Rheumatol Int (2017) 37:999–1005
DOI 10.1007/s00296-017-3720-7

Rheumatology INTERNATIONAL

OBSERVATIONAL RESEARCH

Use of bisphosphonate might be important to improve bone mineral density in patients with rheumatoid arthritis even under tight control: the TOMORROW study

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Received: 14 November 2016 / Accepted: 7 April 2017 / Published online: 12 April 2017

Abstract Although patients with rheumatoid arthritis (RA) are prone to osteoporosis, tight control of disease activity might have a positive effect on bone metabolism. We aimed to determine whether bisphosphonate use is still important to improve bone mineral density (BMD) in RA patients whose disease activity was tightly controlled and the dose of glucocorticoid was reduced. This study was a sub-analysis of the 10-year prospective cohort TOtal Management Of Risk factors in Rheumatoid arthritis patients to lOWer morbidity and mortality: the TOMORROW which started from 2010. We compared BMD between 192 patients with RA and age- and sex-matched volunteers between 2010 and 2013 using dual-energy X-ray absorptiometry (DXA) in whole body mode. We then determined ratios of changes in BMD (%ΔBMD) to assess factors influencing increases in BMD among the patients using multivariate logistic regression analysis. The BMD was significantly lower in the patients than in the controls at all sites surveyed during 2010 and 2013. The %ΔBMD of the total spine was significantly higher among the patients treated with, than without bisphosphonate (6.2 vs. 1.8%, $P = 0.0001$). Multivariate logistic regression analysis revealed that use of bisphosphonate was a significant factor contributing to BMD increase (odds ratio 2.13; 95% confidence interval, 1.03–4.38, $P = 0.041$). Meanwhile, use of biologic agents, reducing glucocorticoid dose, and control of disease activity were not significant factors for gain of BMD. The BMD was lower among patients with RA than non-RA controls. Use of bisphosphonate significantly increased the BMD of the spine in patients over a period of 3 years and was important for maintaining the BMD among patients with RA under the control of inflammation and disease activity.

Keywords Cohort · Fragile fracture · Osteoporosis · Inflammatory disease · Dual-energy X-ray absorptiometry

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Introduction

Rheumatoid arthritis (RA) is typically complicated with secondary osteoporosis [1] and the rate of fragile fractures caused by osteoporosis is higher among patients with RA than among non-RA individuals. The risk of hip and vertebral fractures increases approximately two- to six-fold in patients with RA compared with control [2–4]. Rheumatoid arthritis is an independent risk factor for fragile fractures that has been assessed using the Fracture Risk Assessment Tool (FRAX) [5, 6].

Other factors influencing bone metabolism in patients with RA other than primary osteoporosis that increases with advancing age include peri-articular osteoporosis due to local inflammation [7], glucocorticoid-induced

osteoporosis [8] and systemic osteoporosis due to inactivity [9]. The likelihood of fragile fractures needs to be decreased in patients with RA by preventing osteoporosis. Our previous retrospective study found that bisphosphonate and reducing glucocorticoids improve bone mineral density (BMD) in patients with RA [10]. Controlling disease activity helps to prevent a decrease in BMD [11] and biological disease-modifying anti-rheumatic drugs (bDMARDs) help to increase BMD [12]. If disease activity is sufficiently controlled by such as bDMARDs and glucocorticoids are also reduced, is it not necessary to administer bisphosphonate for the treatment of osteoporosis?

We launched a prospective cohort in 2010, the TOtal Management Of Risk factors in Rheumatoid arthritis patients to lOWer morbidity and mortality: the TOMORROW study [13]. In this cohort, among other objectives, we aimed to determine which risk factors affect osteoporosis and fracture in patients with RA. In a previous step, we identified a relationship between reducing the glucocorticoid dosage and bone metabolic markers (BMM) in patients with RA from the database of the TOMORROW study [14]. Is the rate of BMD loss higher in RA than in persons without the disease? Unfortunately, we only have indirect evidence that this may be the case. We made a hypothesis that use of bisphosphonate was still important to improve BMD among patients with RA whose disease activity was tightly controlled by bDMARDs and the dose of glucocorticoid was reduced. To validate a hypothesis, we compared secular changes in BMD between patients with RA and healthy individuals, and investigated whether use of bisphosphonate was influenced factor for increase of BMD among patients with RA using a logistic regression analysis.

Materials and methods

Study design and participants

The present study is a sub-analysis of a prospective 10-year cohort study (TOMORROW) that started in 2010. The study is registered with the UMIN Clinical Trials Registry [http://www.umin.ac.jp/ctr/] (UMIN000003876) and it was designed to evaluate risk factors associated with osteoporosis and metabolic syndrome in patients with RA.

This study included 208 patients with RA (177 women, 31 men) in general clinical practice at our hospital and 205 age- and sex-matched non-RA volunteers (172 women, 33 men) who were recruited via mass media (total, 413 participants). All patients with RA were between 20- and 80-years-old and fulfilled the American College of Rheumatology (ACR) criteria (1987) for RA [15]. To investigate the long-term effects of bDMARDs on bone and lipid metabolism, we recruited RA patients receiving bDMARDs as half of the patients with RA (Table 1).

Table 1 Baseline demographics and clinical characteristics of patients with rheumatoid arthritis and healthy volunteers (controls)

	Patients ($n = 192$)	Controls ($n = 194$)	P*
Age (years)	60.4 ± 12.6	59.8 ± 12.4	0.677
Women, *n* (%)	162 (84.4)	162 (83.5)	0.816
Height (cm)	155.0 ± 8.9	157.1 ± 7.7	0.345
Weight (kg)	54.7 ± 10.1	56.7 ± 11.1	0.126
BMI (kg/m^2)	23.1 ± 3.5	22.3 ± 3.3	0.298
Osteoporosis, *n* (%)	21 (11.0)	14 (7.2)	0.285
Bisphosphonate, *n* (%)	60 (31.3)	10 (5.2)	<0.001
PSL, *n* (%)	62 (32.3)	0 (0)	<0.001
PSL dose (mg/day)	3.9 ± 1.8		
OC (ng/mL)	7.33 ± 2.69	7.26 ± 2.22	0.796
uNTx (nmol BCE/mmol Cr)	57.1 ± 34.6	43.8 ± 21.9	0.001
Whole lean body mass (Kg)	36.7 ± 7.2	39.0 ± 7.8	0.004
Ratio of whole body fat (%)	29.9 ± 7.2	28.1 ± 6.6	0.009
Disease duration (years)	14.4 ± 11.7		
mHAQ	0.47 ± 0.41		
bDMARDs, *n* (%)	86 (44.8)		
MTX, *n* (%)	161 (83.9)		
MTX dose (mg/week)	7.8 ± 3.7		

Data are shown as mean ± standard deviation (SD) or as ratios of patients with measured values compared with total number of patients: *n* (%)

bDMARD biological disease modifying anti-rheumatic drugs, *BMI* body mass index, *mHAQ* modified health assessment questionnaire, *MTX* methotrexate, *OC* serum osteocalcin, *PSL* prednisolone, *RA* rheumatoid arthritis, *uNTx* urinary cross-linked *N*-telopeptide of type I collagen

* Continuous and categorical variables were analyzed using unpaired Student's *t* test and Fisher's exact test, respectively

Clinical assessment

Baseline clinical and laboratory data were collected at the first presentation between January and March of 2010. The attending rheumatologist of each patient decided the treatment strategy based on clinical disease activity during the observation period. All participants completed a self-administered questionnaire about general health status, history of comorbidities, and present and past medications. The activity of RA was measured as a disease activity score (DAS) composite index of the erythrocyte sedimentation

rate (ESR) and a 28-joint score (DAS28-ESR) [16]. Functional status was also measured in patients with RA based on modified health assessment questionnaire (mHAQ) scores [17].

Bone mineral density

We measured BMD at three sites (whole body, lower limb, and total spine) in the patients with RA and controls by dual-energy X-ray absorptiometry (DXA) using a QDR 4500 system (Hologic, Waltham, MA) in whole body mode. The whole body included all skeletal bone. The lower limb was defined as the left limb bones excluding the femoral neck. The total spine consisted of bone from the cervical, to the lumbar spine. These definitions were based on the manual provided with the QDR 4500 system. The approximate coefficient of variation (CV) of the total spine was 1%. The BMD was compared between 2010 and 2013 at three sites in patients with RA and in controls. If any of the participants had surgically implanted metal, DXA data from the site were excluded. We compared ratios of changes in BMD (%ΔBMD) among patients administered with or without bisphosphonate and bDMARDs. The increase of BMD in total spine was defined that BMD increased above LSC (least significant change). Since the CV value of total spine BMD measurement at our facility was 1%, LSC was calculated as 2.8% (95% CI; confidence interval).

Statistical analysis

Differences in demographic and clinical variables between patients with RA and controls were analyzed using unpaired Student's t tests or Fisher's exact test for continuous or categorical variables, respectively. The significance of differences in BMD between 2010 and 2013, and the %ΔBMD between patients with RA and controls was tested using Mann–Whitney U tests. Values for %ΔBMD with or without bisphosphonate and bDMARDs were compared among patients with RA using Mann–Whitney U test. Correlations between %ΔBMD and ΔDAS28-ESR values (continuous variable) or ΔPSL (prednisolone) dose were examined using Spearman's correlation coefficients. Multivariate logistic regression models were prepared to estimate the influencing factors for the increase of total spine BMD associated with potential predictors, adjusting for disease duration and total spine BMD at baseline. Because those two factors were significant for the increase of total spine BMD by univariate logistic regression analysis. Inclusion of variables in the modes was based on existing knowledge of risk factors. All data are presented as mean ± standard deviation (SD) and were statistically analyzed using IBM SPSS Statistics (ver. 22, IBM, Armonk, New York). A value of $P < 0.05$ was considered significant.

Results

During 3 years, sixteen patients with RA dropped out of the study based on their own wishes (ten women and one man), death (three women) or a change in hospitals (two women), and 11 controls decided to withdraw (nine women and two men). Therefore, we analyzed data from 192 patients with RA (162 women, 30 men) and 194 controls (162 women, 32 men). The three-year follow-up rates for the patients and controls were 92.7 and 94.6%, respectively. Table 1 shows the baseline demographics and clinical characteristics of the study participants. The demographic characteristics of the two study groups were similar, because the controls were recruited to match the age and sex of the patients. Whole body lean mass was significantly lower, whereas the ratio (%) of whole body fat was significantly higher among the patients than the controls. We could analyze 134 cases in whole BMD, 164 in lower limb BMD, and 186 in total spine BMD among 192 patients with RA. On the other hand, BMD of almost cases and sites were analyzed in non-RA volunteers except two people by implantation.

Comparison of BMD between patients with RA and controls

The BMD was significantly lower in the patients than in the controls at all measured sites in 2010 and in 2013 (Fig. 1) and that of the whole body and lower limb did not significantly change within each group between 2010 and 2013. However, the BMD of total spine significantly increased between 2010 and 2013 in the patients ($P = 0.038$) and controls ($P = 0.041$). The change in BMD did not significantly differ between the patients and the controls (%ΔBMD of whole body, lower limb and total spine in patients: -0.2 ± 4.0, -0.1 ± 9.2 and 3.1 ± 6.9%, respectively, controls: 0.4 ± 3.9, -0.1 ± 6.0 and 2.2 ± 7.1%, respectively.

Factors influencing changes in BMD among patients with RA

Table 2 shows the effects of bisphosphonate. The %ΔBMD of only the total spine was significantly higher in patients administered with, than without bisphosphonate (Mann–Whitney U test). The tendency was the same in the controls.

Table 3 shows that bDMARDs did not significantly affect %ΔBMD at any measured site. Table 4 shows the relationship between %ΔBMD and the ΔDAS28-ESR as well as the ΔPSL. Neither ΔDAS28-ESR nor ΔPSL correlated with %ΔBMD at any of the three sites.

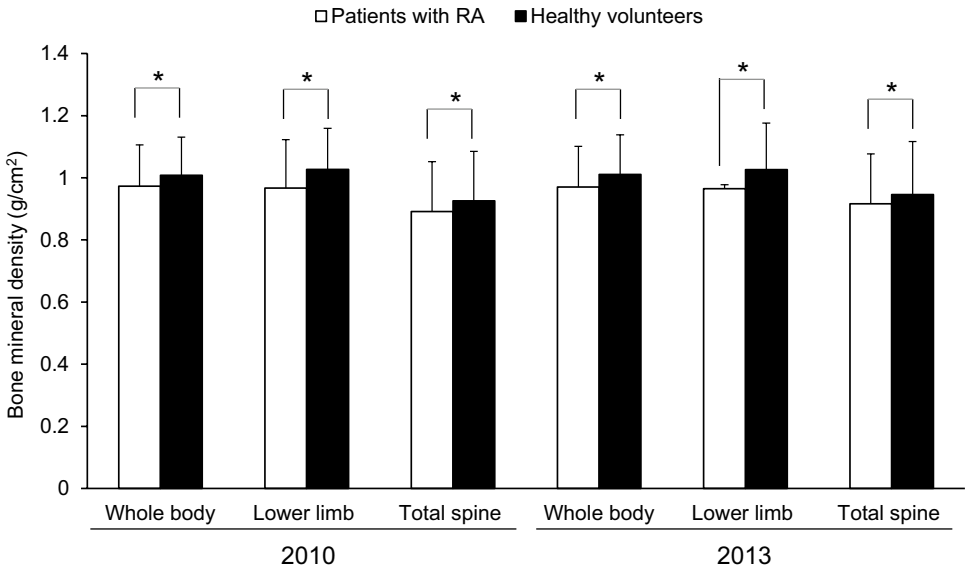

Fig. 1 Bone mineral density at whole body, lower limb, and total spine in 2010 and 2013. Bone mineral density of patients with rheumatoid arthritis is significantly lower than that of controls at all sites. *Columns* and *bars*, mean ± standard deviation (SD) in both groups. *$P < 0.05$. *RA* rheumatoid arthritis

Table 2 Influence of bisphosphonate on percent changes of bone mineral density in patients with rheumatoid arthritis and healthy controls

	Patients			Controls		
	Bisphosphonate+ ($n = 60$)	Bisphosphonate − ($n = 132$)	P*	Bisphosphonate+ ($n = 10$)	Bisphosphonate− ($n = 184$)	P*
Whole body	0.33 ± 5.19	−0.53 ± 3.13	0.387	1.20 ± 2.75	0.50 ± 4.43	0.125
Lower limb	1.45 ± 15.27	−0.80 ± 4.73	0.482	0.18 ± 1.83	−0.09 ± 6.13	0.488
Total spine	6.21 ± 7.35	1.81 ± 6.21	0.001	8.86 ± 11.27	1.86 ± 6.63	0.038

Data are shown as mean ± standard deviation (SD)

* Mann–Whitney *U* test

Table 3 Influence of biological DMARDs on percent changes of bone mineral density in patients with rheumatoid arthritis

	Biological DMARDs+ ($n = 86$)	Biological DMARDs− ($n = 106$)	P*
Whole body	0.27 ± 4.18	−0.75 ± 3.72	0.180
Lower limb	0.49 ± 12.08	−0.77 ± 4.51	0.879
Total spine	3.52 ± 6.97	2.68 ± 6.74	0.589

Data are shown as mean ± standard deviation (SD)

DMARDs disease-modifying anti-rheumatic drugs

* Mann–Whitney *U* test

Table 4 Correlations between percent change in bone mineral density and changes in DAS28-ESR and PSL in patients with rheumatoid arthritis

	ΔDAS28-ESR		ΔPSL	
	Correlation	P	Correlation	P
Whole body ($n = 134$)	0.128	0.154	−0.006	0.948
Lower limb ($n = 164$)	0.006	0.942	0.085	0.279
Total spine ($n = 186$)	0.028	0.712	−0.084	0.258

ΔDAS28-ESR change in disease activity score-erythrocyte sedimentation rate, *ΔPSL* change in prednisolone

Factors affecting %ΔBMD over the whole body comprised low-density lipoprotein ($R = -0.279$, $P = 0.001$), total cholesterol ($R = -0.331$, $P = 0.001$) and gender (woman) ($R = -0.245$, $P = 0.005$). Factors affecting %ΔBMD at the lower limb comprised MTX ($R = 0.173$, $P = 0.028$), osteocalcin ($R = -0.241$, $P = 0.002$) and alkaline phosphatase ($R = -0.302$, $P = 0.001$), and those affecting %ΔBMD at the total spine were alkaline phosphatase ($R = -0.160$, $P = 0.034$), height ($R = -0.219$, $P = 0.003$), and baseline age ($R = 0.146$, $P = 0.045$).

Table 5 Logistic regression analysis of risk factors for increase in BMD of total spine in patients with RA

	Univariate		Multivariate	
	OR (95%CI)	*P*	OR (95%CI)	*P*
Use of bisphosphonate (yes; 1, no; 0)	2.26 (1.17–4.58)	0.023	2.13 (1.03–4.38)	0.041
Use of bDMARDs (yes; 1, no; 0)	1.26 (0.69–2.30)	0.456	1.12 (0.60–2.08)	0.719
ΔDAS28-ESR	0.91 (0.68–1.21)	0.500	0.94 (0.70–1.26)	0.665
Reduction of PSL dose (yes; 1, no; 0)	1.19 (0.58–2.43)	0.642	1.13 (0.54–2.36)	0.741

Increase of BMD was defined as an increase above LSC and ΔDAS28-ESR was treated as a continuous variable. ORs were adjusted for duration of disease and BMD of total spine at baseline

BMD bone mineral density, *RA* rheumatoid arthritis, *OR* odds ratio, *bDMARDs* biological disease-modifying anti-rheumatic drugs, *ΔDAS28-ESR* change in disease activity score-erythrocyte sedimentation rate, *PSL* prednisolone, *LSC* least significant change

Table 5 shows the results of logistic regression analysis for the increase of total spine BMD. The use of bisphosphonate significantly increased the BMD of the total spine in the patients (odds ratio 2.13; 95% CI 1.03–4.38, $P = 0.041$). However, use of bDMARDs, change of DAS28-ESR, and reduction of PSL dose did not increase the BMD of the total spine after adjusting with disease duration and baseline total spine BMD (Table 5). However, if the dependent variable was changed to "BMD did not decrease (i.e. $\%\Delta\text{BMD} > -2.8$)", the significance of all factors disappeared (data not shown).

Discussion

This study showed that BMD was significantly lower among patients with RA than controls at three sites at baseline and after 3 years, and that bisphosphonate significantly increased the BMD of the total spine in both groups. The results of multivariate logistic regression analyses supported our hypothesis that the use of bisphosphonates might be still important if we aim to increase BMD even under tight control of disease activity in patients with RA. Only one longitudinal, population-based study has investigated BMD in patients with RA [18]. The present study is the first cohort comparison of secular changes in BMD between patients with RA and healthy persons.

The BMD of the total spine in the patients and in the controls significantly increased between 2010 and 2013. Degenerative changes might influence BMD of the total spine, especially the lumbar spine. Steiger et al. found that the relationship between age and bone mass was weakest for degenerative changes in the lumbar spine [19]. This point should be taken into account when interpreting the results of our study.

Tumor necrosis factor (TNF) inhibitors exerts limited effects on BMD, as one study showed that they maintained the BMD of the lumbar spine and hip for 6 months, but did not significantly increase BMD compared with baseline [20]. We also reported that a TNF inhibitor suppressed a decrease in BMD at the lumbar spine and femoral neck. However, that agent did not increase the BMD in patients with RA [10]. The results of the present cohort study also indicated that the BMD of patients administered without bDMARDs decreased at the whole body and lower limb over the 3-year study period. In contrast, BMD slightly increased in patients treated with bDMARDs without significant difference between two groups. Baseline disease activity scores of the patients with RA were relatively low (mean DAS28-ESR, 3.47). This could explain why disease activity and bDMARDs did not influence BMD.

We previously found from the TOMORROW study that reducing glucocorticoid dosages improves serum osteocalcin in patients with rheumatoid arthritis [14]. However, the present study did not find that decreasing glucocorticoids improved the BMD. The proportion of PSL users was only 32.3% in RA patients, and the average dose was as low as 3.9 mg/day. It was considered to be one of the reasons why reduction of PSL dose was not extracted as a significant factor. Regardless of this result, if disease activity is well controlled, dose reduction of PSL should be considered.

Changes in disease activity, treatment with bDMARDs and decreasing glucocorticoids did not affect changes in the BMD of the spine among patients with RA. In contrast, bisphosphonate significantly increased the BMD of the spine. We previously found that bisphosphonate was more important than biological agents for increasing BMD [10] and the present results supported this finding.

Patients with RA who were administered with bisphosphonate had lower BMD at baseline compared with those who were not. Treating patients with a lower BMD using bisphosphonate is important to retard the progression of osteoporosis. A few patients with RA in the present study were administered with vitamin D, denosumab, teriparatide or selective estrogen receptor modulators to prevent osteoporosis. However, the sample of patients was too small to determine the influence of these agents on changes in BMD.

Changes in low-density lipoprotein and total cholesterol correlated negatively with changes in BMD at the whole body. Patients with RA with higher values for low-density lipoprotein and total cholesterol had lower BMD. These findings reflect degenerative changes in women with RA, because 80% of the participants of the present study were women.

The present study has some limitations that must be considered. The baseline disease activity score of patients with RA was relatively low (mean DAS28-ESR, 3.47) and disease activity did not change very much over 3 years. Thus, changes in disease activity did not influence changes in BMD. Half of the patients with RA were under bDMARD therapy. This rate is higher than the general average in the real world [21, 22]. Conversely, the rate of administration and the dosages of glucocorticoids were lower in this study than in the real world [22]. We calculated DXA in whole body mode. The standard routine procedure is to assess the lumbar spine and hip. We used whole body mode to investigate not only BMD, but also fat and lean body mass. We could not determine the prevalence of fragile fractures among patients with RA who were administered with bisphosphonate. The relationship between the prevalence of fragile fractures and bisphosphonate intake will be important to determine in the future. It was reported that smoking adversely affected BMD [23]. However, we did not get continuous smoking information except baseline, and this time we did not add smoking as a factor in the analysis. This study was sub-analysis of a cohort investigation. We need to perform a prospective randomized study to investigate the effect of bisphosphonate for maintenance of the BMD in patients with RA in new era.

In conclusion, our findings indicated that the BMD was lower for patients with RA than for healthy individuals and bisphosphonate significantly increased the BMD at the total spine of patients with RA over a period of 3 years. Changes in disease activity, bDMARDs and decreasing glucocorticoids did not influence changes in BMD. Use of bisphosphonate is still important to improve BMD in patients with RA under the tight control of disease activity and reducing glucocorticoid.

Acknowledgements We thank Atsuko Kamiyama, Tomoko Nakatsuka and the Center for Drug and Food Clinical Evaluation, Department of Radiology and Department of Central Clinical Laboratory in Osaka City University Hospital for serving as research coordinators in terms of recruiting participants, collecting data and managing the quality of the data. We greatly appreciate the cooperation of the patients with RA and the healthy volunteers who participated in this study.

Author contribution statement Study design: M.T. and T.K., Study implementation: T.K., Data collection: T.O., Y.S., S.A, and K.M., Data analysis: M.T. and T.K., Data interpretation: M.T., T.K., and K.I., Drafting the manuscript: M.T., T.K., and K.I., Approving the final version of the manuscript: all authors.

Compliance with ethical standards

Conflict of interest Dr. Koike has received grant fees, research fees, consulting fees, or other remuneration from AbbVie, Astellas Pharma Inc., Bristol-Myers Squibb, Chugai Pharmaceutical, Eisai, Janssen, Lilly, Mitsubishi Tanabe Pharma Corporation, MSD, Ono Pharmaceutical, Pfizer, Roche, Takeda Pharmaceutical, Teijin Pharma, and UCB. None of the other authors has any conflict of interest to disclose.

Ethical standards The Ethics Committee at Osaka City University approved the study protocol. We obtained written informed consent from all patients and volunteers to participate in this study in accordance with the Declaration of Helsinki.

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