



Original article

Rheumatoid arthritis in tight disease control is no longer risk of bone mineral density loss

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ABSTRACT

Objectives: Rheumatoid arthritis (RA) is an independent risk factor of osteoporosis. However, if disease activity is successfully controlled using the treat-to-target (T2T) strategy, the risk of bone mineral density (BMD) loss can be diminished. We evaluated if RA is a risk factor even when the T2T is applied in clinical cases.

Methods: From September 2017 to August 2019, 741 patients were examined using dual-energy X-ray absorptiometry; of these, 279 were diagnosed with RA who attained clinical remission within 6 months (RA-rem) and 53 could not attain clinical remission (RA-nonrem), while 409 were not diagnosed with RA (non-RA). The following characteristics between RA-rem and non-RA were matched using the propensity score matching (PSM) technique: age, sex, past bone fragility fracture experience, osteoporosis drug intervention ratio, glucocorticoid administration ratio, mean dose, Barthel Index score, body mass index, serum-creatinine-to-cystatin C ratio, and the number of comorbidities. The BMDs and changes of the lumbar spine, femoral neck, total hip, and greater trochanter were statistically compared between the RA-rem and the non-RA after PSM, and between RA-nonrem and RA-rem after PSM using the Mann-Whitney U test.

Results: In total, 107 patients of RA-rem and 108 of non-RA were recruited. BMDs and changes of every part demonstrated no significant differences between the 2 groups. BMDs in every part of RA-rem after PSM were significantly greater than those in every part of RA-nonrem, while no significant difference in change during follow-up.

Conclusions: If disease activity is controlled in clinical remission, RA will not contribute to BMD reduction.

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1. Introduction

It is widely accepted that rheumatoid arthritis (RA) is a determinant risk factor of osteoporosis [1–11]. Since the past 10 years, FRAX has been globally used as an investigative tool for determining the risk of osteoporotic fractures. It includes a questionnaire with items such as glucocorticoid administration, current smoking habits, and bone fragility fracture history of both the patients and their parents, at the same time, suffering from RA is included [12].

RA, is associated with a high risk of osteoporotic fracture; this is because of the identification of many other risk factors of osteoporosis that involved in RA such as glucocorticoid administration [13–15], chronic inflammation [16], impaired mobility due to joint deformity [3,17], sarcopenia (likely to be caused by decreased mobility), polypharmacy, and malnutrition cachexia [18]. However, most of these risk factors may also arise from inadequate or inappropriate treatment, resulting in continuously high levels of inflammation or inert glucocorticoid steroid (GCS) use [6,16,19]. Since the recommendation of the treat-to-target (T2T) strategy by the European League Against Rheumatism and American College of Rheumatology in 2010 [20], a targeted treatment aiming for clinical remission or low disease activity within 3–6 months from treatment initiation has become the gold standard for RA [21]. Approximately 10 years since its implementation, the T2T strategy

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is being widely accepted. Strictly controlled disease activity should improve inflammation associated with RA and thus improve the activities of daily living (ADLs) [22]. Moreover, improved disease control may contribute to the remodeling of bone metabolism to form normal bone structure not only in the joints but also in the entire body [23], which will subsequently normalize bone mineral density (BMD). In this study, we investigated if RA is associated with a high risk of osteoporosis even when disease activity is well-controlled by determining if patients with RA have a lower BMD than those without RA.

We attempted to evaluate the risk of lower BMD in patients with RA under strictly controlled disease activity versus that in patients without RA both before and after treatment using the propensity score matching (PSM) technique [24,25]. We hypothesize that strictly controlling RA activity can result in equivalent BMD in patients with and without RA.

2. Methods

From September 2017 to August 2019, 741 patients underwent dual-energy X-ray absorptiometry (DXA) in the main institute of corresponding author. The BMDs of lumbar spine (LS), femoral neck (FN), total hip (TH), and greater trochanter (GT) were measured in a similar manner by the same radiology technician using the DPX Bravo bone densitometer (GE Health Care, Chicago, IL, USA). Coefficients of variation were 2.7% on LS, 2.4% on FN, 2.2% on TH, and 1.9% on GT. Patients were divided into groups based on whether or not they were diagnosed with RA (i.e., RA or non-RA group, respectively). Diagnosis of RA was judged with American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria [26].

Our screening and treatment protocol of osteoporosis is as follows: First, X-ray pictures of LS and both sides of the hip joint are taken. And risk factors for osteoporosis such as past bone fragility fracture history, family history, current smoke, diabetes mellitus, arteriosclerosis, chronic obstructive pulmonary disease, are identified at baseline with interview. Subjects were followed up in every 6 months with DXA if subject's BMD demonstrated less than 80% of mean value in 30s in any part, in accordance with the institute's own protocol. No arbitrary was considered for diagnosed as RA.

Before comparing the 2 groups, a multivariate regression analysis was conducted whether the BMD of each bone as a dependent variable correlated the patient's clinical background associated with RA to identify significant independent variables.

First, the BMDs and its change with every 6 months interval of the 2 groups were compared using the Mann-Whitney U-test. Patients in the RA group who were consecutively treated for >1 year and achieved clinical remission by means of a 28-joints disease activity score with C-reactive protein (DAS28-CRP) of lower than 2.3 within 6 months (RA-rem) were recruited, and they were compared with the patients in the non-RA group using the Mann-Whitney U-test. Second, both the groups were compared for the patients' clinical characteristics at baseline: sex distribution, average age, past bone fragility fracture experience, glucocorticoid administration ratio, the number of comorbidities, Barthel Index score, body mass index (BMI), serum-creatinine-to-cystatin C ratio, and osteoporosis drug intervention rate. Third, the BMDs of the 2 groups after these clinical characteristics matched each other with the PSM technique were statistically compared using the Mann-Whitney U-test.

Additionally, to compare BMDs of the RA patients between groups who could and could not attain clinical remission, patients in the RA group for whom the average score of DAS28-CRP in the recent 6 months exceeded 2.3 were selected (RA-nonrem). The BMDs and its change with every 6 months interval of RA-nonrem

were compared with those of the RA-rem after PSM using the Mann-Whitney U-test. Bone fragility fractures during observational period was confirmed with medical record.

All statistical analyses were performed using the StatPlus software (AnalystSoft Inc., Walnut, CA, USA).

2.1. Ethical approval

The study was conducted in compliance with the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects as well as according to the principles of the Declaration of Helsinki. The study protocol and consent forms were approved by the ethics committee of the institution (Yoshii Hospital; approval number: Y-OP-002). Both the patients and their families were informed that personal information would be kept anonymous and would only be used for research purposes. Data were included in this study only after obtaining written informed consent of the patient and his/her family.

3. Results

The study enrolled 741 patients, of which 332 were diagnosed with RA; among these patients, 279 patients were included in RA-rem, while 53 were included in RA-nonrem, and 409 patients were included in non-RA. The multiple linear regression analysis conducted for all patients revealed the BMD of LS was a significantly and positively correlated with BMI and the number of comorbidities ($P < 0.05$). Alternatively, the BMD of FN demonstrated significant positive correlation in the presence of RA and negative correlation with osteoporosis drug intervention ($P < 0.05$). The BMD of TH demonstrated a significant positive correlation with being RA, present GCS administration dose, Barthel Index score, and BMI and negative correlation with osteoporosis drug intervention ($P < 0.05$). The BMD of GT demonstrated a significant positive correlation with being RA, age, male sex, present GCS administration dose, and BMI and demonstrated a significant negative correlation with osteoporosis drug intervention ratio ($P < 0.05$) (Table 1).

The clinical characteristics of the RA and non-RA groups are shown in Table 2. Of the 332 patients in the RA group, 279 were RA-rem. The average age of patients in the non-RA group was 81.5 ± 9.5 . It was significantly older than that of those in the RA group, which was 75.7 ± 10.3 ($P < 0.05$). The glucocorticoid administration ratio was significantly higher in the RA-rem than in the non-RA group ($P < 0.01$). The number of comorbidities that had been informed from medical record and average Barthel Index score were significantly higher in the RA-rem group than that in the non-RA group ($P < 0.01$). Osteoporosis drug administration rate, BMI, and serum-creatinine-to-cystatin C ratio did not significantly differ between the 2 groups. The BMDs of all the assessed bones were higher in the RA-rem group than those in the non-RA group ($P < 0.05$).

PSM revealed that average age, glucocorticoid administration ratio, the number of comorbidities, and average Barthel Index score were approximately equal between the 2 groups. The number of patients with past bone fragility fracture, who were eliminated from both the 2 groups, was 107 and 108 in the RA-rem and non-RA groups, respectively. The clinical characteristics of patients in both the groups after PSM are shown in Table 3 and the clinical background of patients in the RA-rem group before and after PSM are shown in Table 4. Background disease for administrating GCS in the non-RA group configured systemic lupus erythematosus for 8 and 2, polymyalgia rheumatica for 7 and 2, systemic sclerosis for 4 and 2, giant cell arteritis for 2 and 1, and polyarthritis nodosa for 1 and 1, in whom before and after PSM, respectively.

Table 1

Correlation between bone mineral density magnitude and factors of all subjects in each part with P-value.

Factor	Population or mean value	LS	FN	TH	GT
Being RA patient	323 (43.6)	0.126	0.001	0.001	0.003
Age	79.2 ± 10.2	0.216	0.792	0.330	0.021
Being male	72 (9.7)	0.136	0.356	0.151	0.001
Current GCS administration	42 (5.7)	0.099	0.315	0.629	0.357
Current GCS dose, mg/day	3.5 ± 2.6	0.084	0.078	0.037	0.003
GCS administrated	228 (30.8)	0.366	0.732	0.752	0.305
Mean cumulative GCS dose, mg	203.8 ± 604.7	0.129	0.603	0.853	0.554
Osteoporosis drug intervention	522 (70.4)	0.527	0.001	0.001	0.001
Past bone fragility fracture	223 (30.1)	0.914	0.276	0.443	0.934
Frailty score	2.4 ± 2.3	0.224	0.212	0.311	0.152
Barthel Index	70.1 ± 25.8	0.985	0.401	0.015	0.156
Body mass index	21.9 ± 10.2	0.005	0.231	0.049	0.006
Cr/CysC	0.661 ± 0.134	0.316	0.104	0.852	0.554
Dementia treated	205 (27.5)	0.723	0.545	0.642	0.504
No. of comorbidities	11.4 ± 6.2	0.001	0.553	0.929	0.925

Values are presented as number (%) or mean ± standard deviation.

LS, lumbar spine; FN, femoral neck; TH, total hip; GT, greater trochanter; RA, rheumatoid arthritis; GCS, glucocorticoid steroid; Cr/CysC, serum creatinine to cystatin C ratio. In LS, FN, TH, and GT columns, P-value with multiple linear regression analysis are shown.

Plain style shows positive correlation and italic style shows negative correlation.

Bold style with large points shows significant positive correlation ($P < 0.05$), and bold style with large points and with underline shows significant negative correlation ($P < 0.05$). Small pointed number shows no significant correlation ($P > 0.05$).**Table 2**

Background data of each group before propensity score matching procedure.

Variable	RA	Non-RA	P-value
No. of cases	279	409	
Women	256 (91.8)	375 (91.7)	5.279×10^{-1}
Age, yr	75.7 ± 10.3	81.5 ± 9.5	$<1.000 \times 10^{-12}$
Past bone fragility fracture	49 (17.6)	174 (42.5)	$<1.000 \times 10^{-12}$
Osteoporosis drug administration	191 (68.5)	279 (68.2)	9.930×10^{-1}
GCS administration	108 (38.7)	22 (5.4)	$<1.000 \times 10^{-12}$
GCS dose, mg/day	2.4 ± 1.6	4.7 ± 2.8	2.144×10^{-3}
Mean cumulative GCS dose, mg	337.2 ± 547.4	153.7 ± 224.0	$<1.000 \times 10^{-12}$
number of comorbidities	13.5 ± 6.2	10.0 ± 5.8	$<1.000 \times 10^{-12}$
Barthel Index	75.5 ± 22.3	67.7 ± 26.9	2.046×10^{-2}
Body mass index	21.9 ± 2.9	21.9 ± 4.0	6.823×10^{-1}
Cr/CysC	0.67 ± 0.12	0.65 ± 0.14	3.914×10^{-1}
BMD in LS, g/cm ²	0.996 ± 0.199	0.931 ± 0.219	1.090×10^{-5}
BMD in FN, g/cm ²	0.671 ± 0.130	0.615 ± 0.132	1.332×10^{-8}
BMD in TH, g/cm ²	0.721 ± 0.127	0.666 ± 0.144	1.856×10^{-8}
BMD in GT, g/cm ²	0.596 ± 0.121	0.557 ± 0.134	3.750×10^{-5}

Values are presented as number (%) or mean ± standard deviation.

RA, a patient group who is suffered from rheumatoid arthritis; non-RA, a patient group who is not suffered from rheumatoid arthritis; GCS, glucocorticoid steroid; Cr/CysC, serum creatinine to cystatin C ratio; BMD, bone mineral density; LS, lumbar spine; FN, femoral neck; TH, total hip; GT, greater trochanter.

Table 3

Background of each group after propensity score matching procedure.

Variable	RA	Non-RA	p-value
No. of cases	107	108	
Women	102 (95.3)	116 (89.2)	4.776×10^{-1}
Age, yr	73.8 ± 8.8	74.3 ± 10.2	7.520×10^{-1}
Past bone fragility fracture	0 (0)	0 (0)	N/A
Osteoporosis drug administration	69 (64.8)	70 (64.9)	5.973×10^{-1}
GCS administration	10 (9.3)	12 (9.2)	9.312×10^{-1}
GCS dose, mg/day	2.5 ± 1.2	2.7 ± 2.1	8.142×10^{-2}
Mean cumulative GCS dose, mg	132.8 ± 134.0	127.1 ± 162.4	5.854×10^{-1}
number of comorbidities	11.3 ± 3.9	11.0 ± 5.7	8.438×10^{-1}
Barthel Index	78.0 ± 19.0	79.2 ± 16.9	8.022×10^{-1}
Body mass index	22.9 ± 2.8	22.2 ± 4.9	2.908×10^{-1}
Cr/CysC	0.69 ± 0.13	0.67 ± 0.16	2.270×10^{-1}
BMD in LS, g/cm ²	0.994 ± 0.179	0.960 ± 0.235	5.352×10^{-2}
BMD in FN, g/cm ²	0.690 ± 0.122	0.666 ± 0.141	9.793×10^{-2}
BMD in TH, g/cm ²	0.745 ± 0.122	0.722 ± 0.153	1.959×10^{-1}
BMD in GT, g/cm ²	0.611 ± 0.121	0.597 ± 0.142	2.863×10^{-1}

Values are presented as number (%) or mean ± standard deviation.

RA, a patient group who is suffered from rheumatoid arthritis; non-RA, a patient group who is not suffered from Rheumatoid arthritis; GCS, glucocorticoid steroid; Cr/CysC, serum creatinine to cystatin C ratio; BMD, bone mineral density; LS, lumbar spine; FN, femoral neck; TH, total hip; GT, greater trochanter; N/A, not applied. There is no significant difference in the parameters between the 2 groups.

Table 4
Clinical characteristics of the RA group before and after propensity score matching.

Index	Before PSM	After PSM	P-value
No. of cases	279	107	
Age, yr	75.7 ± 10.3	73.8 ± 8.8	5.972 × 10 ⁻²
Women	256 (91.8)	102 (95.3)	6.233 × 10 ⁻¹
Disease duration	11.9 ± 7.7	11.1 ± 7.5	2.874 × 10 ⁻¹
DAS28-CRP	1.79 ± 0.71	1.55 ± 0.40	1.012 × 10 ⁻²
mHAQ	0.596 ± 0.689	0.420 ± 0.650	1.237 × 10 ⁻²
SHS	65.0 ± 73.0	51.2 ± 60.1	1.643 × 10 ⁻¹
Pain VAS	26.1 ± 23.7	21.6 ± 21.3	1.120 × 10 ⁻¹

Values are presented as mean ± standard deviation or number (%).

RA, a patient group who is suffered from rheumatoid arthritis; PSM, Propensity score matching; DAS28-CRP, 28-joints disease activity score with C-reactive protein; mHAQ, modified Health Assessment Questionnaire; SHS, Sharp/van der Heijde Score; Pain VAS, pain score with visual analogue scale.

In statistical significance column, before > after demonstrates significantly greater in before propensity score matching than in after within 5%, and after > before demonstrates significantly greater in after propensity score matching than in before within 5%.

All parameters demonstrated no significant differences between the RA-rem and non-RA groups. The osteoporosis drug administration ratio as a whole as well as the administration ratio of each drug demonstrated no significant difference between the 2 groups (Table 5).

Following PSM, the BMDs of all the assessed bones showed no significant differences between the RA-rem and the non-RA group (Table 3).

The BMDs and clinical characteristics of the RA-rem group after PSM and the RA-nonrem group are shown in Table 6. Number of cases, number of females, and Barthel Index score of the RA-rem demonstrated significantly greater than of the RA-nonrem, while past bone fragility fracture experienced patients were significantly more in the RA-nonrem than in the RA-rem. The Health Assessment Questionnaire (HAQ) score and DAS28-CRP in recent 6 months were significantly greater in the RA-nonrem than in the RA-rem ($P < 0.05$). BMD of LS, FN, and GT in RA-rem was significantly greater than that in the RA-nonrem; however, after age and sex correction was performed, BMDs of all parts in the RA-rem were significantly greater than those in the RA-nonrem ($P < 0.05$).

Table 5
Osteoporosis drug administration before and after propensity score matching for each group.

Adminstrated drug	RA	Non-RA	P-value
Before propensity score matching			
Denosumab	168 (60.2)	227 (55.5)	2.195 × 10 ⁻¹
Bisphosphonate	7 (2.5)	39 (9.5)	2.912 × 10 ⁻²
SERM	6 (2.2)	3 (0.7)	1.082 × 10 ⁻¹
Daily teriparatide	2 (0.7)	5 (1.2)	5.164 × 10 ⁻¹
Weekly teriparatide	1 (0.4)	5 (1.2)	2.314 × 10 ⁻¹
Drug naïve	88 (31.5)	130 (31.8)	9.462 × 10 ⁻¹
Total	279	409	
After propensity score matching			
Denosumab	66 (60.7)	65 (50.0)	7.186 × 10 ⁻²
Bisphosphonate	1 (0.9)	2 (3.8)	7.286 × 10 ⁻¹
SERM	2 (1.9)	0 (0)	N/A
Daily teriparatide	0 (0)	0 (0)	N/A
Weekly teriparatide	0 (0)	1 (1.9)	N/A
Drug naïve	38 (35.5)	40 (37.0)	5.565 × 10 ⁻¹
Total	107	108	

Values are presented as number (%).

RA, a patient group who was suffered from rheumatoid arthritis; non-RA, a patient group who was not suffered from rheumatoid arthritis; SERM, selective estrogen-receptor modulator; N/A, not applicable.

In statistical significance column, RA > non-RA demonstrates significantly greater in the RA group than in the non-RA group within 5%, and RA < non-RA demonstrates significantly greater in the non-RA group than in the RA group within 5%.

BMDs were measured in total number of subjects with 108, 98, 84, and 62 in the non-RA, 107, 79, 62, and 50 in the RA-rem, and 53, 44, 39, and 34 in the RA-nonrem group, at the baseline, month 6, 1 year, and 1 and a half year, respectively. The change of BMDs at 6 months and at 1 year after baseline demonstrated no significant difference in both of between the RA-rem and non-RA groups, and between the RA-rem and RA-nonrem group (Supplementary Figs. 1 and 2). Bone fragility fractures during the observational period were confirmed in 3 cases for the non-RA, in 2 for the RA-rem, and in 3 for the RA-nonrem.

4. Discussion

RA is the disease that is independently associated with a high risk of osteoporosis, which is evident both for the risk of fracture [1,4,6,8,9] and BMD loss [2,3,5,7,27]. Reasons contributing to this risk are as follows: (1) severe continual inflammation within the entire body, (2) decreased mobility due to joint deformation, polypharmacy, or cachexia, and leded muscle weakness [18], (3) the frequent use of GCS, and (4) anticyclic citrullinated peptide antibodies, which has recently been identified as a causative factor [28]. Numerous studies have reported on the high risk of fracture and BMD loss in patients with RA. In summary, the potential factors contributing to these risk include: (1) increasing age and female sex as well as postmenopausal status [1–3,5,8,9,17,29–32], (2) higher disease activity [7,13,16,19,28,31–33], (3) high physical disability complicating ADLs or increased HAQ score [1–3,17,30,32,34], (4) long disease duration [6,17,19,29,32], (5) relatively young onset age [32], (6) low body weight [1–3,5,6,17,29,30], (7) grip strength weakness or muscle power weakness [29], and (8) current GCS use and the cumulative dose of GCS [1,2,6,13–15,19,29–31]. Among these factors, (2) is considered essential for inflammation; (3) is thought to result in severe inflammation; (4) and (5) indicate a high risk of unresolved inflammation; (8) is often viewed as an anti-inflammatory therapy; and (1), (6), and (7) are physical problems and are commonly listed regardless of RA [35–38]. Accordingly, inflammation is the primary cause for RA being the risk factor of osteoporosis.

As the T2T strategy has resulted in a paradigm shift, RA treatment has drastically improved and clinical remission has become a routine treatment target in daily clinical practice. Currently, in our institute, 90% of patients with RA are treated to control disease activity or to achieve clinical remission. Alternatively, in RA treatment, inflammation has become a potential target for ensuring strict control over disease activity. Under these situations, it is unclear if being affected with RA is still a risk factor of osteoporosis. Patients with RA are also exposed to many other risk factors associated with osteoporosis. However, most of these risk factors come from long-lasting inflammation and inappropriate treatment, including unnecessary glucocorticoid administration. If inflammation of RA is strictly controlled, the risk of osteoporosis should be diminished.

Before comparing patients with RA with those without RA, multivariate linear regression analysis was conducted to clarify significant factors affecting the BMD of each of the assessed bone. We evaluated the relationship between the BMD of the assessed bones along with risk factors such as the presence of RA, age, sex, current GCS administration and dosage, past GCS administration and total administered dose, osteoporosis drug intervention, bone fragility fracture history, frailty score, BMI, serum-creatinine-to-cystatin C ratio (as an index for sarcopenia), and the number of comorbidities. The results demonstrated that having RA, male sex, present GCS dosage, higher Barthel Index score, and higher BMI were significantly correlated with higher BMD of all the assessed bones. The number of comorbidities demonstrated a significant,

Table 6
Background of each patient group with rheumatoid arthritis in remission and nonremission.

Variable	RA-rem	RA-nonrem	P-value
No. of cases	107	53	
Women	102 (95.3)	43 (81.1)	1.269×10^{-1}
Age, yr	73.8 ± 8.8	78.6 ± 8.1	5.499×10^{-2}
Past bone fragility fracture	0 (0)	6 (11.3)	$<1.000 \times 10^{-12}$
osteoporosis drug administration	69 (64.8)	37 (67.9)	9.134×10^{-1}
GCS administration	10 (9.3)	5 (9.4)	8.573×10^{-1}
GCS dose, mg/day	2.5 ± 1.2	2.7 ± 2.4	0.999×10^{-1}
Mean cumulative GCS dose, mg	132.8 ± 134.0	148.5 ± 320.8	4.953×10^{-1}
number of comorbidities	11.3 ± 3.9	11.5 ± 5.7	9.974×10^{-1}
Barthel Index	78.0 ± 19.0	62.2 ± 26.3	2.543×10^{-2}
HAQ score in recent 6 months	0.420 ± 0.650	1.040 ± 0.782	6.524×10^{-6}
DAS28-CRP in recent 6 months	1.55 ± 0.34	2.99 ± 0.90	$<1.000 \times 10^{-12}$
Body mass index	22.9 ± 2.8	21.1 ± 2.8	2.922×10^{-1}
Cr/CysC	0.69 ± 0.13	0.67 ± 0.13	9.795×10^{-1}
BMD in LS, g/cm ²	0.994 ± 0.179	0.938 ± 0.209	1.151×10^{-2}
BMD in FN, g/cm ²	0.690 ± 0.122	0.627 ± 0.150	2.393×10^{-3}
BMD in TH, g/cm ²	0.745 ± 0.122	0.686 ± 0.153	8.746×10^{-3}
BMD in GT, g/cm ²	0.611 ± 0.121	0.594 ± 0.144	8.957×10^{-2}
BMD in LS after age and sex correction, %mean	100.3 ± 18.5	96.9 ± 22.6	1.653×10^{-2}
BMD in FN after age and sex correction, %mean	95.3 ± 16.1	89.3 ± 21.9	2.431×10^{-2}
BMD in TH after age and sex correction, %mean	86.7 ± 14.8	80.3 ± 19.4	1.149×10^{-2}
BMD in GT after age and sex correction, %mean	101.6 ± 17.4	93.6 ± 22.6	9.230×10^{-3}

Values are presented as number (%) or mean \pm standard deviation.

RA-rem, a RA patient group of whom clinical remission in past 6 months have been attained; RA-nonrem, a RA patient group of whom clinical remission in past 6 months could not be attained; GCS, glucocorticoid steroid; HAQ, Health Assessment Questionnaire; DAS28-CRP, 28-joints disease activity score with C-reactive protein; Cr/CysC, serum creatinine to cystatin C ratio; BMD, bone mineral density; LS, lumbar spine; FN, femoral neck; TH, total hip; GT, greater trochanter.

RA-rem > RA-nonrem; in the RA-rem greater value is demonstrated than in the RA-nonrem. RA-rem < RA-nonrem; in the RA-rem smaller value is demonstrated than in the RA-nonrem. All the statistical procedures were performed with Mann-Whitney U-test. Statistical significance was set within 5%.

positive correlation with the BMD of LS. Aging and osteoporosis drug intervention demonstrated a negative correlation with higher BMD in FM, TH, and GT. We selected these factors as targets for PSM.

The PSM method is a statistical technique that uses with 2 groups with different levels of background data and is typically used for statistically comparing observational data [24]. Using this technique, 2 groups of different clinical backgrounds, such as those in this study, can be compared without case bias. However, this method may result in the elimination of participants; thus, there is an inherent disadvantage of reduction in the number of cases. Fortunately, the sample size in the present study in each group was >100, which was adequate for comparison using this technique.

Age did not contribute to low BMD in LS; however, a lower BMI did contribute to low BMD in every assessed bone. These results may result from the fact that the patients included in this study were relatively old, with average and median ages of 79.2 and 81 years, respectively. Thus, the data may not be strong enough to demonstrate age as a significant factor affecting BMD in LS. The mean age of the RA group was significantly lower than that of the non-RA group, and mean BMD of the RA group was higher than that of the non-RA group. Thus, as we believed that age differences may affect BMD results, age was adjusted for in PSM.

Serum-creatinine-to-cystatin C ratio has recently been highlighted as a surrogate marker of relative muscle volume. Cystatin C is a protein that is widely used as a biomarker for renal function. Creatinine is also widely used for renal function assessment. However, creatinine differs from cystatin C as it is produced only from cross-striated muscle tissue, and therefore, serum creatinine is affected by muscle volume. Serum-creatinine-to-cystatin C ratio can be calculated and is presently in focus as it reflects muscle volume and can be specifically utilized as an index of sarcopenia [39,40]. There was no significant difference in the serum-creatinine-to-cystatin C ratio between the RA and non-RA groups. So, attention was paid not to make a significant difference between values before and after within the PSM procedure for each group.

With regard to sex, changes in BMD were demonstrated in the GT in the present study with multivariate regression analysis. However, in the present study, no significant difference was noted with regard to sex distribution between the 2 groups. Thus, we had to ensure that there were no significant differences in for serum-creatinine-to-cystatin C ratio comparing before and after the PSM.

Body weight is major factor determining BMI and affecting bones. Bone remodeling is activated by gravity, and higher body weight results in increased gravity load on the bone. In this study, no significant difference was observed in BMI between the 2 groups before PSM; thus, attention was paid not to make significant difference between the 2 groups after score matching as well as for serum-creatinine-to-cystatin C ratio and sex distribution.

Osteoporosis drug administration at the time of measurement is a very important contributing factor of BMD change [27]. In this multivariate regression analysis, drug intervention was significantly and negatively correlated with the BMD of the entire proximal femur. This may be because the BMD of the patients, who were administered with osteoporosis drugs, was so low that they had to be treated with antiosteoporosis therapy.

ADL or physical dysfunction is also an important factor affecting BMD in all bones [1–3,17,30,32,34]. The most popular index of ADL for patients with RA is the HAQ. However, it is not universally used for patients without RA. Therefore, as a substitute, the Barthel Index was employed in the present study. This index consists of a ten-item questionnaire and scores ADL levels from 0 to 100 points [41]. The Barthel Index score of the RA group was significantly greater than that of the non-RA group before PSM. Thus, Barthel Index score made no significant difference after score matching in that there was no significant difference between the 2 groups.

In addition to Barthel Index score, bone fragility fracture history [6], frailty score, treated dementia, and the number of comorbidities were all evaluated before comparing the 2 groups; however, except for the number of comorbidities, no significant correlation was obtained between any of the factors noted above. Thus, the number of comorbidities was selected as a variable in PSM. We

eliminated past bone fragility fracture cases in PSM procedures; therefore, we did not need further correction regarding prevalence of bone fragility fracture. Although this variable was significantly higher in the RA-rem group than that in the non-RA group before PSM, after matching no significant difference was noted between the groups.

It is convincing that GCS administration affects osteoporosis. There are many instances when GCS can be administered to decrease inflammation and control disease activity during treatment. Many reports have suggested that the risk of osteoporosis in patients with RA is contributed by GCS administration, especially in terms of longevity and the total amount of drugs administered [1,2,6,13–15,19,29–31]. However, studies suggesting that current GCS administration as a risk factor are few [5,42–44]. It is still unclear whether low-dose administration of GCS is a risk factor of low BMD. Some studies have reported that low-dose GCS administration is not a risk factor [5,42]. In contrast, another study suggested that low-dose GCS administration can prevent BMD loss, primarily due to inflammation control [43]. GCS administration is a risk factor of osteoporotic fractures; however, the effect of low-dose GCS administration on BMD remains unclear. In this study, GCS administration and dosage did not influence BMD in either of the groups. This may be because of the fact that the dosage, both before and after PSM procedure in both groups, was relatively low, as shown in Tables 2 and 3

We attempted to evaluate whether patients with RA treated using the T2T strategy and with sustained clinical remission acquire no specific disadvantage regarding bone metabolism. Our results revealed no significant differences in BMD in patients with RA compared with that in patients without RA. Moreover, we compared BMDs in patients whose disease activity could not attain clinical remission with those in patients who were in clinical remission. We found that patients who were in clinical remission could achieve greater BMD values than those who were not in clinical remission. The results of these findings supported our hypothesis that patients with RA treated with the T2T strategy and with well-controlled disease activity demonstrate no significant difference in BMD when compared with patients without RA. Moreover, it has been suggested that disease activity is a significant determinant of bone turnover in RA, and first priority must be given to controlling disease activity to prevent systemic bone loss [33]. Prior to PSM, the BMDs of every assessed bone were significantly higher in the RA-rem group than those in the non-RA group. However, this may be due to a significantly lower average age and higher Barthel Index score in the RA-rem group than those in the non-RA group. After PSM, these differences were diminished.

Our study has some limitations. Ethnicity, frailty, dementia, and large joint involvement in patients with RA were not considered. The major limitation is that this was not a randomized controlled study. BMDs for each group were followed but, number of measured cases decreased as the period progressed. Number of bone fragility fracture was confirmed from medical record, however, cases lost to follow-up was not included. Thus, future bone fragility fractures could not be taken into consideration. Presently, improvement in RA disease activity does not result in a decrease in the prevalence of vertebral fractures [45]. Second limitation is relatively small number in the RA-nonrem group. This may interfere accuracy of statistical results. However, these limitations do not impede arrival to the conclusion that RA alone is not a risk factor for decreased BMD; thus, as long as the RA disease activity is strictly controlled, RA will not contribute to low BMD.

5. Conclusions

In conclusion, although RA is threatened by strong osteoporosis risk, as long as disease activity is well controlled and inflammation

caused by RA is settled, risk of bone mineral density loss is diminished. Therefore, disease activity control is essentially important not only for ADL maintenance but also osteoporosis control.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

CRedit author statement

Ichiro Yoshii: Conceptualization, Formal analysis, Writing – Original Draft. **Tatsumi Chijiwa:** Methodology, Validation, Formal analysis, Data Curation. **Naoya Sawada:** Investigation, Resources, Writing – Review & Editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.afos.2020.04.002>.

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