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# Risk factors for bone loss in patients with rheumatoid arthritis treated with biologic disease-modifying anti-rheumatic drugs

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## Abstract

**Objective:** Osteoporosis is a complication of rheumatoid arthritis. We examined the risk factors for bone loss in rheumatoid arthritis patients receiving biological disease-modifying anti-rheumatic drugs. Lumbar spine and femoral neck bone mineral density was measured at two time points in 153 patients with rheumatoid arthritis managed with biological disease-modifying anti-rheumatic drugs. We examined patients' variables to identify risk factors for least significant reduction of bone mineral density.

**Results:** Least significant reduction of lumbar spine bone mineral density ($\leq -2.4\%$) was seen in 13.1% of patients. Least significant reduction of femoral neck bone mineral density ($\leq -1.9\%$) was seen in 34.0% of patients. Multiple logistic regression analysis showed that a risk factor for least significant reduction of the lumbar spine was high-dose methylprednisolone use. Multiple regression analysis showed that a risk factor for least significant reduction of the femoral neck was short disease duration. Our findings showed that a risk factor for femoral neck bone mineral density reduction was a short disease duration. These findings suggest that rheumatoid arthritis patients receiving treatment with biological disease-modifying anti-rheumatic drugs may benefit from earlier osteoporosis treatments to prevent femoral neck bone loss.

**Keywords:** Biological disease-modifying anti-rheumatic drugs (bDMARDs), Osteoporosis, Rheumatoid arthritis (RA), Risk factors

## Introduction

Rheumatoid arthritis (RA) is an autoimmune disease that promotes joint inflammation and destruction. It has been reported that 15–20% of RA patients are affected by osteoporosis of the hip and spine [1, 2]. Inflammation plays a key role in RA activity, as well as in bone resorption and osteoporosis [3]. The treatment of RA has advanced significantly by targeting key molecules including tumor necrosis factor alpha (TNF-α) or interleukin 6 (IL-6) using a group of drugs called biological

disease-modifying anti-rheumatic drug (bDMARDs) [4–6]. There is also evidence suggesting that bDMARDs may have beneficial effects on bone metabolism and bone remodeling [3, 5, 7–13]. Transgenic mice expressing soluble TNF-α receptor were protected from bone loss caused by estrogen-deficiency-related osteoporosis [14]. The blockade of inflammatory cytokines in RA may therefore not only reduce inflammation but also generalized bone loss. In this study, we examined changes in the bone mineral density (BMD) of patients with RA being treated with bDMARDs. We aimed to identify specific patient factors associated with least significant reduction (LSR) of BMD in the lumbar spine and femoral neck.

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## Main text

### Methods

#### Patients

We retrospectively examined the records of 153 consecutive patients with RA diagnosed using American College of Rheumatology/European League Against Rheumatism classification criteria [15]. All consecutive patients who underwent DXA scanning of the lumbar spine and femoral neck were included. Inclusion criteria for the study were that the patients (1) had undergone bDMARDs therapy for $\geq 1$ year; (2) had undergone dual-energy X-ray absorptiometry (DXA) as a baseline study and again after 1 year and/or during long-term follow-up; and (3) had all parameters recorded in an electronic medical record. The patients for whom some of these data were missing were excluded from the study. All patients diagnosed and started medication at the Japanese Red Cross Kagoshima Hospital. When conventional DMARDs treatment led to a Disease Activity Score 28-C-reactive protein (DAS28-CRP) value of < 2.6 or a Simplified Disease Activity Index of $\leq 3.3$, bDMARDs were not needed [16, 17]. If the disease activity was not lowered sufficiently to meet these criteria, therapy with bDMARDs was started. The choice of bDMARDs was made by the attending physician. The bDMARDs used for treatment in this study included infliximab, adalimumab, golimumab, etanercept, tocilizumab, and abatacept. All treatments were undertaken at the Japanese Red Cross Kagoshima Hospital, as previously reported [18]. Demographic and disease-related data were collected retrospectively from the medical records. We examined age, sex, disease duration, body mass index (BMI), average prescribed dose of methylprednisolone, serum C-reactive protein (CRP), Disease Activity Score 28-CRP, simplified disease activity index, duration of bDMARDs therapy, and the type of anti-osteoporosis drugs to identify risk factors for LSR of BMD. We calculated changes in BMD over a 12-month period. Anti-osteoporosis drugs were used according to the guideline for treating osteoporosis and glucocorticoid-induced osteoporosis [19–22]. In addition, if blood tests showed a significant reduction in the $1.25(OH)_2$ vitamin D level, a vitamin D formulation was administered. All patients gave written informed consent for their records to be published in this study.

#### BMD of the lumbar spine and femoral neck

BMD was examined between December 2011 and December 2013 by the Discovery DXA system (Hologic, Waltham, MA, USA). The BMD of the lumbar spine (L2–L4) and femoral neck ($g/cm^2$) were measured. The mean duration between each BMD examination was 12 (range 11–13) months.

#### Criteria for reduction of BMD

Judgment of treatment results using BMD was offered by the Scientific Task Force Group of the International Osteoporosis Foundation (IOF) [23], which was based on the notion of least significant change (LSC). Therefore, the LSC is calculated by the coefficient of variation of BMD measurement, a value that exceeds the LSC can be recognized as a significant reduction in BMD during short duration. The LSR of BMD was used as the criterion for judging BMD reduction. Reduced BMD was defined as previously reported [23, 24]. The BMD coefficient of variation was 2.0% for the lumbar spine and 1.6% for the femoral neck [24]. The LSC with a one-tailed test would be 1.19 times for evaluation of individual cases, with 80% confidence. The LSR of BMD was $\leq - 2.4\%$ for the lumbar spine and $\leq - 1.9\%$ for the femoral neck [24].

#### Statistical analysis

Univariate and multivariate stepwise binomial logistic regression were performed to correlate demographic and patient-reported outcome metrics with changes in LSR of BMD. Because of the relatively small number of patients and the large number of confounding factors, we applied a stepwise variable selection method to identify significant factors, as previously described [25]. Stepwise variable selection is a method of fitting regression models in which choice of variables is performed by an automatic procedure. Because of potential confounding factors between the variables, we did not exclude any variables according to the results of the univariate analyses. In the stepwise model, all variables are included to the model at first but may also be removed until the current model is identical to the model estimated in the previous model. For a variable to enter or stay in the model, we defined a p value of 0.2 as cut-off for variables to enter in the model. p < 0.05 was determined as statistically significant. Analysis was performed using BellCurve for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan).

### Results

The demographic and clinical characteristics of the 153 patients who underwent DXA scanning of the lumbar spine and femoral neck are shown in Table 1. LSR of lumbar spine ($\leq - 2.4\%$) BMD was seen in 13.1% (20/153) of patients, and LSR of femoral neck BMD ($\leq - 1.9\%$) was seen in 34.0% (52/153) of patients. Scatter plots were shown in Additional file 1: Figure S1. Univariate analysis detected no risk factors for 12-month LSR of lumbar spine and femoral neck BMD (Table 2). Multiple stepwise binomial logistic regression analysis showed that a risk factor for bone loss of the lumbar spine was the use of high dose of methylprednisolone (Table 3). Multiple

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## Table 1 Patient demographic and clinical characteristics

| | |
|---|---|
| Age (year) | 60.8 ± 10.5 |
| Proportion of female | 83.0% |
| Disease duration (year) | 10.0 (5.0–17.0) |
| BMI | 22.8 ± 3.4 |
| Average dose of prednisolone (mg) | 0.0 (0.0–2.0) |
| CRP (mg/dL) | 0.12 (0.03–0.38) |
| DAS28-CRP | 2.39 (1.62–3.47) |
| SDAI | 6.07 (2.35–14.32) |
| MHAQ | 4.0 (0.0–10.0) |
| Duration of bDMARDs therapy | 4.0 (3.0–6.0) |
| Type of anti-osteoporosis drugs | PTH: 3.5% Bisphosphonate: 47.1% Others: 14.4% None: 35.3% |
| Change of lumbar spine BMD/12 months (g/cm$^2$) | 0.004 (− 0.080 to 0.018) |
| Percent of least significant reduction of lumber spine BMD | 13.1% (20/153) |
| Change of femoral neck BMD/12 months (g/cm$^2$) | − 0.001 (− 0.025 to 0.019) |
| Percent of least significant reduction of femoral neck BMD | 34.0% (52/153) |

*BMI* body mass index, *CRP* serum C-reactive protein concentration, *DAS28-CRP* Disease Activity Score-28-CRP, *SDAI* simplified disease activity index, *MHAQ* modified Health assessment questionnaire, *bDMARDs* biologic disease-modifying anti-rheumatic drugs, *PTH* parathyroid hormone, *BMD* bone mineral density

## Table 2 Univariate analysis of risk factor for LSR of BMD

| | Lumber spine | | Femoral neck | |
|---|---|---|---|---|
| | Odds ratio | p value | Odds ratio | p value |
| Age (year) | 0.98 (0.94–1.02) | 0.28 | 0.98 (0.95–1.02) | 0.34 |
| Sex | 0.71 (0.21–2.34) | 0.57 | 2.25 (0.79–6.42) | 0.13 |
| Disease duration | 1.03 (0.97–1.08) | 0.34 | 0.96 (0.92–1.01) | 0.10 |
| BMI | 1.04 (0.90–1.19) | 0.61 | 0.97 (0.88–1.07) | 0.53 |
| Average dose of prednisolone | 1.18 (0.99–1.41) | 0.06 | 1.10 (0.95–1.27) | 0.22 |
| CRP | 1.51 (0.99–2.30) | 0.05 | 1.04 (0.70–1.53) | 0.85 |
| DAS28-CRP | 1.33 (0.91–1.96) | 0.14 | 1.00 (0.76–1.33) | 0.99 |
| SDAI | 1.03 (0.98–1.08) | 0.20 | 1.00 (0.97–1.04) | 0.92 |
| MHAQ | 1.03 (0.95–1.11) | 0.46 | 0.99 (0.93–1.05) | 0.68 |
| Duration of bDMARDs therapy | 0.98 (0.81–1.19) | 0.83 | 0.91 (0.79–1.05) | 0.18 |
| Type of anti-osteoporosis drugs | 1.26 (0.77–2.05) | 0.36 | 0.93 (0.66–1.32) | 0.68 |

Univariate analysis detected no risk factors for 12-month LSR of lumbar spine (≤ − 2.4%) and femoral neck (≤ − 1.9%) BMD

*LSR* least significant reduction, *BMD* bone mineral density, *BMI* body mass index, *CRP* serum C-reactive protein concentration, *DAS28-CRP* Disease Activity Score-28-CRP, *SDAI* simplified disease activity index, *MHAQ* modified health assessment questionnaire, *bDMARDs* biologic disease-modifying anti-rheumatic drugs

regression analysis showed that a risk factor for LSR of the femoral neck was a short disease duration (Table 3).

## Discussion

Advanced age, female sex, longer disease duration, history of past thoracic or lumbar vertebral fractures, higher Steinbrocker classification, and lower BMI were previously determined to be associated with low femoral neck BMD in patients with RA treated with bDMARDs [18]. As these factors were correlated with a one-time examination of BMD, there is a possibility that other factors may confound those results. In this study, we examined LSR of BMD in the lumbar spine and femoral neck in RA patients treated with bDMARDs as measured at two time points. In this report, we showed that a high dose of methylprednisolone is a risk factor for LSR of BMD in the lumbar spine. This finding is consistent with previous studies [18, 26, 27]. Several studies showed that glucocorticoid therapy increase intensely risk of vertebral fracture [28–30]. Mori et al. reported in a multivariate linear regression analysis that longer RA disease duration was significantly related to the loss of BMD in the femoral neck and total femur [31]. Our findings showed that a risk factor for femoral neck BMD reduction was a short disease duration. There is a discrepancy between our results and the findings of previous reports [18, 31]. Bone loss was observed in patients with recently diagnosed rheumatoid arthritis, suggesting that the start of the femoral neck bone loss may be much earlier than previously anticipated [32].

It has been reported that bisphosphonates prevent bone loss of the lumbar spine and femoral neck in RA patients treated with bDMARDs [33, 34]. Although we could not detect the type of anti-osteoporosis drug as a significant risk factor, anti-osteoporosis drug therapy is necessary for some patients receiving bDMARDs. Further studies are needed to determine which anti-osteoporosis drugs are suitable to increase BMD in RA patients being treated with bDMARDs.

## Conclusions

Our findings showed that a risk factor for femoral neck BMD reduction was a short disease duration. These findings suggest that RA patients receiving treatment with bDMARDs may benefit from earlier osteoporosis treatments to prevent femoral neck bone loss.

### Limitations

Our study has several limitations. Data collection was retrospective. The duration and kinds of bDMARDs used varied. It is better to examine BMD when patients begin taking bDMARDs. The Binary logistic regression analysis causes loss of information as it analyses a dichotomous

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### Table 3 Multivariate analysis for LSR reduction of lumber spine and femoral neck BMD

| Nagelkerke $R^2$: 0.10 | Lumber spine | |
|---|---|---|
| | Odds ratio | p value |
| Average dose of prednisolone | 1.22 (1.02–1.50) | 0.03 |
| Type of anti-osteoporosis drugs | 1.52 (0.87–2.65) | 0.14 |
| CRP | 1.46 (0.95–2.25) | 0.08 |
| Nagelkerke $R^2$: 0.08 | Femoral neck | |
| | Odds ratio | p value |
| Sex | 2.37 (0.82–6.90) | 0.11 |
| Disease duration | 0.95 (0.91–0.10) | 0.04 |
| Average dose of prednisolone | 1.13 (0.97–1.32) | 0.11 |

The stepwise binomial logistic regression detected high dose of prednisolone use is a risk factors for 12-month LSR of lumbar spine ($\leq -2.4\%$). The stepwise binomial logistic regression analysis detected short disease duration is a risk factors for 12-month LSR of femoral neck ($\leq -1.9\%$)

*LSR* least significant reduction, *BMD* bone mineral density, *CRP* serum C-reactive protein concentration

outcome variable rather than the continuous bone loss measurement. We did not measure changes in biomarkers associated with bone remodeling in the blood or urine. Although prior studies did not find a difference in the levels of bone turnover markers after 1 year of treatment with bDMARDs [13, 35], we are now examining longitudinal changes in BMD and bone turnover markers in a prospective study.

### Additional file

**Additional file 1: Figure S1.** These scatter plot show the reduction of BMD in lumber spine (A) and femoral neck (B).

### Abbreviations
RA: rheumatoid arthritis; bDMARDs: biological disease-modifying anti-rheumatic drugs; LSR: least significant reduction; RANKL: receptor activator of nuclear factor-kappa B ligand; BMD: bone mineral density; DXA: dual X-ray absorptiometry; BMI: body mass index; CRP: serum C-reactive protein; DAS28-CRP: Disease Activity Score 28 CRP; SDAI: simplified disease activity index; TNFα: tumor necrosis factor-alpha; PTH: parathyroid hormone.

### Authors' contributions
TS conceived of and designed the examinations. HT, YA, HO, MA, YI, SN, ET, and NS collected and analyzed the data. SK and TS wrote the manuscript. All authors read and approved the final manuscript.

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