as assessed by visual analog scale and visual rating scale, has been reported with clodronate and etidronate, two bisphosphonates which were not included in our study.

Our study has several limitations. Antiresorptive users, and especially those taking bisphosphonates, are more likely to have low BMD and osteoporosis, which may protect these individuals from the development of OA (63,64). Although our analyses were adjusted for hip BMD and history of fractures, the possibility of confounding by indication remains. There were few African American women who reported use of antiresorptive agents, particularly bisphosphonates, in this study; however, the African American women did not have more severe disease than did the white women, and similar trends in the findings were present when African American women were excluded from the analysis. Nevertheless, due to the small numbers of African American women who were antiresorptive users, more data would be needed before any definitive statements could be made about the relationship of antiresorptive drug use to OA in African American women.

We analyzed each individual drug, and duration of use for estrogen. There were too few long-term ($\geq$6 years) users of alendronate (n = 13) or raloxifene (none) to analyze the effects of duration of use of these agents on MRI findings and WOMAC scores. This situation occurred most likely because these agents had only recently become available when the Health ABC Study was launched. Different relationships might be observed if the drugs had been taken for longer periods of time. Collagen markers were not obtained in this study; therefore, the effect of antiresorptive agent use on collagen markers could not be assessed. In addition, alendronate was the only bisphosphonate being taken by our study population, and other bisphosphonates might be associated with different results.

We recognize that the standard deviations are large in Table 3, reflecting somewhat skewed distributions of MRI features. Therefore, we also dichotomized the MRI scores and analyzed the data by logistic regression (Table 4). The differences observed for the presence of bone marrow edema–like lesions may be clinically important, since previous studies have shown that these lesions assessed by MRI are associated strongly with knee pain and structural progression (54,55). However, whether the differences in bone attrition are clinically significant requires further research. Finally, we only assessed the knee joint in our study; other joints, particularly non–weight-bearing joints, might be influenced differently by antiresorptive agent use.

In conclusion, our study has shown that older women who were receiving estrogen or alendronate had significantly fewer OA-related subchondral bone abnormalities in the knee, including bone attrition and bone marrow edema–like abnormalities, compared with women who were not taking any bone antiresorptive drugs. Those receiving alendronate also had less knee pain (as indicated by WOMAC scores) compared with nonusers. However, there was no association of either alendronate use or estrogen use with changes in cartilage lesions, and no association of use of another

antiresorptive agent, raloxifene, with any structural findings of knee OA or knee symptoms. Our study suggests that alendronate and estrogen may protect against the development of bone abnormalities associated with knee OA, which may have a beneficial effect on the overall course of the disease. Further studies with longitudinal data and randomized trials are needed to evaluate the potential of using alendronate, estrogen, and other bone antiresorptive agents for the prevention or treatment of knee OA.

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