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ORIGINAL ARTICLE

Bone mineral density of postmenopausal women with rheumatoid arthritis depends on disease duration regardless of treatment

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Abstract The aim of this study was to determine the associations of disease activity and disease duration with the bone mineral density (BMD) in rheumatoid arthritis (RA) patients. We also evaluated the associations of biological drugs with bone loss. A total of 138 postmenopausal RA patients were retrospectively assessed to identify the associations of disease activity, disease duration, and biological drug use with BMD. We assessed the associations of disease duration, a C-reactive protein based disease activity score in 28 joints (DAS28), simplified disease activity index, clinical disease activity index, health assessment questionnaire scores, and the use of biological drugs with the lumbar spine, total hip, and femoral neck BMDs using univariate and multivariate linear regression analyses in bisphosphonate treatment and non-bisphosphonate treatment groups at 1 year of follow-up. The multivariate linear regression analyses showed that disease duration was significantly related to the BMD of the femoral neck and total hip regardless of bisphosphonate treatment. The use of biological drugs was not significantly associated with BMD. Hip BMD in postmenopausal women with RA depends on the disease duration regardless of bisphosphonate use. Biological drugs for RA treatment were not negatively associated with general bone loss.

Keywords Rheumatoid arthritis · Osteoporosis · Disease activity · Bisphosphonates · Biologics

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Introduction

Osteoporosis is a well-known complication of rheumatoid arthritis (RA) [1]. The frequencies of osteoporosis in RA patients are reported to be 15–20 % in the hip and lumbar spine [1, 2]. Osteoporosis increases the risk of fragile fractures in patients with RA [3–6]. Osteoporosis-related fractures are strongly associated with morbidity, death, and health care costs. Further, osteoporosis in RA patients may be associated with increases in inflammatory cytokine levels, decreased physical activity, and the use of glucocorticoids and disease-modifying antirheumatic drugs, in addition to the more general risk factors for osteoporosis, including age and postmenopausal status [7].

A number of studies have shown that both disease-related and demographic variables are associated with bone mineral density (BMD) in RA patients. However, the findings from studies on the risk factors for BMD loss have been somewhat inconsistent because of differences in patient selection, sample size, and study design [8–10]. Moreover, the complex interactions between disease activity, physical activity, and use of medications, including glucocorticoids, biological drugs, and bisphosphonates, may affect the BMD variables [11]. The associations between disease activity, physical activity, and generalized bone loss have not yet been reported.

Over the past decade, several biological agents have been developed with the goal of controlling RA disease activity. Many studies have reported that such agents reduce disease activity, prevent joint destruction, and improve physical activity in patients with active arthritis. Several studies have also indicated that tumor necrosis factor prevents both joint destruction and generalized bone loss [12, 13]. However, only a few reports have examined the effects of biological drugs on bone loss, and all of those

reports were based on rather small patient populations. Therefore, it remains unclear whether biological drugs can prevent generalized bone loss.

Thus, the aim of the present study was to determine the association of RA clinical parameters, including disease duration and disease activity scores, with the lumbar spine and hip BMD in postmenopausal patients. We also assessed the relationship between the use of biological drugs and the lumbar spine and hip BMD. We hypothesized that a negative association of disease duration and disease activity exists for hip BMD. We also hypothesized that biological drugs do not negatively relate to the BMD of the lumbar spine and hip.

Materials and methods

Patients

The present study was a cross-sectional, retrospective study. The protocol for this retrospective study was approved by the Institutional Review Board of Tohoku University Hospital. All patients provided written informed consent. The study population included 138 Japanese postmenopausal female patients with RA, all of whom fulfilled the American College of Rheumatology criteria (1987) for RA [14]. We included patients who had been treated with non-bisphosphonates or who had been treated with bisphosphonates for less than 3 years at the baseline. Patients were enrolled from September 2011 through August 2014 at Tohoku University Hospital. We excluded patients with parathyroid disease, chronic kidney disease, and malabsorption disease, as well as patients who had undergone parathyroid hormone treatment. We also excluded patients who had vertebral fractures from high-velocity injuries.

Assessment of RA disease activity

We measured the RA disease activity by calculating composite disease activity scores (DAS). DAS28 includes the number of swollen and tender joints (out of a total of 28), a global visual analog scale score, and the C-reactive protein level [15]. The simplified disease activity index (SDAI) and clinical disease activity index (CDAI) were also used calculated to assess disease activity [16, 17]. The Health Assessment Questionnaire (HAQ) was administered to assess functional disability [18]. All assessments were performed at the baseline and at 1 year of follow-up.

BMD, radiography, and evaluation of markers of bone metabolism

At the baseline and at 1 year of follow-up, we measured BMD (g/cm^2) in the lumbar spine (vertebrae L2–L4) and the left hip (total hip and femoral neck) by dual-energy X-ray absorptiometry using a Discovery DXA system (Hologic, Waltham, MA, USA). All procedures were performed according to the manufacturer's standardized protocols. At the baseline, the serum levels of the bone metabolism markers procollagen type 1 N-terminal propeptide and tartrate-resistant acid phosphatase 5b were also measured when BMD and RA disease activity were assessed. At the baseline, all patients were examined by thoracolumbar radiographs to detect vertebral fractures, including both painful vertebral fractures and asymptomatic morphological vertebral fractures.

Statistical methods

Comparisons between the patient groups that received bisphosphonate treatment and non-bisphosphonate treatment at the baseline were performed by the Mann–Whitney U test. To determine the associations between BMD and the clinical parameters, including age, disease duration, DAS28, CDAI, SDAI, HAQ score, and use of biological drugs, we conducted univariate and multivariate linear regression analyses on the 1-year follow-up data in the bisphosphonate treatment and the non-bisphosphonate treatment groups. We performed stepwise multivariate linear regression analyses to evaluate the significance of the relationships between the clinical parameters and total hip, femoral neck, and lumbar spine BMD to determine what variables were important and influenced the clinical outcome. Those variables selected as independent factors were analyzed by stepwise linear regression. All the statistical tests were two-sided, and p values less than 0.05 were considered statistically significant. All analyses were performed with JMP version 10 (SAS, Cary, NC, USA).

Results

Patient demographics

The study population included 138 postmenopausal female patients. The baseline characteristics of these patients, including age, sex, disease duration, BMD, any history of glucocorticoid treatment (more than 5 mg/day), and the number of previous fractures, are shown in Table 1. The patients were divided into two groups on the basis of treatment with ($n = 75$) and without ($n = 63$) bisphosphonates. Significant differences in age, BMD of the femoral neck and total hip, DAS28, and HAQ score were found between the two groups (Table 2). The BMD of the femoral neck and total hip, DAS28, and HAQ score were significantly higher in the group treated with bisphosphonates. However, patients in the bisphosphonate treatment group had severer

restrictions of their physical activity and less bone loss at the baseline. In both groups, the amount of bone loss in the lumbar spine was less than the amount of bone loss in the femoral neck and total hip. Any degenerative changes in the spine would affect the lumbar spine BMD measurement, leading to differences in the amount of bone loss between the hip and the spine. These results suggested that the total hip and femoral neck BMDs reflected the generalized bone loss in these postmenopausal RA patients.

Table 1 Baseline characteristics of the patient cohort ($n = 138$)

Patient characteristics	Values
Mean age (years)	68.2 (9.8)
Mean disease duration (years)	14.1 (8.7)
Disease activity	
DAS28	2.4 (0.8)
SDAI	6.9 (4.5)
CDAI	6.4 (4.7)
HAQ score	0.82 (0.78)
Bone mineral density (g/cm^2)	
Lumbar spine	0.82 (0.18)
Femoral neck	0.63 (0.12)
Total hip	0.69 (0.14)
Glucocorticoid use	56 (40.6 %)
TRAP-5b (mU/dl)	319.5 (133.5)
P1NP (μg/l)	30.8 (14.2)
Vertebral fractures	24
Hip fractures	5

The standard deviation is given in *parentheses*, except for glucocorticoid use, where the percentage of patients is given.

CDAI clinical disease activity index, *HAQ* health assessment questionnaire, *P1NP* procollagen type 1 N-terminal propeptide, *SDAI* simplified disease activity index, *TRAP-5b* tartrate-resistant acid phosphatase 5b

Association between BMD and clinical variables in postmenopausal RA patients

The univariate linear regression analyses of the bisphosphonate treatment group showed that disease duration and age were negatively associated with the BMD of the femoral neck, disease duration and age were negatively associated with the BMD of the total hip, and age was negatively associated with the BMD of the lumbar spine (Table 3). The univariate linear regression analyses of the non-bisphosphonate treatment group showed that disease duration and HAQ score were negatively associated with the BMD of the femoral neck, disease duration and HAQ score were negatively associated with the BMD of the total hip, and no variable was negatively associated with the BMD of the lumbar spine (Table 4). The multivariate linear regression analyses of the bisphosphonate treatment group showed that disease duration and age were negatively associated with the BMD of the femoral neck and total hip and no variable was associated with the BMD of the lumbar spine (Table 5). The multivariate linear regression analyses of the non-bisphosphonate treatment group showed that disease duration was negatively associated with the BMD of the femoral neck and total hip and no variable was associated with the BMD of the lumbar spine (Table 6). These results indicated that disease duration was negatively associated with the BMD of the femoral neck and total hip regardless of bisphosphonate treatment and that the use of biological drugs was not significantly associated with BMD.

Discussion

Several previous studies showed that high HAQ scores predicted generalized bone loss in patients with established

Table 2 Clinical parameters of the bisphosphonate and non-bisphosphonate treatment groups at the baseline shown as means

Measurements	Bisphosphonate group ($n = 75$)	Non-bisphosphonate group ($n = 63$)	p
Age (years)	69.2 (10.2)	65.7 (7.8)	0.004
Femoral neck BMD (g/cm^2)	0.64 (0.17)	0.61 (0.14)	0.03
Total hip BMD (g/cm^2)	0.73 (0.13)	0.65 (0.16)	0.01
Lumber spine BMD (g/cm^2)	0.84 (0.19)	0.81 (0.21)	0.14
Disease duration (years)	14.5 (8.6)	13.6 (8.9)	0.62
DAS28	2.56 (0.88)	2.21 (0.75)	0.03
SDAI	7.64 (5.4)	6.12 (4.5)	0.19
CDAI	7.26 (5.2)	5.64 (4.7)	0.14
HAQ score	0.98 (0.82)	0.66 (0.63)	0.03
TRAP-5b (mU/dl)	276.2 (108.2)	356.7 (158.2)	0.07
P1NP (μg/l)	28.2 (10.2)	35.2 (15.2)	0.17

Mann–Whitney *U* tests were used to determine statistical significance. The standard deviation is given in *parentheses*

BMD bone mineral density, *CDAI* clinical disease activity index, *HAQ* health assessment questionnaire, *P1NP* procollagen type 1 N-terminal propeptide, *SDAI* simplified disease activity index, *TRAP-5b* tartrate-resistant acid phosphatase 5b

Table 3 Univariate linear regression analyses of bone mineral density (*BMD*) shown as the regression coefficient in the bisphosphonate treatment group

	Disease duration	Age	DAS28	CDAI	SDAI	HAQ score	Biological drug use
Femoral neck BMD							
Coefficient	−0.0032 (0.0015)	−0.0026 (0.0013)	0.012 (0.014)	0.0004 (0.0026)	0.001 (0.0025)	0.0051 (0.015)	−0.0044 (0.012)
p	0.03*	0.04*	0.42	0.89	0.72	0.74	0.73
Total hip BMD							
Coefficient	−0.0036 (0.0018)	−0.0031 (0.0015)	0.013 (0.017)	−0.001 (0.0032)	−0.001 (0.003)	−0.001 (0.018)	−0.013 (0.015)
p	0.04*	0.04*	0.45	0.78	0.91	0.94	0.4
L2–L4 spine BMD							
Coefficient	−0.002 (0.0021)	−0.0042 (0.0017)	0.009 (0.02)	−0.001 (0.0037)	−0.001 (0.0035)	−0.016 (0.021)	−0.037 (0.024)
p	0.35	0.02*	0.67	0.92	0.85	0.44	0.13

The standard error is given in *parentheses*

* $P < 0.05$

Table 4 Univariate linear regression analyses of bone mineral density (*BMD*) shown as the regression coefficient in the non-bisphosphonate treatment group

	Disease duration	Age	DAS28	CDAI	SDAI	HAQ score	Biological drug use
Femoral neck BMD							
Coefficient	−0.0038 (0.0012)	−0.0007 (0.0016)	−0.027 (0.018)	−0.0023 (0.0028)	−0.003 (0.0027)	−0.04 (0.018)	−0.022 (0.014)
p	0.003**	0.65	0.13	0.4	0.25	0.03*	0.12
Total hip BMD							
Coefficient	−0.0057 (0.0016)	−0.0012 (0.0021)	−0.036 (0.023)	−0.0016 (0.0036)	−0.003 (0.0035)	−0.05 (0.024)	−0.018 (0.015)
p	<0.001***	0.56	0.11	0.65	0.4	0.04*	0.24
L2–L4 spine BMD							
Coefficient	0.0007 (0.0019)	−0.0018 (0.0024)	0.003 (0.026)	0.004 (0.004)	0.0032 (0.0039)	0.01 (0.027)	−0.0055 (0.017)
p	0.72	0.44	0.91	0.32	0.42	0.72	0.75

The standard error is given in *parentheses*

*** $P < 0.001$; ** $P < 0.01$; * $P < 0.05$

Table 5 Multivariate linear regression analyses of bone mineral density (*BMD*) with disease duration, DAS28, Health Assessment Questionnaire (*HAQ*) score, and biological drug use selected as independent variables shown as the regression coefficient in the bisphosphonate treatment group

	Disease duration	Age	DAS28	HAQ score	Biological drug use
Femoral neck BMD					
Coefficient	−0.004 (0.0015)	−0.031 (0.0013)	0.029 (0.02)	−0.019 (0.021)	0.012 (0.013)
p	0.01**	0.02*	0.15	0.38	0.35
Total hip BMD					
Coefficient	−0.0045 (0.0018)	−0.0034 (0.0016)	0.041 (0.024)	−0.034 (0.026)	0.006 (0.016)
p	0.01**	0.04*	0.11	0.19	0.71
L2–L4 spine BMD					
Coefficient	−0.0025 (0.0021)	0.0034 (0.0019)	0.048 (0.028)	−0.052 (0.029)	−0.021 (0.018)
p	0.24	0.07	0.1	0.08	0.26

The standard error is given in *parentheses*

** $P < 0.01$; * $P < 0.05$

Table 6 Multivariate linear regression analyses of bone mineral density (*BMD*) with disease duration, DAS28, Health Assessment Questionnaire (*HAQ*) score, and biological drug use selected as independent variables shown as the regression coefficient in the non-bisphosphonate treatment group

	Disease duration	Age	DAS28	HAQ score	Biological drug use
Femoral neck BMD					
Coefficient	−0.0033 (0.0015)	−0.001 (0.017)	−0.0057 (0.024)	−0.0075 (0.027)	−0.017 (0.013)
p	0.04*	0.71	0.81	0.78	0.2
Total hip BMD					
Coefficient	−0.0055 (0.002)	0.001 (0.0022)	−0.0062 (0.031)	−0.0014 (0.035)	−0.011 (0.016)
p	0.01**	0.63	0.85	0.96	0.5
L2–4 spine BMD					
Coefficient	0.0014 (0.0025)	−0.0022 (0.0026)	0.0074 (0.038)	−0.001 (0.042)	−0.0038 (0.02)
p	0.57	0.4	0.84	0.97	0.85

The standard error is given in *parentheses*

** $P < 0.01$; * $P < 0.05$

RA [19, 20]. The HAQ scores were negatively correlated with the BMD of the femoral neck and forearm. However, only a few studies have assessed disease activity parameters as predictors of generalized bone loss, and the patient populations in those studies were rather small. In the present study, we determined whether BMD was negatively correlated with HAQ score, DAS28, CDAI, SDAI, age, disease duration, and use of biological drugs with or without bisphosphonate treatment. The efficacies of biological drugs for preventing generalized bone loss have been examined in previous studies, which showed that tumor necrosis factor inhibitors prevented generalized bone loss [12, 13], as did tocilizumab [21]. However, only a few reports have assessed the efficacy of biological drugs for preventing bone loss, and the effects of such drugs on osteoporosis remain unclear. Further randomized controlled studies are needed.

Here, we evaluated the association between BMD and various clinical parameters in 138 patients with RA. The disease duration of RA was negatively associated with the BMD of the total hip and femoral neck regardless of bisphosphonate treatment. DAS28, SDAI, CDAI, and HAQ score were not significantly associated with generalized bone loss. Similarly, the use of biological drugs was not associated with generalized bone loss. The results of this study indicate that a long disease duration of RA induces bone loss in the hip regardless of treatment with bisphosphonates. Because increasing the BMD of the total hip and femoral neck is more difficult than increasing the BMD of the lumbar spine, postmenopausal RA patients should begin treatment of osteoporosis to prevent bone loss at the early stages of osteopenia. We also determined the efficacies of biological drugs for the prevention of bone loss. We found no significant negative association between the use of biological drugs and BMD. The effects of biological drugs on osteoporosis should be further evaluated in large-scale prospective studies.

There are several limitations to the present study. The size of our patient population was relatively small, and the study was retrospective and cross-sectional in nature. To determine the associations of RA clinical parameters with BMD, further large-scale prospective studies should be performed.

In summary, we found a significant negative association of RA disease duration with the BMD of the hip in postmenopausal RA patients regardless of treatment with bisphosphonates. We found no significant association between biological drug use and BMD. A few observational studies, but no large-scale investigations, have reported the efficacies of biological drugs in osteoporosis in RA patients. However, the effects of such drugs remain unclear. Randomized controlled studies with larger numbers of patients are needed to adequately address this question. Additionally, further studies are needed to determine the effects of tumor necrosis factor inhibitors and tocilizumab on osteoporosis in RA patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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