

Time-averaged disease activity of rheumatoid arthritis associated with long-term bone mineral density changes

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Abstract

Background: Rheumatoid arthritis (RA) is associated with poor bone mineral density (BMD). We designed the current study owing to the lack of long-term prospective studies regarding whether a high disease activity leads to increased bone loss.

Methods: We have continually enrolled patients with RA. According to the average disease activity score in 28 joints based on the erythrocyte sedimentation rate (DAS28-ESR) during follow-up, the patients were classified into remission, low disease activity, and moderate or high disease activity groups. Patients were examined with dual-energy X-ray absorptiometry at baseline and after 3 years of follow-up. BMD changes were compared among the groups.

Results: We have studied 477 patients. Overall BMD was significantly reduced from baseline to the 3-year follow-up ($p < 0.05$). After stratifying according to the time-averaged DAS28-ESR levels and use of anti-osteoporosis treatment (AOT), the BMD values of the femur and spine significantly increased in patients in the remission group with AOT. The BMD changes of different DAS28-ESR patients were further compared using the generalized estimation equation model. For the patients on AOT, the negative change in femoral BMD values of the moderate or high activity group was significant when compared with the remission group with positive BMD changes (regression coefficient, -0.038 ; 95% confidence interval, -0.055 to -0.021).

Conclusion: For RA patients, if remission is achieved, AOT can better improve BMD, especially in the femur. In addition, moderate or high disease activity will lead to significant bone loss; therefore, disease activity must be actively controlled.

Keywords: arthritis, bone density, osteoporosis, rheumatoid disease activity

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Introduction

Osteoporosis is a bone disease that increases bone fragility and the risk of fractures, resulting in increased morbidity and mortality. In the United States and Europe, approximately 30% of postmenopausal women have osteoporosis.¹ In Taiwan, with the rapidly aging population, the impact of osteoporosis and hip fractures will become apparent in the coming years.² There are several clinical risk factors associated with osteoporosis on the Fracture Risk Assessment Tool

(FRAX[®]),³ and rheumatoid arthritis (RA) is one of them.

Although severe RA can cause joint deformities and disability, this situation can be addressed with the early use of disease-modifying antirheumatic drugs and biologics to control the disease. Aggressive treatment with biologics also reduces the rate of bone deterioration although the effect of anti-osteoporosis treatment (AOT) may be better than that of biologics.⁴ By controlling

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disease activity and inflammation, the development of osteoporosis can be prevented.⁵

Disease activity is an important determinant of RA bone turnover.⁶ Moreover, a previous study indicated an association between high-radiological RA damage and low hip bone mineral density (BMD).⁷ It suggested an association between RA severity and general risk of bone loss. Disease activity is often mentioned in studies on the risk factors for osteoporosis in patients with RA.⁸ However, these retrospective or cross-sectional studies do not provide sufficient information on whether controlled disease activity affects changes in the BMD.^{7–12} In contrast, some studies using baseline Disease Activity Score (DAS) to represent disease activity do not account for the impact of disease activity over time.^{8,9}

In addition, AOT is the most important treatment for osteoporosis. However, there are no reports on whether AOT induces different effects in different disease activity groups. Therefore, we designed a prospective study to observe changes in BMD between different time-averaged disease activity groups. Furthermore, we analyzed the differences in the effect of AOT between these groups.

Materials and methods

This was a 3-year prospective study designed to analyze changes in BMD in RA patients registered with Kaohsiung Chang Gung Memorial Hospital (KCGMH). We registered consecutive RA patients who had been at the KCGMH Rheumatology Clinic since 1 September 2014 and met the 1987 American Rheumatology Association (ACR) revised criteria¹³ or the 2010 ACR/European League against Rheumatism classification criteria.¹⁴ Patients aged <20 years, those who had had any malignancy within the last 5 years, those who may not be able to complete the 3-year follow-up (those with major organ failure or bedridden), and those who were unwilling to participate in the study were excluded from the registration plan.

In addition, because we wanted to compare the 3-year change in BMD, the data of patients who did not complete the 3-year follow-up could not be used for analysis because there was no second set of BMD data.

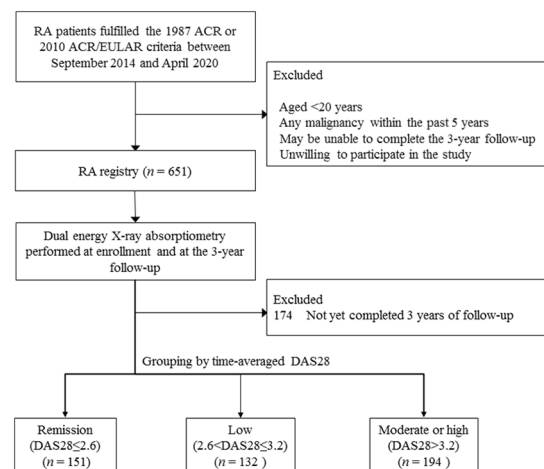


Figure 1. Enrollment of the patients in the study. ACR, American College of Rheumatology; DAS, Disease Activity Score; EULAR, European League Against Rheumatism; RA, rheumatoid arthritis.

All participants provided written informed consent. The KCGMH Institutional Review Board approved the study (104-3530B), which was conducted in accordance with the guidelines of the Declaration of Helsinki.

Clinical assessments included demographic data, anti-citrullinated protein antibodies (ACPAs), rheumatoid factor (RF), and duration of disease. We collected information about current medications at the time of registration. In addition, lifestyle, previous fragility fractures, and risk factors for fragility fractures based on the FRAX[®] tool were recorded. We used the DAS in 28 joints based on the erythrocyte sedimentation rate (DAS28-ESR) to assess RA DAS at least every 3 months. The participants were categorized according to the 3-year time-averaged DAS28-ESR as follows: group 1 – disease remission (DAS28-ESR ≤ 2.6), group 2 – low disease activity (2.6 < DAS28-ESR ≤ 3.2), and group 3 – moderate or high disease activity (DAS28-ESR > 3.2; Figure 1).

The change in BMD was the primary outcome. Therefore, the BMDs of the hip (total), femur, and lumbar spine (L1–L4) were measured using a dual-energy X-ray absorptiometry scanner (Delphi A; Hologic Corp., Waltham, MA, USA) at enrollment and after the 3-year follow-up. We calculated and compared the BMD changes between and within the different DAS groups. In

addition, since the use of AOT was one of the main factors affecting BMD, we stratified the main analysis by AOT. The use of AOT was defined as the use of any AOT including bisphosphonates, denosumab, raloxifene, estrogen, or teriparatide within the 3-year period.

Statistical analysis

The patient characteristics among different time-averaged DAS levels (remission, low, and moderate or high) were compared using the chi-square test for categorical variables, one-way analysis of variance for continuous variables that were normally distributed, and the Kruskal–Wallis test for continuous variables that were non-normally distributed (e.g. alanine aminotransferase and C-reactive protein). Pairwise comparisons between any two groups were made using Bonferroni adjustment. The changes in the BMD values from baseline to the third-year values were compared using the paired-sample *t*-test. This analysis was further stratified by time-averaged DAS and using AOT. The changes in the BMD values from baseline to the third year among patients with different time-averaged DAS (as categorical factor) were analyzed using one-way analysis of variance with Bonferroni-adjusted multiple comparison. In addition, the different time-averaged DAS was also treated as an ordinal variable in the one-way analysis of variance with linear contrast. Finally, the generalized estimating equation (GEE) model was used to evaluate the changes in the BMD values during the 3-year follow-up among patients with different time-averaged DAS, after adjustment for the potential confounding factors. The selected covariates are the parameters in the FRAX[®] assessment,³ including age, sex, body mass index, previous fractures, parental hip fractures, current smoking and drinking status, and lifestyle,^{15,16} such as coffee and tea consumption and vegetarianism. In addition, other covariates were also adjusted, including RF, anti-cyclic citrullinated peptide, disease duration, and daily prednisolone equivalent dose. Postmenopausal women are a group of patients susceptible to osteoporosis; therefore, a subgroup analysis for postmenopausal women alone was performed.

The GEE model included the intercept, the main effect of time (third year *versus* baseline) and different time-averaged DAS levels (categorical factor: remission, low, and moderate or high), and two-way interactions of time by different time-averaged

DAS levels. In an alternative GEE model, the different time-averaged DAS was treated as an ordinal variable in order to assess trends over categories of DAS. A two-sided *p*-value < 0.05 was considered statistically significant. These are exploratory analyses; thus, there was not enough power to adjust for multiple testing. Data analyses were conducted using SPSS 25 (IBM SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

A total of 477 patients with RA completed 3 years of follow-up since September 2014 at our hospital. The average age was 57.8 years and the cohort was predominantly female (85.1%); 65.6% of the patients were positive for RF and 67.9% had ACPAs. Within 3 years, 32.9% of patients had used AOT. Of these, 16.4% (29 patients) did not use AOT at baseline and received AOT during the subsequent study period. For a few patients who started receiving AOT during the subsequent study period, the time of initiating AOT was inconsistent and depended on the doctor's judgment. According to the mean DAS28-ESR during the 3-year follow-up, the patients were divided into Group 1 (151 patients in disease remission), group 2 (132 patients with low disease activity), and group 3 (194 patients with moderate or high disease activity). The low and moderate or high groups were more predominantly female and less likely to have current smoking status than the remission group. The moderate or high group was more likely to be prescribed AOT than the other groups. In addition, the moderate or high group also had greater numbers of postmenopausal women, patients previously using AOT, patients with the possibility of being prescribed glucocorticoids, and patients with higher daily prednisolone equivalent doses than the remission group (Table 1).

In addition, 174 patients did not complete the 3-year follow-up and were therefore not included in the analysis. The characteristics between the group without complete follow-up and the analyzed cohort were compared and are listed in Supplemental material Table 1 online. The results showed that patients who did not complete the follow-up were older and had lower body mass index values, more menopausal women, longer

Table 1. Characteristics of the study patients with different mean DAS levels during 3-year follow-up.

Variable	Total N=477	Remission n=151	Low n=132	Moderate or high n=194	p value
Characteristic					
Age, years	57.8 ± 10.5	56.3 ± 11.0	57.2 ± 10.6	59.3 ± 9.8	0.025
Female	406 (85.1)	117 (77.5)	116 (87.9) ^a	173 (89.2) ^a	0.008
Body mass index, kg/m ²	23.7 ± 3.9	23.9 ± 4.1	23.7 ± 3.6	23.6 ± 4.0	0.840
Previous fracture	151 (31.7)	43 (28.5)	38 (28.8)	70 (36.1)	0.238
Parent fractured hip	37 (7.8)	13 (8.6)	15 (11.4)	9 (4.6)	0.069
Current smoking	31 (6.5)	19 (12.6)	4 (3.0) ^a	8 (4.1) ^a	0.002
Alcohol	7 (1.5)	1 (0.7)	2 (1.5)	4 (2.1)	0.567
Coffee	76 (15.9)	26 (17.2)	26 (19.7)	24 (12.4)	0.169
Tea	88 (18.4)	30 (19.9)	31 (23.5)	27 (13.9)	0.075
Vegetarian	26 (5.5)	8 (5.3)	4 (3.0)	14 (7.2)	0.257
Menopause; total female = 406	319 (78.6)	85 (72.6)	86 (74.1)	148 (85.5) ^a	0.012
Previous AOT	132 (27.7)	31 (20.5)	35 (26.5)	66 (34.0) ^a	0.020
Disease duration, year	13.8 ± 9.1	12.5 ± 9.1	14.2 ± 8.2	14.7 ± 9.5	0.070
DAS					
At baseline	3.3 ± 1.2	2.5 ± 0.8	3.1 ± 0.9 ^a	4.1 ± 1.2 ^{a,b}	<0.001
Average during follow-up	3.1 ± 0.9	2.1 ± 0.4	2.9 ± 0.2 ^a	4.0 ± 0.7 ^{a,b}	<0.001
Laboratory					
RF	300 (65.6)	83 (57.6)	83 (67.5)	134 (70.5) ^a	0.044
Anti-CCP	320 (67.9)	92 (61.3)	89 (68.5)	139 (72.8)	0.082
iPTH, pg/ml	42.2 ± 22.6	40.9 ± 19.2	40.9 ± 17.3	44.1 ± 27.6	0.319
25-OH-Vitamin D, ng/ml	22.6 ± 7.5	22.3 ± 6.9	22.9 ± 7.8	22.7 ± 7.8	0.847
Creatinine, mg/dl	0.73 ± 0.22	0.73 ± 0.23	0.70 ± 0.18	0.74 ± 0.23	0.235
ALT, U/l	21.0 (14.0, 32.0)	24.0 (15.0, 38.0)	20.0 (14.0, 27.0)	21.0 (14.0, 32.0)	0.091
WBC, 10 ³ /mm ³	7.0 ± 2.2	7.1 ± 2.1	7.1 ± 2.4	6.7 ± 2.0	0.145
Hemoglobin, g/dl	12.9 ± 1.5	12.8 ± 1.4	12.9 ± 1.6	12.9 ± 1.5	0.952
Blood platelet, 10 ³ /μl	248 ± 71	244 ± 65	260 ± 73	244 ± 73	0.102
ESR, mm/h	23.1 ± 20.3	23.8 ± 20.6	23.4 ± 20.9	22.4 ± 19.7	0.818
CRP, mg/dl	2.3 (0.8, 7.3)	1.8 (0.8, 5.7)	2.5 (0.9, 8.9)	2.7 (0.8, 7.2)	0.279

(Continued)

Table 1. (Continued)

Variable	Total N=477	Remission n=151	Low n=132	Moderate or high n=194	p value
Baseline bone mineral density, g/cm ²					
Femoral	0.63 ± 0.12	0.65 ± 0.14	0.64 ± 0.10	0.61 ± 0.11 ^a	0.004
Hip	0.79 ± 0.14	0.81 ± 0.14	0.80 ± 0.13	0.76 ± 0.14 ^{a,b}	0.001
Spine	0.87 ± 0.17	0.89 ± 0.17	0.89 ± 0.17	0.84 ± 0.16 ^{a,b}	0.003
Medication					
AOT	157 (32.9)	43 (28.5)	33 (25.0)	81 (41.8) ^{a,b}	0.003
Biological agent	123 (25.8)	32 (21.2)	39 (29.5)	52 (26.8)	0.251
Glucocorticoid	436 (91.4)	128 (84.8)	121 (91.7)	187 (96.4) ^a	0.001
Daily prednisolone equivalent dose	4.3 ± 2.2	3.8 ± 2.4	4.2 ± 2.1	4.7 ± 2.0 ^a	0.001
Data are presented as frequency (%), mean ± standard deviation or median (25th, 75th percentiles).					
^a Significant difference <i>versus</i> the "remission" group in the Bonferroni multiple comparison.					
^b Significant difference <i>versus</i> the "low" group in the Bonferroni multiple comparison.					
ALT, alanine aminotransferase; Anti-CCP, anti-cyclic citrullinated peptide; AOT, anti-osteoporosis therapy; BMD, bone mineral density; CRP, C-reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; iPTH, intact parathyroid hormone; RF, rheumatoid factor; WBC, white blood cells.					

disease duration, lower hemoglobin level, and lower baseline BMD values at the femoral and hip were more likely to have received previous AOT treatment and were less likely to have received glucocorticoids.

Changes in BMD of the femur, hip, and spine during the 3-year follow-up period

During the 3-year follow-up, there was a significant decrease in the BMD values of the femur, hip, and spine ($p < 0.05$) in the whole cohort. After stratification by the use of AOT, we found that the BMD values did not decrease from baseline to follow-up in the femur, hip, and spine, and the BMD had even significantly increased in the spine ($p = 0.044$) in the group with AOT use. When the analysis was stratified by the time-averaged DAS level, even with AOT, the femoral BMD value of patients in the moderate or high group was significantly reduced ($p = 0.017$). However, the BMD values of the femur ($p = 0.001$) and spine ($p = 0.021$) of patients in the remission group who received AOT increased significantly. In contrast, regardless of whether AOT was used, the BMD value in the moderate or high group did not increase significantly or it even decreased (Table 2).

The changes in the BMD of patients with different time-averaged DAS during the 3-year follow-up were compared. Patients on AOT in the moderate or high group showed a greater decrease in the BMD values of the femur than patients in the remission group ($p = 0.001$). Patients not on AOT in the moderate or high group showed a greater decrease in the BMD values of the hip than patients in the remission group ($p = 0.023$). Differences in the BMD changes in the spine were not observed among the different time-averaged DAS levels, regardless of the use of AOT. When treating the different time-averaged DAS as an ordinal factor, similar results were observed – that the change in femoral BMD in patients with AOT and the change in hip BMD in patients without AOT was toward a greater decrease with the higher time-averaged DAS level (Table 3).

The GEE model, after adjustment for possible confounding factors, confirmed the results of the previous univariate analysis, irrespective of the time-averaged DAS level, and was treated as a categorical or ordinal factor (Table 4). In addition, there was a significant trend of bone density loss as disease activity increased. The changes in the BMD values among the different time-averaged

Table 2. The change in bone mineral density of patients according to different mean Disease Activity Score levels during 3-year follow-up.

BMD, g/cm ²	Total N=477			Remission n=151			Low n=132			Moderate or high n=194		
	Baseline	3rd year	p	Baseline	3rd year	p	Baseline	3rd year	p	Baseline	3rd year	p
Femoral												
Total	0.63 ± 0.12	0.62 ± 0.11	<0.001	0.65 ± 0.14	0.65 ± 0.13	0.110	0.64 ± 0.10	0.62 ± 0.10	<0.001	0.61 ± 0.11	0.59 ± 0.11	<0.001
AOT	0.56 ± 0.08	0.56 ± 0.09	0.893	0.56 ± 0.09	0.58 ± 0.09	0.001	0.57 ± 0.08	0.58 ± 0.08	0.709	0.56 ± 0.08	0.55 ± 0.10	0.017
Non-AOT	0.66 ± 0.12	0.64 ± 0.11	<0.001	0.69 ± 0.14	0.67 ± 0.13	0.001	0.66 ± 0.10	0.63 ± 0.10	<0.001	0.65 ± 0.11	0.63 ± 0.11	<0.001
Hip												
Total	0.79 ± 0.14	0.78 ± 0.13	0.024	0.81 ± 0.14	0.81 ± 0.14	0.981	0.80 ± 0.13	0.79 ± 0.12	0.246	0.76 ± 0.14	0.75 ± 0.13	0.011
AOT	0.71 ± 0.11	0.72 ± 0.12	0.099	0.73 ± 0.11	0.74 ± 0.11	0.375	0.73 ± 0.11	0.74 ± 0.10	0.260	0.69 ± 0.11	0.70 ± 0.12	0.325
Non-AOT	0.82 ± 0.14	0.81 ± 0.13	<0.001	0.85 ± 0.14	0.84 ± 0.14	0.596	0.82 ± 0.13	0.81 ± 0.12	0.070	0.81 ± 0.13	0.78 ± 0.13	<0.001
Spine												
Total	0.87 ± 0.17	0.86 ± 0.17	0.037	0.89 ± 0.17	0.89 ± 0.17	0.439	0.89 ± 0.17	0.87 ± 0.18	0.054	0.84 ± 0.16	0.84 ± 0.17	0.301
AOT	0.78 ± 0.14	0.80 ± 0.16	0.044	0.80 ± 0.16	0.82 ± 0.17	0.021	0.77 ± 0.13	0.77 ± 0.14	0.565	0.76 ± 0.14	0.79 ± 0.16	0.136
Non-AOT	0.91 ± 0.16	0.89 ± 0.17	<0.001	0.93 ± 0.16	0.92 ± 0.17	0.011	0.93 ± 0.16	0.91 ± 0.17	0.060	0.89 ± 0.16	0.86 ± 0.17	0.002

AOT, anti-osteoporosis therapy; BMD, bone mineral density.

Table 3. The change of bone mineral density during 3-year follow-up among patients with different mean Disease Activity Score levels stratified by the use of anti-osteoporosis agent.

Outcome/ subgroup	Total N=477	Remission n=151	Low n=132	Moderate or high n=194	p value	p trend
Change of femoral BMD, g/cm ²						
Total	-0.014 ± 0.051	-0.008 ± 0.057	-0.017 ± 0.047	-0.018 ± 0.047	0.140	0.063
AOT	-0.001 ± 0.049	0.022 ± 0.041	0.003 ± 0.045	-0.014 ± 0.051 ^a	0.001	<0.001
Non-AOT	-0.021 ± 0.050	-0.019 ± 0.059	-0.024 ± 0.045	-0.020 ± 0.045	0.775	0.825
Change of hip BMD, g/cm ²						
Total	-0.007 ± 0.064	0.0001 ± 0.0644	-0.006 ± 0.057	-0.013 ± 0.067	0.188	0.069
AOT	0.009 ± 0.063	0.009 ± 0.065	0.009 ± 0.047	0.008 ± 0.068	0.991	0.922
Non-AOT	-0.014 ± 0.063	-0.003 ± 0.064	-0.011 ± 0.059	-0.026 ± 0.063 ^a	0.023	0.007
Change of spine BMD, g/cm ²						
Total	-0.007 ± 0.071	-0.004 ± 0.064	-0.011 ± 0.066	-0.006 ± 0.078	0.682	0.806
AOT	0.014 ± 0.079	0.025 ± 0.065	-0.007 ± 0.067	0.016 ± 0.090	0.229	0.587
Non-AOT	-0.016 ± 0.064	-0.015 ± 0.060	-0.013 ± 0.066	-0.020 ± 0.066	0.694	0.568
^a Significant difference <i>versus</i> the "remission" group in the Bonferroni multiple comparison. AOT, anti-osteoporosis therapy; BMD, bone mineral density.						

DAS levels stratified by the use of AOT are shown in Figure 2.

Subgroup analysis for postmenopausal women was also performed using the GEE model. For patients receiving AOT, the femoral BMD value of the moderate or high group decreased more than that of the remission group ($p < 0.001$). In an alternative model that treated disease activity as an ordinal variable, there was also a trend in the BMD loss as disease activity increased (p trend < 0.001) (Supplemental Table 2).

Discussion

To the best of our knowledge, the current prospective study provides 3-year large-scale results on the impact of RA disease activity on changes in BMD. Overall, although the BMD decreased significantly in the femur, hip, and spine in the remission group, there was a significant increase in bone density in the femoral and spinal areas of patients on AOT. In contrast, for patients in the

moderate or high activity group receiving AOT, the femoral BMD values decreased significantly. After adjustment for confounding factors, there was still a significant difference in the change in femoral bone mass between patients in remission and those in the moderate-high activity group receiving AOT. If AOT was not used, the hip BMD in the higher disease activity group also decreased more. For RA patients, these findings indicate that good control of disease activity has a positive effect on BMD.

In previous cross-sectional studies, with small samples or short follow-up time, the correlation between disease activity of RA and bone loss has been mentioned.^{7,17} In the study by Krieckaert *et al.*, even in a 1-year follow-up period, the decrease in the hip BMD was more pronounced in non-responders than in RA patients with good response.¹⁷ However, 1 year is a short time to determine changes in BMD, and the small changes in BMD may have led to inconsistent results.¹⁸ Some studies examined the effect of

Table 4. The generalized estimating equation for the change of bone mineral density during 3-year follow-up among patients having different mean Disease Activity Score levels with adjustment of potential confounders^a.

Outcome/ interaction effect	Remission n= 151		Low n= 132		Moderate or high n= 194		
	B (95% CI)	p value	B (95% CI)	p value	B (95% CI)	p value	p trend
Femoral, g/cm ²							
Total	Reference	–	–0.013 (–0.026, –0.000)	0.044	–0.011 (–0.023, 0.001)	0.065	0.076
AOT	Reference	–	–0.022 (–0.042, –0.001)	0.036	–0.038 (–0.055, –0.021)	<0.001	<0.001
Non-AOT	Reference	–	–0.009 (–0.024, 0.006)	0.259	–0.001 (–0.016, 0.013)	0.871	0.885
Hip, g/cm ²							
Total	Reference	–	–0.012 (–0.026, 0.003)	0.117	–0.012 (–0.027, 0.002)	0.094	0.105
AOT	Reference	–	–0.006 (–0.031, 0.020)	0.668	–0.002 (–0.027, 0.023)	0.861	0.901
Non-AOT	Reference	–	–0.013 (–0.031, 0.004)	0.133	–0.022 (–0.039, –0.005)	0.011	0.011

For the sake of saving space, only the estimates of interaction effect are showed.

^aThe analysis adjusted for age, sex, body mass index, previous fracture, parent fractured hip, current smoking, alcohol, coffee, tea, vegetarian, rheumatoid factor, anti-cyclic citrullinated peptide, disease duration, and daily prednisolone equivalent dose.

AOT, anti-osteoporosis therapy; B, regression coefficient, CI, confidence interval.

disease activity on bone turnover⁶ and changes in local bone density in the hands.^{19,20} All of this information provided ideas for designing the current prospective study in order to observe patients and to understand bone loss status and disease activity over a long period of time. In addition, we used time-averaged DAS to better represent the true disease status of these patients. Three years of follow-up and a large sample size can help provide robust conclusions.

Osteoporosis is a well-known complication of RA. First, glucocorticoid drugs often prescribed for the treatment of RA may cause severe bone loss. In addition, pain caused by disease and loss of joint function can lead to immobility, further increasing the risk of osteoporosis. Studies also indicate that bone loss in RA may be a direct result of inflammation.^{21,22} Therefore, reducing disease activity as much as possible can improve the above-mentioned adverse conditions, thereby reducing bone loss. Especially in the era of biologics, early and persistent remission is easier to achieve than before. In the current study, there was no significant decrease in the BMD at 3 years in the remission group receiving AOT (Table 2). Therefore, for patients in remission, we believe that the adverse effects of RA on bone density can

be alleviated, which is similar to the conclusions of previous reviews.²³ Further research comparing the decline in bone density of RA patients in remission and that of the general population can provide insight on this view.

Treat-to-target (T2T) focuses on the rapid reduction of disease activity and has been established as the guiding principle for the treatment of RA. Because the T2T approach produces good results, ACR, European League Against Rheumatism, and other professional organizations have recognized it as the basic treatment strategy for RA. T2T strategies have been shown to significantly reduce radiographic damage at the group level.²⁴ In addition, the reduction in disease activity over time in RA is associated with fewer cardiovascular events.²⁵ The evidence provided by the current study on the benefits of changes in the BMD for RA patients will increase our confidence in using T2T in clinical practice.

With respect to BMD, poor bone quality, or osteoporosis, in addition to non-pharmacological interventions (such as weight-bearing activities and nutrition), AOT is always considered the first option for treating patients. However, as RA itself is a clinical risk factor for osteoporosis, different

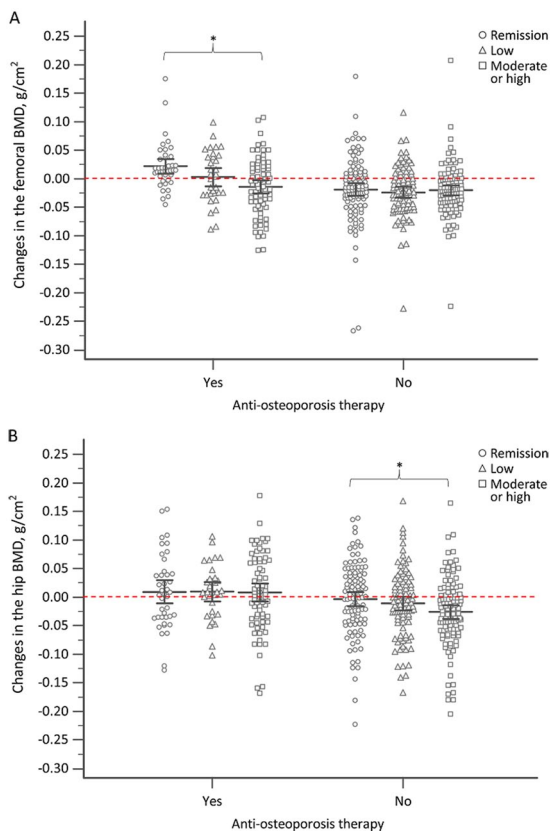


Figure 2. Changes in the bone mineral density (BMD) of the femur (A) and hip (B) during the 3-year follow-up among patients with different time-averaged Disease Activity Score levels stratified using anti-osteoporosis agent.

The horizontal line represents the mean and the error bar represents 95% confidence intervals for the means. Each symbol represents a single data point.

*Indicates significant difference between the "remission" and "moderate or high" groups.

treatment strategies should be adopted for patients with RA. It is important to control moderate or high disease activity. In addition, because osteoporosis treatment of RA patients often fails, disease activity should be considered when initially treating osteoporosis in RA cases.²⁶ According to the results of the current study, patients with higher disease activity experienced long-term BMD loss in the femoral region even though they were receiving AOT, in contrast to patients in remission (Tables 3 and 4). Although in clinical practice the absolute difference in BMD levels is relatively small, the difference is significant and worthy of attention. Previous cross-sectional studies also showed that high RA disease activity was independently associated with

low BMD.²⁷ Therefore, to improve the BMD of RA patients, both disease activity and AOT should be considered simultaneously.²⁸

RA itself, and even its disease activity, seems to have varying degrees of influence on the BMD of different parts. In patients with RA, cortical areas (such as the distal bone and neck of the femur) are more likely to develop osteoporosis than trabecular areas (such as the lumbar spine).^{29–31} This result is different from other inflammatory diseases. One of the possible reasons is that bone damage in RA is caused not only by inflammation, but also by the independent influence of ACPAs.³² In fact, before the clinical onset of RA, ACPAs have caused significant thinning and fenestration of cortical bone, but the changes in trabecular bone are slight.³³ In a study by Lodder *et al.*, higher disease activity was significantly associated with lower hip BMD, but this correlation was not significant in the spine.⁷ In the current study, compared with patients in remission, the femur and hip BMD of more severe patients tended to decrease more, but there was no such tendency in the spine area (Table 3). All results indicate that RA activity has a greater impact on the femur or hip area than on the spine area. Nonetheless, compared with the hip or femoral area, the spinal BMD value of patients using AOT increased even more (Table 3). This is consistent with the following view: the effect of bisphosphonates on trabecular bone is more pronounced than on cortical bone.³⁴

Glucocorticoids are widely used in patients with RA. They have certain disease-modifying effects, and their introduction at the beginning of RA treatment may increase the remission rate.³⁵ However, this group of medications is a double-edged sword because it also causes glucocorticoid-induced osteoporosis. The rate of glucocorticoid use varies greatly, but the global average is about 60–70%,³⁶ and this percentage is higher in the current study than the global average (91.4%). For women with early RA, previous studies mentioned that disease activity and disability may predict a decrease in BMD, and glucocorticoid therapy may not be possible.³⁷ It is difficult to determine the correlation between changes in BMD and disease activity in established RA patients without considering the effect of glucocorticoids. The use of glucocorticoids in severe cases and during induction seems reasonable, but long-term use of glucocorticoids is not

recommended.^{35,38} Given the long-term side effects of glucocorticoids on BMD, biologics should be used as soon as possible because they have a certain bone protection effect.³¹

It should be noted that BMD is related to aging because without additional intervention, most people will lose BMD with age. In fact, age is one of the parameters in the FRAX[®] evaluation.³ In this study, the mean age of patients with more severe arthritis is higher, as mentioned in previous studies.³⁹ The first possible reason is that ESR increases significantly with age, so for older men with low disease activity, the increase in ESR may underestimate the remission rate.⁴⁰ According to the study by Marloes *et al.*, age is significantly positively correlated with DAS28-ESR, while elderly patients have higher 28-SJC and ESR than younger patients.³⁹ Another possible cause is the duration of the disease. RA patients with longer disease duration do not respond well to treatment.⁴¹ Both of these reasons can lead to severe arthritis with an older baseline age. Therefore, to avoid the influence of age, we also included age in the multivariate analysis to correct the results.

According to the characteristics data, patients with a higher average DAS level did not have a higher proportion of biological agent use. There was no obvious positive relationship between them. We believe that this may be related to socioeconomic status and patient preferences. After all, this is a real-world study, and there will be a decision-making situation between doctors and patients. Another possible reason is that, due to the good effects of biological agents, the average disease activity of patients using biological agents will not be too high. In fact, the effect of disease activity on bone density seems to be more important than the immune-modulating agent we chose. A tight control strategy appears to be more important than control of RA with specific drugs.⁴²

There were some limitations to the current study. First, as the effect of AOT on BMD is obvious, we must consider it an important variable. Approximately 30% of the patients were on AOT; therefore, our cohort was not as consistent as we initially believed. Therefore, we stratified the main analysis by AOT to address this problem. Although there were some significant findings, the number of cases in each group was small, making the study less powerful. In any case, the

study used real-world data to provide doctors with important information.

Second, all the participants had established RA, so the external validity of the results for patients with early RA is doubtful. The destruction of RA is cumulative, and the inactivity caused by RA may cause further bone loss, which is relatively rare in early RA. In previous studies, early RA resulted in significant male bone loss in the femoral neck.⁴³ The relationship between disease activity and bone loss in early RA is inconsistent.^{37,44,45} Therefore, whether different stages of RA are correlated with different bone loss rates requires further observation and research.

Third, the current prospective study used only DAS28-ESR to measure disease activity while ignoring other scoring systems, such as the Clinical Disease Activity Index (CDAI) and van der Heijde-modified Total Sharp Score (TSS). Because ESR contributes to the DAS28-ESR score, different therapies have remarkably different effects on DAS28-ESR.⁴⁶ The actual disease activity of some patients may be distorted and misclassified. Furthermore, changes in basic radiology may affect the results of the study,⁴⁷ but only baseline and time averaged DAS can be provided in the current study. Therefore, in the future registration form, CDAI and TSS should also be included to draw clearer conclusions. Finally, we did not adjust for multiple testing (multiplicity) in the GEE model due to the limited sample size; therefore, the current conclusions might be optimistic and further larger-scale studies are warranted.

In conclusion, the disease activity of RA affects bone density significantly, although the clinical difference in BMD and the study power are relatively small for clinical practice. Higher RA disease activity may offset the benefits of AOT. Thus, even with AOT use, only the BMD of patients in the remission group showed a significant increase after 3 years of follow-up. Compared with the moderate or high activity group, AOT in the remission group can better improve BMD, especially in the femur. Therefore, active treatment of RA to disease remission is beneficial for bone health.

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Conflict of interest statement


The authors declare that there is no conflict of interest.

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Supplemental material

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