



Bone Loss and Radiographic Damage Profile in Rheumatoid Arthritis Moroccan Patients

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Received: February 26, 2021

Revised: April 27, 2021

Accepted: May 2, 2021

Background: Rheumatoid arthritis (RA) is a known cause of joint destruction and systemic bone loss. In this study, we aimed to evaluate the bone damage and bone loss profiles of established RA patients. **Methods:** We designed a cross-sectional study on a cohort of established RA patients. The bone evaluation was performed by obtaining standard X-ray images of hands and feet combined with bone mineral density (BMD) measurements. Radiographic joint damage was calculated by the modified total Sharp / van der Heijde score (mTSS). BMD was obtained by performing dual energy X-ray absorptiometry of the lumbar spine and femoral neck. Data on age, smoking, alcoholism, steroid prescription, body mass index (BMI), disease duration, disease activity, and functional disability were collected. **Results:** A total of 93 RA patients were recruited. Their mean age was 51.59 ± 12.38 years, with a mean disease duration of 12.07 ± 9.19 years. A total of 36.6% of patients had osteoporosis, and the mean mTSS was 70.33 ± 48.93 . Both hip ($P=0.0005$) and lumbar BMD ($P=0.0005$) were correlated with mTSS. Backward regression analyses determined that bone damage was associated with high titers of rheumatoid factor, low lumbar BMD, and low BMI. General bone loss was associated with gender, steroid dose, steroid duration, menopause, and BMI. **Conclusions:** Bone damage was associated with low BMI and axial bone loss in our RA population.

Key Words: Arthritis, rheumatoid · Bone density · Disability evaluation

INTRODUCTION

Rheumatoid arthritis (RA) is a frequent connective tissue disease, which results in disability and bone damage. Inflammation in the synovial membrane of joints explains bone damage in situ. The general bone loss in RA is very intricate. Several combined factors (e.g., inflammation, glucocorticoid (GC) chronic use, menopause, and disease-related weight loss) are the main factors leading to bone loss in RA.[1,2]

Inflammation and bone loss in RA are closely linked processes. The systemic inflammatory condition observed in RA leads to generalized reduced bone quality by encouraging osteoclast activity and inhibiting the reparative activity of osteoblasts.[3] Although focal and generalized bone loss is a combined phenomenon in RA, which is partially explained by the underlying inflammatory process, their correlation is subject to various modifying factors, such as treatments,[4,5] and tends to vary according to the disease course.[6] Furthermore, sex and ethnic differences regarding bone constitution and formation are well documented.[7,8]

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Men and those with African origins exhibit larger bone surfaces and higher trabecular bone density than females or other races (Caucasian), respectively.[7] This may result in different RA profiles regarding bone loss. Studies on bone loss and damage profiles in established RA are scarce, especially in our context. We hypothesized that bone damage is associated with bone loss in our RA patients. Therefore, our objective was to evaluate bone destruction and osteoporosis profile in our established RA patients, determine their relationship, and investigate the associated factors with radiographic joint damage and bone loss.

METHODS

1. Study design

We performed a cross-sectional study on established RA patients seeking care at our Rheumatology Department. We have included in the study the patients that were seen from October to December 2015.

2. Subjects

RA diagnosis was made according to the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) 2010 criteria. The patients with prior specific bone treatment, liver cirrhosis, renal insufficiency, primary hyperparathyroidism, and cancer were excluded. The study was conducted in accordance with the declaration of Helsinki, and all patients provided informed written consent prior to the study.

3. Bone evaluation

The bone mineral density (BMD) was measured with a dual energy X-ray absorptiometry (DXA) Lunar Prodigy DXA system version 12.3 (GE Healthcare, Madison, WI, USA) in 2 sites (femur and lumbar spine). Femur neck (FN) BMD was determined on the basis of a dual femur technique in g/cm²; lumbar BMD was evaluated from an anteroposterior view of L1–4. Hip BMD refers to the mean value of both FN BMDs. Osteoporosis was defined according to the World Health Organization classification (*t*-score < -2.5 in the spine and/or hip). The structural evaluation was performed simultaneously with BMD determination. The bone damage (erosion and joint narrowing) in hands and feet was calculated based on X-ray images according to the modified Sharp van der Heijde score (mTSS).[9] Two rheumatologists (M.L.

and L.L after a period of training) separately performed the calculation; in the case of non-concordance, a third rheumatologist performed the calculation, and an average estimation was obtained.

4. Data collection

The demographic data on age, gender, smoking, alcoholism status, and menopause were collected. In addition, the patients were asked whether they performed regular physical activity (more than 30 min of jogging per day or equivalent). Information on the disease duration, GC prescription (actual dosage, duration, withdrawal), and disease-modifying anti-rheumatic drug treatments were assessed. The body mass index (BMI) was calculated from each patient's height and weight (weight/height²); the latter 2 measurements used the same scale as that for BMD calculation. We used a composite index, the disease activity score for 28 joints for RA with erythrocyte sedimentation rate (DAS28-ESR).[10] The components of DAS28 were obtained within the current evaluation. The ESR was measured for each patient. Remission was defined by DAS28 < 2.6. Whereas low disease activity was considered when DAS28 was between 2.6 and 3.2, mild disease activity ranged from 3.2 to 5.1, and high disease activity was attributed to DAS28 > 5.1. We had concomitantly assessed functional disability using the health assessment questionnaire (HAQ).[11] The latter's final score ranged from 0 (no handicap) to 3 (highly impaired). Information on the rheumatoid factor (RF) titer and anti-Cyclic Citrullinated Peptide Antibodies was extracted from the patients' medical records.

5. Statistical analysis

The data were analyzed by the Statistical Package for the Social Sciences 20 software (SPSS Inc., Chicago, IL, USA). First, a descriptive study was made for each variable. Then, bivariate correlation (Pearson or Spearman test) was performed between 2 continuous variables to identify any significant association with bone damage (mTSS) or bone loss. We used analysis of variance (ANOVA) for quantitative variable analysis. Shapiro-Wilk test was used to evaluate normality. Multiple backward linear (mTSS, BMD) and logistic (osteoporosis) regressions were performed to identify factors associated with radiographic damage and osteoporosis in our patients. We used the variance inflation factor (VIF) test to study multicollinearity. The VIF test demon-

strated null multicollinearity (VIF=1) for the independent variables studied. There was modest multicollinearity detected for menopause duration and age (VIF=5) that did not affect other independent factors at the used models. A *P* value under 0.05 was considered to be statistically significant.

RESULTS

1. RA population characteristics

The study included 93 RA patients. They were middle-aged patients (51.59 ± 12.38 years old) with a mean disease duration of 12.07 ± 9.19 years. The diagnosis of RA was made

Table 1. Demographic and disease characteristics of our population

Characteristic	Mean \pm SD or N (%) (N=93)
Age (yr)	51.59 \pm 12.38
Women	82 (88.2)
BMI (kg/m ²)	25.42 \pm 5.01
Positive RF	77 (82.8)
Positive ACPA	74 (79.6)
ESR (mm/h)	31.4 \pm 27.1
Disease duration (yr)	12.07 \pm 9.19
Current steroid use	71 (76.3)
Steroid use duration, median (min-max) (month)	36 (0-360)
DMARDs	
MTX monotherapy	88 (94.6)
Combined MTX with sulfasalazine or HCQ	11 (11.8)
HCQ	23 (24.7)
Biologic DMARDs	8 (8.6)
Comorbidities	
Diabetes	6 (6.5)
Hypertension	9 (9.7)
Thyroid disease	5 (5.4)
DAS28	3.93 \pm 1.81
HAQ (range 0-3)	1.08 \pm 0.99
mTSS (hands and feet, range 0-448)	70.33 \pm 48.93
Osteoporosis	34 (36.6)
Hip BMD (g/cm ²)	0.884 \pm 0.163
Lumbar spine T-score	-1.72 \pm 1.43
Hip T-score	-1.15 \pm 1.33

BMI, body mass index; RF, rheumatoid factor; ACPA, anti-Cyclic Citrullinated Peptide Antibody; ESR, erythrocyte sedimentation rate; DMARDs, disease modifying anti-rheumatic drugs; MTX, methotrexate; HCQ, hydroxychloroquine; DAS28, disease activity score 28; HAQ, health assessment questionnaire; mTSS, modified total Sharp-van der Heijde score; BMD, bone mineral density; SD, standard deviation.

24 (12–72) months, as a median, after the onset of symptoms. The patients were slightly disabled (the mean of HAQ was 1.08 ± 0.99). Patients were in a remission state in 30.1% (28) and low disease activity in 16.1% (15). Mild and high disease activity was found in 22 (23.7%) and 28 (30.1%) patients, respectively. Comorbidities were present in 18 (19.3%) patients. They were a majority to receive methotrexate (94.6%). Osteoporosis was present in 36.6% of our patients, and their average mTSS score was 70.33 ± 48.93 (Table 1).

2. Osteoporosis classical factors

A total of 86.8% of our patients used or were using GC at the moment of the study; 13 patients smoked, and 3 were alcoholics. Menopause was recorded among 43 patients with a mean duration of 8.15 ± 7.71 years. We have assessed 6 cases of body thinness (BMI under 19). Only 12% of our patients declared to perform regular physical activity. There was no significant difference when comparing RA osteoporotic and non-osteoporotic patients regarding smoking, alcoholism, physical activity, and body thinness. However, women with osteoporosis were predominantly menopausal (61.8%), while 37.3% had menopause in the non-osteoporotic group.

3. Predictors of radiographic damage

Age, functional disability (HAQ), disease duration, GC use duration, and menopause duration were positively corre-

Table 2. Associated factors with mTSS, hip and spine BMD using correlations

	<i>P</i> -value		
	mTSS	Hip BMD	Lumbar BMD
Age	0.293 ^{a)}	-0.306 ^{a)}	-0.406 ^{b)}
Disease duration	0.475 ^{b)}	-0.233 ^{a)}	-0.178 ^{c)}
BMI	-0.257 ^{a)}	0.474 ^{b)}	0.306 ^{a)}
HAQ	0.307 ^{a)}	-0.209 ^{c)}	-0.247 ^{a)}
DAS28	0.128 ^{c)}	-0.180 ^{c)}	-0.210 ^{c)}
GC use duration	0.290 ^{a)}	-0.289 ^{a)}	-0.329 ^{a)}
GC dose	0.200 ^{c)}	-0.155 ^{c)}	-0.214 ^{c)}
Menopause duration	0.259 ^{a)}	-0.326 ^{a)}	-0.364 ^{a)}
Hip BMD	-0.479 ^{b)}	-	-
Spine BMD	-0.379 ^{b)}	-	-

^{a)} < 0.05. ^{b)} < 0.001. ^{c)} > 0.05.

BMI, body mass index; HAQ, health assessment questionnaire; DAS28, disease activity score 28; GC, glucocorticoid; BMD, bone mineral density; mTSS, modified total Sharp-van der Heijde score.

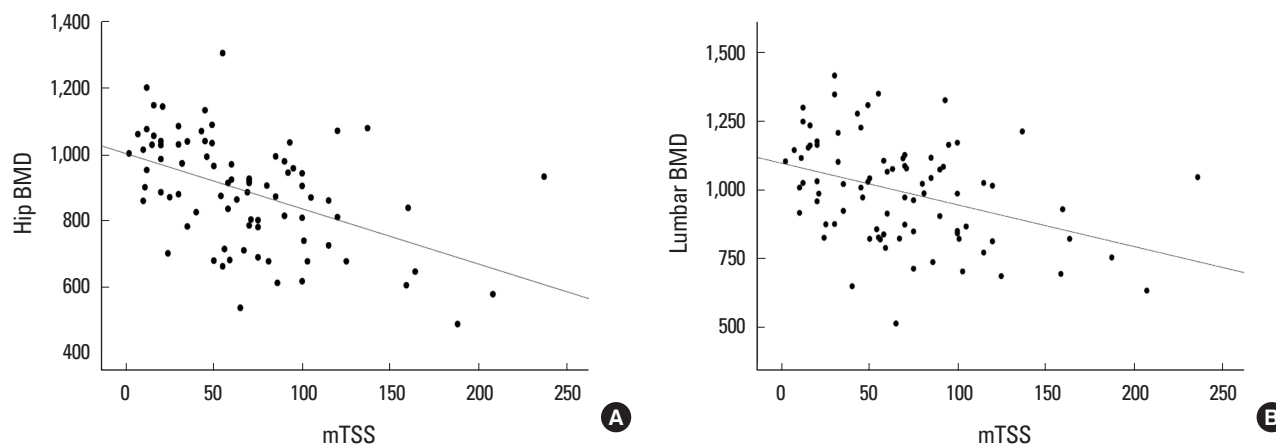


Fig. 1. Scatter plots of the modified total Sharp-van der Heijde score (mTSS) with (A) hip bone mineral density (BMD) and (B) lumbar BMD in our population.

lated with mTSS. On the other side, BMI and BMD (hip and spine) were negatively correlated with mTSS (Table 2 and Fig. 1). These variables were associated with bone damage, as determined by univariate linear regression (Table 3).

However, only high titer of RF with low lumbar BMD and low BMI were associated with mTSS in the multivariate backward regression model, including all associated factors (Table 3). Smoking was included in that model but did not reach significance.

4. Factors associated with bone loss

RA osteoporotic patients had significantly ($P=0.001$) higher mean mTSS (91.97 ± 46.85) than those without osteoporosis (57.86 ± 46.02). In logistic multivariate backward regression, osteoporosis was associated with gender ($P=0.01$), GC use duration ($P=0.028$), GC dose ($P=0.01$), menopause ($P=0.003$), and BMI ($P=0.001$; Table 4).

Age, disease, menopause, and steroid use duration, were negatively correlated to hip and lumbar BMD. Only BMI demonstrated a positive correlation with BMD (hip and lumbar) in our study (Table 2). At regressions, menopause was negatively associated with lumbar BMD ($P=0.02$), while disease duration was unassociated (Table 3). Multivariate backward linear regression revealed that lumbar BMD was best explained by age, GC dose, and BMI (Table 3).

DISCUSSION

In this study, Bone damage was best explained by positive RF, smoking, lumbar BMD, and BMI. Nevertheless, it was

positively associated with age, functional disability, GC use duration, and disease duration. On top of that, bone loss was associated with age, menopause, GC dose, and GC duration. BMI was a protective factor of both bone loss and bone damage in our study. These findings were in perfect agreement with the results reported in the literature. Late-onset [12,13] and longstanding RA disease [14] are known to be aggressive. On top of that, GC use duration was positively associated with mTSS. This could be explained by the heterogeneity of this population regarding disease duration and recent introduction of synthetic DMARDs. In our area, the diagnosis delay of RA was long (i.e., 24 [12-72] months), and many recruited patients were only on GC auto medication and never received a prior DMARD treatment (data not shown). The association between disability and joint destruction is controversial in the literature. We determined a positive significant association between HAQ and mTSS, which was also shown by Sivas et al. [14]; a positive significant association was also observed between disability scores and other measurement methods of radiographic damage. In addition, HAQ was also individualized as an independent predictor of radiographic progression in a Korean cohort.[15] It is possible that other studies [16,17] did not observe this association owing to the duration of studies and baseline HAQs. Severe disease is associated with a high HAQ score at the baseline,[18] which can explain the predictive ability of HAQ for joint damage.

Interestingly, BMI was inversely correlated with the Sharp scores. In our study, obesity appeared to be a protective factor for joint destruction in established RA. Several stud-

Table 3. Results of linear univariate and multivariate backward regression analyses for mTSS and BMD

	mTSS		Hip-BMD		Lumbar-BMD	
	Univariate β (95% CI)	Multivariate β (95% CI)	Univariate β (95% CI)	Multivariate β (95% CI)	Univariate β (95% CI)	Multivariate β (95% CI)
Age	0.290 (0.37 to 1.95) ^(a)	EV	-0.306 (-0.007 to -0.001) ^(b)	EV	-0.406 (-0.009 to -0.003) ^(b)	-0.491 (-0.01 to -0.004) ^(b)
Gender	0.012 (-29.5 to 33.2)	EV	0.010 (-0.1 to 0.11)	EV	0.039 (-0.1 to 0.143)	EV
DAS28	0.128 (-2.12 to 9.02)	EV	-0.180 (-0.03 to 0.003)	EV	-0.210 (0.04 to 0.0005)	EV
ACPA	-0.240 (-0.08 to -0.001) ^(a)	EV	0.170 (0)	EV	0.119 (0)	EV
RF	0.116 (+0.03 to 0.08)	0.327 (0.019 to 0.128) ^(a)	0.050 (0)	EV	0.103 (0)	EV
Smoking	-0.121 (-21.7 to 5.7)	-0.226 (-24.8 to 0.91)	-0.020 (-0.05 to 0.04)	EV	-0.002 (-0.05 to 0.05)	EV
Disease duration	0.475 (1.55 to 3.50) ^(b)	EV	-0.233 (-0.009 to -0.0004) ^(a)	EV	-0.178 (-0.009 to 0.001)	EV
GC use duration	0.222 (0.01 to 0.26) ^(a)	EV	-0.289 (-0.01 to -0.0002) ^(a)	-0.203 (-0.001 to 0)	-0.329 (-0.001 to -0.0003) ^(b)	EV
GC dose	0.200 (-0.28 to 5.23)	EV	-0.155 (-0.01 to 0.003)	EV	-0.214 (-0.02 to 0.001)	-0.329 (-0.02 to -0.005) ^(b)
HAQ	0.307 (5.33 to 24.82) ^(b)	EV	-0.209 (-0.07 to 0.001)	EV	-0.215 (-0.08 to 0)	EV
Hip BMD	-0.479 (-193.2 to -82.3) ^(b)	EV	-	-	-	-
Lumbar BMD	-0.379 (-145.7 to -43.9) ^(b)	-0.333 (-157.3 to -22.27) ^(a)	-	-	-	-
BMI	-0.219 (-4.32 to -0.06) ^(a)	-0.387 (-5.58 to -1.18) ^(b)	0.474 (0.009 to 0.02) ^(b)	0.570 (0.009 to 0.023) ^(b)	0.329 (0.004 to 0.02)	0.400 (0.006 to 0.02) ^(b)
Menopause	0.125 (-5.92 to 24.16)	EV	-0.110 (-0.07 to 0.03)	EV	-0.231 (-0.12 to -0.005) ^(a)	EV
Duration of menopause	0.259 (0.36 to 3.67) ^(a)	EV	-0.326 (-0.01 to -0.003) ^(b)	-0.334 (-0.014 to -0.002) ^(a)	-0.364 (-0.02 to -0.004) ^(b)	EV

^{a)}P<0.05. ^{b)}P<0.005.

DAS28, disease activity score 28; ACPA, anti-cyclic citrullinated peptide antibody; RF, rheumatoid factor; GC, glucocorticoid; HAQ, health assessment questionnaire; BMD, bone mineral density; BMI, body mass index; mTSS, modified total Sharp-van der Heijde score; CI, confidence interval; EV, excluded variable in the final model.

Table 4. Univariate and multivariate backward logistic regressions for osteoporosis

	Osteoporosis	
	Univariate OR (95% CI)	Multivariate OR (95% CI)
Age	1.06 (1.02 to 1.1) ^{b)}	EV
mTSS	1.016 (1.005 to 1.026) ^{b)}	EV
Gender (female)	1.01 (0.27 to 3.73)	71.52 (2.48 to 2055.6) ^{a)}
BMI	0.88 (0.79 to 0.97) ^{a)}	0.71 (0.58 to 0.86) ^{b)}
Menopause	1.72 (0.9 to 3.27)	12.46 (2.34 to 66.26) ^{b)}
Duration of menopause	1.1 (1.01 to 1.18) ^{a)}	EV
ACPA positivity	0.94 (0.3 to 2.8)	EV
RF positivity	0.70 (0.22 to 2.27)	EV
DAS28	1.21 (0.95 to 1.54)	EV
Smoking	1.06 (0.6 to 1.87)	EV
Disease duration	1.01 (0.96 to 1.06)	EV
GC use duration	1.007 (1.001 to 1.01) ^{a)}	1.009 (1.001 to 1.02) ^{a)}
GC dose	1.13 (0.99 to 1.27)	1.24 (1.04 to 1.48) ^{a)}
HAQ	1.39 (0.9 to 2.14)	EV

^{a)} $P < 0.05$. ^{b)} $P < 0.005$.

mTSS, modified total Sharp-van der Heijde score; BMI, body mass index; ACPA, anti-cyclic citrullinated peptide antibody; RF, rheumatoid factor; DAS28, disease activity score 28; GC, glucocorticoid; HAQ, health assessment questionnaire; OR, odds ratio; CI, confidence interval; EV, excluded variable in the final model.

ies have shown this association between BMI and bone damage.[19-21] It has been also reported that low BMI is a significant predictor of radiographic progression in Caucasian and Korean populations with early RA.[15,22] To explain this paradoxical fact, some theories have been proposed such as the mechanical effect of greater weight and greater muscle mass on bone remodeling,[22] or the effect of aggressive therapy conducted in obese patients based on their habitual high DAS activity.[21] Studies focusing on adipocytokines in RA indicated that the levels of adiponectin [23,24] or leptin [25] could be associated with radiological damage. The molecular mechanism of this association is yet unknown.

A high titer of the RF was associated with mTSS in this study. Studies suggested that RF and anti-cyclic citrullinated proteins antibodies had a potentially significant role in erosion even in the absence of inflammation.[26] RF even determines radiographic progression independently of disease activity in a study of 5 RA clinical trials.[27] These clinical observations are supported by the increased Fc-receptor expression during osteoclastogenesis and the effective stimulation of osteoclasts differentiation by immune

complexes *in vivo* and *in vitro* studies.[26]

We have demonstrated a good correlation between hip, lumbar BMD, and joint damage, but only lumbar BMD remained negatively associated with mTSS at the multivariate model. This association has been previously reported in studies focusing on established RA.[28,29] While in early RA, this finding seems to be more evident, especially in hands.[30,31] In established RA, this association is diluted by emergent confounding factors, especially for hip BMD. [28] Moreover, Zhang et al. [29] showed that generalized bone loss was an independent predictor of joint radiographic progression.

Several studies have shown lower BMD in RA than that in controls; the largest effect has been measured in the hip.[2,32] In the current study, the lumbar–spine *t*-score was lower than the total hip *t*-score and was affected by menopause. Hip BMD was associated with disease duration and not menopause status. This can be explained by the osteoporosis profile seen in RA, which is more pronounced in cortical bone.[1,33] In our RA patients, we observed factors associated with bone loss that were similar to those cited in the literature. Steroid dose and use duration were associated with bone loss. Some studies have shown that GC use was not an overall predictor of BMD loss, rather its use duration was a predictor.[34] The impact of steroids on bone health is also complex. GCs are known to induce osteoporosis in healthy bone,[35] it is a dose- and duration-dependent effect. In RA, steroids reverse inflammation, which is the direct cause of bone loss and damage by the disease. A recent longitudinal study (10 years of follow-up) has shown that the use of steroids was not associated with bone loss; however, the cumulative steroid dose was significantly associated with the total hip BMD in the first 2 years of RA evolution.[36] The effect of steroids on RA bone is not only a dose- and duration-dependent effect but also probably a site-effect. Engvall has determined that low-dose Prednisolone in early RA counteracts the negative effects of rheumatoid inflammation in bone tissue in the hip but not in the lumbar spine, especially in postmenopausal women.[5] These data show the multifaceted condition of bone loss in RA.

In this study, BMI was highly correlated with BMD and had a protective effect on bone loss in our RA patients. The association between obesity and RA appeared to be controversial. Although both diseases are inflammatory and

result in high morbidity and mortality, obesity is associated with less bone erosion and osteoporosis in patients with RA.[37] The effect of high BMI on bone can be partially explained by the estrogenic role in bone remodeling and the mechanical bone loading effect.

Finally, our study's objective was to develop a profile of factors associated with bone loss and joint damage in established RA. Some limits should be mentioned. Specifically, the cross-sectional design would not permit prediction models. Besides, we used backward regression analysis to make easily interpretable models; however, stepwise analyses were criticized for possible false inclusion or exclusion of correlated independent variables.[38] Also, hand BMD could not be measured at the time of the study.

CONCLUSION

In this study, joint damage was associated with BMD loss in our established RA patients. The generalized bone loss was also predicted by steroid dose, steroid duration, menopause, and gender; high BMI was a protective factor for bone loss and local damage in our RA population.

DECLARATIONS

Acknowledgments

The authors acknowledge the contribution made by Drs. O. Akkar, M. Lehraiki, L. Lehlou, and L. Boutouala in data acquisition. The paper was presented at the 2016 ARLAR meeting and accepted as an abstract at the 2016 EULAR annual congress.

Funding

The authors received no financial support for this article.

Ethics approval and consent to participate

This study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved.

Conflict of interest

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

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