Bone Mineral Density in Older Adult Patients with Rheumatoid Arthritis: An Analysis of NHANES III

MITSUYO KINJO, SOKO SETOGUCHI, and DANIEL H. SOLOMON

ABSTRACT. ***Objective.*** Several studies suggest that bone mineral density (BMD) is reduced in rheumatoid arthritis (RA). However, it is unclear whether this relationship holds in a representative community-based typical RA population. We examined the relationship between BMD and RA in a representative US population-based sample from the Third National Health and Nutrition Examination Survey (NHANES III: 1988-1994).

Methods. We selected subjects over age 60 with RA from NHANES III using previously described methods. Femoral neck BMD (FN-BMD) measured by dual-energy x-ray absorptiometry was compared for the RA (n = 106) and non-RA cohorts (n = 4,277). Multivariable linear regression models included known risk factors for osteoporosis. Further adjusted analyses compared the BMD among subgroups of patients with RA, such as those taking methotrexate (MTX), those with positive rheumatoid factor (RF), and those with elevated C-reactive protein (CRP).

Results. Patients with RA more frequently reported poor health, a history of falling, cognitive impairment, early menopause, a history of chronic obstructive lung disease, higher total calcium intake, and thiazide use than the non-RA subjects (all $p < 0.05$). Adjusted FN-BMD was similar between the patients with RA (0.71 g/cm^2) and non-RA subjects (0.72 g/cm^2; $p = 0.5$). Among patients with RA, reduced BMD tended to be seen with MTX use (0.60 g/cm^2, $p = 0.07$), CRP above 1 mg/dl (0.66 g/cm^2, $p = 0.09$), and positive RF in female patients (0.68 g/cm^2, $p = 0.056$). However, none of these findings reached statistical significance.

Conclusions. Among a US population-based representative sample, FN-BMD was similar in RA and non-RA patients. Several characteristics of patients with RA may be associated with reduced BMD. (First Release Sept 15 2007; J Rheumatol 2007;34:1971–5)

Key Indexing Terms:
BONE DENSITY | RHEUMATOID ARTHRITIS | NHANES III
METHOTREXATE | C-REACTIVE PROTEIN

There are data suggesting an association between rheumatoid arthritis (RA) and osteoporosis[1,2]. Possible reasons for RA patients to have reduced bone mineral density (BMD) include inflammation, reduced physical activity, and medications[3,4]. Inflammatory cytokines may play an important role in the localized bone destruction of RA[5,6] and may also accelerate generalized bone loss[7]. Systemic signs of inflammation, presence of rheumatoid factor (RF), and greater disability have been shown to predict lower BMD in prior studies[1,8]. An association between glucocorticoid use and reduced BMD among patients with RA has been suggested[8,9], but low-dose glucocorticoids may retard disease-related bone loss by suppressing inflammation[10].

Previous studies of osteoporosis in RA consist of patients from referral centers[10-12] or several population-based cohorts[1,13-16]. We compared BMD among RA and non-RA subjects in the Third National Health and Nutrition Examination Survey (NHANES III: 1988-1994), a representative US population-based sample. We also examined the association of several RA-related factors with reduced BMD.

MATERIALS AND METHODS

Data source. NHANES III was conducted by the US National Center for Health Statistics of the Centers for Disease Control and Prevention between 1988 and 1994. The sample represents the civilian, noninstitutionalized population in the 50 United States[11]. Subjects aged ≥ 60 years had a standardized joint examination. We chose to examine subjects in this age group who had undergone dual-energy x-ray absorptiometry (DEXA) of the femoral neck and thus had femoral neck bone mineral density (FN-BMD) data available.

Definition of RA and non-RA cohort. We identified subjects with RA by described methods[12]. Only 5 of the 7 components of the American College of Rheumatology (ACR) criteria for RA were available in NHANES III[13]: morning stiffness, presence of 3 or more joints swelling, hand arthritis, symmetrical arthritis, and rheumatoid nodule. Anteroposterior radiographs of the hands and wrists were substituted by the presence of metacarpophalangeal swelling

From Teine Keijinkai Hospital, Teine-ku Sapporo city, Japan; and Divisions of Pharmacoepidemiology and Rheumatology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA.

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M. Kinjo, MD, MPH, Teine Keijinkai Hospital; S. Setoguchi, MD, DrPH, Msc, Division of Pharmacoepidemiology; D.H. Solomon, MD, MPH, Divisions of Pharmacoepidemiology and Rheumatology, Brigham and Women's Hospital.

Address reprint requests to Dr. M. Kinjo, Teine Keijinkai Hospital, 1-40 Maeda 1 jou 12 chome, Teine-ku, Sapporo, Hokkaido 006-8555, Japan. E-mail: mitsuyos220@worldnet.att.net

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on examination. If subjects had missing RF titers, the presence of wrist swelling on examination substituted this criterion. Previous methods[12] employ a decision tree algorithm using self-reported RA status, the 5 ACR criteria, and use of disease modifying antirheumatic drugs (DMARD) including auranofin, gold sodium thiomalate, methotrexate (MTX), azathioprine, penicillamine, sulfasalazine, chloroquine phosphate, and hydroxychloroquine sulfate. Based on those validated methods, subjects regardless of self-reported RA present were considered to have RA if they were using DMARD and met at least one ACR criterion or if they met 3 of 5 of these available criteria. Subjects who self-reported RA and took DMARD were also considered as having RA. Subjects in the non-RA cohort included those without any of the available ACR criteria, who did not self-report RA, and did not report DMARD use. A group of patients with ambiguous clinical criteria were left unclassified by this method (e.g., patients with no criteria who were receiving DMARD, patients with 1 or 2 criteria but no DMARD, and patients with no criteria or DMARD, who self-reported RA).

Covariates. Demographic and medical risk factors predictive of reduced BMD were considered potential confounders. In addition to sex, age, and race, other important covariates included: body mass index (BMI) (kg/m^2), smoking (current vs former or never), alcohol intake (number of drinks in the prior month), self-reported health (poor vs other), history of hip or wrist fracture, and history of fall within the previous year. We also noted the following chronic medical conditions: myocardial infarction, congestive heart failure, peripheral vascular disease, stroke, hemiparesis, diabetes, nonintegumentary cancer, and chronic obstructive pulmonary disease (COPD). Cognitive impairment was assessed by either a physician's impression or East Boston Memory Test for recent memory (2 or fewer recalls with 6 questions)[14]. We also assessed menopause before age 40, serum 25-hydroxy-vitamin D level (ng/ml), and total calcium intake (combined dietary and supplements, in mg/day). Medication use 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?" and each medication container was checked by the interviewer. Medications such as thiazide diuretics, hormone replacement therapy (HRT), and oral glucocorticoids were considered. Participants were also asked to report a health problem and duration for the medication they take.

RA disease variables such as MTX use, serum C-reactive protein (CRP) level determined by latex-enhanced nephelometry[15], RF measured by the Singer-Plotz latex agglutination test[15], and RA disease duration in years were available for analyses. In addition, daily physical activity was assessed with a Health Assessment Questionnaire (HAQ), with a score 0–3 based on 6 out of 8 categories in the HAQ, higher score indicating greater disability[16].

Statistical analysis. Femoral neck BMD (FN-BMD) measured by DEXA (Hologic QDR 1000, Waltham, MA, USA) was the primary outcome for all analyses[17]. The BMD at other anatomical sites was not available in NHANES III. Baseline characteristics of patients with RA and non-RA subjects were compared by Student's t-test for continuous variables and Pearson's chi-square test for categorical variables. We used a multivariable linear regression model to assess the relationship between RA and BMD. Regression models included age, sex, and all non-RA related factors for osteoporosis when comparing RA and non-RA. In the primary models, RA-related factors such as MTX use, CRP, RF, daily physical activity, and RA disease duration were not included because these variables may mediate the effect of RA on BMD. These RA-related factors were included in an analysis restricted to the RA cohort.

To determine whether our results were sensitive to the definition of RA, we repeated our analyses on the subjects who had at least 3 ACR criteria for RA. All analyses were run in SAS (Cary, NC, USA).

RESULTS

The eligible cohort included 6,596 participants 60 years or older. We identified 144 (2%) subjects with RA and 4,802 (73%) without RA, and the remaining 1650 (25%) subjects could not be classified. Our analysis was limited to the 106 subjects with RA and 4,277 controls who underwent DEXA. There were no significant differences in patient characteristics between those with and without DEXA (data not shown). Among those with a BMD measurement, the baseline characteristics were compared between the RA and non-RA cohorts (Table 1). Patients with RA more frequently reported many health conditions, including poor health, a history of falls, cognitive impairment, menopause before age 40, and COPD. They also noted higher total calcium intake, more frequent thiazide use, and poorer physical activity (all p values < 0.05). The distribution of age, sex, race, BMI, smoking, alcohol, history of hip or wrist fractures, comorbid illnesses, serum 25-hydroxy-vitamin D level, and HRT use was similar between RA and non-RA subjects. Among patients with RA, 11 (10%) took glucocorticoids, 5 (5%) took MTX, and 33 (31%) had positive RF; the mean disease duration was 11.3 years. Median duration of oral glucocorticoid use was 1095 days in patients with RA.

Unadjusted FN-BMD was lower for the RA (0.69 g/cm^2) than the non-RA cohort (0.72 g/cm^2, p = 0.069). However, after adjustment for all available relevant covariates, patients with RA had FN-BMD (0.71 g/cm^2) similar to that of non-RA subjects (0.72 g/cm^2; p = 0.5) (Table 2). We analyzed the relationship between disease-related variables and FN-BMD among patients with RA (Table 3): those who used MTX had a trend toward lower FN-BMD (0.60 g/cm^2) than those not

Table 1. Baseline characteristics of subjects with and without rheumatoid arthritis.

Variable	Non-RA, n = 4277	RA, n = 106
Age, yrs	71.7 ± 8.1	73.1 ± 8.1
Female	2134 (50)	60 (57)
Caucasian	2528 (59)	68 (64)
Body mass index, kg/m^2	26.9 ± 4.9	26.3 ± 5.0
Tobacco, current use	651 (15)	12 (11)
Alcohol, drinks/mo	9.3 ± 30.0	9.2 ± 29.4
Self-reported health, poor	329 (8)	21 (20)†
Hip or wrist fracture	459 (10)	12 (11)
Fall, at least 1 in previous year	940 (22)	36 (34)†
Chronic obstructive pulmonary disease	620 (15)	26 (24)†
Cognitive impairment*	784 (18)	29 (27)†
Menopause before age 40 yrs	445 (21)	18 (30)†
Serum 25(OH) vitamin D, ng/ml	26.5 ± 10.5	26.9 ± 10.6
Total calcium intake, mg/day	702 ± 481	738 ± 513†
Hormone replacement therapy use	129 (3)	4 (4)
Thiazide diuretic use	618 (14)	24 (22)†
Oral glucocorticoid use	78 (2)	11 (10)†
Methotrexate use	0 (0)	5 (5)†
Serum C-reactive protein, mg/dl	0.4 ± 1.0	0.8 ± 1.4†
Rheumatoid factor present	231 (5)	33 (31)†
Physical function score**	0.4 ± 0.3	0.7 ± 0.4†

* Physician's impression or East Boston Memory Test for recent memory (2 or less recall with 6 questions). ** 6 out of 8 categories in Health Assessment Questionnaire, average score range 0–3, higher score indicating worse disability. † p ≤ 0.05 compared with non-RA.

Table 2. Femoral neck bone mineral density (g/cm^2) among non-RA and RA subjects.

	Non-RA, n = 4277	RA, n = 106	p
Unadjusted	0.72 (0.71, 0.72)	0.69 (0.66, 0.71)	0.069
Age, sex adjusted	0.72 (0.71, 0.72)	0.71 (0.68, 0.73)	0.4
Fully adjusted*	0.72 (0.71, 0.72)	0.71 (0.68, 0.73)	0.5

Values are mean (95% confidence interval). * Adjusted for age, sex, race, number of comorbidity, chronic obstructive lung disease, smoking, alcohol, self-reported health, hip and wrist fracture, fall, menopause before age 40, cognitive impairment, BMI, exercise, serum vitamin D level, total calcium intake, use of glucocorticoid, hormone replacement therapy, and thiazide diuretics.

Table 3. Femoral neck bone mineral density (BMD, g/cm^2) in subgroups of patients with RA by methotrexate use, CRP level, and RF status.

RA Variable	N	BMD	p
Methotrexate use*			
No use	101	0.70 (0.68, 0.71)	
Current use	5	0.60 (0.51, 0.70)	0.07
CRP**, mg/dl			
0–0.99	74	0.70 (0.68, 0.72)	
1.0–8.9	23	0.66 (0.61, 0.70)	0.09
RF status†			
Negative	65	0.70 (0.68, 0.73)	
Positive	33	0.67 (0.63, 0.70)	0.11

Values are mean (95% confidence interval). All models were adjusted for age, sex, race, BMD, comorbidity, chronic obstructive lung disease, smoking, alcohol, self-reported health, hip and wrist fracture, fall, menopause before age 40 yrs, cognitive impairment, serum vitamin D level, total calcium intake, use of glucocorticoid, hormone replacement therapy, and thiazide diuretics. * Additional adjustment for CRP, RF, physical function, and disease duration. ** Data for 9 subjects are missing; additional adjustment for methotrexate use, RF, physical function, and disease duration. † Data for 8 subjects are missing; additional adjustment for methotrexate use, CRP, physical function, and disease duration.

using MTX (0.70 g/cm^2, p = 0.07). A similar trend toward lower BMD was seen in patients with CRP ≥ 1 mg/dl (BMD = 0.66 g/cm^2) versus CRP < 1 (BMD = 0.70 g/cm^2, p = 0.09), as well as among those who were RF positive (0.67 g/cm^2) compared with those who were RF negative (0.70 g/cm^2, p = 0.11). Women who were RF positive had lower FN-BMD (0.63 g/cm^2) than those who were RF negative (0.68 g/cm^2, p = 0.056).

In multivariable analysis among patients with RA, predictors for reduced BMD included female sex, lower BMI, and no use of thiazide or HRT (all p values < 0.01) (Table 4). When the multivariable model was repeated on subjects who had strictly defined criteria for RA present (n = 88), our findings were unchanged, indicating that these results were not sensitive to the definition of RA. Further, we have re-analyzed data including the unclassified subjects in the non-RA cohort; the reclassification does not change our results (FN-BMD: RA 0.71 g/cm^2 vs non-RA 0.72 g/cm^2, p = 0.6). To examine the effect of vitamin D, a subgroup analysis on subjects with normal serum vitamin D levels above 30 ng/ml (n = 1,424) also showed no association between RA and FN-BMD.

Table 4. Adjusted association between femoral neck bone mineral density (BMD, g/cm^2) and relevant covariates among patients with rheumatoid arthritis.

Covariate	Difference in BMD*, g/cm^2	p
Age, per 5 yrs	–0.007 (–0.023, 0.010)	0.4
Female (vs male)	–0.103 (–0.154, –0.052)	≤ 0.001
Caucasian (vs others)	–0.029 (–0.081, 0.024)	0.29
Body mass index (per + 1 kg/m^2)	0.009 (0.005, 0.013)	≤ 0.001
Current tobacco use (vs others)	–0.038 (–0.026, 0.104)	0.2
Self-reported health, poor (vs others)	–0.006 (–0.064, 0.0531)	0.2
Hip fracture (vs none)	–0.015 (–0.035, –0.054)	0.7
Cognitive impairment (vs none)	–0.040 (–0.089, 0.008)	0.1
Serum 25(OH) vitamin D (per + 1 ng/ml)	0.001 (–0.001, 0.003)	0.17
Total calcium intake (per + 100 mg/day)	0.001 (0.0003, 0.0001)	0.017
Thiazide use (vs no use)	0.103 (0.055, 0.151)	≤ 0.001
Hormone therapy (vs no use)	0.096 (0.009, 0.183)	0.003
Oral glucocorticoid use (vs no use)	0.001 (–0.066, 0.068)	0.9
Methotrexate use (vs no use)	–0.067 (–0.167, 0.032)	0.07
CRP ≥ 1 mg/dl (vs < 1 mg/dl)	–0.047 (–0.099, 0.006)	0.09
Poor physical function ** (vs better)	–0.025 (–0.083, 0.034)	0.4
Positive rheumatoid factor (vs negative)	–0.037 (–0.084, 0.009)	0.11
Disease duration (per 10 yrs)	–0.011 (–0.004, 0.026)	0.4

Values are mean (95% confidence interval); these estimates were generated using multivariate linear regression model. Osteoporotic risk factors (non-RA factors) and all RA risk factors are shown. * The differences in BMD are equal to the beta coefficients estimated in the model. ** Median physical function score or higher (6 out of 8 HAQ score, 0–3, higher score indicating poor function).

DISCUSSION

In a representative US cohort, we found no significant differences in FN-BMD among patients with RA ≥ 60 years of age compared within non-RA subjects. Among patients with RA, MTX use, higher CRP, and presence of RF appear related to reduced FN-BMD. Our results differ somewhat from prior work that showed lower BMD in patients with RA than in healthy controls. Several of these studies concentrated on RA populations from referral centers[18-20] who often have more severe disease with higher levels of inflammation and more frequent use of glucocorticoids. Our findings are not surprising if referral bias overestimates the relationship between BMD and RA. The NHANES sample may be more representative of RA in the general population than previous populations studied. Subjects in NHANES had less severe RA than the RA population in other studies[21]. Only 30% of the patients

with RA in NHANES III had positive RF and the interquartile range of CRP was 0–0.99 mg/dl (median = 0), raising the possibility that some of the RA patients did not actually have RA. We followed described methods of selecting for RA[12], and the prevalence of RA in our population was similar to that reported in earlier studies[22,23]. When we conducted sensitivity analysis for strictly defined RA subjects who met at least 3 ACR criteria, our results were unchanged.

Population-based studies from Finland and Norway[1,24] comparing RA patients with non-RA controls showed reduced BMD at spine and hip in RA. However, these studies used controls from distinct populations that did not necessarily mirror the demographics of their RA cohorts. Using non-RA controls from distinct sources may introduce bias from unmeasured confounders such as different ethnicity and geography[25,26]. Since the NHANES III is a population-based random sample, such bias is unlikely. A report from the Study of Osteoporotic Fractures Research Group showed that the total hip BMD was not significantly reduced in the subgroup of patients with RA using steroids compared with non-RA controls[27], which is consistent with our observations. Another source of the apparent discrepancy between our study and previous ones may be that we studied FN-BMD, whereas others examined different anatomic sites.

RA disease variables such as active inflammation, positive RF, immobility, and use of glucocorticoids have been associated with reduced BMD in RA[10,28,29]. Our results suggest that MTX use, higher CRP, and positive RF may be associated with reduced bone mass in patients with RA in NHANES. Chronic inflammation may contribute to increased bone turnover resulting in reduced bone mass[30,31]. Upregulation of inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor-α in RA increases CRP and induces bone resorption via osteoclast upregulation.

Fragility fractures have been reported in patients receiving MTX for chemotherapy or longterm use for rheumatic disease[32-34]. More recent studies suggest that MTX exerts minimal effect on bone mass[34,35]. Our patients with RA who took MTX appear to have lower BMD than who did not. Our methodology does not allow us to address whether MTX directly affected bone or MTX use was simply a marker for more active disease. Yet, CRP levels were not different between RA subjects taking MTX and those not. Taking MTX may be a surrogate marker for severe activity with longer disease duration but better controlled activity at the time of the study, which would be associated with lower BMD.

Several limitations in our study merit discussion. First, causal associations between factors cannot be inferred in a cross-sectional study. RA disease activity changes over time and the cumulative effects of inflammation may affect BMD. Serial evaluation of patients with active disease might produce different results. Nonetheless, in our cross-sectional study, we found a possible association between RA disease characteristics and FN-BMD. Second, medication dosages were not recorded in NHANES III. Thus, cumulative effect of oral glucocorticoids on BMD cannot be assessed. Third, our RA cohort is limited to those aged ≥ 60 because of the availability of examination data. Our results may not be generalizable to RA patients younger than 60 years old. Finally, about one-fourth of the study sample could not be classified as either RA or non-RA, and this might have potential influence on our finding. When we included the unclassified subjects in non-RA, the results were unchanged.

Our study has important strengths. We studied a large representative population-based sample with standardized data collection including a representative cross section of typical RA patients, not only those attending academic rheumatology practices. Many important variables were considered in this analysis, and the associations between several disease-related covariates and bone loss are notable. Our results are also free from a confounding effect of bisphosphonate use, as these agents were not commonly prescribed at the time of this study.

FN-BMD in elderly patients with RA participating in NHANES III was similar to that in subjects without RA. Female sex, positive RF, and higher levels of CRP appeared to have more reduced FN-BMD. Although our finding may not apply to more severe RA among younger patients in referral settings or different anatomical sites, larger longitudinal studies with information on inflammation and bone turnover are needed to better define the relationship between RA and osteoporosis.

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